

Université de Montréal

Les mécanismes neurophysiologiques sous-jacents aux effets hypoalgésiques de la manipulation
vertébrale dans le soulagement de la douleur au dos

Par

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Thèse présentée
en vue de l'obtention du grade de Philosophiæ Doctor (Ph.D.)
en sciences biomédicales

Février 2026

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Université du Québec à Trois-Rivières

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Cette thèse intitulée

**Les mécanismes neurophysiologiques sous-jacents aux effets hypoalgésiques de la
manipulation vertébrale dans le soulagement de la douleur au dos**

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Résumé

La lombalgie chronique constitue la principale cause mondiale d'années vécues avec des incapacités et représente un fardeau socio-économique majeur. La thérapie par manipulation vertébrale (TMV) figure parmi les interventions recommandées pour le soulagement de la lombalgie chronique. Toutefois, son efficacité clinique demeure relativement modeste, possiblement en raison d'une utilisation sous-optimale. Une meilleure connaissance des mécanismes d'action de la TMV permettrait de l'offrir de manière ciblée aux personnes dont la lombalgie repose sur des mécanismes physiopathologiques sur lesquels cette intervention devrait agir.

L'objectif principal de cette thèse était de mieux caractériser les mécanismes neurophysiologiques sous-jacents aux effets hypoalgésiques de la TMV dans le soulagement de la douleur au dos, en mettant un accent particulier sur son influence sur les processus neuronaux d'amplification de la douleur associés à l'activation des fibres C nociceptives, puisque les résultats d'études antérieures suggèrent que ces mécanismes sont impliqués dans le soulagement de la douleur par cette intervention.

Quatre études ont été réalisées afin d'atteindre cet objectif. Durant la première étude, en utilisant un modèle expérimental de douleur au dos, il a été démontré que la TMV n'influence pas le traitement nociceptif spinal lorsque les afférences nociceptives sont amplifiées par des mécanismes de sensibilisation périphérique. La deuxième étude a permis de développer et de valider une méthode visant à mesurer les réponses cérébrales évoquées par la stimulation des fibres C nociceptives. Ces réponses, ainsi que plusieurs facteurs associés à la douleur chronique, ont ensuite été comparées dans une troisième étude entre des individus atteints de lombalgie primaire chronique et des participants asymptomatiques appariés pour l'âge et le sexe. Les résultats n'ont révélé aucune différence significative entre les groupes en ce qui concerne la sommation temporelle de la douleur ni les réponses cérébrales évoquées par la stimulation des fibres C nociceptives. En revanche, les individus atteints de lombalgie primaire chronique présentaient une hyperalgésie diffuse, de même que des niveaux plus élevés de dramatisation de

la douleur, de vigilance à la douleur et de symptômes dépressifs. Enfin, les résultats d'un essai contrôlé randomisé indiquent que la TMV module le traitement nociceptif spinal lorsque les afférences des fibres C nociceptives sont amplifiées par des mécanismes centraux. Ce mécanisme neurophysiologique contribuerait à la réduction à long terme de l'intensité de la douleur chez les individus atteints de lombalgie primaire chronique. Des effets non spécifiques, possiblement attribuables aux facteurs contextuels, participent également aux effets hypoalgésiques observés, particulièrement après 12 séances d'intervention. De plus, l'application de l'intervention au-delà de la région symptomatique est associée à une diminution supplémentaire de l'intensité de la lombalgie au cours du premier mois d'intervention, et possiblement au-delà.

Ces résultats contribuent à une meilleure compréhension des mécanismes d'action de la TMV et pourraient permettre d'optimiser les soins offerts aux personnes atteintes de douleurs vertébrales chroniques.

Mots-clés : lombalgie, chiropratique, manipulation vertébrale, douleur chronique, thérapie manuelle, laser, fibres C nociceptives, activité cérébrale, électroencéphalographie.

Abstract

Chronic low back pain is the leading global cause of years lived with disability and represents a major socioeconomic burden. Spinal manipulative therapy (SMT) is among the recommended interventions for the management of chronic low back pain. However, its clinical effectiveness remains relatively modest, possibly due to suboptimal use. A better understanding of the mechanisms of action of SMT could allow for a more targeted application of the intervention to individuals whose low back pain is driven by pathophysiological mechanisms that are responsive to this treatment.

The primary objective of this doctoral thesis was to better characterize the neurophysiological mechanisms underlying the hypoalgesic effects of SMT in the treatment of low back pain, with a particular focus on its influence on neuronal pain amplification processes associated with the activation of nociceptive C fibers, as previous studies suggest that these mechanisms play a role in pain relief induced by this intervention.

Four studies were conducted to achieve this objective. In the first study, using an experimental model of low back pain, SMT was shown not to influence spinal nociceptive processing when nociceptive afferents were amplified by peripheral sensitization mechanisms. The second study involved the development and validation of a method to measure cortical responses evoked by stimulation of nociceptive C fibers. These responses, along with several factors associated with chronic pain, were subsequently compared in a third study between individuals with chronic primary low back pain and pain-free participants matched for age and sex. The results revealed no significant between-group differences in temporal summation of pain or in brain responses evoked by nociceptive C fibers stimulation. In contrast, individuals with chronic primary low back pain exhibited diffuse hyperalgesia, as well as higher levels of pain catastrophizing, pain vigilance, and depressive symptoms. Finally, results from a randomized controlled trial indicate that SMT modulates spinal nociceptive processing when nociceptive C fibers afferents are amplified by centrally mediated mechanisms. This neurophysiological mechanism appears to contribute to the long-term reduction of pain intensity in individuals with

chronic primary low back pain. Non-specific effects, possibly attributable to contextual factors, also contribute to the observed hypoalgesic effects, particularly following 12 treatment sessions. Moreover, applying the intervention beyond the symptomatic region was associated with an additional reduction in low back pain intensity during the first month of treatment, and possibly beyond.

These findings contribute to a better understanding of the mechanisms of action of SMT and may help optimize care for individuals with chronic spinal pain.

Keywords: low back pain, chiropractic, spinal manipulation, chronic pain, manual therapy, nociceptive C fibers, laser, brain activity, electroencephalography.

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Liste des sigles et abréviations

ANOVA: analysis of variance

ANCOVA: analysis of covariance

AINS: anti-inflammatoires non stéroïdiens

IASP: International Association for the Study of Pain

CONSORT: Consolidated Standards of Reporting Trials

EEG: électroencéphalographie / electroencephalography

EOG: electrooculography

ERSP: event-related spectral perturbation

ERD: event-related desynchronization

ERS: event-related synchronization

ICD: International Classification of Disease

IMMPACT: Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials

LEP: laser-evoked potential

LPB: low back pain

CLBP: chronic low back pain

CPLBP: chronic primary low back pain

Nd:YAP: yttrium aluminium pérovskite dopé au néodyme

NMDA: N-methyl-D-aspartate

NRS: numeric rating scale

NSAID: non-steroidal anti-inflammatory drugs

OMS: Organisation mondiale de la santé

PPT: pressure pain threshold

QST: quantitative sensory testing

SD: standard deviation

SM: spinal manipulation

SMT: spinal manipulative therapy

TMV: thérapie par manipulation vertébrale

TNF- α : tumor necrosis factor alpha

TRPV1: transient receptor potential vanilloid 1

TSSP: temporal summation of second pain

VAS: visual analog scale

WHO: World Health Organization

Remerciements

J'aimerais d'abord exprimer ma profonde gratitude envers la Fondation Chiropratique du Québec, le département d'anatomie, le décanat des études, la Fondation de l'UQTR, ainsi que le Réseau de Bio-Imagerie du Québec et le Fonds de recherche du Québec – Santé (FRQS) pour leur précieux soutien financier, sans lequel il m'aurait été impossible de poursuivre mes ambitions.

Je tiens également à remercier mon directeur, le Pr Mathieu Piché, pour sa confiance, son accompagnement, son support et la possibilité qu'il m'a offerte de réaliser un tel projet.

Un immense merci à toutes les personnes qui ont participé à ces études — sans vous, aucune recherche ne pourrait voir le jour.

Enfin, un merci tout particulier à ma famille, pour son soutien indéfectible tout au long de cette longue aventure.

Chapitre 1 – Introduction

1.1 La douleur

1.1.1 Douleur et nociception

La douleur constitue l'un des motifs de consultation les plus fréquents en soins de première ligne (Finley et al., 2018). Bien qu'extrêmement répandue, elle demeure une expérience fondamentalement subjective, puisqu'il est impossible de l'inférer en se basant uniquement sur l'activité neuronale (Raja et al., 2020; Treede, 2018). En ce sens, la douleur correspond à une expérience personnelle dont chacun fait l'apprentissage à travers les divers événements de sa vie et cette expérience est influencée par de multiples facteurs biologiques, psychologiques et sociaux (MacMahon et al., 2013; Raja et al., 2020; van Strien & Hollmann, 2025).

Malgré certaines critiques (Cohen et al., 2018), la définition de la douleur la plus largement utilisée demeure celle proposée par l'International Association for the Study of Pain (IASP) en 1979, puis révisée en 2020 afin de reconnaître explicitement que la capacité à communiquer n'est pas une condition nécessaire à l'expérience douloureuse. La définition actuelle stipule que la douleur est « une expérience sensorielle et émotionnelle désagréable associée ou ressemblant à celle associée à une lésion tissulaire réelle ou potentielle » (Raja et al., 2020). Bien que désagréable par nature, la douleur remplit une fonction biologique essentielle : son caractère aversif signale au système nerveux la présence de stimuli nocifs — qu'ils correspondent à des lésions avérées ou à des menaces potentielles — et permet ainsi l'élaboration de réponses de protection adaptées (MacMahon et al., 2013). À court terme, la douleur est donc fondamentale à la survie.

La nociception, quant à elle, est définie comme « le processus neuronal d'encodage des stimuli nocifs » (International Association for the Study of Pain, 1979). Elle repose sur l'activation de neurones sensitifs spécialisés, les fibres nociceptives, qui détectent les stimuli potentiellement dommageables au niveau des tissus et transmettent cette information au système nerveux central (Fenton et al., 2015; MacMahon et al., 2013). Ces neurones seront décrits plus en détail

dans la section suivante. Il est essentiel de distinguer la nociception de la douleur, car ces deux phénomènes peuvent survenir de manière indépendante (van Strien & Hollmann, 2025). La nociception correspond à un processus neurophysiologique inconscient, susceptible — mais non nécessairement — de donner lieu à une expérience douloureuse, tandis que la douleur est, par définition, une expérience consciente pouvant survenir même en l’absence de nociception (MacMahon et al., 2013; Treede, 2018; van Strien & Hollmann, 2025). Sur la base des mécanismes impliqués, l’IASP reconnaît trois grandes catégories de douleur, présentées au **Tableau 1.1**.

Tableau 1.1 – Les catégories de douleur selon les mécanismes impliqués

Catégorie	Définition et exemples
Douleur nociceptive	Douleur résultant d’une lésion réelle ou potentielle à un tissu autre que nerveux et due à l’activation des nocicepteurs → traumatisme physique, arthrose
Douleur neuropathique	Douleur causée par une lésion ou une pathologie du système nerveux somatosensoriel → radiculopathie, névralgie trigéminal, douleur liée à la sclérose en plaques, etc.
Douleur nociplastique	Douleur résultant d’une nociception altérée, sans preuve claire de lésion tissulaire réelle ou potentielle pouvant activer les nocicepteurs, ni de maladie ou de lésion du système nerveux somatosensoriel pouvant expliquer la douleur → fibromyalgie, syndrome de l’intestin irritable, lombalgie primaire chronique, etc.

Tableau traduit et adapté de (International Association for the Study of Pain, 1979; Jensen et al., 2011; Kosek et al., 2016; Scholz et al., 2019; van Strien & Hollmann, 2025).

L’information nociceptive emprunte principalement les voies antérolatérales pour atteindre l’encéphale (Blumenfeld, 2011). Les cornes dorsales de la moelle épinière reçoivent les afférences de nombreux neurones sensitifs, incluant les fibres nociceptives, lesquelles établissent des synapses avec des neurones de projection localisés principalement dans les lames I, II et V de Rexed (Fenton et al., 2015; Karcz et al., 2024; MacMahon et al., 2013). Ces neurones de 2^e ordre décussent au niveau de la commissure antérieure et rejoignent différentes voies ascendantes controlatérales — notamment les tractus spinothalamique, spinoparabrachial, spinomésencéphalique et spinoréticulaire — assurant ainsi la transmission de l’information nociceptive vers de multiples structures sous-corticales, telles que le noyau parabrachial, la région bulbaire rostro-ventrale et la substance grise périaqueducule. Le thalamus y joue un rôle central

en recevant à la fois des projections directes du tractus spinothalamique et des projections indirectes en provenance des voies spinomésencéphalique et spinoréticulaire. Il agit ainsi comme un relais majeur, un site d'intégration et un filtre de l'information sensorielle (Blumenfeld, 2011; Fenton et al., 2015; Karcz et al., 2024; MacMahon et al., 2013; van Strien & Hollmann, 2025).

L'information nociceptive est ensuite transmise à un réseau distribué de structures télencéphaliques interconnectées — incluant les cortex somatosensoriels primaire et secondaire, le cortex préfrontal, le cortex cingulaire, l'insula et l'amygdale — où elle sera interprétée et contribuera potentiellement à l'élaboration de l'expérience douloureuse (MacMahon et al., 2013; van Strien & Hollmann, 2025). Il convient de souligner qu'aucune de ces régions n'est exclusivement dédiée au traitement de l'information nociceptive et que les patrons d'activité cérébrale associés à la douleur peuvent varier considérablement d'un individu à l'autre (van Strien & Hollmann, 2025). Les principales voies impliquées dans le traitement de l'information nociceptive sont illustrées à la **Figure 1.1B**. De plus, tout au long de ces circuits complexes, les afférences nociceptives sont modulées par des voies descendantes (MacMahon et al., 2013; van Strien & Hollmann, 2025). L'issue de ce traitement nociceptif peut être la perception d'une douleur dite nociceptive.

Les mécanismes sous-jacents à la douleur neuropathique sont, pour leur part, moins bien élucidés, mais impliquent une activité anormale et inappropriée des fibres nociceptives lésées et intactes, ainsi que des altérations du traitement nociceptif qui en découlent (MacMahon et al., 2013). Enfin, la douleur nociplastique résulte principalement d'un dysfonctionnement de mécanismes centraux de transmission et de modulation de l'information nociceptives, lesquels seront abordés plus en détail à la section 1.2.

Au-delà de cette classification mécanistique, la douleur peut également être catégorisée selon sa durée. On distingue ainsi la douleur aiguë, persistant depuis moins de trois mois, et la douleur chronique, présente depuis plus de trois mois (Treede et al., 2019). La douleur aiguë peut être de nature nociceptive ou neuropathique (Bouhassira, 2019; Treede et al., 2019) et joue un rôle d'alarme essentiel à la préservation de l'intégrité de l'organisme (MacMahon et al., 2013). À l'inverse, bien que la douleur chronique puisse parfois refléter la persistance d'un processus

pathologique sous-jacent — auquel cas elle sera de nature nociceptive ou neuropathique —, elle correspond le plus souvent à une entité pathologique à part entière et sera alors de nature nociplastique (Treede et al., 2019). Cette distinction sera approfondie à la section 1.4.

1.1.2 Les fibres nociceptives

Les neurones sensitifs peuvent être classés selon différents critères, mais ils sont le plus souvent regroupés en fonction de leur vitesse de conduction, laquelle dépend essentiellement du diamètre de l'axone et de son degré de myélinisation (MacMahon et al., 2013). Cette classification distingue quatre grandes catégories de fibres sensibles — A α , A β , A δ et C — classées des plus rapides aux plus lentes (Blumenfeld, 2011; MacMahon et al., 2013; Sneddon, 2018). Chacune de ces catégories regroupe des populations hétérogènes de neurones sensitifs présentant des seuils d'activation variables et répondant à différents types de stimuli (MacMahon et al., 2013).

Ainsi, chacune de ces catégories peut inclure des fibres capables d'encoder des stimuli nocifs ou inoffensifs. Toutefois, les fibres A α et A β répondent principalement à des stimuli mécaniques inoffensifs, tandis que la majorité des fibres A δ et C, en raison de leur seuil d'activation relativement élevé, encodent préférentiellement des stimuli nocifs (MacMahon et al., 2013). Ainsi, dans le cadre de cette thèse, seules ces dernières seront considérées. Les principales caractéristiques des fibres nociceptives A δ et C sont présentées au **Tableau 1.2**.

Les différences de vitesse de conduction entre ces deux types de fibres expliquent l'apparition d'une double sensation douloureuse aux caractéristiques distinctes lorsque celles-ci sont activées de manière concomitante (Julius & Basbaum, 2001; MacMahon et al., 2013). La stimulation des fibres A δ est perçue en premier et se manifeste par une sensation brève et bien localisée, souvent décrite comme une piqûre, alors que l'activation des fibres C engendre, avec un léger délai, une sensation plus diffuse et prolongée, typiquement décrite comme une brûlure ou une pression (Ploner et al., 2002; Weiss et al., 2008). Ce phénomène est classiquement décrit en termes de première et de seconde douleur et est illustré à la **Figure 1.1C**.

Tableau 1.2 – Caractéristiques principales des fibres nociceptives A δ et C

Type de fibres	A δ	C
Classification alternative	Groupe III	Groupe IV
Sous-classification	Type I ou type II (selon leur vitesse de conduction et leur patron de réponse aux stimuli thermiques)	Peptidergiques ou non-peptidergiques
Innervation	Peau, tissus musculosquelettiques (à l'exception du cartilage articulaire) et viscères. Les fibres A δ de type II sont absentes de la peau glabre.	Peau, tissus musculosquelettiques (à l'exception du cartilage articulaire) et viscères
Myélinisation	Présente, mais fine	Absente
Diamètre axonal	1-5 μ m	0,2-1,5 μ m
Vitesse de conduction moyenne	Type I: 25 m/s Type II: 15 m/s	<2 m/s
Sensation perçue	Première douleur : brève et localisée de type piqûre ou pincement	Seconde douleur : lente et diffuse de type brûlure ou pression
Modalité d'activation	Polymodales (stimuli mécaniques, thermiques et chimiques)	Polymodales (stimuli mécaniques, thermiques et chimiques)
Seuil d'activation à la chaleur (stimuli brefs)	Type I: > 53 °C Type II: $\approx$ 47 °C	37 à 49 °C

Tableau traduit et adapté de (Blumenfeld, 2011; Julius & Basbaum, 2001; MacMahon et al., 2013; Schepers & Ringkamp, 2010; Sneddon, 2018; Varga & Mravec, 2015).

Enfin, il convient de souligner que les fibres A δ (type I) et les fibres C peuvent être sensibilisées, ce qui module de manière importante l'intensité de la douleur perçue (MacMahon et al., 2013). Les mécanismes neurophysiologiques sous-jacents à cette sensibilisation sont abordés dans la section suivante.

1.2 Les mécanismes de sensibilisation à la douleur

L'une des propriétés fondamentales des neurones impliqués dans l'encodage et la transmission de l'information nociceptive est leur capacité à être sensibilisés (Battaglia, 2016; MacMahon et al., 2013). En présence de facteurs pro-inflammatoires ou à la suite de stimulations nocives soutenues ou répétées, leur seuil d'activation s'abaisse. Ils deviennent alors plus facilement excitables, peuvent s'activer de manière spontanée et répondent de façon amplifiée

aux stimuli dépassant leur seuil d'activation (Battaglia, 2016; MacMahon et al., 2013). Le corrélat perceptuel de ce phénomène neurophysiologique est l'hyperalgésie, caractérisée par une diminution du seuil de douleur, une augmentation de la réponse douloureuse à un stimulus donné et la présence de douleur spontanée (MacMahon et al., 2013). La sensibilisation peut survenir à la fois au niveau du système nerveux périphérique et du système nerveux central; ces deux formes sont décrites ci-après.

1.2.1 La sensibilisation périphérique

La sensibilisation périphérique correspond à une augmentation de l'excitabilité des fibres nociceptives (Battaglia, 2016; Karcz et al., 2024; MacMahon et al., 2013). Elle survient à la suite d'une lésion tissulaire, lorsque les tissus endommagés — nerveux ou non — ainsi que les cellules impliquées dans la réparation tissulaire libèrent une variété de facteurs pro-inflammatoires, tels que l'acide arachidonique, les prostaglandines, la bradykinine, les protons, la sérotonine, l'histamine, les purines, les cytokines, le NGF (*nerve growth factor*) et la substance P (Karcz et al., 2024; MacMahon et al., 2013; Pak et al., 2018). Ces médiateurs inflammatoires modifient l'expression génique et protéique au niveau des fibres nerveuses périphériques, notamment celle de certains canaux ioniques et récepteurs membranaires (Karcz et al., 2024; MacMahon et al., 2013; van Strien & Hollmann, 2025). Ces altérations entraînent une diminution du seuil de réponse — habituellement élevé chez les fibres nociceptives —, une augmentation de la réponse à un stimulus supra-seuil, ainsi qu'un élargissement du champ récepteur des fibres nociceptives locales (MacMahon et al., 2013). La sensibilisation périphérique affecte exclusivement les nocicepteurs exposés aux facteurs pro-inflammatoires; l'hyperalgésie primaire qui en résulte est donc circonscrite à la région lésée.

Bien que la sensibilisation périphérique soit essentielle à la compréhension de nombreuses conditions douloureuses, en particulier en contexte de douleur nociceptive, elle ne permet pas à elle seule d'expliquer l'ensemble des signes et symptômes observés chez les personnes atteintes de douleur persistante (Woolf, 2011). Néanmoins, l'augmentation des afférences nociceptives vers la moelle épinière qu'elle induit contribue au développement de la

sensibilisation centrale, un mécanisme permettant de rendre compte d'une plus grande part des manifestations cliniques observées (Latremoliere & Woolf, 2009).

1.2.2 La sensibilisation centrale

La sensibilisation centrale résulte d'une plasticité neuronale des voies nociceptives, définie comme un changement durable du fonctionnement des neurones persistant au-delà de la cause initiale (Latremoliere & Woolf, 2009; MacMahon et al., 2013). Elle se caractérise par trois altérations majeures au niveau des neurones nociceptifs des cornes dorsales de la moelle épinière : 1) une augmentation de leur excitabilité, 2) un élargissement de leur champ récepteur et 3) l'acquisition d'une capacité à répondre à des stimuli normalement inoffensifs (Battaglia, 2016; MacMahon et al., 2013). Sur cette base, la sensibilisation centrale est définie opérationnellement comme « une amplification de la signalisation neuronale au sein du **système nerveux central**, entraînant une hypersensibilité à la douleur » (Woolf, 2011).

Les mécanismes précis à l'origine de ce phénomène ne sont pas encore entièrement élucidés, mais impliquent une facilitation des afférences nociceptives combinée à une diminution de la modulation descendante (Harte et al., 2018; Karcz et al., 2024; van Strien & Hollmann, 2025). Dans le premier cas, l'activation des récepteurs *N-methyl-D-aspartate* (NMDA) exprimés par les neurones nociceptifs des cornes dorsales — notamment par la liaison du glutamate, un neurotransmetteur excitateur libéré par l'ensemble des fibres nociceptives — joue un rôle central dans le développement et le maintien de la sensibilisation centrale (Karcz et al., 2024; MacMahon et al., 2013). Ce processus est le plus souvent initié par une activation intense et/ou prolongée des fibres C nociceptives (Battaglia, 2016; Karcz et al., 2024; MacMahon et al., 2013). Une fois installée, la sensibilisation centrale peut se maintenir avec un niveau très faible d'afférences nociceptives (Woolf, 2011). Parallèlement, un dysfonctionnement des voies de la modulation descendante est fréquemment observé. Celles-ci activent normalement la libération d'opioïdes endogènes — incluant les endorphines, les dynorphines et les enképhalines — et projettent vers les cornes dorsales de la moelle épinière (Karcz et al., 2024; van Strien & Hollmann, 2025). En

conditions normales, ces substances exercent un effet inhibiteur sur la nociception et la douleur; leur diminution entraîne l'effet inverse (Karcz et al., 2024).

Sur le plan perceptuel, l'hyperalgésie primaire — correspondant à une augmentation de la sensibilité thermique et mécanique au niveau des tissus lésés — résulte d'une sensibilisation périphérique et/ou centrale (Treede et al., 1992). La sensibilisation centrale se manifeste également par une hyperalgésie secondaire et par une allodynie mécanique (MacMahon et al., 2013). L'hyperalgésie secondaire correspond à une augmentation de la sensibilité mécanique, mais non thermique, dans les régions adjacentes à la lésion. Elle ne résulte pas de la diffusion de médiateurs inflammatoires, mais plutôt de l'élargissement du champ récepteur des neurones de projection nociceptifs (Battaglia, 2016; Treede et al., 1992). L'allodynie mécanique, quant à elle, se définit comme une douleur provoquée par un stimulus normalement inoffensif, tel qu'un toucher léger. Elle découle d'une potentialisation hétérosynaptique associée à une désinhibition des interneurons excitateurs reliant les fibres A β , de sorte que leur activation engage désormais des neurones de projection nociceptifs sensibilisés (Battaglia, 2016; MacMahon et al., 2013).

Enfin, l'hyperalgésie diffuse — soit une augmentation de la sensibilité thermique et mécanique dans plusieurs régions corporelles éloignées — constitue une manifestation clinique typiquement associée à la douleur nociplastique, une condition dans laquelle la sensibilisation centrale joue un rôle prépondérant (Kaplan et al., 2024; Kosek, 2024). Une diminution de la modulation descendante figure parmi les mécanismes contribuant à cette forme d'hyperalgésie (Yarnitsky, 2010).

Le wind-up est un phénomène neurophysiologique étroitement lié à la sensibilisation centrale, dont le corrélat perceptuel est la sommation temporelle de la douleur (Bosma et al., 2015; Herrero et al., 2000). Il correspond à une augmentation progressive de l'activité des neurones nociceptifs des cornes dorsales de la moelle épinière en réponse à l'activation répétée de fibres C nociceptives par des stimuli d'intensité constante, administrés à une fréquence supérieure ou égale à 0,33 Hz (Baron et al., 2013; Herrero et al., 2000; Li et al., 1999). Afin de souligner la contribution des fibres C nociceptives, la sommation temporelle de la douleur est également désignée sous le terme de sommation temporelle de la seconde douleur (Anderson et

al., 2013; Bosma et al., 2015; Wakui et al., 2025). Contrairement à la sensibilisation centrale, qui persiste au-delà de la cause initiale, le wind-up ne se manifeste que pendant la répétition des stimuli et ne constitue pas un état durable (Woolf, 2011). Il ne reflète pas non plus une amplification des réponses aux afférences sensibles non stimulées, qu'elles soient nociceptives ou non (Woolf, 2011). Néanmoins, il est probable que le wind-up contribue au développement et au maintien de la sensibilisation centrale (Herrero et al., 2000). Facilement reproductible en laboratoire, il constitue ainsi un modèle expérimental pertinent pour l'étude de plusieurs de ses mécanismes (Arendt-Nielsen, 2015; Herrero et al., 2000; Li et al., 1999; Staud et al., 2007).

Cette distinction est particulièrement importante, puisque la sensibilisation centrale est fortement impliquée dans le développement de plusieurs syndromes douloureux chroniques (Nijs et al., 2021; Nijs et al., 2023; Woolf, 2011). À cet égard, il est de plus en plus courant de situer les personnes atteintes de douleur chronique sur un continuum en fonction du degré de sensibilisation centrale observé (Harte et al., 2018; Nijs et al., 2021). Bien que le concept de sensibilisation centrale présente une utilité clinique indéniable (Nijs et al., 2023), il serait néanmoins réducteur de rendre compte de toute la complexité des syndromes douloureux chroniques en se fondant exclusivement sur des mécanismes neurophysiologiques (Cayrol et al., 2021). Cette perspective sera approfondie à la section 1.4.

1.3 L'étude de la douleur

1.3.1 Le laser pour l'étude de la douleur et du traitement nociceptif

Pour évaluer adéquatement le traitement nociceptif, il est nécessaire de stimuler préférentiellement les fibres nociceptives tout en minimisant l'activation d'autres modalités sensibles, telles que la mécanoréception et la proprioception (Plaghki & Mouraux, 2003). Différentes méthodes — incluant l'application de stimuli électriques, thermiques (chaud ou froid), chimiques ou mécaniques — permettent d'activer les fibres nociceptives et d'induire une douleur expérimentale chez les participants. Chacune de ces approches présente des avantages

et des limites, et le choix de la méthode dépend essentiellement de ses propriétés et des objectifs spécifiques de l'expérience (MacMahon et al., 2013).

Dans ce contexte, l'utilisation de stimuli thermiques chauds produits par un laser infrarouge constitue un outil particulièrement pertinent pour l'étude de la douleur et du traitement nociceptif (Plaghki & Mouraux, 2003). Ces stimuli permettent une élévation très rapide de la température d'une région cutanée restreinte au moyen d'une lumière invisible, ce qui entraîne l'activation sélective et synchrone d'un nombre suffisant de fibres nociceptives pour permettre la mesure de leurs réponses (Bromm et al., 1984; Cruccu & García-Larrea, 2004; Plaghki & Mouraux, 2003). La chaleur générée par l'impulsion laser active les fibres nociceptives par l'ouverture des canaux cationiques *transient receptor potential vanilloid 1* (TRPV1), des récepteurs fortement exprimés par ces fibres et sensibles à la température ainsi qu'à certains stimuli chimiques (Greffrath et al., 2002; Ilie et al., 2019). Un autre avantage majeur de cette méthode réside dans la possibilité d'ajuster précisément l'intensité des stimuli afin d'induire une perception douloureuse chez les participants, offrant ainsi l'opportunité d'évaluer simultanément la douleur rapportée et le traitement nociceptif sous-jacent (Hu et al., 2014; Plaghki & Mouraux, 2003). Cet aspect est particulièrement important, puisque, comme mentionné précédemment, la douleur et la nociception ne sont pas toujours corrélées, notamment lorsque des mécanismes nociplastiques sont en jeu. De plus, plusieurs paramètres de stimulation — tels que la durée de l'impulsion, la taille du stimulus ou la région d'application — peuvent être modulés afin de cibler préférentiellement les fibres nociceptives A δ ou C (Hu et al., 2014; Verdugo et al., 2022).

L'ensemble de ces caractéristiques fait du laser infrarouge un outil de choix pour évaluer le système nociceptif, tant en contexte expérimental qu'en milieu clinique (Cruccu & García-Larrea, 2004; de Tommaso et al., 2020; Plaghki & Mouraux, 2005; Treede et al., 2003; Verdugo et al., 2022). Son principal inconvénient réside toutefois dans l'impossibilité de déterminer avec précision si les altérations observées dans les réponses mesurées sont d'origine périphérique, spinale ou supraspinale (Verdugo et al., 2022). En effet, il a été rapporté que les réponses induites par des stimuli laser — détaillées dans la section suivante — reflètent l'état général du système nociceptif plutôt qu'un niveau spécifique de son organisation fonctionnelle (de Tommaso et al., 2020). Par ailleurs, bien que plusieurs types de lasers infrarouges soient disponibles, le laser à

yttrium aluminium pérovskite dopé au néodyme (Nd:YAP) présente certains avantages. Il permet notamment une meilleure synchronisation des afférences nociceptives, facilitant ainsi la détection des réponses évoquées (Perchet et al., 2008). De plus, il est associé à un risque réduit de lésions cutanées (Cruccu et al., 2003; Iannetti et al., 2004), et des recommandations spécifiques ont été formulées quant à son utilisation afin de minimiser ce risque (Madden et al., 2016).

1.3.2 L'électroencéphalographie pour l'étude du traitement nociceptif

L'électroencéphalographie (EEG) constitue l'un des outils de mesure de l'activité cérébrale les plus anciens et les plus largement utilisés (Schomer, 2018). Le signal EEG brut est toutefois difficile, voire impossible, à interpréter directement, puisqu'il résulte de la superposition de multiples processus sensoriels, moteurs et cognitifs intégrés (Luck, 2014). Néanmoins, diverses techniques d'analyse permettent de décomposer ce signal afin d'étudier de nombreuses fonctions du système nerveux, incluant le traitement nociceptif (MacMahon et al., 2013; Schomer, 2018; Treede et al., 2003; Verdugo et al., 2022). Parmi ces techniques, l'analyse des potentiels évoqués et les analyses temps-fréquence figurent parmi les approches les plus couramment utilisées pour étudier le traitement nociceptif (Cohen, 2014; Luck, 2014; Nuwer, 1998). Elles sont présentées ci-dessous.

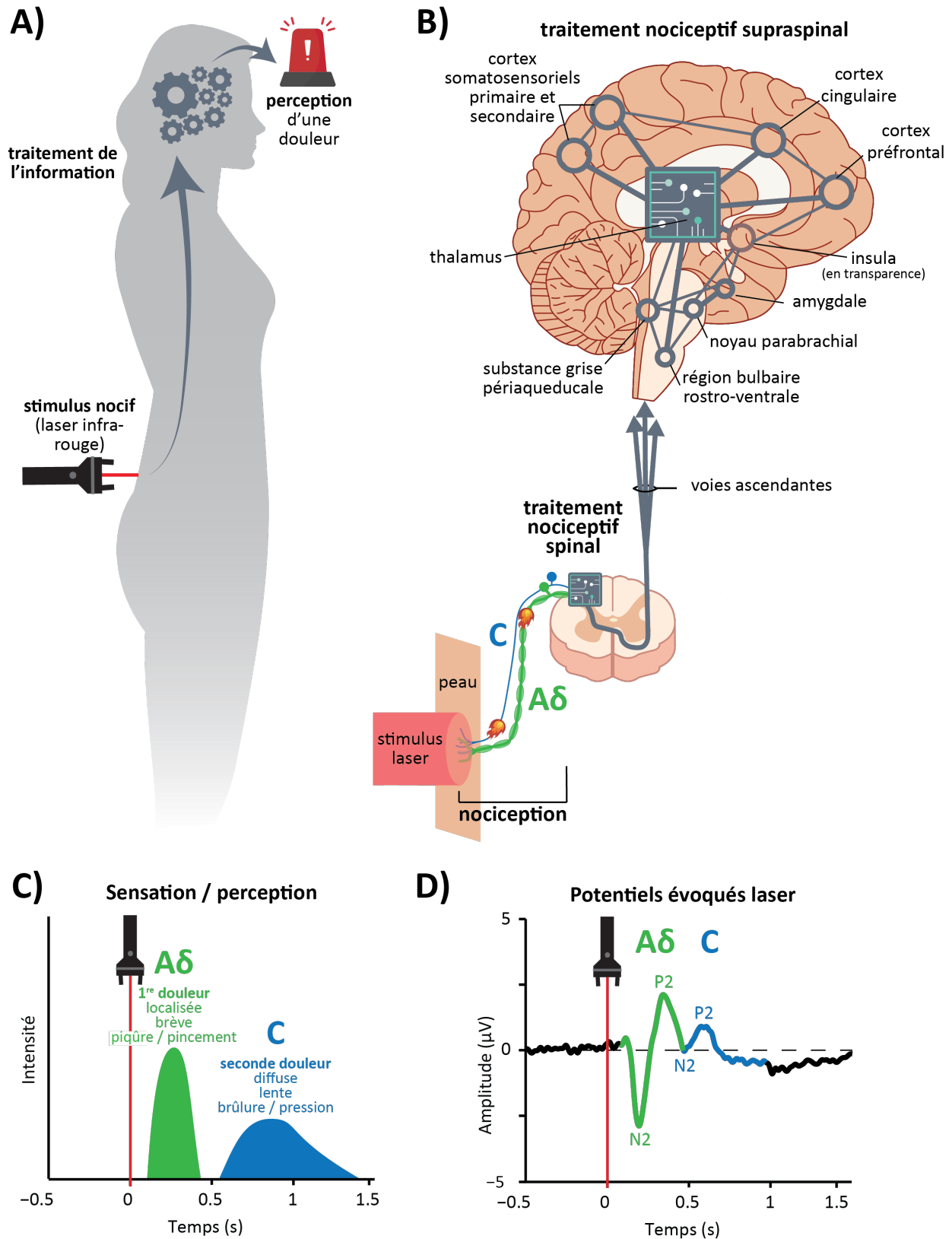
1.3.2.1 Les potentiels évoqués

Les neurones communiquent entre eux par de faibles courants électriques qui se superposent. La différence de potentiel générée par cette activité, mesurée par rapport à une référence donnée, peut être enregistrée quasi instantanément à l'aide d'électrodes placées sur le scalp (Buzsáki et al., 2012; Schomer, 2018). Bien que des courants électriques provenant de toutes les cellules excitables contribuent au voltage extracellulaire (Buzsáki et al., 2012), il est généralement admis que les potentiels évoqués résultent principalement de la sommation de potentiels postsynaptiques issus de populations de neurones pyramidaux présentant une orientation et une localisation corticales similaires (Luck, 2014; Schomer, 2018). Les potentiels évoqués sont obtenus en moyennant l'activité cérébrale enregistrée en réponse à un stimulus

répété un nombre de fois variable, selon la nature de ce dernier. Lorsque le stimulus est appliqué par un laser, on parle alors de potentiels évoqués laser (*laser-evoked potentials*, LEP). Le moyennage des essais permet d'atténuer fortement l'activité cérébrale spontanée, dont les fluctuations sont aléatoires dans le temps, tout en préservant l'activité évoquée par le stimulus, qui survient dans une fenêtre temporelle relativement constante après celui-ci. Cette procédure améliore ainsi le rapport signal/bruit du signal EEG (Luck, 2014; Schomer, 2018).

L'atténuation de l'activité qui n'est pas associée au stimulus permet de faire émerger des composantes des potentiels évoqués, correspondant à des inflexions positives ou négatives observées à des latences spécifiques dans le signal EEG moyenné (Luck, 2014). Les LEP sont présentement le meilleur outil pour l'évaluation fonctionnelle des voies nociceptives (Cruccu et al., 2010; de Tommaso et al., 2020; Treede et al., 2003). Ces réponses cérébrales, bien qu'elles soient hautement influencées par la saillance des stimuli, représentent une mesure indirecte du traitement nociceptif (Iannetti et al., 2008; Lenoir et al., 2020; Peng & Tang, 2016). L'utilisation des LEP a contribué de manière significative à l'avancement des connaissances en neurophysiologie de la douleur (Garcia-Larrea & André-Obadia, 2025; MacMahon et al., 2013). Les principales composantes des LEP présentent généralement une amplitude maximale au niveau du vertex et sont classiquement désignées sous les appellations N2 et P2 (Cruccu & García-Larrea, 2004; Plaghki & Mouraux, 2005; Schomer, 2018; Treede et al., 2003; Verdugo et al., 2022). Un exemple de LEP illustrant ces composantes est présenté à la **Figure 1.1D**.

Figure 1.1 – Sommaire des concepts fondamentaux pour l'étude de la douleur



A) Illustration schématique des principales étapes menant à la perception d'une douleur nociceptive. **B)** Représentation des voies ascendantes impliquées dans la nociception et le traitement nociceptif. **C)** Illustration de la double sensation douloureuse perçue lors de la stimulation concomitante des fibres nociceptives A δ et C. **D)** Exemple de potentiel évoqué par laser (LEP) présentant ses principales composantes (N2–P2) chez un participant représentatif. Cette figure a été créée à l'aide d'images provenant d'Adobe Stock (stock.adobe.com), utilisées conformément aux conditions de la licence.

Comme illustré dans cette figure, il est possible d'observer des LEP distincts associés à l'activation des fibres A δ ou C. Les composantes liées aux fibres C nociceptives présentent toutefois des latences plus tardives, en raison de la vitesse de conduction moindre de ces fibres (Bromm & Treede, 1987; Hu et al., 2014; Plaghki & Mouraux, 2005). La mise en évidence du complexe N2–P2 associé aux fibres C représente néanmoins un défi technique. Pendant longtemps, il a été suggéré que l'activation concomitante des fibres A δ devait être évitée afin de pouvoir observer clairement les réponses liées aux fibres C (Bragard et al., 1996; Bromm & Treede, 1987; Magerl et al., 1999; Opsommer et al., 2021; Plaghki & Mouraux, 2005). Cette idée est d'ailleurs encore relayée dans un important ouvrage de référence en EEG (Schomer, 2018).

Cependant, des travaux ont montré que la difficulté à observer l'activité évoquée par les fibres C est principalement attribuable à une sélection inadéquate des paramètres de stimulation, plutôt qu'à l'activation concomitante des fibres A δ (Mouraux & Plaghki, 2007a, 2007b; Truini et al., 2007). Ce défi méthodologique a d'ailleurs été rencontré au cours de la réalisation de la présente thèse et le chapitre 3 décrit en détail les stratégies mises en œuvre pour y répondre.

1.3.2.2 Les analyses temps-fréquences

Le cerveau présente une activité oscillatoire riche et complexe, reflétant divers processus neuronaux distincts (Buzsáki, 2006; Schomer, 2018). Cette activité rythmique résulte en grande partie de la synchronisation périodique de l'activité neuronale au sein de populations de neurones (Ploner et al., 2017). Elle est détectable dans le signal EEG et peut être caractérisée en termes de fréquence, d'amplitude et de phase des oscillations (Cohen, 2014; Schomer, 2018).

Les oscillations cérébrales sont généralement regroupées en bandes de fréquences : delta (0,5–3,5 Hz), thêta (4–7 Hz), alpha (8–13 Hz), bêta (14–29 Hz) et gamma (30–100 Hz) (Cohen, 2014; Schomer, 2018). La synchronisation et la désynchronisation de ces oscillations au sein de différentes bandes de fréquences contribuent au transfert dynamique de l'information entre les régions cérébrales (Ploner et al., 2017). Un événement ponctuel, tel qu'un stimulus douloureux, peut perturber cette activité rythmique et induire une synchronisation ou une désynchronisation transitoire de populations neuronales spécifiques (Neuper & Pfurtscheller, 2001; Pfurtscheller & Lopes da Silva, 1999). L'application de méthodes d'analyse fréquentielle au signal EEG permet de caractériser ces perturbations spectrales dans le temps (Cohen, 2014). Contrairement à l'analyse des potentiels évoqués, les analyses temps-fréquence sont particulièrement adaptées à l'étude de l'activité cérébrale qui n'est pas strictement synchronisée dans le temps avec le stimulus (Morales & Bowers, 2022; Pfurtscheller & Lopes da Silva, 1999). C'est notamment le cas des réponses cérébrales induites par la stimulation des fibres C nociceptives, dont la faible vitesse de conduction engendre une importante variabilité inter-essai dans la latence des réponses (Hu et al., 2014). Dans ce contexte, le moyennage des essais lors de l'analyse des potentiels évoqués tend à réduire artificiellement l'amplitude des réponses mesurées, en raison de cette variabilité temporelle. Bien que la réduction de la taille de la région stimulée puisse atténuer partiellement cette variabilité (Hu et al., 2014), cette approche présente elle-même des limites, ce qui confère aux analyses temps-fréquence un intérêt particulier pour l'étude de la douleur et du traitement nociceptif (Ploner et al., 2017).

Les changements observés dans les analyses temps-fréquence dépendent à la fois du type de stimulus appliqué et des catégories de fibres nociceptives recrutées (Jankovski et al., 2013; Ploner et al., 2017). De plus, ces réponses oscillatoires sont modulées par l'intensité du stimulus,

reflétant ainsi la quantité d'afférences nociceptives recrutées (Domnick et al., 2009; Ploner et al., 2017). Enfin, il est important de noter que la synchronisation transitoire de l'activité neuronale dans les basses fréquences (< 10 Hz) correspond, dans le domaine fréquentiel, à l'activité neuronale synchronisée associée aux potentiels évoqués (Jankovski et al., 2013; Mouraux et al., 2003; Ploner et al., 2017).

1.3.3 Les méthodes psychophysiques

En complément des mesures neurophysiologiques — telles que la microneurographie, les réflexes nociceptifs spinaux ou les mesures de l'activité cérébrale dont celles décrites à la section précédente —, il existe des méthodes psychophysiques et des modèles expérimentaux permettant d'étudier le système nociceptif de manière non invasive (MacMahon et al., 2013). Bien que de nombreuses approches soient utilisées en recherche animale (Sandkühler, 2009), seuls les outils employés chez l'humain sont abordés ici.

Ces méthodes reposent principalement sur l'évaluation quantitative sensorielle (*quantitative sensory testing*, QST), qui consiste à appliquer des stimuli mécaniques ou thermiques calibrés afin d'évaluer les seuils de perception d'un individu sur différentes régions du corps (Mücke et al., 2021; Starkweather et al., 2016; van Driel et al., 2024). L'existence de protocoles standardisés, combinée à une bonne fiabilité test-retest et interexamineur, fait de ces approches des outils particulièrement utiles pour évaluer la fonction des neurones sensitifs (fibres A β , A δ et C) et pour inférer les mécanismes sous-jacents à la douleur, notamment la présence de sensibilisation périphérique ou centrale (Knutti et al., 2014; Marcuzzi et al., 2017; Nothnagel et al., 2017; Owens et al., 2025; Paungmali et al., 2012; Starkweather et al., 2016).

L'évaluation quantitative sensorielle permet d'examiner plusieurs modalités somatosensorielles (Mücke et al., 2021; van Driel et al., 2024). Toutefois, dans le cadre de cette thèse, seules les mesures les plus couramment utilisées en lien avec la perception de la douleur seront considérées. Celles-ci, ainsi que leur signification clinique et mécanistique, sont résumées au **Tableau 1.3**. Les mécanismes neurophysiologiques inférés à partir des mesures psychophysiques doivent être interprétés avec prudence, puisqu'un même résultat peut refléter

des contributions périphériques et centrales variables selon le contexte clinique ou expérimental. Il importe également de souligner que les résultats de l'évaluation quantitative sensorielle sont influencés par des facteurs psychologiques tels que la dramatisation de la douleur, l'anxiété et la peur du mouvement (Owens et al., 2025). Ainsi, cette approche ne reflète pas uniquement des mécanismes neurophysiologiques. Cette caractéristique en ferait d'ailleurs, selon certains auteurs, un outil particulièrement pertinent pour l'étude de la douleur nociplastique (Owens et al., 2025).

Tableau 1.3 – Éléments de l'évaluation quantitative sensorielle utilisés pour l'étude des mécanismes de la douleur

Tests → fibres évaluées	Région évaluée	Signe clinique détectable	Mécanismes neuro-physiologiques inférés
Seuil de douleur à la chaleur → C et A δ	Site lésionnel	Hyperalgésie primaire (thermique cutanée)	Sensibilisation périphérique
Seuil de douleur mécanique (filaments de Von Frey) → A δ > C	Site lésionnel	Hyperalgésie primaire (mécanique cutanée)	Sensibilisation périphérique
	Peau non lésée avoisinante	Hyperalgésie secondaire (mécanique cutanée)	Sensibilisation centrale
Seuil de douleur à la pression (algomètre) → C et A δ	Site lésionnel	Hyperalgésie primaire (mécanique des tissus profonds [muscles])	Sensibilisation périphérique
	Peau non lésée avoisinante	Hyperalgésie secondaire (mécanique des tissus profonds [muscles])	Sensibilisation centrale
Réponse à un toucher léger → A β	-	Allodynie mécanique dynamique	Sensibilisation centrale
Ratio wind-up → C	-	Sommation temporelle de la douleur	Sensibilisation centrale et wind-up
Modulation conditionnée de la douleur → voies de la modulation descendante de la douleur	-	Diminution de la modulation conditionnée de la douleur	Dysfonction de la modulation descendante (associée à la sensibilisation centrale)

Les fibres et mécanismes indiqués correspondent aux contributions dominantes rapportées dans la littérature. Tableau traduit et adapté de (Mücke et al., 2021; van Driel et al., 2024).

L'évaluation quantitative sensorielle peut être utilisée tant chez des individus présentant une douleur clinique que dans des contextes expérimentaux, lorsque des modèles de sensibilisation sont appliqués chez des sujets sains afin d'étudier les mécanismes sous-jacents à la douleur. À cet égard, plus d'une quinzaine de modèles expérimentaux de sensibilisation centrale ont été recensés, parmi lesquels l'application de capsaïcine demeure le plus couramment utilisée (Quesada et al., 2021). La capsaïcine est une molécule naturellement présente dans les piments forts. Elle se lie aux récepteurs TRPV1 — également activés par la chaleur des stimuli laser — qui sont fortement exprimés au niveau des fibres C nociceptives (Ilie et al., 2019). Son application induit une réaction inflammatoire locale qui active les fibres nociceptives et provoque une douleur expérimentale, ainsi qu'une hyperalgésie primaire et secondaire (Ilie et al., 2019; LaMotte et al., 1992).

1.3.4 Les principales mesures d'intérêt en recherche clinique sur la douleur chronique

Les mesures neurophysiologiques et psychophysiques présentées jusqu'à présent sont généralement considérées comme des mesures secondaires, en ce sens qu'elles relèvent principalement de la recherche fondamentale et visent avant tout à approfondir la compréhension des mécanismes sous-jacents à la douleur. Toutefois, dans le contexte de la recherche appliquée — c'est-à-dire lorsque l'objectif est d'évaluer des interventions destinées à traiter des individus atteints de douleur, en particulier de douleur chronique — l'évaluation d'un ensemble minimal de variables cliniques standardisées devient essentielle.

Une telle approche permet d'obtenir une appréciation plus globale de l'état des participants, tout en facilitant la comparaison entre les études, la mise en commun des données dans le cadre de méta-analyses et le transfert des connaissances vers les milieux cliniques (Turk et al., 2003). À cet égard, le groupe Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) a souligné l'importance d'évaluer systématiquement chacun des six domaines d'intérêt qu'il a identifiés comme essentiels aux essais cliniques en douleur (Turk et al., 2003). Par ailleurs, des recommandations spécifiquement dédiées à la recherche clinique sur la

douleur sont venues compléter les lignes directrices Consolidated Standards of Reporting Trials (CONSORT), afin d'améliorer la qualité méthodologique, la comparabilité des études et la transparence des publications dans ce domaine (Gewandter et al., 2019; Hopewell et al., 2025). Ces bonnes pratiques en recherche clinique sur la douleur sont synthétisées dans les sections suivantes.

1.3.4.1 La douleur

Plusieurs dimensions peuvent être prises en compte afin d'évaluer la douleur dans son ensemble, notamment son intensité, son décours temporel, sa localisation et son caractère (Turk et al., 2003). Parmi celles-ci, l'intensité de la douleur constitue la dimension la plus fréquemment évaluée en recherche clinique. À cet égard, le groupe IMMPACT recommande l'utilisation d'une échelle numérique de 11 points (0 à 10, où 0 correspond à « aucune douleur » et 10 à « la pire douleur imaginable ») afin de quantifier l'intensité de la douleur (Dworkin et al., 2005).

Cette mesure devrait également être utilisée pour définir et rapporter de manière explicite les critères d'inclusion des participants (Gewandter et al., 2019), par exemple, en précisant que ceux-ci ont été recrutés s'ils rapportaient une douleur moyenne $\geq 3/10$ au cours des 24 heures précédentes. Par ailleurs, l'utilisation d'interventions concomitantes visant à réduire la douleur — en particulier la prise d'analgésiques — devrait être documentée de façon détaillée, puisqu'elle constitue un indicateur indirect de l'intensité de la douleur et de son évolution dans le temps (Dworkin et al., 2005). Cet élément a d'ailleurs été explicitement intégré à la plus récente révision des lignes directrices CONSORT (Hopewell et al., 2025).

Bien que moins fréquemment évalué dans les essais cliniques portant sur la douleur chronique, le décours temporel de la douleur peut également représenter un indicateur pertinent du changement clinique. Celui-ci inclut notamment des variables telles que la fréquence des épisodes douloureux, leur durée et le délai avant l'obtention d'un soulagement (Dworkin et al., 2005). Plusieurs échelles validées permettent de recueillir ces informations de manière standardisée (Jumbo et al., 2021; Salamon et al., 2014).

1.3.4.2 La fonction physique

Au-delà de la réduction des symptômes, un objectif central des soins de santé consiste à améliorer la capacité des individus à fonctionner dans leur vie quotidienne (Turk et al., 2003). L'évaluation de la fonction physique revêt une importance particulière dans le contexte de la douleur chronique, puisque celle-ci est fréquemment associée à une incapacité fonctionnelle marquée, que la réduction de l'intensité douloureuse demeure parfois limitée et que la corrélation entre l'intensité de la douleur et la fonction est généralement modeste (Dworkin et al., 2005).

Ainsi, plusieurs interventions cliniques visent principalement à réduire les interférences de la douleur sur les activités de la vie quotidienne plutôt qu'à éliminer complètement la douleur (Taylor et al., 2016; Turk et al., 2003). Les outils d'évaluation de la fonction physique se répartissent en deux grandes catégories : les mesures de résultats rapportés par les patients (*patient-reported outcome measures*, PROMs), qui prennent généralement la forme de questionnaires, et les mesures basées sur la performance, qui évaluent la capacité des individus à réaliser des tâches ou des épreuves physiques spécifiques (Taylor et al., 2016). Ces deux types de mesures fournissent des informations complémentaires et leur combinaison permet une appréciation plus complète de la fonction (Taylor et al., 2016). Dans chacune de ces catégories, il existe des instruments génériques ainsi que des instruments spécifiques à la condition de santé étudiée. Lorsque disponibles, les mesures spécifiques à la condition sont à privilégier, car elles présentent une meilleure sensibilité à la détection de changements cliniques pertinents (Turk et al., 2003).

1.3.4.3 La fonction émotionnelle

L'évaluation de la fonction émotionnelle constitue un élément essentiel de la recherche clinique sur la douleur chronique, puisque de nombreuses études ont mis en évidence une association étroite entre l'expérience douloureuse et la détresse psychologique (Dworkin et al., 2005; Rogers & Farris, 2022; Turk et al., 2003). Cette relation est d'ailleurs explicitement reconnue

dans la définition de la douleur chronique primaire, laquelle intègre la détresse émotionnelle comme composante centrale de cette expérience (Treede et al., 2019).

Dans cette perspective, le groupe IMMPACT recommande l'utilisation du questionnaire de dépression de Beck afin d'évaluer la présence et la sévérité des symptômes dépressifs chez les participants (Beck et al., 1961; Bourque & Beaudette, 1982; Dworkin et al., 2005). Selon les objectifs spécifiques de l'étude et les caractéristiques de la population investiguée, d'autres instruments validés peuvent également être utilisés afin d'objectiver des dimensions émotionnelles complémentaires, telles que l'anxiété, la colère ou d'autres symptômes pertinents.

1.3.4.4 L'amélioration globale et la satisfaction

Malgré l'apparente exhaustivité des mesures précédemment décrites, celles-ci ne permettent pas de saisir pleinement l'expérience subjective des participants ni l'importance relative qu'ils accordent aux différents aspects évalués (Dworkin et al., 2005; Turk et al., 2003). Afin de pallier cette limite, il est recommandé d'inclure au minimum une mesure de l'impression globale de changement.

Cette mesure permet aux participants d'intégrer, en un score unique, l'ensemble des composantes de leur expérience, incluant la perception de l'amélioration ou de la détérioration, la présence d'effets secondaires et la satisfaction à l'égard de l'intervention reçue (Dworkin et al., 2005). L'amélioration globale est généralement évaluée à l'aide d'une échelle numérique ou ordinale comportant des ancrages allant de « détérioration considérable » à « amélioration considérable », en passant par « aucun changement » (Cormier et al., 2016; Dworkin et al., 2005).

1.3.4.5 Les événements indésirables

Tous les essais cliniques, y compris ceux portant sur la douleur, devraient rapporter de manière systématique les effets secondaires observés (Dworkin et al., 2005; Hopewell et al., 2025; Schulz et al., 2010; Turk et al., 2003). Ces effets correspondent à des manifestations inattendues et involontaires associées aux interventions utilisées et peuvent être de nature

positive ou négative (Ioannidis et al., 2004). Toutefois, le terme « événement indésirable » est réservé aux effets secondaires négatifs, c'est-à-dire à ceux qui entraînent une détérioration de l'état de la personne (Ioannidis et al., 2004).

Les événements indésirables ont un impact important sur l'adhérence au protocole de l'étude et leur prise en compte influence directement l'interprétation des résultats, l'évaluation du rapport risque-bénéfice des interventions ainsi que les décisions cliniques qui en découlent (Turk et al., 2003). Il est donc recommandé de documenter rigoureusement la nature, la fréquence et la sévérité des événements indésirables, puis de les rapporter séparément pour chacun des groupes expérimentaux, en fournissant le plus de détails possible (Hopewell et al., 2025; Ioannidis et al., 2004; Schulz et al., 2010). Il est également essentiel de décrire explicitement les méthodes employées pour recueillir ces informations et d'indiquer comment elles ont été analysées lors de la publication des résultats (Dworkin et al., 2005; Hopewell et al., 2025).

1.3.4.6 L'adhérence au protocole de l'étude

En lien avec la section précédente, et afin de se conformer aux lignes directrices CONSORT, tout essai clinique doit également rapporter de manière détaillée, pour chacun des groupes, le nombre de participants inclus et exclus, ainsi que les justifications correspondantes à chaque étape du protocole, depuis le recrutement jusqu'aux analyses statistiques finales (Dworkin et al., 2005; Hopewell et al., 2025; Turk et al., 2003).

Ces informations incluent notamment les procédures de randomisation, les abandons et exclusions post-randomisation, ainsi que toute déviation par rapport aux interventions prévues, qu'elle concerne l'adhérence des participants ou la fidélité de l'intervention au protocole établi (Dworkin et al., 2005; Hopewell et al., 2025). Une telle transparence méthodologique favorise la reproductibilité des résultats, permet une meilleure évaluation des biais potentiels et contribue de manière significative à la qualité scientifique et à la crédibilité générales des publications issues des essais cliniques (Hopewell et al., 2025).

1.4 La lombalgie

La lombalgie est un terme générique utilisé pour décrire une douleur localisée inférieurement aux 12^e côtes et supérieurement aux sillons glutéaux (Hartvigsen et al., 2018; Vlaeyen et al., 2018). C'est un symptôme tellement commun qu'il est estimé que toute personne souffrira d'au moins un bref épisode de lombalgie au cours de sa vie (Hartvigsen et al., 2018; Vlaeyen et al., 2018). Selon la durée de l'épisode douloureux, la lombalgie est traditionnellement catégorisée comme aiguë ou chronique. Par définition, une douleur lombaire persistant depuis plus de trois mois est qualifiée de lombalgie chronique (Treede et al., 2019).

Si la majorité des individus récupèrent favorablement à la suite d'un épisode de lombalgie aiguë, environ une personne sur cinq verra sa douleur persister au-delà de trois mois (Kongsted et al., 2016; Meucci et al., 2015). Dans ces cas, les répercussions de la douleur sur la vie personnelle, professionnelle et sociale peuvent devenir considérables, contribuant à une altération durable du fonctionnement et de la qualité de vie.

1.4.1 Le fardeau de la lombalgie chronique

Depuis plus de 30 ans, la lombalgie chronique constitue la principale cause d'incapacité à l'échelle mondiale. En 2021, elle représentait à elle seule 7,7 % des années vécues avec incapacité, toutes causes confondues (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018; GBD 2021 Diseases and Injuries Collaborators, 2024). Elle figure également parmi les dix principales causes mondiales d'années de vie corrigées de l'incapacité (*disability-adjusted life years, DALY*), une mesure globale du fardeau des maladies combinant mortalité et incapacité, surpassant notamment les accidents de la route, le cancer du poumon et le sida (GBD 2021 Diseases and Injuries Collaborators, 2024).

Les projections indiquent que le fardeau associé à la lombalgie chronique continuera de croître au cours des prochaines décennies, en particulier au sein de la population en âge de travailler, chez qui la prévalence est la plus élevée (GBD 2021 Forecasting Collaborators, 2024; Hartvigsen et al., 2018; Li et al., 2024; Zhang et al., 2025). Ces données sont particulièrement

préoccupantes, considérant qu'au Québec, environ un tiers des travailleurs âgés de 15 ans et plus rapportent déjà des troubles musculosquelettiques d'origine non traumatique liés au travail, dont 18,3 % correspondent à des douleurs au dos (15,1 % chez les hommes et 21,8 % chez les femmes) (Camirand & collaborateurs, 2023).

Par ailleurs, les coûts directs — liés aux soins de santé — et indirects — liés notamment à la perte de productivité — associés à la lombalgie imposent un fardeau économique majeur aux systèmes de santé et aux sociétés. En 2016, aux États-Unis, la lombalgie et la cervicalgie représentaient les affections pour lesquelles les dépenses estimées en soins de santé étaient les plus élevées, pour un total excédant 134 milliards de dollars (Dieleman et al., 2020). Ce montant surpassait notamment les coûts combinés de l'ensemble des autres troubles musculosquelettiques (130 milliards), du diabète (111 milliards) et des maladies coronariennes (89 milliards) (Dieleman et al., 2020). Bien que les États-Unis consacrent davantage de ressources financières aux soins de santé que tous les autres pays (Chang et al., 2019), le fardeau économique de la lombalgie se chiffre également en dizaines de milliards de dollars dans des pays tels que le Royaume-Uni et l'Australie (Knezevic et al., 2021; Maher et al., 2017).

Au Canada, en 2019, les coûts associés à la douleur chronique — incluant la lombalgie chronique — étaient estimés entre 38,2 et 40,3 milliards de dollars, et une augmentation de plus de 30 % est anticipée d'ici 2030 (Campbell et al., 2021). Face à l'ampleur de ce fardeau personnel, social et économique, il apparaît essentiel de mieux comprendre les mécanismes sous-jacents à la lombalgie chronique afin d'orienter efficacement les stratégies de prévention et de prise en charge.

1.4.2 L'étiologie de la lombalgie

La douleur lombaire peut constituer le symptôme de pathologies spécifiques affectant le rachis lombaire, l'abdomen ou le bassin, notamment les fractures vertébrales, la sténose du canal vertébral, certaines arthrites inflammatoires, des atteintes néoplasiques ou infectieuses, les hernies discales, ou encore des affections viscérales, telles qu'un anévrisme de l'aorte abdominale, une prostatite, l'endométriose ou des calculs rénaux (Hartvigsen et al., 2018;

Knezevic et al., 2021; Maher et al., 2017; Vlaeyen et al., 2018). Toutefois, ces causes spécifiques demeurent relativement rares. Par exemple, une étude australienne ayant évalué 1 172 cas de lombalgie aiguë n'a identifié que 11 cas de pathologie grave (prévalence de 0,9 %), dont huit étaient des fractures vertébrales (Henschke et al., 2009). Il est généralement rapporté que, dans environ 90 % des cas de lombalgie, aucune pathologie spécifique ni lésion tissulaire identifiable ne peut être mise en évidence à l'aide des examens cliniques ou de l'imagerie diagnostique, d'où l'appellation de « lombalgie non spécifique » (Chiarotto & Koes, 2022; Maher et al., 2017; Vlaeyen et al., 2018). Lorsque cette douleur persiste au-delà de trois mois, on utilise le terme de « lombalgie chronique non spécifique » (Chiarotto & Koes, 2022; Maher et al., 2017).

Cependant, s'appuyant sur des études longitudinales portant sur le décours temporel de la lombalgie, plusieurs auteurs ont remis en question la pertinence d'une classification strictement binaire opposant les formes aiguës et chroniques. Ils suggèrent plutôt de concevoir la lombalgie comme une condition persistante caractérisée par des symptômes fluctuants dans le temps (Kongsted et al., 2016). En effet, l'observation des trajectoires à long terme révèle que la majorité des individus présentent une douleur persistante d'intensité variable, généralement faible à modérée, plutôt qu'une résolution complète ou une douleur constante sévère (Ailliet et al., 2018; Downie et al., 2016; Kongsted et al., 2016; Kongsted et al., 2015). Malgré ces données, la classification binaire demeure largement utilisée en recherche et en pratique clinique, probablement en raison de la complexité méthodologique associée aux approches longitudinales (Nguena Nguetack et al., 2020).

Dans ce contexte, et en cohérence avec la nature durable et fluctuante de la lombalgie chronique, il est généralement admis qu'une lombalgie chronique non spécifique ne correspond pas au symptôme direct d'une pathologie sous-jacente identifiable, mais constitue plutôt un problème en soi, résultant de l'interaction de multiples facteurs indépendants de la cause initiale (Vlaeyen et al., 2018). Ainsi, la lombalgie chronique est aujourd'hui conceptualisée à travers un modèle biopsychosocial, dans lequel des facteurs biologiques, psychologiques et sociaux interagissent et contribuent à la pathogenèse et à la pérennité de la condition (Hartvigsen et al., 2018; Nicholas, 2022). Les principaux facteurs relevant de chacune de ces dimensions sont détaillés dans les sections suivantes.

1.4.2.1 Les facteurs biologiques et physiques

En l'absence d'étiologie spécifique identifiable (rhumatologique, infectieuse, néoplasique, etc.), la lombalgie a longtemps été considérée comme la conséquence d'un traumatisme ou de l'accumulation de microtraumatismes ayant entraîné des lésions des tissus vertébraux et paravertébraux (Vlaeyen et al., 2018). En effet, ces structures — incluant les plateaux vertébraux, les disques intervertébraux, les articulations zygapophysiales, les muscles, les tendons, les ligaments et les fascias — sont innervées, et leur atteinte peut engendrer une douleur nociceptive (Knezevic et al., 2021; Nijs et al., 2024; Vlaeyen et al., 2018).

En appui à cette idée, de nombreux facteurs de risque biologiques et physiques associés à l'apparition d'une lombalgie ont été décrits, tels que la station debout prolongée, les antécédents de tabagisme, la manutention de charges lourdes ou éloignées du corps, l'exposition professionnelle aux vibrations, la surreprésentation de gènes impliqués dans la réponse inflammatoire, ainsi que des altérations de la composition et de la morphologie des muscles érecteurs du rachis (Green et al., 2018; Hartvigsen et al., 2018; Steffens et al., 2015; Vlaeyen et al., 2018). Certains de ces facteurs — notamment le sexe féminin, la sédentarité, l'obésité et le tabagisme — sont également associés à un risque accru de chronicisation de la lombalgie (Knezevic et al., 2021).

Toutefois, en opposition à cette théorie d'une blessure initiale persistante, il est fréquemment impossible d'identifier une lésion tissulaire précise permettant d'expliquer la douleur ou, d'un point de vue strictement biologique, de justifier sa persistance au-delà du temps normal de guérison des tissus (Nijs et al., 2024). De plus, près d'un tiers des personnes atteintes de lombalgie aiguë sont incapables d'identifier un facteur déclencheur spécifique (do Carmo Silva Parreira et al., 2015). Enfin, il a été démontré que l'exposition à certains facteurs psychologiques augmente significativement le risque de développer une lombalgie (Steffens et al., 2015), suggérant que les mécanismes en jeu ne peuvent être réduits à des facteurs biologiques ou physiques seuls.

1.4.2.2 Les facteurs psychologiques et comportementaux

La fatigue ainsi que le fait d'être distrait lors de la réalisation d'une tâche sont deux facteurs psychologiques qui sont associés à un risque accru d'avoir une lombalgie aiguë (Steffens et al., 2015). Par ailleurs, les principaux facteurs psychologiques impliqués dans la chronicisation de la douleur — incluant la lombalgie — sont regroupés au sein du modèle cognitivo-comportemental de la peur liée à la douleur, illustré à la **Figure 1.2** (Vlaeyen & Crombez, 2009; Vlaeyen & Linton, 2000). Ce modèle décrit comment, chez certaines personnes, un affect négatif et des croyances erronées à propos de la douleur favorisent l'émergence de la peur liée à la douleur, c'est-à-dire la crainte que certains mouvements ou activités provoquent ou aggravent la douleur

Figure 1.2 – Modèle cognitivo-comportemental de la peur liée à la douleur.

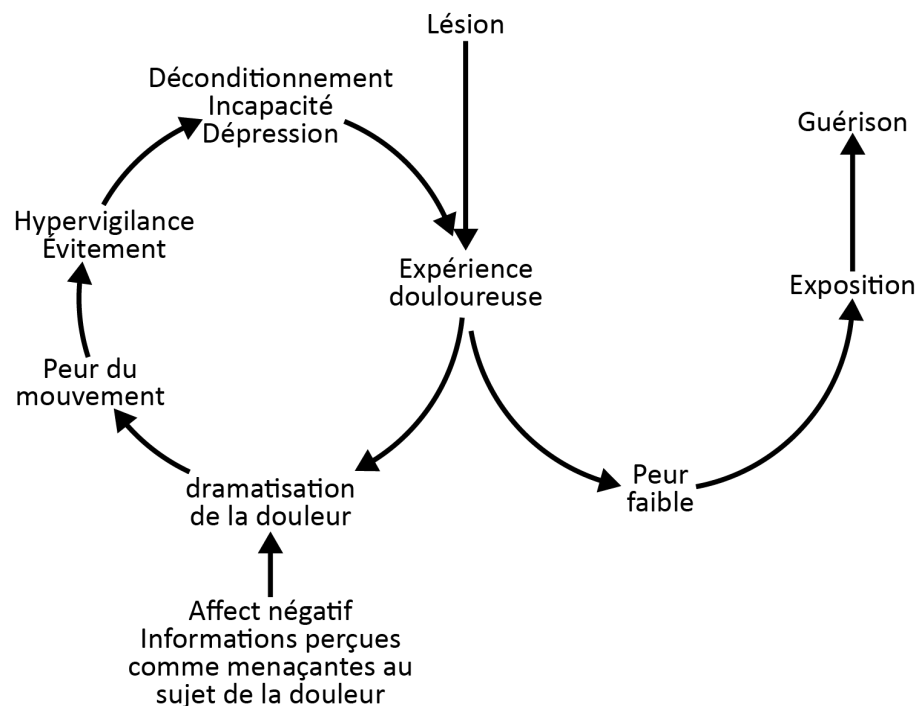


Figure traduite et adaptée de (Vlaeyen & Linton, 2000).

Cette peur conduit à des comportements d'évitement, à une hypervigilance et à des incapacités fonctionnelles. La réduction des activités qui en résulte favorise un état dépressif et un déconditionnement physique, lesquels exacerbent l'expérience douloureuse et entretiennent

un cercle vicieux nuisant à la récupération et favorisant la persistance de la douleur (Crombez et al., 2012; Vlaeyen & Crombez, 2009; Vlaeyen et al., 2016; Vlaeyen & Linton, 2000).

D'autres facteurs psychologiques sont également associés à la chronicisation de la douleur de manière plus générale, notamment la détresse émotionnelle — souvent évaluée par des mesures d'anxiété et de dépression —, les antécédents de traumatismes vécus durant l'enfance et un faible sentiment d'auto-efficacité (Edwards et al., 2016). Par ailleurs, divers facteurs sociaux contribuent également à ce processus.

1.4.2.3 Les facteurs sociaux

Bien que les facteurs sociaux aient longtemps été moins étudiés que les dimensions biologiques et psychologiques, une revue narrative récente a identifié 28 facteurs sociaux contribuant au développement de la lombalgie chronique (Sonjon et al., 2025). Plusieurs de ces facteurs ont déjà été évoqués dans les sections précédentes, mais Sonjon et collaborateurs les ont abordés sous une perspective sociologique, d'où leur inclusion dans la revue narrative.

Parmi les facteurs sociaux les plus fréquemment associés à la chronicisation de la lombalgie figurent le genre, le statut socio-économique (faible niveau d'éducation, faible revenu, accès limités aux soins de santé), l'absence de soutien social — qu'il soit familial ou professionnel —, le statut d'emploi, les conditions de travail et l'insatisfaction au travail (Sonjon et al., 2025).

1.4.2.4 La classification de la lombalgie chronique

Compte tenu de son caractère multifactoriel, la lombalgie chronique se manifeste par une grande hétérogénéité de présentations cliniques. La majorité des guides de pratique recommandent de classer les individus atteints de lombalgie en trois grandes catégories : la lombalgie non spécifique, le syndrome radiculaire et la lombalgie spécifique (Mathieu et al., 2023). Cette approche revient essentiellement à classer la lombalgie selon les mécanismes physiopathologiques prédominants, à savoir nociceptifs, neuropathiques ou nociplastiques (Nijs et al., 2024; Wirth & Schweinhardt, 2024). Récemment, un consortium international d'experts —

le Low Back Pain Phenotyping (BACPAP) Consortium — a publié des recommandations visant à faciliter le phénotypage des individus atteints de lombalgie, dans le but de faciliter la personnalisation des soins (Nijs et al., 2024; Wirth & Schweinhardt, 2024). Le **Tableau 1.4** présente une synthèse des trois principaux phénotypes de la lombalgie.

Tableau 1.4 – Les phénotypes de la lombalgie

Phénotypes	Caractérisé par des mécanismes nociceptifs	Caractérisé par des mécanismes neuropathiques	Caractérisé par des mécanismes nociplastiques
Caractéristiques principales	La douleur est proportionnelle aux afférences nociceptives.	- Une lésion du système nerveux (périphérique ou central) est identifiable. - La douleur a une distribution dermatomale au niveau des membres inférieurs et peut s’accompagner de paresthésies. - Des signes d’un déficit sensitif et/ou moteur peuvent être démontrés à l’examen.	- La douleur ne peut s’expliquer entièrement par des mécanismes nociceptifs ou neuropathiques. - Hyperalgésie diffuse démontrable à l’examen. - Allodynie démontrable à l’examen. - Hypersensibilité à des stimuli non-musculosquelettiques (lumières, sons, odeurs, etc.) rapportée lors de l’anamnèse. - Présence de comorbidités (troubles du sommeil, fatigue, atteinte cognitive, etc.).
Distribution de la douleur	Douleur localisée et limitée à la région lombaire.	Douleur distribuée sur un territoire neuroanatomiquement plausible	Douleur localisée, multifocale ou diffuse.

Tableau traduit et adapté de (Nijs et al., 2024).

Selon cette classification, la majorité des cas de lombalgie chronique non spécifique — qui représentent la majorité des lombalgies chroniques — serait caractérisée par des mécanismes

nociplastiques. Cette proposition est appuyée par une revue systématique récente montrant qu'au moins une comorbidité est présente dans 49 à 92 % des cas de lombalgie chronique (Gandløse et al., 2025). Parmi celles-ci, la présence de douleur chronique dans d'autres régions du corps est l'une des plus fréquentes (5,4 % à 65,7 % des cas), un constat compatible avec le phénotype nociplastique (Gandløse et al., 2025).

Enfin, la reconnaissance de la douleur chronique comme une pathologie à part entière a conduit à l'introduction de nouveaux codes diagnostiques dans la 11^e édition de la Classification internationale des maladies (ICD-11) de l'Organisation mondiale de la Santé (Treede et al., 2019).

1.4.3 Les diagnostics associés à la lombalgie chronique

1.4.3.1 Le processus d'évaluation

La lombalgie chronique non spécifique constitue, par définition, un diagnostic d'exclusion. Autrement dit, il est nécessaire d'évaluer en premier lieu la présence d'une pathologie spécifique susceptible d'expliquer les symptômes avant de poser ce diagnostic (Chiarotto & Koes, 2022; Maher et al., 2017). À cette fin, la majorité des guides de pratique recommandent la réalisation d'une anamnèse détaillée et d'un examen physique afin d'éliminer les conditions spécifiques du diagnostic différentiel (Oliveira et al., 2018).

L'anamnèse vise notamment à identifier les « drapeaux », soit les indices cliniques suggérant la présence d'une pathologie grave, ainsi que les facteurs associés au risque de chronicisation, dans le but d'orienter le diagnostic et la prise en charge (Knezevic et al., 2021; Maher et al., 2017; Oliveira et al., 2018; Vlaeyen et al., 2018). Une synthèse des principaux drapeaux associés à la lombalgie est présentée au **Tableau 1.5**. En présence de drapeaux rouges — indiquant une suspicion de pathologie grave —, des examens complémentaires peuvent être requis selon le contexte clinique, tels que des analyses de laboratoire ou des examens d'imagerie diagnostique (Maher et al., 2017). En revanche, lorsque la lombalgie chronique non spécifique constitue le diagnostic le plus probable, l'ensemble des guides de pratique recommandent d'éviter le recours systématique à l'imagerie (Oliveira et al., 2018).

Tableau 1.5 – Principaux drapeaux associés à la lombalgie

Drapeau	Nature	Exemples
Rouge	Indicateurs d'un problème biologique grave	En lien avec l'histoire de cas ▪ Historique de cancer → néoplasie ▪ Traumatisme physique récent → fracture ▪ Âge ○ > 50 ans → néoplasie ○ > 50 ans + sexe féminin → fracture ○ > 70 ans → fracture / sténose du canal vertébral ▪ Historique d'ostéoporose → fracture ▪ Infection récente → infection ▪ Indice de masse corporelle < 22 → fracture ▪ Douleur inflammatoire^a → arthrite inflammatoire
		En lien avec l'historique pharmacologique ▪ Usage de drogues injectables → infection ▪ Usage de corticostéroïdes → fracture ▪ Usage de médicaments immunosuppresseurs → infection
		En lien avec les signes et symptômes ▪ Présence de fièvre (> 38°C) → infection ▪ Douleur pire au repos ou la nuit → arthrite inflammatoire / néoplasie ▪ Anesthésie en selle → syndrome de la queue de cheval ▪ Douleur radiculaire bilatérale aux membres inférieurs → sténose du canal vertébral ▪ Déficits moteurs aux membres inférieurs → syndrome de la queue de cheval ▪ Dysfonction urinaire ou intestinale (incontinence ou rétention) → syndrome de la queue de cheval ▪ Perte de poids soudaine et inexpliquée → néoplasie ▪ Sueurs nocturnes → infection / néoplasie
Orange	Symptômes psychiatriques	▪ Dépression clinique ▪ Troubles de la personnalité
Jaune	Facteurs psychosociaux qui peuvent retarder la guérison et entraîner la chronicisation	▪ Niveaux initiaux élevés de douleur et d'incapacité ▪ Dramatisation de la douleur ▪ Peur du mouvement ▪ Affect négatif ▪ Anxiété ▪ Comportements d'évitement

^a Une douleur est considérée comme inflammatoire si au moins quatre des cinq éléments suivants sont présents : 1) le premier épisode lombalgique est survenu avant l'âge de 40 ans, 2) la douleur a débuté insidieusement, 3) la douleur s'améliore avec l'activité physique, 4) la douleur ne s'améliore pas avec le repos, 5) la douleur est présente la nuit, mais s'améliore au lever (déverrouillage matinal) (Maher et al., 2017).

		▪ Une préférence marquée pour les traitements passifs (sacs chaud/froid, analgésiques, etc.) ▪ Insatisfaction au travail ▪ Faible statut socio-économique ▪ Faible support social
Bleu	Perceptions concernant la relation entre le travail et la santé	▪ Croyance que les tâches au travail sont lourdes et susceptibles d'aggraver le problème ▪ Croyance que les collègues et les employeurs n'offriront pas de support
Noir	Obstacles contextuels ou systématiques	▪ La législation restreint les options de retour au travail ▪ Conflit avec l'assureur au sujet d'une réclamation en lien avec le problème ▪ Avoir des proches ou des professionnels de la santé trop attentionnés et protecteurs ▪ Travail exigeant avec peu de possibilités d'alléger les tâches

Les drapeaux présentés dans ce tableau correspondent soit à des facteurs de risque suggérant que la lombalgie pourrait être associée à une pathologie grave sous-jacente (drapeaux rouges), soit à des facteurs de risque liés à la chronicisation de la lombalgie (drapeaux orange, jaunes, bleus et noirs). Pour chaque drapeau rouge, les pathologies sous-jacentes potentiellement associées sont précisées à droite des exemples, après la flèche. Tableau inspiré et traduit de (Chiarotto & Koes, 2022; Hartvigsen et al., 2018; Knezevic et al., 2021; Maher et al., 2017; Vlaeyen et al., 2018; Whalen et al., 2022).

Au-delà de l'identification des drapeaux, l'anamnèse doit inclure un historique précis des symptômes, comprenant les caractéristiques de la douleur — son caractère, son intensité, sa fréquence, sa durée, sa localisation (lombaire ou irradiant au membre inférieur) et sa distribution (dermatomale ou non, unilatérale ou bilatérale) — ainsi que les facteurs aggravants et atténuants, de même que les traitements antérieurs et concomitants (Mathieu et al., 2023; Whalen et al., 2022). Bien que l'identification des facteurs de risque constitue une étape importante de l'anamnèse, il convient de souligner que les faux positifs sont fréquents (Vlaeyen et al., 2018). En effet, près de 80 % des personnes présentant une lombalgie rapportent au moins un drapeau rouge, alors que moins de 1% présentent une pathologie grave sous-jacente (Henschke et al., 2009).

Par ailleurs, le triage des individus à risque élevé de chronicisation peut être facilité par l'utilisation de questionnaires validés, tels que le STarT Back Screening Tool (Bruyère et al., 2014). L'utilisation de ces outils est d'ailleurs appuyée par plusieurs guides de pratique (Oliveira et al., 2018), l'objectif étant d'adapter les interventions au profil de risque des individus afin d'optimiser les résultats cliniques. Toutefois, bien que cette approche soit intuitivement attrayante, les résultats d'une méta-analyse récente indiquent que la stratification des patients selon leur niveau de risque n'entraîne qu'un effet faible et non cliniquement significatif sur les résultats cliniques (Tagliaferri et al., 2022). Dans ce contexte, une anamnèse approfondie combinée à un examen physique rigoureux demeure l'approche privilégiée.

L'examen physique devrait inclure, en plus des mesures de routine telles que les signes vitaux, un examen neurologique comprenant l'évaluation de la motricité, de la sensibilité et des réflexes ostéotendineux des membres inférieurs, ainsi qu'un test d'élévation de la jambe tendue afin de dépister une atteinte neuropathique potentielle (Oliveira et al., 2018). Toutefois, les données probantes concernant la précision diagnostique de ces évaluations demeurent non concordantes (Mathieu et al., 2023). Les autres composantes de l'examen physique — telles que la mesure des amplitudes de mouvement du rachis, l'évaluation de la posture et la palpation —, bien que recommandées par certains guides de pratique, présentent généralement une faible valeur diagnostique (Chiarotto & Koes, 2022; Mathieu et al., 2023; Oliveira et al., 2018). En l'absence de signes cliniques suggérant une pathologie spécifique, la douleur est alors attribuée à une lombalgie chronique non spécifique (Chiarotto & Koes, 2022; Maher et al., 2017).

1.4.3.2 Diagnostiquer en fonction de la classification internationale des maladies

Bien qu'encore largement employé en clinique et en recherche, le diagnostic de «lombalgie chronique non spécifique» est imprécis et devrait être remplacé par des alternatives plus actuelles et conceptuellement plus justes. D'une part, la douleur chronique constitue un problème de santé à long terme qui nécessite une prise en charge spécifique (Nicholas et al., 2019). D'autre part, elle représente une condition pathologique à part entière, associée à une détresse émotionnelle et à une incapacité fonctionnelle significatives, des dimensions qui devraient être explicitement intégrées au diagnostic (Nicholas et al., 2019; Treede et al., 2019).

Dans cette optique, un groupe de travail de l'IASP a collaboré avec l'Organisation mondiale de la Santé afin de développer une classification diagnostique de la douleur chronique reflétant l'état actuel des connaissances, intégrée à la 11^e édition de la Classification internationale des maladies (ICD-11). C'est d'ailleurs dans le cadre de ces travaux que la durée de trois mois a été officiellement établie comme critère distinctif entre douleur aiguë et douleur chronique (Treede et al., 2019).

Plusieurs codes diagnostiques ont ainsi été introduits afin de classer les différents troubles douloureux chroniques. De plus, l'outil de codage de l'ICD-11 permet d'ajouter, aux diagnostics principaux, des descripteurs précisant les caractéristiques de la douleur (sévérité, décours temporel), la présence de facteurs psychosociaux ainsi que le niveau d'incapacité fonctionnelle, offrant ainsi une description plus complète et cliniquement pertinente de la condition (Treede et al., 2019). Sans entrer dans le détail de la structure complète de l'ICD-11, il importe de souligner que cette classification est organisée de manière hiérarchique, allant de catégories générales vers des diagnostics de plus en plus spécifiques. L'arborescence diagnostique pertinente à la lombalgie chronique est illustrée à la **Figure 1.3**. Seuls les éléments nécessaires à la compréhension de la présente thèse sont développés ci-dessous.

Figure 1.3 – Structure générale de l'ICD-11 en lien avec la lombalgie chronique

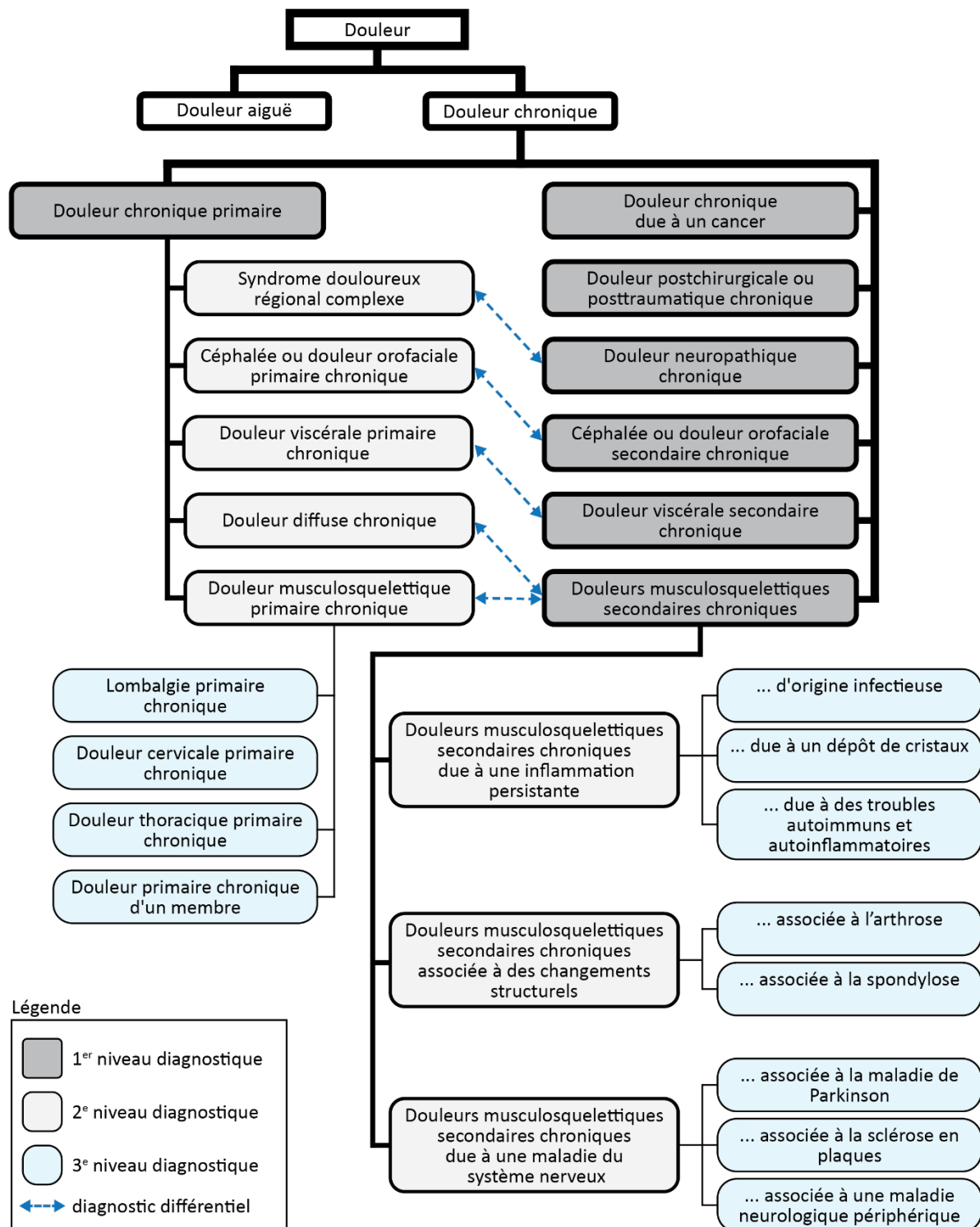


Figure adaptée de (Nicholas et al., 2019; Perrot et al., 2019; Treede et al., 2019; World Health Organisation (WHO), 2019).

Dans l'ICD-11, la douleur chronique primaire est définie comme suit :

Une douleur chronique dans une ou plusieurs régions anatomiques qui est caractérisée par une détresse émotionnelle significative (anxiété, colère/frustration ou humeur dépressive) ou un handicap fonctionnel (interférence dans les activités de la vie quotidienne et participation réduite aux rôles sociaux). La douleur chronique primaire est multifactorielle : des facteurs biologiques, psychologiques et sociaux contribuent au syndrome douloureux. Le diagnostic est approprié indépendamment des facteurs biologiques ou psychologiques identifiés, à moins qu'un autre diagnostic ne permette de mieux expliquer les symptômes présentés. (World Health Organisation (WHO), 2019)

La douleur chronique primaire est subdivisée en cinq sous-groupes (voir **Figure 1.3**), dont fait partie la douleur musculosquelettique primaire chronique. Celle-ci est ensuite précisée selon la localisation anatomique de la douleur. C'est à ce niveau de la classification qu'apparaît le diagnostic de **lombalgie primaire chronique**, qui se substitue à l'appellation de « lombalgie chronique non spécifique » et qui sera désormais employé dans cette thèse.

Pour sa part, la douleur musculosquelettique secondaire chronique est définie comme :

Une douleur chronique provenant d'un ou de plusieurs os, d'une ou de plusieurs articulations, d'un ou de plusieurs muscles, de la colonne vertébrale, d'un ou de plusieurs tendons ou de tissus mous connexes. Il s'agit d'un groupe hétérogène d'affections douloureuses chroniques ayant pour origine une nociception persistante dans les articulations, les os, les muscles, la colonne vertébrale, les tendons et les tissus mous apparentés, avec des étiologies locales et systémiques, mais également liées à des lésions somatiques profondes. La douleur peut être spontanée ou provoquée par un mouvement. (World Health Organisation (WHO), 2019).

Bien qu'il soit parfois difficile de distinguer cliniquement la douleur musculosquelettique secondaire chronique de la douleur chronique primaire — ce qui explique qu'elles fassent partie d'un même diagnostic différentiel —, la première repose, par définition, sur une étiologie identifiable et ne correspond pas au phénotype nociplastique caractéristique de la lombalgie primaire chronique. L'établissement d'un diagnostic précis est essentiel, puisqu'il conditionne le choix d'interventions adaptées à la condition et aux besoins spécifiques de l'individu (Nijs et al., 2024).

1.4.4 La prise en charge de la lombalgie primaire chronique

1.4.4.1 Les défis associés à cette prise en charge

Il est d'abord essentiel que la prise en charge de la lombalgie primaire chronique tienne compte du fait qu'il s'agit d'une condition multifactorielle évoluant sur le long terme (Treede et al., 2019). Dans ce contexte, il serait inapproprié de viser les mêmes objectifs thérapeutiques que pour une douleur aiguë, lesquels reposent généralement sur un soulagement rapide et complet. Une cible thérapeutique plus réaliste consiste plutôt à réduire l'intensité de la douleur chronique à un niveau jugé « léger », soit $\leq 3/10$ sur une échelle numérique (Moore et al., 2013). Ce seuil est simple à utiliser en pratique clinique et a été associé à une amélioration significative de la qualité de vie ainsi que du fonctionnement physique et social (Moore et al., 2013).

Plusieurs interventions peuvent être mises en œuvre afin d'atteindre cet objectif. Il existe en effet une multitude de guides de pratique clinique, tant nationaux qu'internationaux, portant sur la gestion pharmacologique et non pharmacologique de la lombalgie primaire chronique. Toutefois, les recommandations formulées par ces guides sont fréquemment discordantes (Lim et al., 2025; Oliveira et al., 2018; Zaina et al., 2023). Cette discordance s'explique en partie par la variabilité de la qualité méthodologique des guides disponibles (Lim et al., 2025). À cet égard, une revue systématique récente a montré que, même en ne retenant que 22 guides de pratique jugés de haute qualité, seulement 65 % des recommandations relatives à la prise en charge de la lombalgie étaient concordantes entre au moins deux guides (McKenzie et al., 2025). Cette variabilité semble également découler des différences dans les données probantes incluses, ainsi que de l'expertise des auteurs dans l'interprétation des résultats et la formulation des recommandations (McKenzie et al., 2025).

Par ailleurs, malgré l'existence de recommandations de haute qualité fondées sur les données probantes, celles-ci demeurent souvent peu appliquées en pratique clinique (Lim et al., 2025). À ce sujet, une revue systématique regroupant 26 études et incluant 194 388 personnes atteintes de lombalgie a révélé qu'en clinique médicale et aux urgences, seulement une personne sur cinq reçoit de l'information et des conseils conformes aux données probantes, alors que l'imagerie diagnostique et la prescription d'opioïdes sont fréquemment surutilisées (Kamper et

al., 2020). Parmi les facteurs susceptibles de contribuer à cette faible applicabilité figure le fait que la majorité des guides de pratique ne tiennent pas suffisamment compte des préférences des patients et des cliniciens lors de l'élaboration de leurs recommandations (Lim et al., 2025).

Néanmoins, les interventions recommandées dans les guides de pratique clinique correspondent à celles pour lesquelles une efficacité supérieure a été démontrée. À ce titre, elles sont synthétisées dans les sections suivantes.

1.4.4.2 Recommandations fondées sur les données probantes pour la gestion de la lombalgie primaire chronique

Les interventions pharmacologiques disponibles pour la gestion de la lombalgie sont nombreuses et demeurent parmi les options les plus fréquemment utilisées en pratique clinique, malgré le fait que plusieurs d'entre elles aient démontré une efficacité limitée ou un profil de risque défavorable (Cashin et al., 2023). En conséquence, la majorité des guides de pratique clinique de haute qualité — incluant le guide récemment publié par l'Organisation mondiale de la Santé — déconseillent l'utilisation de la plupart de celles-ci comme interventions de première ligne dans la prise en charge de la lombalgie primaire chronique (McKenzie et al., 2025; World Health Organization, 2023; Zaina et al., 2023).

Ces recommandations concernent notamment les opioïdes, les antidépresseurs (tricycliques et inhibiteurs de la recapture de la sérotonine), les anticonvulsivants, les relaxants musculaires ainsi que les glucocorticoïdes, qu'ils soient administrés par voie orale ou par injection (McKenzie et al., 2025; World Health Organization, 2023). En ce qui concerne le paracétamol (acétaminophène), aucune recommandation ne peut actuellement être formulée, puisqu'aucun essai clinique n'a évalué son efficacité spécifique dans le soulagement de la lombalgie primaire chronique (Cashin et al., 2023). En somme, les anti-inflammatoires non stéroïdiens (AINS) sont les seules interventions pharmacologiques recommandées, lorsqu'ils sont intégrés comme l'une des composantes d'une prise en charge globale, en raison de leur efficacité supérieure au placebo pour réduire la douleur et de l'absence d'augmentation significative du risque d'événements indésirables à moyen terme (Cashin et al., 2023; World Health Organization, 2023).

Concernant les interventions non pharmacologiques, la majorité des guides de pratique de haute qualité recommandent d'éviter certaines modalités, notamment le port de corsets ou de ceintures lombaires, les tractions, ainsi que les thérapies par ultrasons ou par courants interférentiels (Lim et al., 2025; McKenzie et al., 2025; World Health Organization, 2023; Zaina et al., 2023). À l'inverse, la recommandation la plus fortement appuyée par les données probantes — et en cohérence directe avec la nature multifactorielle de la douleur chronique — consiste à privilégier une approche multimodale. Celle-ci repose sur la combinaison de différentes interventions non pharmacologiques, incluant les exercices thérapeutiques, les thérapies manuelles (telles que la thérapie par manipulation vertébrale, la mobilisation et le massage) et les interventions psychologiques, notamment la thérapie cognitivo-comportementale (Lim et al., 2025; McKenzie et al., 2025; World Health Organization, 2023; Zaina et al., 2023).

Il importe toutefois de souligner que chacune de ces interventions, lorsqu'utilisées isolément, bénéficie également d'un appui scientifique, tout comme l'éducation des patients concernant leur condition et les recommandations visant à demeurer actif (Lim et al., 2025; McKenzie et al., 2025; World Health Organization, 2023). Dans cette perspective — et puisque cette modalité constitue l'objet principal de la présente thèse — la section suivante s'attardera plus spécifiquement à la thérapie par manipulation vertébrale (TMV).

1.4.4.3 Thérapie par manipulation vertébrale et lombalgie primaire chronique

Un essai clinique randomisé a évalué la supériorité d'une approche interdisciplinaire par rapport à une approche unidisciplinaire chez 201 adultes, dont 97 % présentaient une lombalgie primaire chronique^b (Bronfort et al., 2022). Les participants ont été affectés aléatoirement à l'une de deux interventions administrées pendant 12 semaines : 1) une approche intégrative interdisciplinaire comprenant de l'acupuncture, des soins chiropratiques incluant la TMV, une thérapie cognitivo-comportementale, des exercices de réadaptation, des massages thérapeutiques, de la médication (AINS ou autres analgésiques), ainsi que des conseils ergonomiques et posturaux, le tout dispensé par une équipe de 13 intervenants ; ou 2) des soins

^b Pour les 3 % restants, la durée de la lombalgie se situait entre 6 semaines et 3 mois.

chiropratiques unidisciplinaires prodigués par trois chiropraticiens, incluant principalement des manipulations et des mobilisations vertébrales ainsi que des exercices thérapeutiques. Les résultats indiquent qu'à l'issue des 12 semaines d'intervention, aucune différence significative n'était observée entre les groupes. En revanche, un an après la randomisation, un léger avantage en faveur de l'approche interdisciplinaire a été observé, correspondant à une différence moyenne de 0.5/10 d'intensité de douleur (Bronfort et al., 2022). Toutefois, les auteurs concluent que, compte tenu de la faible ampleur de cet effet ainsi que des ressources humaines et financières considérables nécessaires à la mise en place de soins interdisciplinaires, ceux-ci pourraient ne pas en valoir les efforts lorsque comparés à une approche unidisciplinaire comme les soins chiropratiques dans le soulagement des lombalgies (Bronfort et al., 2022).

Il est intéressant de noter que, dans cette étude, les soins chiropratiques reposaient essentiellement sur deux des interventions de première ligne — les exercices thérapeutiques et la TMV — pour lesquelles les bénéfices excèdent probablement les risques selon un outil décisionnel en gestion de la lombalgie primaire chronique destiné aux médecins de famille canadiens (Kirkwood et al., 2021; Kolber et al., 2021; Korownyk et al., 2022). Par ailleurs, une analyse récente des guides de pratique clinique portant sur la TMV montre que ce n'est que récemment que les recommandations ont évolué en faveur de son intégration au sein d'approches multimodales, plutôt que de son utilisation en tant qu'intervention isolée (Trager et al., 2024). Cette évolution explique pourquoi la TMV figure aujourd'hui comme la deuxième intervention non pharmacologique la plus fréquemment recommandée dans les guides de pratique pour la prise en charge de la lombalgie primaire chronique, juste après l'approche multimodale — laquelle inclut d'ailleurs l'utilisation de manipulations vertébrales. (Lim et al., 2025). Toutefois, des revues systématiques et méta-analyses récentes rapportent que, bien que la TMV soit plus efficace qu'un placebo pour réduire l'intensité de la lombalgie chronique (Cashin et al., 2025; Conde-Vázquez et al., 2026), son efficacité demeure comparable à celle d'autres interventions recommandées, telles que les exercices, les AINS ou les soins usuels (Rizzo et al., 2025).

Au-delà des recommandations cliniques, les préférences des patients constituent un élément important à considérer. À cet égard, un sondage mené auprès de 424 Québécois atteints

de lombalgie chronique a mis en évidence une grande hétérogénéité dans les préférences thérapeutiques (Morillon et al., 2023). Néanmoins, la majorité des répondants rapportaient préférer recevoir des manipulations physiques (Morillon et al., 2023), ce qui témoigne de la popularité des thérapies manuelles, dont la TMV. Cette information revêt une importance clinique, puisque l'adaptation des interventions en fonction des préférences et du profil des individus constitue un élément central de la personnalisation des soins en lombalgie primaire chronique (Wirth & Schweinhardt, 2024).

Malgré l'ensemble des données probantes soutenant l'utilisation de la TMV dans la prise en charge de la lombalgie primaire chronique, son efficacité clinique demeure modeste. En effet, il est estimé qu'environ 55 % des patients obtiennent un soulagement d'au moins 30 % de leur douleur (Kirkwood et al., 2021; Korownyk et al., 2022). Un des facteurs contribuant à limiter l'efficacité de cette intervention réside dans la compréhension encore incomplète de ses mécanismes d'action sur la douleur (Gevers-Montoro et al., 2021a). L'acquisition de ces connaissances est essentielle pour plusieurs raisons. D'une part, la personnalisation des soins est de plus en plus préconisée dans la prise en charge de la lombalgie chronique (Wirth & Schweinhardt, 2024). Or, une telle personnalisation nécessite une compréhension fine des mécanismes impliqués tant dans la pathophysiologie de la condition que dans les effets de l'intervention, afin de pouvoir les faire correspondre de manière optimale (Bialosky et al., 2018). D'autre part, bien que des avancées importantes aient été réalisées dans la compréhension des mécanismes sous-jacents à la lombalgie — permettant notamment le phénotypage des individus (Nijs et al., 2024) —, les mécanismes spécifiques par lesquels la TMV module la douleur demeurent incertains (Gevers-Montoro et al., 2021a). Cette lacune limite actuellement la possibilité d'offrir cette intervention de manière ciblée aux personnes étant le plus susceptible d'en bénéficier pour ainsi maximiser son efficacité clinique (Alanazi et al., 2025).

Une meilleure compréhension des mécanismes faciliterait également l'optimisation des paramètres d'application de cette intervention, tels que la dose, la fréquence ou la région manipulée, dans le but d'accroître ses effets cliniques. À ce jour, peu d'études se sont penchées sur ces aspects, et ceux-ci ne sont pas pris en compte dans des lignes directrices récentes destinées aux chiropraticiens (Whalen et al., 2022). En pratique, le choix de ces paramètres

repose donc principalement sur l'expérience clinique des intervenants (Clijsters et al., 2014). Dans ce contexte, il apparaît essentiel d'approfondir la compréhension des mécanismes par lesquels la TMV influence la douleur. La section suivante présente donc l'état actuel des connaissances à ce sujet.

1.5 La thérapie par manipulation vertébrale et ses mécanismes hypoalgésiques

1.5.1 La manipulation vertébrale

La section précédente a présenté les bénéfices de la TMV dans la prise en charge de la lombalgie primaire chronique, en évitant de la définir. Cette omission était intentionnelle, puisqu'une certaine controverse persiste quant à la définition précise de la manipulation vertébrale (Evans, 2022). Dans le cadre de cette thèse, la manipulation vertébrale est définie comme l'application, par un clinicien, d'une force de haute vélocité et de faible amplitude sur une ou plusieurs vertèbres, entraînant momentanément une séparation des facettes articulaires ainsi qu'une réduction de la rigidité segmentaire (Evans, 2010; Herzog, 2010; Young et al., 2024). Cette force est le plus souvent appliquée manuellement, bien que l'utilisation d'instruments spécialisés soit également courante en pratique clinique (Beliveau et al., 2017).

La manipulation vertébrale est fréquemment accompagnée d'un bruit audible communément appelé « craquement », correspondant au phénomène de cavitation (Dunning et al., 2017; Herzog, 2010). Celui-ci résulte de la séparation rapide des facettes articulaires durant l'application de la force et, bien qu'il soit souvent perçu comme un marqueur du succès de la manœuvre, ce bruit ne semble pas être associé à l'effet thérapeutique de la manipulation (Cramer et al., 2012; Evans, 2022; Herzog, 2010; Moorman & Newell, 2022). Cet effet serait plutôt initié – du moins en partie – par la modulation des afférences mécaniques issues des tissus paravertébraux pendant la manœuvre, ou par les modifications de la biomécanique vertébrale qu'elle pourrait induire (Pickar & Bolton, 2012).

Au cours de la manipulation, ces afférences mécaniques proviennent de l'activation synchrone de différents récepteurs somatosensoriels, notamment les fuseaux neuromusculaires, les organes tendineux de Golgi et des mécanorécepteurs à haut seuil. Ces structures répondent au mouvement rapide imposé à la colonne vertébrale et génèrent une décharge d'activité à haute fréquence transmise vers les cornes dorsales de la moelle épinière (Pickar & Bolton, 2012). Ainsi, la TMV consiste en l'application, à des fins thérapeutiques, d'une ou de plusieurs manipulations vertébrales chez un individu, sur un nombre variable de séances.

Comme mentionné précédemment, cette intervention a démontré son efficacité pour réduire certaines douleurs cliniques (Gevers-Montoro et al., 2024; Minnucci et al., 2023), mais également pour atténuer une douleur expérimentale chez des sujets sains (Coronado et al., 2012; Provencher et al., 2021; Randoll et al., 2017). Pendant de nombreuses années, les effets hypoalgésiques de la manipulation vertébrale ont été expliqués par une combinaison de mécanismes biomécaniques et neurophysiologiques (Evans, 2002; Evans & Breen, 2006; Herzog, 2010; Pickar, 2002). Toutefois, cette perspective a évolué, et les données probantes actuelles convergent vers l'hypothèse que les mécanismes d'action de la manipulation vertébrale seraient principalement d'ordre neurophysiologique (Bialosky et al., 2018; Gyer et al., 2019; Keter et al., 2025; Kovanur Sampath et al., 2024; Wirth et al., 2019; Young et al., 2024). L'origine précise de ces mécanismes hypoalgésiques est détaillée dans les sections suivantes.

1.5.2 Les mécanismes périphériques

Une méta-analyse publiée en 2017 et mise à jour en 2024 a montré que la manipulation vertébrale entraîne des modifications significatives des concentrations de cortisol et de plusieurs cytokines pro-inflammatoires — principalement le TNF- α (*tumor necrosis factor alpha*) et certaines interleukines — immédiatement après son exécution, comparativement à une condition de contrôle. Toutefois, le niveau global d'évidences demeure faible (Kovanur Sampath et al., 2024; Kovanur-Sampath et al., 2017).

De plus, la direction et l'amplitude des changements observés varient considérablement d'une étude à l'autre et ne s'inscrivent pas systématiquement dans un cadre mécanistique

cohérent permettant d'expliquer une diminution de la douleur (Gevers-Montoro et al., 2021a; Kovanur Sampath et al., 2024). La portée clinique de ces modifications, mesurées dans des contextes expérimentaux et à très court terme, demeure également incertaine (Keter et al., 2025).

Dans l'ensemble, les données probantes actuelles sont insuffisantes pour soutenir de manière convaincante la contribution de mécanismes périphériques aux effets hypoalgésiques de la manipulation vertébrale. Néanmoins, ce domaine de recherche demeure en développement. Par ailleurs, il est plausible que la manipulation vertébrale déclenche avant tout une cascade de réponses neurophysiologiques au niveau spinal et supraspinal. Dans cette perspective, les modifications observées au niveau des marqueurs biochimiques périphériques pourraient être des conséquences de mécanismes centraux plutôt que des mécanismes périphériques (Gyer et al., 2019; Keter et al., 2025; Kovanur Sampath et al., 2024).

1.5.3 Les mécanismes spinaux

L'inhibition spinale de l'activité musculaire figure parmi les mécanismes proposés dans plusieurs modèles théoriques expliquant les effets de la manipulation vertébrale (Bialosky et al., 2018; Gyler et al., 2019). De nombreuses études ont quantifié l'activité de différents muscles à la suite d'une manipulation vertébrale segmentaire ou d'autres thérapies manuelles (Keter et al., 2025). Bien que les résultats soient variables et parfois contradictoires, une tendance générale vers une réduction de l'activité musculaire est observée (Alanazi et al., 2025; Keter et al., 2025). Cette diminution a d'ailleurs été théorisée comme l'un des mécanismes contribuant à la réduction de la rigidité segmentaire associée à la manipulation (Jun et al., 2020; Young et al., 2024). Toutefois, il a également été suggéré que la diminution de la rigidité et de l'activité musculaire pourrait être une conséquence de la réduction de la douleur plutôt qu'un mécanisme causal (Jun et al., 2020). De plus, l'impact clinique de ces changements musculaires transitoires demeure incertain (Alanazi et al., 2025). Ainsi, le rôle de l'inhibition de l'activité musculaire comme mécanisme hypoalgésique direct reste à confirmer.

Sur le plan neurophysiologique, la moelle épinière constitue un site clé de modulation de l'information nociceptive (MacMahon et al., 2013). À cet égard, la connectivité corticospinale — mesurée à l'aide de l'imagerie par résonance magnétique fonctionnelle — a récemment été identifiée comme un prédicteur de la sensibilité à la douleur chez l'humain (Lin et al., 2025). La moelle épinière représente donc une cible privilégiée pour l'identification des mécanismes hypoalgésiques de la manipulation vertébrale. En cohérence avec cette idée, une revue des revues portant sur les mécanismes des thérapies manuelles — incluant, mais non limitées à la TMV — indique qu'elles sont associées à une atténuation de l'excitabilité nociceptive au niveau spinal (Keter et al., 2025).

Plusieurs études expérimentales ont rapporté un effet segmentaire de la manipulation vertébrale sur les seuils de douleur à la pression (Alonso-Perez et al., 2017; de Camargo et al., 2011; Dorron et al., 2016; Gevers-Montoro et al., 2024; Laframboise et al., 2016). Toutefois, ces résultats ne sont pas corroborés par les conclusions de deux méta-analyses (Aspinall et al., 2019b; Jung et al., 2023). De plus, une étude menée en contexte clinique auprès de 129 individus atteints de douleur vertébrale n'a observé aucun changement significatif des seuils de douleur à la pression à la suite d'une manipulation vertébrale (Nim et al., 2022). Des études supplémentaires évaluant les effets à plus long terme dans un contexte de soins sont donc nécessaires afin de déterminer si la réduction segmentaire de l'hyperalgésie mécanique constitue un mécanisme hypoalgésique certain.

Par ailleurs, les données issues d'études comportementales suggèrent que la manipulation vertébrale pourrait exercer ses effets hypoalgésiques en modulant des processus spinaux liés au wind-up. En effet, plusieurs études menées chez des participants sains (Bialosky et al., 2008; Bishop et al., 2011; George et al., 2006; Penza et al., 2017; Randoll et al., 2017) ainsi que chez des personnes atteintes de lombalgie (Bialosky et al., 2009; Bialosky et al., 2014) ont rapporté une diminution de la sommation temporelle de la douleur induite par des stimuli thermiques ou électriques à la suite d'une manipulation vertébrale segmentaire, c'est-à-dire appliquée au niveau vertébral correspondant au dermatome stimulé. Comme il a été rapporté dans une revue sur le sujet, ces résultats suggèrent que des mécanismes spinaux sont fortement

impliqués dans les effets hypoalgésiques de la manipulation vertébrale (Gevers-Montoro et al., 2021a).

Certaines de ces études ont également évalué l'effet de la manipulation sur la douleur provoquée par un stimulus unique, sans observer de changement significatif (Bialosky et al., 2009; Bishop et al., 2011; George et al., 2006; Randoll et al., 2017). Étant donné que la sommation temporelle de la douleur est induite par la stimulation répétée des fibres C nociceptives, tandis que, dans ces études, les stimuli uniques recrutaient davantage les fibres A δ , ces résultats suggèrent que la manipulation vertébrale module préférentiellement l'activité des fibres C nociceptives. Cette hypothèse est renforcée par une étude montrant que, chez des participants sains, les réponses cérébrales évoquées par la stimulation des fibres A δ nociceptives demeurent inchangées après une manipulation vertébrale segmentaire, malgré une diminution significative de la douleur associée aux stimuli (Provencher et al., 2021). Toutefois, la démonstration neurophysiologique directe d'un effet de la manipulation vertébrale sur l'activité liée aux fibres C nociceptives reste à établir. À cet égard, un essai contrôlé randomisé chez des personnes atteintes de lombalgie, comparant une manipulation vertébrale à une intervention factice, n'a rapporté aucun changement de la sommation temporelle entre les groupes (Aspinall et al., 2019a). Cette absence d'effet pourrait s'expliquer par l'utilisation d'un stimulus mécanique piquant pour induire la sommation temporelle, une modalité sensorielle médiée exclusivement par les fibres A δ (Magerl et al., 2001). Ce résultat appuie donc indirectement l'hypothèse selon laquelle les effets de la manipulation vertébrale pourraient être spécifiques aux processus spinaux dépendants de l'activité des fibres C nociceptives.

Dans le prolongement de ces observations, une méta-analyse a montré que les thérapies manuelles — incluant, mais non limitées à la TMV — améliorent significativement plusieurs variables associées à la sensibilisation centrale, notamment par une réduction de la sommation temporelle et une augmentation de la modulation conditionnée de la douleur, comparativement à une intervention de contrôle (Arribas-Romano et al., 2020). De plus, des études expérimentales ont montré que la manipulation vertébrale peut réduire l'hyperalgésie secondaire (Gevers-Montoro et al., 2021b; Mohammadian et al., 2004) ainsi que l'allodynie induite par l'application topique de capsaïcine (Mohammadian et al., 2004). Néanmoins, des recherches supplémentaires

sont nécessaires afin de déterminer de manière concluante si la manipulation vertébrale influence durablement ces marqueurs de la sensibilisation centrale.

Enfin, une revue systématique et deux méta-analyses récentes suggèrent que des effets hypoalgésiques peuvent être observés indépendamment du niveau vertébral manipulé, ce qui indique que ces effets ne reposent pas exclusivement sur des mécanismes segmentaires ou strictement spinaux (Nim et al., 2025; Nim et al., 2021; Sørensen et al., 2023).

1.5.4 Les mécanismes supraspinaux

Des modèles théoriques portant sur les mécanismes des thérapies manuelles en général (Bialosky et al., 2018), ou de la manipulation vertébrale plus spécifiquement (Gyer et al., 2019), postulent que des mécanismes supraspinaux contribuent aux effets hypoalgésiques observés. Parmi ceux-ci figurent principalement l'activation des voies descendantes de modulation de la douleur ainsi que la modulation du traitement nociceptif au niveau supraspinal (Bialosky et al., 2018; Gyer et al., 2019).

À cet égard, une revue systématique ayant évalué l'effet de la manipulation vertébrale sur l'activité cérébrale — incluant 18 essais contrôlés, dont une majorité randomisés (14/18) — conclut que cette intervention semble effectivement induire des effets neurophysiologiques supraspinaux mesurables (Meyer et al., 2019). Toutefois, dans la majorité des études incluses, l'absence de précision quant à l'insu des personnes impliquées (participants, thérapeutes, évaluateurs) suggère que des biais ont pu être introduits. Par ailleurs, le lien entre ces altérations de l'activité cérébrale et des changements cliniquement pertinents demeure incertain. Depuis cette revue, d'autres études — principalement menées chez des personnes atteintes de lombalgie — ont également rapporté des modifications de diverses mesures de l'activité cérébrale à la suite de manipulations vertébrales (Didehdar et al., 2020; Isenburg et al., 2021; Tan et al., 2020; Weber li et al., 2019; Wen et al., 2022; Yang et al., 2022; Zhou et al., 2024; Zhou et al., 2025). Toutefois, la mise en évidence de changements neurophysiologiques supraspinaux ne signifie pas nécessairement que ceux-ci sont à l'origine d'effets cliniquement pertinents. La signification fonctionnelle de ces altérations doit donc être interprétée avec prudence. De plus,

ces effets doivent être mis en perspective en les comparant à ceux induits par d'autres types de stimuli physiques comparables ou par d'autres modalités thérapeutiques. En effet, bien qu'annoncée comme une manipulation vertébrale, l'intervention décrite dans certaines de ces études s'apparente davantage à un massage (Tan et al., 2020; Wen et al., 2022; Yang et al., 2022). Il est donc possible que les changements observés dans l'activité cérébrale ne soient pas spécifiques à la manipulation vertébrale en tant que telle, mais reflètent des réponses non spécifiques à une stimulation mécanique. Des études comparatives rigoureuses sont nécessaires afin de vérifier cette hypothèse.

Par ailleurs, l'observation de modifications de l'activité au niveau de régions cérébrales impliquées dans le traitement nociceptif supraspinal ne permet pas de conclure que la manipulation vertébrale agit directement sur ces structures. Il est plausible que ces effets reflètent, au moins en partie, des processus spinaux, c'est-à-dire qu'ils soient secondaires à une modulation des afférences nociceptives ascendantes projetées vers les régions supraspinales impliquées dans le traitement de l'information nociceptive. Cette interprétation alternative est d'ailleurs évoquée dans la majorité des études incluses dans la revue systématique de Meyer et al. (2019).

Ainsi, bien que les données actuelles suggèrent l'existence d'effets supraspinaux associés à la manipulation vertébrale, leur origine exacte — directe ou indirecte — ainsi que leur contribution spécifique aux effets hypoalgésiques cliniquement observés demeurent à clarifier.

1.5.5 Les effets non spécifiques

Outre les mécanismes neurophysiologiques discutés dans les sections précédentes, plusieurs effets dits non spécifiques contribuent également à la diminution de la douleur observée à la suite d'une TMV (Gevers-Montoro et al., 2021a). Ces effets incluent notamment la régression vers la moyenne, l'évolution naturelle de la condition, l'effet placebo et l'influence des facteurs contextuels (Haflíðadóttir et al., 2021; Hohenschurz-Schmidt et al., 2025).

Il est essentiel de distinguer l'effet placebo de la réponse placebo. L'effet placebo correspond aux changements résultant de mécanismes liés aux attentes et à l'apprentissage, tandis que la réponse placebo englobe l'ensemble des changements observés dans le groupe placebo d'un essai clinique, incluant les effets non spécifiques tels que l'évolution naturelle de la condition ou la régression vers la moyenne (Hafliðadóttir et al., 2021; Hohenschurz-Schmidt et al., 2025; Kaptchuk et al., 2020; Wager & Atlas, 2015). Ces distinctions conceptuelles sont illustrées à la **Figure 1.4**. L'analgésie placebo correspond donc à une diminution de la douleur induite par le contexte thérapeutique et médiée, entre autres, par l'activation des voies descendantes de modulation de la douleur (Sherriff et al., 2022; Wager & Atlas, 2015).

Figure 1.4 – Illustration de l'impact des effets non spécifiques sur les résultats

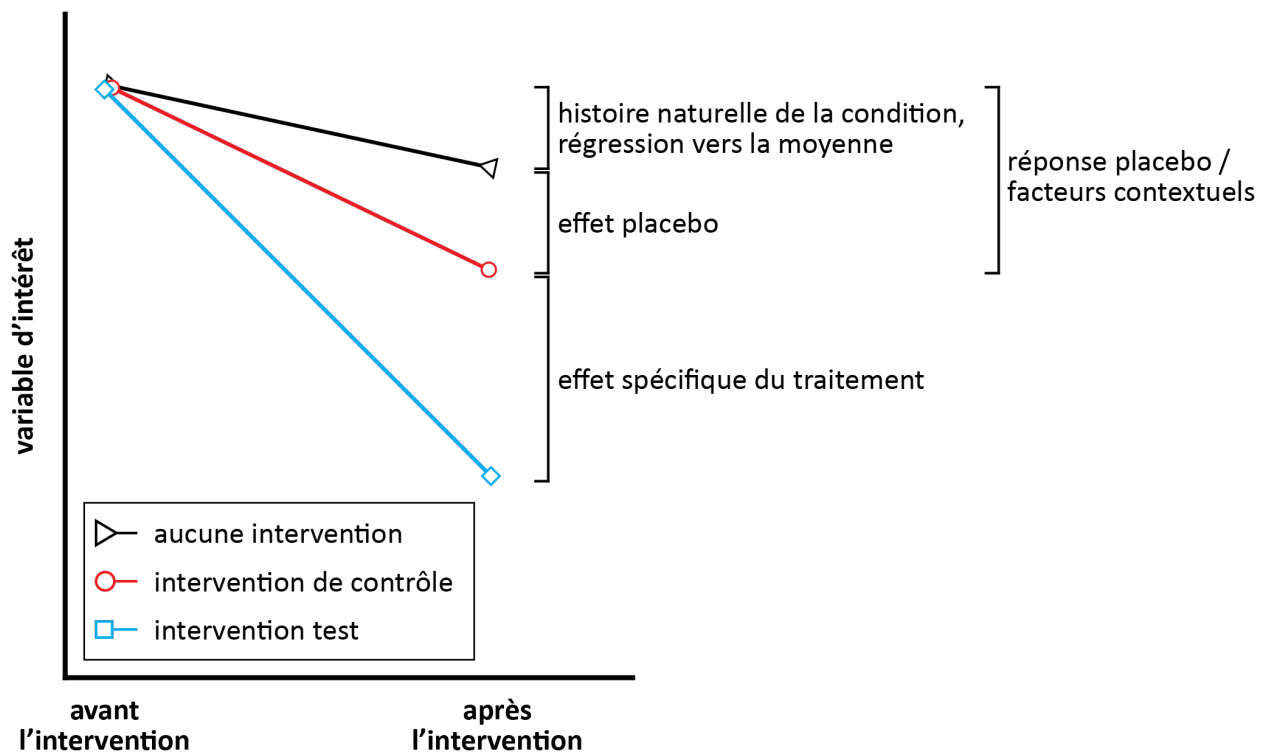


Figure traduite et adaptée de (Hafliðadóttir et al., 2021; Krogsbøll et al., 2009).

Les facteurs contextuels peuvent être décomposés en plusieurs composantes afin d'en faciliter l'étude, incluant les croyances, attentes et caractéristiques des patients, celles des thérapeutes, la qualité de l'alliance thérapeutique (relation patient-thérapeute), l'environnement de soins ainsi que les caractéristiques de l'intervention (Sherriff et al., 2022). Une revue systématique récente portant sur l'impact de ces facteurs dans la gestion conservatrice de la lombalgie, incluant 3075 participants, met en évidence deux constats majeurs : 1) la majorité des participants présentent une amélioration clinique indépendamment de l'intervention reçue, et 2) l'effet d'une intervention peut être significativement amplifié par la modulation des facteurs contextuels (Sherriff et al., 2022). Ces résultats concordent avec ceux d'une méta-analyse portant sur 186 essais contrôlés randomisés, toutes conditions et interventions confondues, qui rapporte qu'en moyenne 54 % des effets thérapeutiques observés sont attribuables aux effets contextuels (Haflíðadóttir et al., 2021). Une autre méta-analyse, spécifiquement consacrée à la lombalgie, suggère que, dans le cas de la lombalgie chronique, jusqu'à 66 % de la variance des changements de douleur pourrait être expliquée par des effets non spécifiques (Menke, 2014).

Les effets non spécifiques sont inhérents à toute intervention thérapeutique et ne peuvent être entièrement éliminés. Il est donc indispensable d'intégrer une ou plusieurs conditions de contrôle appropriées lors de la réalisation d'essais cliniques afin de permettre une interprétation adéquate des effets spécifiques de l'intervention étudiée. À cet égard, des lignes directrices méthodologiques ont récemment été proposées afin d'optimiser la conception des essais cliniques non pharmacologiques et la prise en compte rigoureuse des effets contextuels (Hohenschurz-Schmidt et al., 2023).

1.6 Objectifs et hypothèses

1.6.1 Objectif général

L'objectif général de cette thèse doctorale est de mieux caractériser les mécanismes neurophysiologiques sous-jacents aux effets hypoalgésiques de la TMV dans le soulagement de la douleur au dos, en mettant un accent particulier sur son influence sur les processus neuronaux d'amplification de la douleur liés à l'activation des fibres C nociceptives. Une compréhension approfondie de ces mécanismes pourrait, à terme, permettre d'appliquer cette intervention de manière ciblée aux individus affectés par des mécanismes pathophysiologiques qui peuvent être modulés par la TMV. Cela pourrait également contribuer à l'optimisation des paramètres d'application de la TMV afin d'en améliorer l'efficacité clinique.

Les quatre études présentées dans cette thèse s'inscrivent de manière progressive dans cet objectif général. La première vise à explorer certains mécanismes neurophysiologiques chez des participants sains. La deuxième a pour but de développer et de valider une méthode permettant de mesurer les effets des manipulations vertébrales sur les réponses cérébrales associées à l'activation des fibres C nociceptives. La troisième étude cherche à caractériser les altérations neurophysiologiques et psychologiques présentes chez des personnes atteintes de lombalgie primaire chronique, en les comparant à des participants témoins appariés pour l'âge et le sexe, mais exempts de douleur. Enfin, la quatrième étude examine les effets à plus long terme de la TMV sur un ensemble de variables neurophysiologiques et psychologiques en lien avec la douleur, afin d'en préciser les mécanismes sous-jacents. Tout en s'inscrivant dans cet objectif général, chacune de ces études comporte des objectifs et des hypothèses spécifiques, présentés ci-dessous.

1.6.2 Hypothèse générale

La TMV inhibe les processus neuronaux d'amplification de la douleur liés à l'activation des fibres C nociceptives, ce qui contribue au soulagement de la douleur au dos.

1.6.3 Objectifs et hypothèses spécifiques

Étude 1 : L'objectif de cette étude était d'examiner les effets de la manipulation vertébrale sur l'amplification de la douleur à l'aide d'un modèle de douleur expérimentale capsaïcine-chaueur, dans lequel des impulsions laser sont appliquées sur une peau préalablement traitée à la capsaïcine. La première hypothèse était que la manipulation vertébrale segmentaire réduirait l'amplification de la douleur associée aux stimuli laser qui est induite par la capsaïcine, en diminuant l'augmentation de la transmission nociceptive spinale. La seconde hypothèse était que cette réduction de l'augmentation de la transmission nociceptive spinale se traduirait par une diminution de l'amplitude des potentiels évoqués laser, reflétant en partie l'inhibition segmentaire de l'activité nociceptive spinale.

Étude 2 : L'objectif de cette étude était d'établir un protocole visant à étudier l'activité cérébrale évoquée par l'activation des fibres C nociceptives dans la région lombaire. Sur la base d'études antérieures, des impulsions laser uniques ou répétées (3) ont été utilisées, avec une durée d'impulsion de 7 ou 14 ms. La première hypothèse était que les trains d'impulsions laser susciteraient des réponses liées aux fibres C nociceptives mesurables chez une proportion plus élevée de participants que les impulsions uniques. La seconde hypothèse était que les trains d'impulsions laser à 0,67 Hz entraîneraient une augmentation de l'amplitude des réponses cérébrales liées aux fibres C nociceptives entre la première et la dernière impulsion du train.

Étude 3 : L'objectif de cette étude était de déterminer si la sommation temporelle de la seconde douleur et les réponses cérébrales associées aux fibres C nociceptives sont augmentées chez les personnes atteintes de lombalgie primaire chronique par rapport à des témoins sains appariés pour l'âge et le sexe. L'hypothèse était que les personnes atteintes de lombalgie primaire chronique présenteraient une sommation temporelle de la seconde douleur plus marquée, associée à une augmentation de l'amplitude des réponses cérébrales liées aux fibres C, comparativement aux témoins. De plus, en lien avec la douleur nociplastique, nous nous

attendions à observer une hyperalgésie diffuse ainsi qu'une détresse psychologique chez les personnes atteintes de lombalgie primaire chronique.

Étude 4 : L'objectif principal de cette étude était de déterminer, chez des adultes atteints de lombalgie primaire chronique, si la TMV réduit l'intensité de la douleur clinique et module les mécanismes neurophysiologiques associés à l'amplification de la douleur expérimentale comparativement à une intervention contrôle. L'objectif secondaire était d'évaluer l'influence de la région vertébrale manipulée et du nombre de séances sur la réduction de l'intensité de la lombalgie. Plus précisément, l'étude testait les hypothèses suivantes :

Hypothèses principales :

- 1) La TMV entraînera une diminution plus importante de l'intensité de la lombalgie comparativement à une intervention contrôle.
- 2) La réduction de l'intensité de la lombalgie induite par la TMV sera accompagnée d'une diminution de la sommation temporelle de la seconde douleur, d'une diminution de la sommation temporelle des réponses cérébrales liées aux fibres C nociceptives, ainsi que d'une réduction de la sensibilité mécanique.

Hypothèses secondaires :

- 3) La TMV appliquée de manière globale (à toutes les régions vertébrales) entraînera une diminution plus importante de l'intensité de la lombalgie que la TMV appliquée uniquement à la région lombaire.
- 4) L'intensité de la lombalgie diminuera progressivement au fil du temps, avec des effets cumulatifs sur une période de trois mois.
- 5) Des facteurs psychologiques liés à la douleur modéreront l'effet de la TMV sur l'intensité de la lombalgie.

Chapitre 2: Étude 1 – Segmental Chiropractic Spinal Manipulation Does not Reduce Pain Amplification and the Associated Pain-Related Brain Activity in a Capsaicin-Heat Pain Model

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Provencher, B., Northon, S., & Piché, M. (2021). Segmental Chiropractic Spinal Manipulation Does not Reduce Pain Amplification and the Associated Pain-Related Brain Activity in a Capsaicin-Heat Pain Model. *Frontiers in Pain Research*, 2(86), 733727. <https://doi.org/10.3389/fpain.2021.733727>

Contribution des auteurs:

- Benjamin Provencher : conception de l'étude, collecte, analyse et interprétation des données, rédaction du manuscrit.
- Stéphane Northon : collecte et analyse des données.
- Mathieu Piché : financement et conception de l'étude, collecte, analyse et interprétation des données, révision du manuscrit.

Abstract

Musculoskeletal injuries lead to sensitization of nociceptors and primary hyperalgesia (hypersensitivity to painful stimuli). This occurs with back injuries, which are associated with acute pain and increased pain sensitivity at the site of injury. In some cases, back pain persists and leads to central sensitization and chronic pain. Thus, reducing primary hyperalgesia to prevent central sensitization may limit the transition from acute to chronic back pain. It has been shown that spinal manipulation (SM) reduces experimental and clinical pain, but the effect of SM on primary hyperalgesia and hypersensitivity to painful stimuli remains unclear. The goal of the present study was to investigate the effect of SM on pain hypersensitivity using a capsaicin-heat pain model. Laser stimulation was used to evoke heat pain and the associated brain activity, which were measured to assess their modulation by SM. Eighty healthy participants were recruited and randomly assigned to one of the four experimental groups: inert cream and no intervention; capsaicin cream and no intervention; capsaicin cream and SM at T7; capsaicin cream and placebo. Inert or capsaicin cream (1%) was applied to the T9 area. SM or placebo were performed 25 min after cream application. A series of laser stimuli were delivered on the area of cream application (1) before cream application, (2) after cream application but before SM or placebo, and (3) after SM or placebo. Capsaicin cream induced a significant increase in laser pain ($p < 0.001$) and laser-evoked potential amplitude ($p < 0.001$). However, SM did not decrease the amplification of laser pain or laser-evoked potentials by capsaicin. These results indicate that segmental SM does not reduce pain hypersensitivity and the associated pain-related brain activity in a capsaicin-heat pain model.

Introduction

Musculoskeletal injuries generally lead to an inflammatory response, peripheral sensitization and primary hyperalgesia (1). This occurs with low back injuries, which are associated with acute pain and increased pain sensitivity at the site of injury, and in some cases, this leads to chronic primary low back pain (2–4).

Primary hyperalgesia mostly results from peripheral mechanisms and is caused by nociceptor sensitization (5). The release of pro-inflammatory mediators, including serotonin, bradykinin, prostaglandins, arachidonic acid and substance P was shown to cause nociceptor sensitization in the injured tissues (5, 6). Thus, primary hyperalgesia is limited to the site of injury and is characterized by a decrease in pain threshold, an increased response to suprathreshold stimuli and spontaneous pain in the absence of external stimulation (5–7). When primary hyperalgesia affects the hairy skin, both A δ and C nociceptors are sensitized to heat stimuli (5, 6, 8). If primary hyperalgesia persists, sustained nociceptive inputs from C-nociceptors to spinal cord neurons lead to central sensitization, which can be evidenced by the presence of secondary hyperalgesia (6, 9, 10). Secondary hyperalgesia is usually described as an increased sensitivity to mechanical, but not heat stimuli, in uninjured tissues outside the area of tissue injury (6, 7, 11). Recent studies have shown that this relies on a class of A-nociceptors that project to sensitized spinal neurons in laminae I and IV/V (10, 12, 13). Central sensitization is common in chronic pain conditions (14). Features of central sensitization such as increased temporal summation and decreased pressure pain threshold in remote body parts (secondary hyperalgesia) are also frequently observed in chronic low back pain (15). Thus, reducing the intensity or the duration of primary hyperalgesia to prevent central sensitization and secondary hyperalgesia may limit the transition from acute to chronic pain.

Spinal manipulation (SM) is a form of manual therapy provided by different healthcare professionals, including chiropractors (16). SM has been shown to reduce both experimental and clinical pain (17, 18) and recent clinical practice guidelines recommend the use of SM for the management of back pain (19–22). Although several studies suggest that SM may decrease pain via segmental mechanisms involving the processing of C-nociceptor inputs in the spinal cord (23–

26), these mechanisms are not fully understood, and the effect of SM on primary hyperalgesia remains unclear.

Two systematic reviews reported that SM decreases experimental pain in healthy volunteers (17, 18). Accordingly, several experimental studies demonstrated that SM could decrease experimental cutaneous pain in healthy volunteers (23, 24, 27–30) and in patients with low back pain (25, 26), when the nociceptive activity is amplified by centrally mediated mechanisms like temporal summation and central sensitization. In addition, a recent meta-analysis reported that physical therapy (including manual therapy such as SM) improves nociceptive processing influenced by or related to central sensitization in patients with chronic musculoskeletal pain (31). Although it has never been demonstrated using neurophysiological measures, these findings suggest that SM affects the transmission of nociceptive activity or decreases nociceptive transmission in the dorsal horns of the spinal cord, regardless of the origin of the inputs (cutaneous or myofascial). Besides, a few studies suggest that the hypoalgesic effects of SM are partly due to decreased rigidity of the spine (32, 33). In these studies, however, SM were not performed specifically at one segment. Moreover, a recent study suggests that spinal stiffness is not the most important factor to produce SM-induced hypoalgesia (34). Furthermore, no clinically relevant association was observed between spine stiffness and mechanical pain thresholds (35), where increased stiffness was not associated with increased mechanical pain sensitivity, but rather with increased pain thresholds (lower pain sensitivity). Thus, although mechanical effects cannot be excluded, the hypoalgesic effects of SM may be independent of the improvement in mechanical function and may be produced when applied to joints without restriction, therefore supporting the observed effects in healthy volunteers.

Capsaicin pain models are widely used in pain research for the selective activation of nociceptors (36–38). Capsaicin is a chemical that is naturally present in chili peppers that binds to transient receptor potential vanilloid 1 (TRPV1), which is highly expressed in C-nociceptors (39). Low concentrations ($\leq 1\%$) of capsaicin applied topically initially excite C-nociceptors, resulting in a transient inflammatory response, pain, as well as primary and secondary hyperalgesia (6, 7, 11, 39). To our knowledge, two studies investigated the hypoalgesic mechanisms of SM on capsaicin pain, one reporting that a single SM session reduced capsaicin pain and the other showing no

effect (30, 40). In addition to these conflicting findings that remain to be clarified, the underlying neurophysiological mechanisms of SM on heat pain amplification by capsaicin remain unknown.

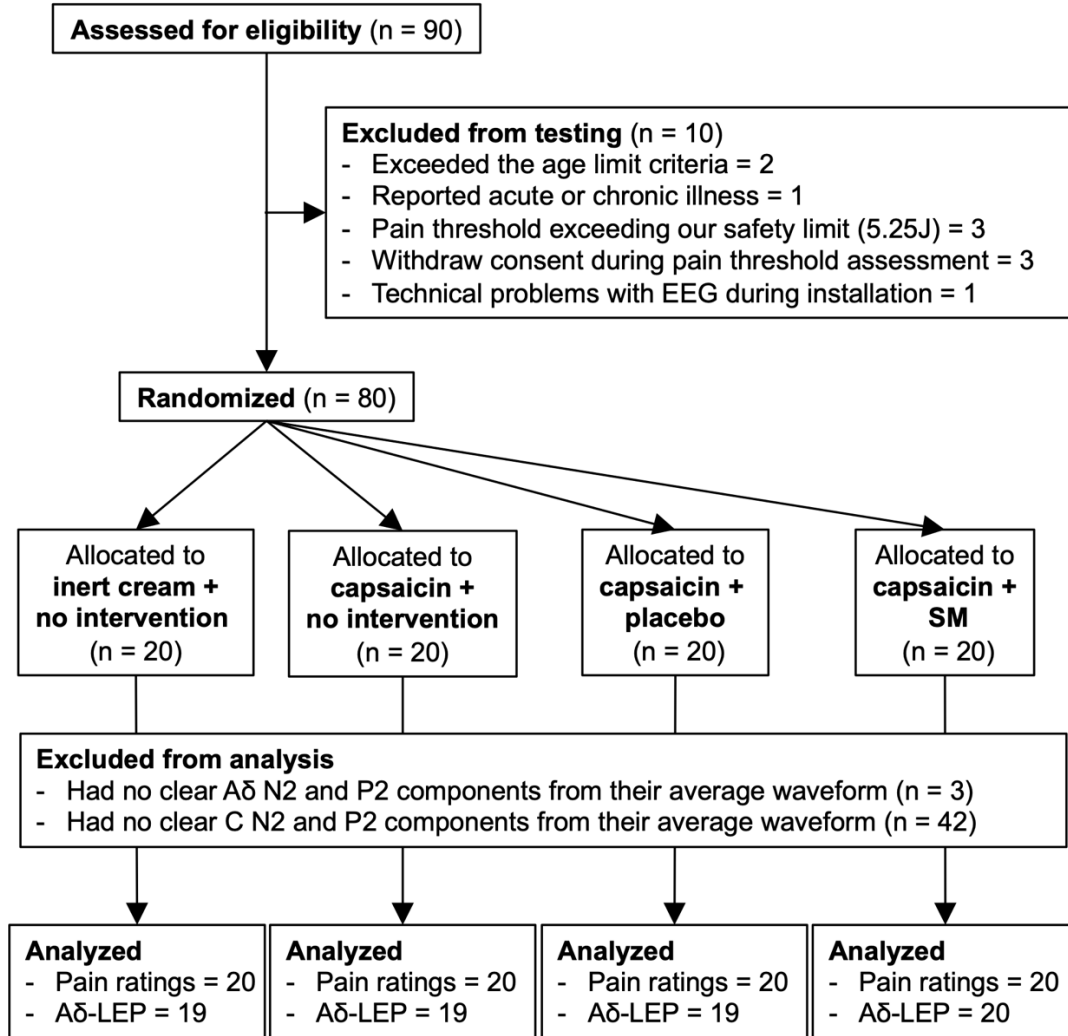
The aim of the present study was to investigate the effects of SM on pain amplification using a capsaicin-heat pain model, in which laser pulses are applied on capsaicin-treated skin. We hypothesized that segmental SM would reduce the capsaicin-induced amplification of laser heat pain, by reducing the associated increase in spinal nociceptive transmission. We also hypothesized that this reduction would result in reduced laser-evoked potentials amplitude, partly reflecting the segmental inhibition of spinal nociceptive activity.

Materials and methods

Participants

Ninety participants were recruited by advertisement on the campus of Université du Québec à Trois-Rivières and on social media. Participants were included if they were between 18 and 55 years old. They were excluded if they reported acute or chronic pain, acute or chronic illness, psychiatric disorders, if they underwent spinal surgery, had a significant injury to the spine in the 3 months preceding the experiment, or took any medication or recreational drug during the 2 weeks prior to experimentation. They were also excluded if they presented a skin of type I on the Fitzpatrick scale, reported having an allergy/intolerance to chili peppers, or if their pain threshold exceeded the safety limit for laser stimulation (see section Painful Laser Stimulation). Eighty healthy volunteers [40 women and 40 men; aged 27.1 ± 6.8 years (mean $\pm$ SD)] were included and completed the study. A flow diagram of participants inclusion is presented in **Figure 2.1**. All experimental procedures conformed to the standards set by the latest revision of the Declaration of Helsinki and were approved by the Research Ethics Board of Université du Québec à Trois-Rivières. All participants gave written informed consent, acknowledging their right to withdraw from the experiment without prejudice, and received a compensation of \$25 for their travel expenses, time and commitment.

Figure 2.1 – Flow diagram of enrollment, allocation, and analyses.



SM, spinal manipulation; LEP, laser-evoked potential.

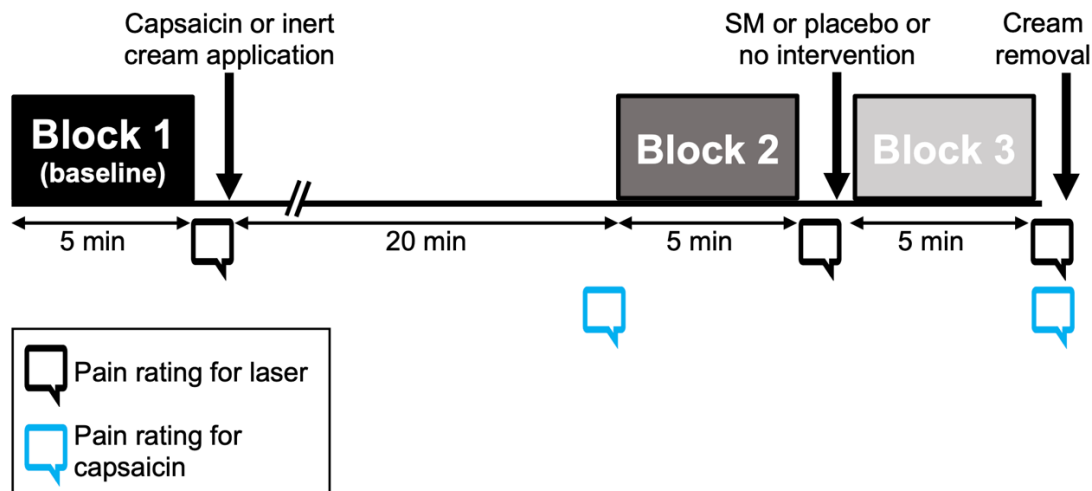
Experimental Design and Protocol

This study relied on a mixed design to compare changes in laser-evoked pain and brain activity between groups. Participants were randomly assigned to one of the four experimental groups using a random-number generator: inert cream with no intervention (n = 20); capsaicin cream and no intervention (n = 20); capsaicin cream and SM at T7 (n = 20); capsaicin cream and placebo intervention (n = 20).

During the experiment, room temperature was kept constant at 24°C. All participants were seated on a regular desk chair with a low backrest (under T9 vertebra) during the first 25 min of the experiment, after which they were instructed to lay prone comfortably on a chiropractic table for the remaining 10 min. This allowed the intervention to be delivered. Their head was slightly elevated by a thick towel placed under their chin to avoid pressure on the electrooculography (EOG) and frontal electroencephalography (EEG) electrodes. The participant and experimenter wore safety glasses designed for a 1,340 nm wavelength laser at all time. In both positions, participants were instructed to keep their eyes open, look at a fixation cross to minimize eye movement, and refrain movement as much as possible during stimulation.

The experimental protocol is illustrated in **Figure 2.2**. The experiment comprised three blocks of 30 laser stimuli delivered to the T9 area. After the first block, inert or capsaicin cream (1%) was applied to the stimulation area and participants waited 20 min before the next block of laser stimuli. After this second block (25 min after cream application), either no intervention, SM or the placebo intervention (sham SM) were performed. For the groups with no intervention, participants simply waited for 60 s before the third block of laser stimuli was delivered. After each stimulation block, participants provided their pain ratings, and they could blink and stretch as needed. The timing of the intervention (25 min after cream application) was based on previous findings, which characterized the time course of tonic pain produced by capsaicin applied to the back (30). After 20 min, capsaicin pain remains relatively stable, which allows to compare laser pain with baseline and pain amplification by capsaicin. This is more clinically relevant to investigate the hypoalgesic mechanisms of SM, since ongoing tonic pain is closer to what patients report with acute back pain. The laser stimulus allows confirming the amplification of pain by capsaicin and the measure of laser evoked potentials and their amplification by capsaicin.

Figure 2.2 – Experimental protocol



Three blocks of 30 laser stimuli were applied to the back, for a total of 90 stimuli. After each block, participants were instructed to rate pain verbally. Inert or capsaicin cream was applied to the stimulation area after block 1 and removed at the end of the experiment. Between blocks 2 and 3, participants received either no intervention, a placebo intervention or a spinal manipulation at T7.

Painful Laser Stimulation

Painful stimuli were produced by laser heat pulses generated by an infrared neodymium-doped yttrium aluminum perovskite laser (Nd:YAP, DEKA 1,340, Electronical Engineering, Florence, Italy). These stimuli have been shown to activate heat sensitive A δ and C fibers selectively, while avoiding the activation of A β fibers (41, 42). The laser beam was transmitted through a 10 m optic fiber cable and was adjusted to 7 mm (≈ 38.5 mm² area), with a pulse duration of 5 ms. Based on our prior experience with this type of laser and safety recommendations for repeated laser stimuli (43), a maximum fluence limit was set to 14 J/cm² (5.25 J intensity limit for a 7 mm laser beam diameter). The laser device was triggered using a stimulus presentation software (Spike2; Cambridge Electronic Design Limited, Cambridge, UK). To avoid stimulation of the same area twice, 25 tiny ink marks were drawn on the skin with a regular Hi-Tecpoint 0.5 mm—Black Pilot pen to guide the experimenter for the area to be stimulated, in

a 5 × 5 cm grid centered around T9 spinous process (T9-T10 dermatome). The laser was moved to the next point of the grid after each stimulus. No adverse event related to laser stimulation was observed by the experimenter during the experiment or reported by participants after the experiment.

The individual pain threshold was determined using a staircase procedure. Before pain threshold assessment, participants were instructed to focus on the warm/burning sensation in their back and to report pain intensity verbally after each stimulus using a numerical rating scale ranging from 0 to 100, 0 indicating “no pain” and 100 “the worse pain imaginable.” Stimuli were delivered at an initial intensity of 0.5 J and stimulus intensity increased sequentially by 0.5 J increments until pain was reported (rating of 1/100 or higher), or until the 5.25 J safety limit was reached. If no pain was reported (rating of 0/100) at the highest energy laser stimulus within our safety limits (5.25 J), the participant was excluded from the study. This was necessary for the purpose of the study, in which we examined pain inhibition and not only LEPs. Three participants were excluded for this reason. Otherwise, the energy was increased sequentially again until a pain rating of at least 30/100 was reported or until the 5.25 J limit was reached. Participants were then familiarized with the selected intensity using five consecutive stimuli with an interstimulus interval varying between 5 and 10 s. If the intensity was deemed acceptable for the participant, the experiment was continued. If the participant judged that the stimulus intensity produced pain that could not be tolerated for the duration of the experiment, stimulus intensity was decreased by 0.5 J and the familiarization procedure resumed until an acceptable stimulus intensity was reached. Once approved by the participant, the stimulus intensity was kept constant throughout the experiment.

Capsaicin and Inert Creams

The 1% capsaicin cream used for this experiment was prepared by a pharmaceutical laboratory (Gentès & Bolduc pharmacists, St-Hyacinthe, QC, Canada). This concentration was used to produce tonic pain and hyperalgesia in prior studies (40, 44–46). The inert cream consisted of the same petroleum jelly-based cream without the active ingredient. After the first

laser stimulation block, ≈ 1 g of cream was applied uniformly to the stimulated area in a layer <1 mm thick and covered with transparent food-grade plastic film secured in place by adhesive tape. This ensured that the cream could not be wiped or spread out. After the experiment, the plastic film was discarded, the remaining cream removed, and the participants back carefully washed with water and soap to eliminate any trace of the cream. The burning sensation induced by capsaicin vanished within 30–120 min after the cream removal.

Instructions given to the participants were scripted for standardization and to minimize the influence of expectations. Participants were told which cream would be applied to their back (inert or capsaicin). However, they were not aware that other participants may receive a different cream. Moreover, none of the participants had used capsaicin cream before. Therefore, they were not aware that it could affect laser-evoked pain. Prior to the experiment, the information given to each participant was as follows: *“After the first series of laser stimuli, we will apply 1 g of inert cream in your back. This will not do anything”* OR *“After the first series of laser stimuli, we will apply 1 g of capsaicin cream in your back. You may feel nothing at all, or you may notice a warm or burning sensation. These sensations are completely normal. We are interested to know how you will react to this cream.”* Later, when it was time to rate the spontaneous pain induced by capsaicin, the experimenter asked the following question: 1- Do you feel something in your back right now? If the participant said yes: 2- Do you consider this painful? If the participant said yes: 3- How painful is it from 0 to 100?

Spinal Manipulation and Placebo Intervention

SM were performed by only one licensed chiropractor and consisted of a preload force followed by a short-duration, high-velocity, low amplitude, posterior to anterior thrust applied with both hands. SM was applied over the transverse processes of T7 vertebra, just outside the area where cream was applied, to generate audible release (cavitation). The contact point at T7-T8 for SM was selected to avoid painful SM due to the application of this mechanical force on the acutely inflamed and sensitized T9 area. SM directly applied at T9 may produce excitatory activity that could counter hypoalgesic effects. Moreover, since a single thrust affects several adjacent

segments (47), SM applied as close as possible to the painful area while being outside the region of hypersensitivity would produce the most favorable outcomes. This type of manipulation lasts <200 ms and involves a force of ~500 N (48–51). The placebo intervention consisted of a sham spinal manipulation performed with the participant in the same position, but the chiropractor contacted the medial border of both scapulae to apply a preload force by moving the scapulae laterally. A high-velocity, low amplitude thrust was then applied in the scapula-thoracic plane. This type of sham manipulation has been used in previous studies and reported successful in blinding most of the participants (52, 53). No adverse event was reported by participants following SM or placebo.

Pain Ratings

After each series of 30 stimuli, participants were instructed to rate laser-induced pain verbally using a numerical rating scale ranging from 0 to 100, 0 indicating “no pain” and 100 “worst pain imaginable.” They were instructed to report the average pain induced by the 30 stimuli. Immediately before the second stimulation block (20 min after cream application), and immediately after the third stimulation block (30 min after cream application), participants with the capsaicin cream were also instructed to rate capsaicin-induced pain using the same pain rating scale.

Expectations of Pain Modulation and Blinding

To limit the effects of expectations, participants were not informed about the specific objective of the study or about the different groups receiving different interventions (SM or sham SM). They were informed that their back would be mechanically stimulated and that we were interested in measuring how this mechanical stimulus may influence pain-related brain activity. Expectations of pain modulation were measured using a visual analog scale (54). Before the second block of laser stimuli, participants were presented a form with the following question: “On the scale below, indicate the change in laser-pain intensity that you expect following the

intervention in your back.” The scale was a horizontal line ranging from -100 to 100 with the following anchors: -100= “maximum decrease,” 0= “no change” and 100= “maximum increase.” Although participants were not aware that they belonged to different groups, we examined “blinding” by asking the following question to the two intervention groups: “Do you believe that the intervention you received was effective?”

Electroencephalographic Recordings

Electroencephalography (EEG) was recorded using a 64-channel BrainVision system with active Ag-AgCl electrodes mounted on an actiCAP, according to the International 10–20 system (Brain Products, Gilching, Germany). Electrodes were nose-referenced, and the ground was set at FPz. Signals were sampled at 1,000 Hz and filtered using a 0.01–100 Hz band-pass filter. Eye movements and blinks were recorded using right eye EOG with electrodes placed at the suborbital ridge and just lateral to the external ocular canthus. Electrode impedance was kept below 20 kΩ.

Laser-Evoked Potentials Analyses

EEG signals were analyzed offline using EEGLAB v2020.0 (55). After applying a 0.5–30 Hz finite impulse response band-pass filter (56–58), data were segmented into epochs extending from -100 ms to +1,500 ms relative to stimulus onset (56, 57, 59, 60). Epochs were baseline corrected using the -100 to 0 ms window (56, 58, 60) and then visually inspected to reject epochs with artifacts (amplitude value exceeding $\pm 100 \mu\text{V}$) (56–58, 61). On average 3.2 ± 2.4 out of 90 epochs (3.5%) were rejected. Data were then re-referenced to the common average and, an Infomax independent component analysis (ICA) was applied using the in-built EEGLAB function Runica to identify and remove components associated with noise (eye movements, eye blinks, cardiac and muscle artifacts) (55).

After data pre-processing, average waveforms were computed for each participant and stimulation block, and LEP components of interest were analyzed, including the A δ and C fibers N2 and P2 (60–62). The A δ -N2 was defined as the first major negative deflection occurring

between 150 and 400 ms with a maximum amplitude at the vertex (Cz), and the A δ -P2 was defined as the first major positive deflection occurring between 250 and 500 ms with a maximum amplitude at the vertex (Cz). The C-N2 was defined as the first major negative deflection following the A δ -P2 and occurring between 350 and 1,500 ms with a maximum amplitude at the vertex (Cz). The C-P2 was defined as the first major positive deflection following the C-N2 and occurring between 400 and 1,500 ms with a maximum amplitude at the vertex (Cz). An independent assessment performed by two of the experimenters (BP and MP) revealed that from the 80 participants tested, 3 ($\approx$ 4%) did not have clear A δ -N2 and A δ -P2 peaks from their average waveforms and a majority of participants did not have clear C-N2 and C-P2 peaks. Thus, the N2 and P2 calculations were performed on data from the remaining 77 participants for A δ fibers and C-LEP analyses are not presented. However, all data are shown in [Supplementary Figure 1](#). For the LEP amplitude analysis, the N2-P2 peak-to-peak amplitude was preferred for quantification to limit inter-individual amplitude variability; in some participants, the N2 was of normal amplitude and latency, normal topographic distribution, but was shifted from baseline, leading to incorrect amplitude measurements. The peak-to-peak analysis counter this issue although the potential effects on specific components cannot be examined. This was a fair compromise since modulation of LEPs in this study is presumed to occur due to spinal modulation of nociceptive transmission and thus to mostly reflect the resulting ascending information.

Statistical Analysis

Statistical analyses were conducted using Statistica v13.5 (Kivuto Solutions Inc., Ottawa, ON, Canada). All results are expressed as mean $\pm$ SD. SD values were corrected to remove between-subject variability (63). Statistical threshold was set at $p < 0.05$. Data distribution was assessed for normality with the Kolmogorov-Smirnov test and homogeneity of variance was assessed using Levene's test. To assess if the amplification of pain and nociceptive brain responses was induced by capsaicin, the data from block 2 relative to block 1 (difference) were compared between the four groups using one-way ANOVAs. To examine the effects of SM on capsaicin pain, and the amplification of pain and nociceptive brain responses, mixed ANOVAs were performed.

These ANOVAs comprised 2 factors: groups (the 3 groups with capsaicin cream) and time (block 2 and 3). Bonferroni-corrected planned contrasts were used to decompose significant effects. Effect sizes are reported based on partial eta-squared (η^2_p).

Results

Laser Stimulation Intensity and Capsaicin Pain

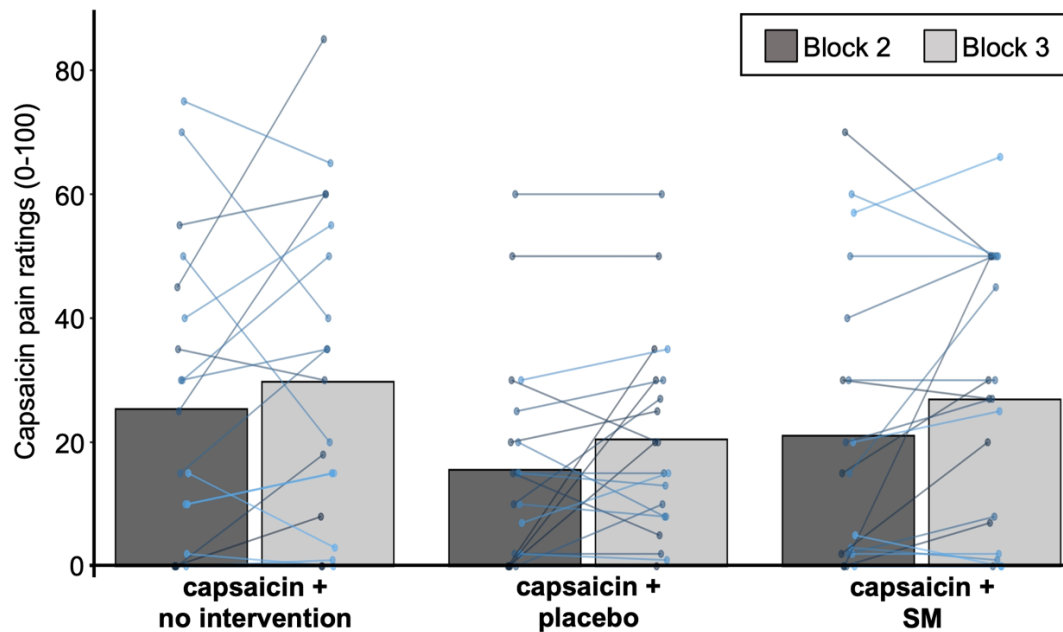
The mean laser stimulation intensity for each group was 4.6 ± 1.0 J for inert cream with no intervention, 4.9 ± 0.5 J for capsaicin cream and no intervention, 4.6 ± 1.0 J for capsaicin cream and SM, and 4.8 ± 0.7 J for capsaicin cream and placebo intervention. A one-way ANOVA revealed no significant difference between groups ($F_{3,76} = 0.81$, $p = 0.49$; $\eta^2_p = 0.03$).

Capsaicin pain ratings are reported in **Table 2.1** and presented in **Figure 2.3**. Capsaicin pain was not significantly different between groups (main effect: $F_{2,50} = 2.3$, $p = 0.11$, $\eta^2_p = 0.09$) or between groups over time (interaction: $F_{2,50} = 0.6$, $p = 0.58$, $\eta^2_p = 0.02$). This indicates that SM did not reduce capsaicin pain.

Table 2.1 – Pain ratings for the four experimental groups (mean $\pm$ SD)

		Inert cream	Capsaicin cream		
		No intervention	No intervention	Placebo	SM
Laser pain	Block 1	22.5 ± 4.8	21.8 ± 12.3	15.9 ± 8.2	24.5 ± 14.3
	Block 2	15.2 ± 2.1	47.3 ± 6.5	32.0 ± 5.0	45.3 ± 8.3
	Block 3	11.8 ± 4.0	51.1 ± 7.9	32.0 ± 5.0	48.0 ± 7.6
Capsaicin pain	Block 2		25.4 ± 8.9	15.6 ± 6.2	21.1 ± 7.4
	Block 3		29.8 ± 8.9	20.5 ± 6.2	26.9 ± 7.4

Figure 2.3 – Capsaicin pain ratings



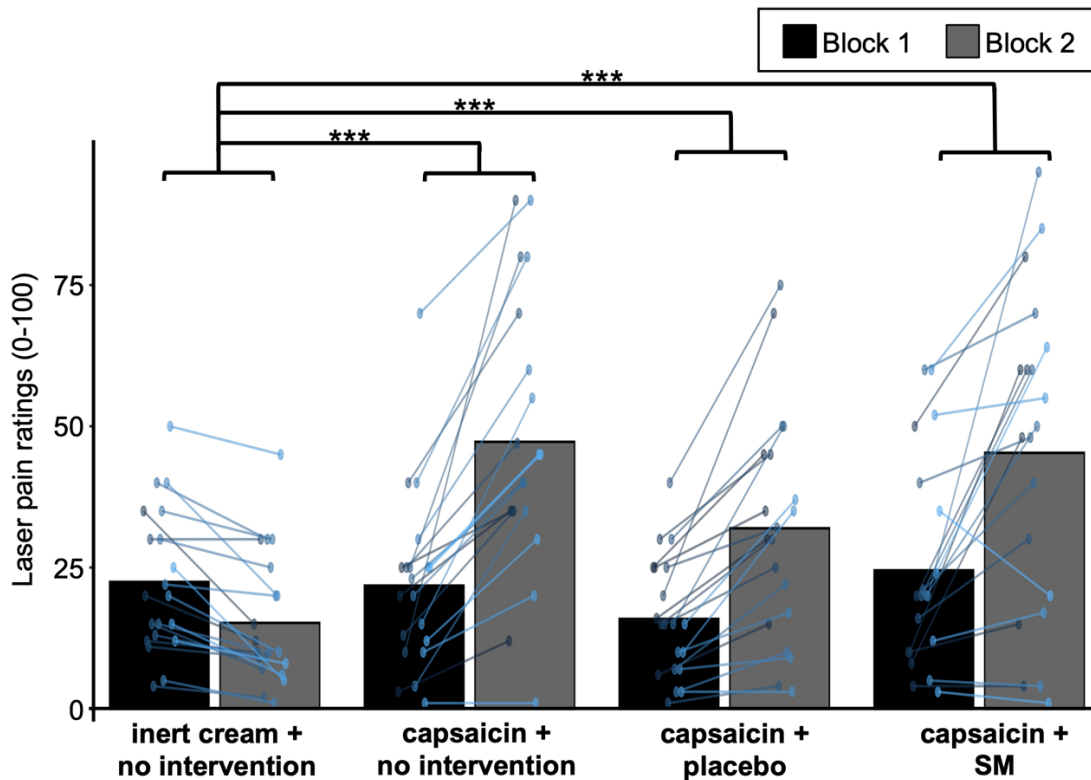
Mean pain ratings for capsaicin pain for the three groups with capsaicin cream. Data from each participant are represented by linked colored points and the mean of these data points for each block is represented by gray bars.

Heat Pain Amplification Induced by Capsaicin

Pain ratings for laser stimulation are reported in **Table 2.1**. Out of the 60 participants on which capsaicin cream was applied, 54 (90%) reported increased sensitivity to laser stimuli during the second block. This number increased to 57 participants (95%) during the third stimulation block. Thus, 3/60 participants (2 in SM and 1 in placebo intervention group) did not show heat pain amplification during the experiment.

To confirm that capsaicin induced heat pain amplification, changes in laser pain after the cream application but before any intervention were compared between groups using a one-way ANOVA (see **Figure 2.4**). The change in laser pain was significantly different between groups ($F_{3,76} = 16.7$, $p < 0.0001$, $\eta^2_p = 0.40$). Bonferroni-corrected planned contrasts revealed that the change in laser pain was greater in the three groups with capsaicin cream compared with the group with inert cream (all $p < 0.001$).

Figure 2.4 – Heat pain amplification induced by capsaicin

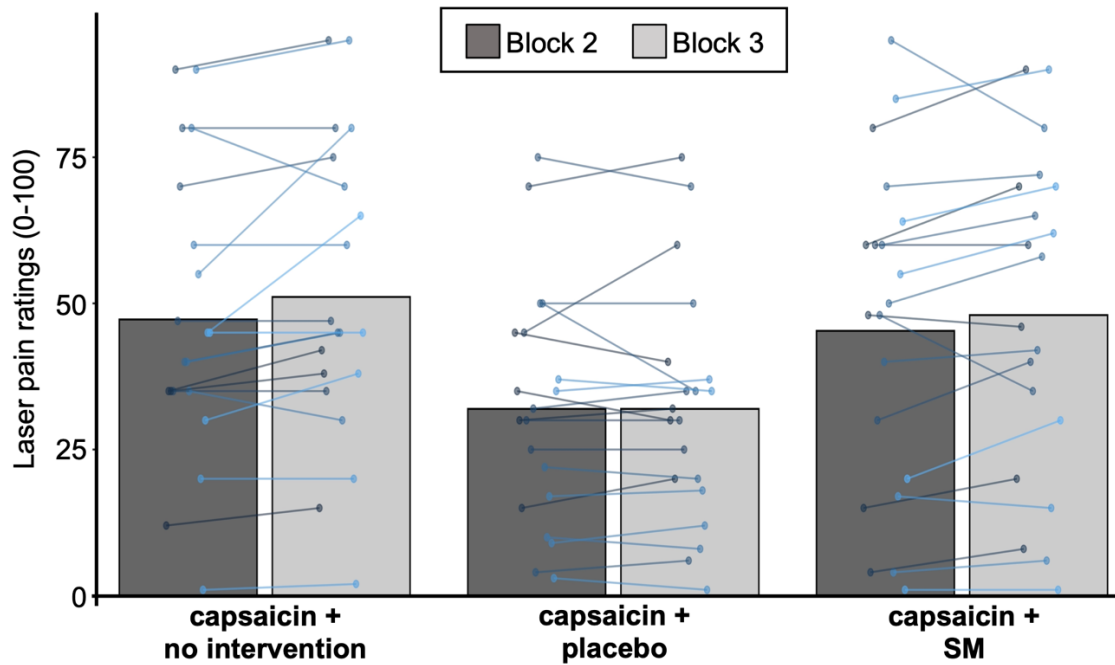


Mean laser pain ratings during block 1 and block 2 (before and after cream application, but before the intervention) for the four experimental groups. Data from each participant are represented by colored points and the mean of these data points for each block is represented by gray bars. *** $p < 0.001$.

Effects of SM on Heat Pain Amplification

To examine the effects of interventions on heat pain amplification, changes in laser-pain relative to baseline were compared between the three groups with capsaicin cream (see **Figure 2.5**). Changes in laser-pain intensity significantly increased between blocks 2 and 3 (main effect: $F_{1,57} = 6.17$, $p = 0.02$, $\eta^2_p = 0.10$). However, this effect was not significantly different between groups (interaction: $F_{2,57} = 1.69$, $p = 0.19$, $\eta^2_p = 0.06$), indicating that heat pain amplification was not reduced by SM.

Figure 2.5 – Effect of SM on heat pain amplification

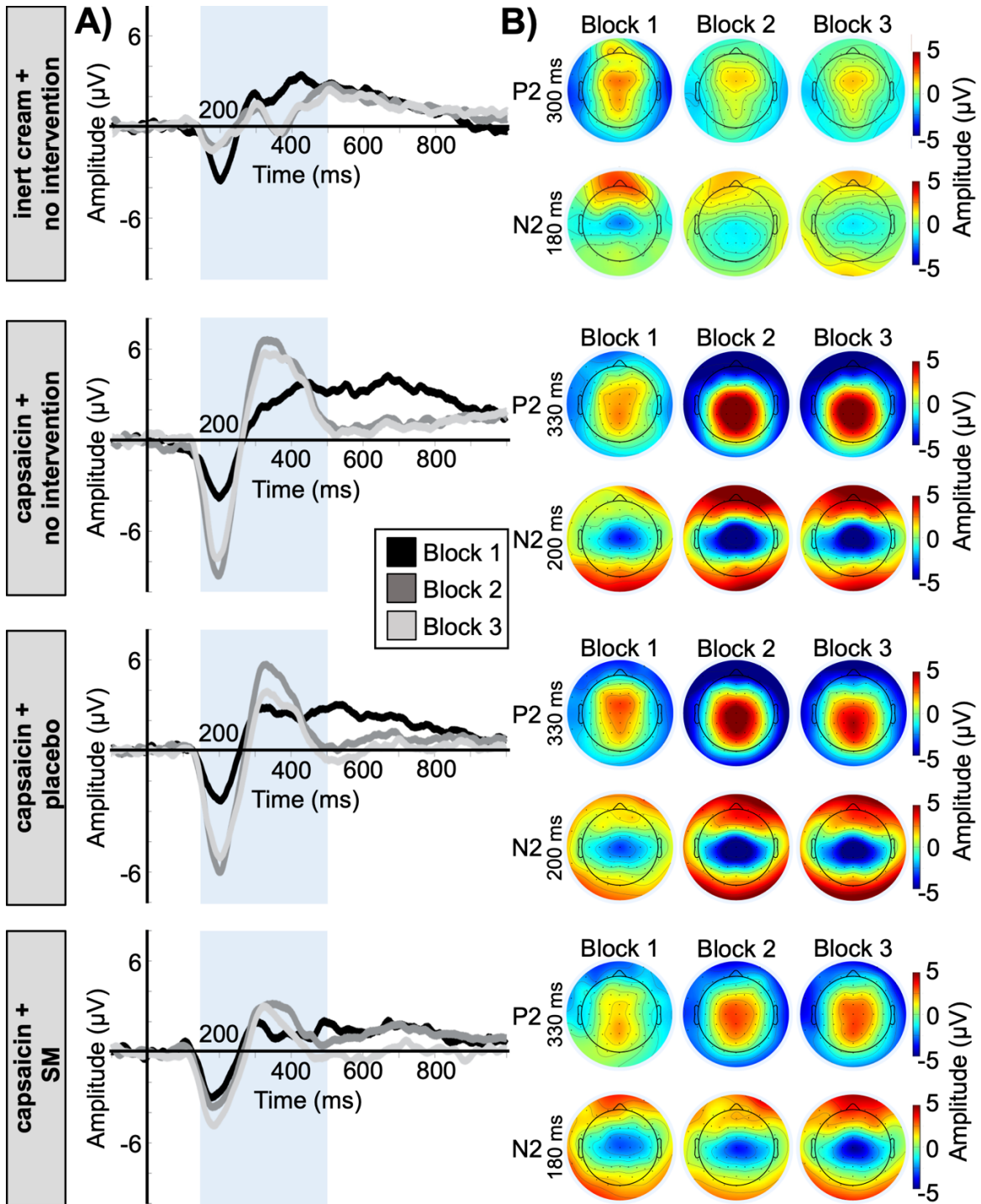


Mean laser pain ratings for the three groups with capsaicin cream during block 2 and block 3 (before and after the intervention). Data from each participant are represented by linked colored points and the mean of these data points for each block is represented by gray bars. Note that the inert cream group did not report heat pain amplification and received no intervention, so it is not included in this analysis.

Amplification of A δ Laser-Evoked Potentials by Capsaicin

Average waveforms and topographic maps for A δ N2 and P2 components for all groups and conditions are presented in **Figure 2.6**. As expected, both components showed a central scalp distribution and were maximal at the vertex.

Figure 2.6 – A δ fiber laser-evoked potentials.



(A) Average waveforms for the N2 and P2 at Cz with a nose reference of the 77 participants included in the A δ fiber LEP analysis, time-locked to the onset of laser stimulation. **(B)** Average topographic maps for the A δ -N2 and A δ -P2 in the four groups.

A δ N2-P2 amplitudes and latencies are reported in **Tables 2.2, 2.3**. The effect of capsaicin on A δ N2-P2 amplitude is presented in **Figure 2.7**. For the change from block 1 to block 2, A δ N2-P2 amplitude was significantly different between groups (main effect: $F_{3,73} = 12.7$, $p < 0.001$, $\eta^2_p = 0.34$). Bonferroni-corrected planned contrasts revealed that compared with the inert cream group, A δ N2-P2 amplitude was significantly increased in the three groups with the capsaicin cream (all $p < 0.001$). Moreover, A δ N2 peak latency was significantly different between groups from block 1 to block 2 (interaction: $F_{3,73} = 6.3$, $p < 0.001$, $\eta^2_p = 0.21$). Bonferroni-corrected planned contrasts revealed that compared with the inert cream group, the A δ N2 peak latency was shorter for block 2 compared with block 1 in the capsaicin with no intervention group ($p < 0.001$), in the placebo intervention groups ($p < 0.001$), but not in the SM group ($p = 0.21$). Similarly, A δ P2 peak latency was significantly different between groups from block 1 to block 2 (interaction: $F_{3,73} = 6.2$, $p < 0.001$, $\eta^2_p = 0.20$). Bonferroni-corrected planned contrasts revealed that the A δ P2 peak latency was shorter at block 2 in the capsaicin with no intervention group ($p = 0.006$), in the placebo intervention group ($p < 0.001$), but not in the SM group ($p = 0.78$) when compared with the inert cream group.

Altogether, these results indicate that heat pain amplification by capsaicin was associated with increased A δ N2-P2 amplitude and decreased A δ N2 and P2 peak latencies.

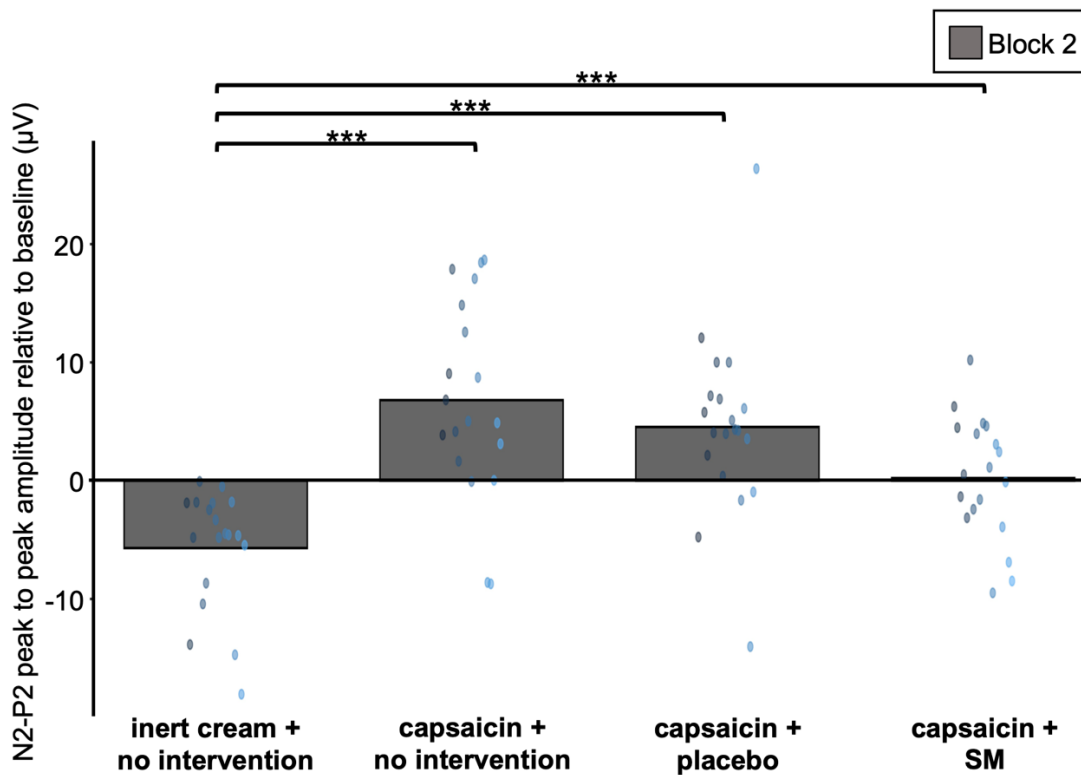
Table 2.2 – A δ N2-P2 peak to peak amplitude (μ V) for the four experimental groups (mean $\pm$ SD).

		Inert cream	Capsaicin cream		
		No intervention	No intervention	Placebo	SM
A δ	Block 1	12.6 $\pm$ 3.5	13.2 $\pm$ 5.3	11.7 $\pm$ 4.9	10.9 $\pm$ 4.1
	Block 2	6.9 $\pm$ 1.7	20.0 $\pm$ 3.4	16.3 $\pm$ 3.4	11.2 $\pm$ 1.9
	Block 3	5.8 $\pm$ 2.2	17.5 $\pm$ 3.1	13.4 $\pm$ 3.3	11.5 $\pm$ 3.6

Table 2.3 – N2 and P2 peak latency (ms) for the four experimental groups (mean $\pm$ SD).

		Inert cream	Capsaicin cream		
		No intervention	No intervention	Placebo	SM
A δ	Block 1	249.1 $\pm$ 42.3	252.4 $\pm$ 49.3	267.3 $\pm$ 53.4	227.7 $\pm$ 40.4
	N2 Block 2	274.5 $\pm$ 31.3	204.4 $\pm$ 22.2	204.7 $\pm$ 27.9	212.1 $\pm$ 20.3
	Block 3	272.1 $\pm$ 46.5	203.3 $\pm$ 29.0	205.2 $\pm$ 26.8	211.5 $\pm$ 23.9
	Block 1	405.4 $\pm$ 39.1	408.9 $\pm$ 52.2	421.6 $\pm$ 55.6	382.3 $\pm$ 51.2
	P2 Block 2	419.2 $\pm$ 36.6	344.0 $\pm$ 31.4	347.3 $\pm$ 30.3	369.2 $\pm$ 23.9
	Block 3	380.8 $\pm$ 51.0	354.5 $\pm$ 26.2	352.7 $\pm$ 30.0	352.4 $\pm$ 40.5

Figure 2.7 – Amplification of A δ fiber LEP by capsaicin



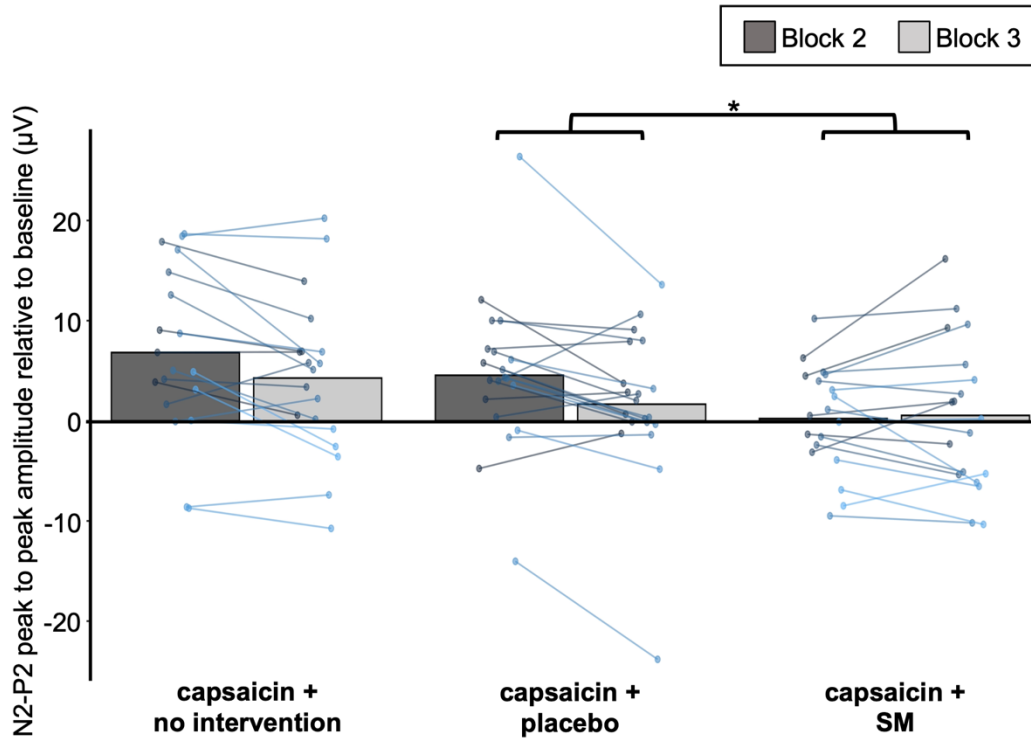
Average A δ fiber N2-P2 peak to peak amplitude values during block 2 for the four experimental groups. These values are relative to baseline (block 2 minus block 1). Data from each participant are represented by colored points and the mean of these data points for each block is represented by gray bars. *** $P < 0.001$.

Effects of SM on the Amplification of A δ Laser-Evoked Potentials by Capsaicin

The effects of interventions on the amplification of A δ -nociceptor activity by capsaicin were examined with the three capsaicin groups (see **Figure 2.8**). A δ N2-P2 amplitude was significantly different between groups over time (interaction: $F_{2,55} = 3.3$, $p = 0.043$, $\eta^2_p = 0.11$). Bonferroni-corrected planned contrasts revealed that the change between block 2 and block 3 was significantly different between the SM and placebo intervention groups ($p = 0.043$), where the SM group did not show a decrease in A δ N2-P2 amplitude. However, no significant difference was observed between the SM and no intervention groups ($p = 0.08$).

Besides, A δ N2 peak latency was not significantly different between groups over time (from block 2 to block 3) (interaction: $F_{2,55} = 0.05$, $p = 0.95$, $\eta^2_p = 0.002$), but the effect was significant for the P2 latency (interaction: $F_{2,55} = 4.1$, $p = 0.02$, $\eta^2_p = 0.13$). However, Bonferroni-corrected planned contrasts revealed that P2 peak latency in block 3 was not significantly different between the SM group compared with the placebo group ($p = 0.06$), although it was significantly different compared with no intervention group ($p = 0.02$).

Figure 2.8 – Effect of SM on A δ fiber LEP



Average A δ fiber N2-P2 peak to peak amplitude values for the three groups with capsaicin cream before (block 2) and after (block 3) the intervention. Data from each participant are represented by linked colored points and the mean of these data points for each block is represented by gray bars. * $P < 0.05$.

Expectations and Blinding

Expectations scores were 1.2 ± 32.4 for the SM group and -5.7 ± 16.6 for the placebo group. An independent t-test revealed no significant difference between groups [$t_{(38)} = 0.83$, $p = 0.41$; $\eta^2_p = 0.02$]. In addition, expectations did not predict changes in capsaicin pain, laser pain or A δ N2-P2 amplitude, induced by SM (all $R^2 < 0.08$, all $p > 0.2$), or by the placebo (all $R^2 < 0.17$, all $p > 0.07$). Regarding blinding, the number of participants reporting that they received an effective intervention was not significantly different between groups [SM: 9/20 (45%); placebo intervention: 7/20 (35%); $\chi^2_{(1)} = 0.36$, $p = 0.55$]. Besides, expectations of pain relief were not significantly different between participants reporting that they received an effective vs.

ineffective intervention for the SM group (Mann-Whitney $U = 42.5$, $p = 0.62$), for the placebo group (Mann-Whitney $U = 32.0$, $p = 0.30$) or both groups combined (Mann-Whitney $U = 182.0$, $p = 0.79$).

Discussion

The aim of the present study was to investigate the effects of segmental chiropractic SM on heat pain amplification produced by capsaicin. The application of topical capsaicin in the back induced heat pain amplification and increased nociceptive brain activity associated with the activation of A- δ fibers. However, contrary to our hypothesis, SM did not reduce heat pain amplification and the associated amplification of nociceptive brain activity.

Heat Pain Amplification Induced by Capsaicin

The tonic pain and heat pain amplification induced by topical capsaicin reported in the present study are consistent with the effects reported previously (37, 39, 64). Moreover, the increase in A δ LEP amplitude is consistent with the effects of nociceptive laser stimuli on capsaicin treated skin (44, 65–67). By contrast, a decrease in A δ LEP amplitude on capsaicin treated skin was reported in one study (68). However, this discrepancy is likely due to the lower concentration of capsaicin [0.1% instead of 0.6% (66) or 1% in the present study and in (44, 65, 67)]. It should be noted that the amplitude of A- δ LEPs in the SM group of the present study was less affected by capsaicin and this may have affected the results. However, capsaicin-evoked pain, laser-evoked pain, laser stimulation intensity, and expectation scores were not significantly different between groups. Therefore, these factors are unlikely to explain the smaller effect of capsaicin on A- δ LEPs in the SM group, which may reflect variability.

Effects of Spinal Manipulation on the Amplification of Heat Pain and Nociceptive Brain Activity by Capsaicin

In the present study, the capsaicin-heat pain model was used for its ability mimic some aspects of pathological pain such as spontaneous pain and increased pain sensitivity (38), which are commonly associated with low back pain (69, 70). Indeed, topical capsaicin has been used in previous studies to induce experimental low back pain (71) and neck pain (72).

The present findings show that SM has no effect on this type of experimental back pain or on the increased sensitivity to painful laser stimuli in the present experimental conditions. This is consistent with results from a recent study in which segmental SM reduced secondary mechanical hyperalgesia induced by capsaicin but not capsaicin pain (30). However, this contrasts with results from a previous study in which capsaicin pain was reduced by SM (40). Nonetheless, several factors may explain these discrepancies.

Firstly, the application of a mechanical force such as SM on an acutely inflamed and sensitized area activates nociceptive afferents, which excitatory activity may counter centrally mediated hypoalgesic effects. Accordingly, in the study that reported a reduction in capsaicin pain, topical capsaicin was applied to the forearm and SMs were not performed on sensitized tissues. This suggests that SM applied close to, but not directly on the acutely inflamed area may produce more favorable outcomes, but this remains to be investigated with a clinical sample. It should be emphasized that topical capsaicin and acute musculoskeletal injury do not sensitize the same tissues, and SM may produce different effects on capsaicin and clinical pain. In line with this idea, it has been shown in patients with chronic back pain that brain activity related to spontaneous clinical pain differs from the brain activity related to experimental pain evoked in their back (73). However, it should be noted that findings from several studies suggest that SM affects the transmission of spinal nociceptive activity, regardless of the origin of the inputs (cutaneous or myofascial) (23–30), although this remains to be confirmed with neurophysiological measures of spinal cord activity. Therefore, the lack of effect in the present study suggests that SM does not influence spinal nociceptive transmission when it is amplified by peripheral

sensitization. Future studies should confirm these findings with other experimental pain models, including muscle pain induced by exercise or intramuscular hypertonic saline.

Secondly, although previous studies have demonstrated that a single SM can decrease experimental pain (23, 74), it is possible that a single SM is not sufficient to reduce peripheral sensitization and pain hypersensitivity. This may explain the discrepancy between the present results and a previous study in which capsaicin pain was reduced by multiple SMs during one session (40). Although the clinical relevance of the present results is limited, it is worth noting that in clinical studies, the number of SM is associated with outcomes. For example, a randomized controlled trial on the dose-response effects of SM for chronic low back pain in which participants received either 0, 6, 12 or 18 sessions of multiple SMs reported that 12 sessions yielded the most favorable improvements in pain level and disability (75). In addition, another study from the same group investigating the effect of the same doses of SM in participants with chronic cervicogenic headache reported a linear dose-response relationship between the number of SM sessions and the number of days per month with cervicogenic headache, the most effective dose being 18 sessions (76).

Altogether, the findings from the present and previous studies suggest that centrally mediated neurophysiological mechanisms independent of primary hyperalgesia may produce the immediate pain reduction by SM, which may add to anti-inflammatory and other effects later on, in line with the current literature (23–26, 77–80). However, this should be confirmed with clinical populations since the effects of SM may be different on primary hyperalgesia associated with clinical pain. In addition, future studies may lead to different results if the modulation of primary hyperalgesia by SM is examined with mechanical stimuli instead of heat stimuli. It should also be emphasized that SM was applied only once and it remains to be determined whether several SM applied on different segments surrounding the hyperalgesic area may be more effective.

Although previous studies have examined brain activity following SM, no study investigated the effects of brain activity associated with capsaicin, which was used in the present study as an experimental model of tonic pain associated with pain hypersensitivity. The present results show that SM did not modulate LEP amplification by capsaicin, in line with the behavioral

results. In two previous EEG studies in healthy volunteers, laser pain (81) and secondary hyperalgesia induced by capsaicin (30) were decreased by SM. However, these studies did not examine if primary hyperalgesia was modulated by SM. Reducing primary hyperalgesia may prevent or reduce the development of secondary hyperalgesia, but the present results indicate that the reduction of secondary hyperalgesia induced by capsaicin (30) cannot be explained by this mechanism. In another study in patients with subclinical pain, pain intensity and cerebral oscillations (1–32 Hz) induced by 80 s of tonic pain (hand cold-pressor test) were not modulated by SM applied on different regions of the spine (82). In functional magnetic resonance imaging (fMRI) studies, a decrease of pain-related activity was observed following a single SM, in healthy individuals (83, 84) and patients with neck pain (85). Other fMRI studies also suggest that SM may reduce chronic low back pain by modulating the saliency network activity or connectivity (86, 87). Thus, far, these conflicting findings highlight the need for further research to examine brain activity with protocols in which SM produces clear pain inhibition. Moreover, it should be emphasized that the present study and our previous reports (30, 81) were designed to examine brain activity evoked by the selective activation of A- δ and C fibers, and its modulation by segmental SM, with the hypothesis that segmental inhibition of nociceptive activity in the spinal cord would be reflected in decreased nociceptive activity in the brain. This does not exclude that cerebral processes non-specific to SM may also modulate nociceptive activity. Accordingly, future studies should include all appropriate controls to examine the effects of SM on pain perception and pain-related processes with well-supported hypothesis-driven experimental designs and a mechanistic approach, as proposed previously (80, 88).

Expectations and Placebo Effects

Expectations did not predict any inter-individual differences in the variables of interest. Although some participants expected a large pain relief by the intervention, this did not lead to better outcomes, either in the SM group or the placebo group. Consistent with these results, less than half of participants reported the intervention as effective, regardless of the intervention group. The fact that participants were not aware of different group allocations and interventions

may contribute to making expectations and placebo effects more comparable between groups. This may be examined and considered in future studies.

It has been shown that the nocebo effect increases pain ratings and LEPs (89). Capsaicin application may have induced such nocebo effects, competing with and hiding the potential inhibition of A δ LEP and pain by SM. A measure of expectations relative to capsaicin in addition to a measure of expectations related to the effects of SM and placebo could clarify this issue in a future study.

Significance

There are several important steps between basic research and clinical practice guidelines, and the objective of this basic study is to provide information on the underlying mechanisms of SM-induced inhibition of pain amplification due to peripheral sensitization. This is essential to feed applied and clinical research, and eventually, to provide a mechanistic rationale to support clinical practice guidelines. Accordingly, experimental pain models are validated in preclinical research on biomarkers, which may be measured in clinical studies, thereby narrowing the gap between basic and clinical findings (38). Recently, three reviews on the mechanisms of SM (80, 90) or manual therapy (91) stated the need for more well-designed mechanistic studies. The present study adds to previous basic studies to guide investigators on which measures should be used in mechanistic clinical trials and which mechanisms may underlie the clinical effects of SM in these clinical trials. Nevertheless, clinical recommendations should be considered cautiously when inferred from experimental pain models that may not completely reflect pathological mechanisms.

Conclusion

In summary, the present results indicate that SM applied segmentally does not reduce the capsaicin-induced amplification of heat pain and the associated nociceptive brain activity. Future studies are needed to examine the modulation of primary heat and mechanical hyperalgesia in patients with chronic spine pain, in whom pathological changes in the dorsal horn of the spinal cord may lead to different results.

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 Comité d'éthique de la recherche chez l'être humain (UQTR). The patients/participants provided their written informed consent to participate in this study.

Author contributions

BP contributed to the study design, data collection, analysis and interpretation, and wrote the preliminary version of the manuscript. SN contributed to data collection and analyses. MP contributed to the study design, data collection, analyses, interpretation, wrote the final version of the manuscript, and obtained funding for the study. Each author has contributed significantly to this work and has read and approved the final version of the manuscript.

Funding

This project was funded by the Fondation Chiropratique du Québec, the Natural Science and Engineering Research Council of Canada (#06659), and the Canadian Foundation for Innovation (#33731). The contribution of Benjamin Provencher was supported by the Fonds de Recherche du Québec – Santé (FRQS) and the Fondation Chiropratique du Québec. The contribution of Stéphane Northon was supported by the Fonds de Recherche du Québec – Nature et Technologie (FRQNT). The contribution of Mathieu Piché was supported by the Fonds de Recherche du Québec – Santé (FRQS).

Supplementary material

The Supplementary Material for this article can be found online at:

<https://www.frontiersin.org/articles/10.3389/fpain.2021.733727/full#supplementary-material>

References

1. Shraim MA, Massé-Alarie H, Hall LM, Hodges PW. Systematic Review and Synthesis of Mechanism-based Classification Systems for Pain Experienced in the Musculoskeletal System. *The Clinical Journal of Pain*. 2020;36(10):793-812.
2. Urits I, Burshtein A, Sharma M, Testa L, Gold PA, Orhurhu V, et al. Low Back Pain, a Comprehensive Review: Pathophysiology, Diagnosis, and Treatment. *Current Pain and Headache Reports*. 2019;23(3):23.
3. Vlaeyen JWS, Maher CG, Wiech K, Van Zundert J, Meloto CB, Diatchenko L, et al. Low back pain. *Nature reviews Disease primers*. 2018;4(1):52-70.
4. Hartvigsen J, Hancock MJ, Kongsted A, Louw Q, Ferreira ML, Genevay S, et al. What low back pain is and why we need to pay attention. *Lancet*. 2018;391(10137):2356-67.
5. Raja SN, Meyer RA, Campbell JN. Peripheral mechanisms of somatic pain. *Anesthesiology*. 1988;68(4):571-90.
6. Treede RD, Meyer RA, Raja SN, Campbell JN. Peripheral and central mechanisms of cutaneous hyperalgesia. *Progress in Neurobiology*. 1992;38(4):397-421.
7. Baumann TK, Simone DA, Shain CN, LaMotte RH. Neurogenic hyperalgesia: the search for the primary cutaneous afferent fibers that contribute to capsaicin-induced pain and hyperalgesia. *Journal of Neurophysiology*. 1991;66(1):212-27.
8. Torebjörk HE, LaMotte RH, Robinson CJ. Peripheral neural correlates of magnitude of cutaneous pain and hyperalgesia: simultaneous recordings in humans of sensory judgments of pain and evoked responses in nociceptors with C-fibers. *Journal of Neurophysiology*. 1984;51(2):325-39.
9. Matsuda M, Huh Y, Ji RR. Roles of inflammation, neurogenic inflammation, and neuroinflammation in pain. *J Anesth*. 2019;33(1):131-9.
10. Hsieh M-T, Donaldson LF, Lumb BM. Differential contributions of A- and C-nociceptors to primary and secondary inflammatory hypersensitivity in the rat. *Pain*. 2015;156(6):1074-83.
11. LaMotte RH, Lundberg LE, Torebjörk HE. Pain, hyperalgesia and activity in nociceptive C units in humans after intradermal injection of capsaicin. *The Journal of Physiology*. 1992;448:749-64.
12. You HJ, Lei J, Sui MY, Huang L, Tan YX, Tjølsen A, et al. Endogenous descending modulation: spatiotemporal effect of dynamic imbalance between descending facilitation and inhibition of nociception. *The Journal of Physiology*. 2010;588(Pt 21):4177-88.

13. Magerl W, Fuchs PN, Meyer RA, Treede RD. Roles of capsaicin-insensitive nociceptors in cutaneous pain and secondary hyperalgesia. *Brain*. 2001;124(9):1754-64.
14. Nijs J, George SZ, Clauw DJ, Fernández-de-las-Peñas C, Kosek E, Ickmans K, et al. Central sensitisation in chronic pain conditions: latest discoveries and their potential for precision medicine. *The Lancet Rheumatology*. 2021;3(5):e383-e92.
15. den Bandt HL, Paulis WD, Beckwée D, Ickmans K, Nijs J, Voogt L. Pain Mechanisms in Low Back Pain: A Systematic Review With Meta-analysis of Mechanical Quantitative Sensory Testing Outcomes in People With Nonspecific Low Back Pain. *The Journal of Orthopaedic and Sports Physical Therapy*. 2019;49(10):698-715.
16. Beliveau PJH, Wong JJ, Sutton DA, Simon NB, Bussières AE, Mior SA, et al. The chiropractic profession: a scoping review of utilization rates, reasons for seeking care, patient profiles, and care provided. *Chiropr Man Therap*. 2017;25:35-52.
17. Millan M, Leboeuf-Yde C, Budgell B, Amorim MA. The effect of spinal manipulative therapy on experimentally induced pain: a systematic literature review. *Chiropractic & manual Therapies*. 2012;20(1):26.
18. Coronado RA, Gay CW, Bialosky JE, Carnaby GD, Bishop MD, George SZ. Changes in pain sensitivity following spinal manipulation: a systematic review and meta-analysis. *Journal of electromyography and kinesiology*. 2012;22(5):752-67.
19. Kolber MR, Ton J, Thomas B, Kirkwood J, Moe S, Dugré N, et al. PEER systematic review of randomized controlled trials: Management of chronic low back pain in primary care. *Canadian Family Physician*. 2021;67(1):e20-e30.
20. Stochkendahl MJ, Kjaer P, Hartvigsen J, Kongsted A, Aaboe J, Andersen M, et al. National Clinical Guidelines for non-surgical treatment of patients with recent onset low back pain or lumbar radiculopathy. *Eur Spine J*. 2018;27(1):60-75.
21. Bussi res AE, Stewart G, Al-Zoubi F, Decina P, Descarreaux M, Haskett D, et al. Spinal Manipulative Therapy and Other Conservative Treatments for Low Back Pain: A Guideline From the Canadian Chiropractic Guideline Initiative. *Journal of Manipulative & Physiological Therapeutics*. 2018;41(4):265-93.
22. Foster NE, Anema JR, Cherkin D, Chou R, Cohen SP, Gross DP, et al. Prevention and treatment of low back pain: evidence, challenges, and promising directions. *The Lancet*. 2018;391(10137):2368-83.
23. Randoll C, Gagnon-Normandin V, Tessier J, Bois S, Rustamov N, O'Shaughnessy J, et al. The mechanism of back pain relief by spinal manipulation relies on decreased temporal summation of pain. *Neuroscience*. 2017;349:220-8.

24. George SZ, Bishop MD, Bialosky JE, Zeppieri G, Jr., Robinson ME. Immediate effects of spinal manipulation on thermal pain sensitivity: an experimental study. *BMC Musculoskeletal Disorders*. 2006;7:68-78.
25. Bialosky JE, Bishop MD, Robinson ME, Zeppieri G, Jr., George SZ. Spinal manipulative therapy has an immediate effect on thermal pain sensitivity in people with low back pain: a randomized controlled trial. *Phys Ther*. 2009;89(12):1292-303.
26. Bialosky JE, George SZ, Horn ME, Price DD, Staud R, Robinson ME. Spinal manipulative therapy-specific changes in pain sensitivity in individuals with low back pain (NCT01168999). *The Journal of Pain*. 2014;15(2):136-48.
27. Bialosky JE, Bishop MD, Robinson ME, Barabas JA, George SZ. The influence of expectation on spinal manipulation induced hypoalgesia: an experimental study in normal subjects. *BMC Musculoskeletal Disorders*. 2008;9:19.
28. Bishop MD, Beneciuk JM, George SZ. Immediate reduction in temporal sensory summation after thoracic spinal manipulation. *The Spine Journal*. 2011;11(5):440-6.
29. Penza CW, Horn ME, George SZ, Bishop MD. Comparison of 2 Lumbar Manual Therapies on Temporal Summation of Pain in Healthy Volunteers. *The Journal of Pain*. 2017;18(11):1397-408.
30. Gevers-Montoro C, Provencher B, Northon S, Stedile-Lovatel JP, Ortega de Mues A, Piché M. Chiropractic Spinal Manipulation Prevents Secondary Hyperalgesia Induced by Topical Capsaicin in Healthy Individuals. *Frontiers in Pain Research*. 2021;2(33).
31. Arribas-Romano A, Fernández-Carnero J, Molina-Rueda F, Angulo-Díaz-Parreño S, Navarro-Santana MJ. Efficacy of Physical Therapy on Nociceptive Pain Processing Alterations in Patients with Chronic Musculoskeletal Pain: A Systematic Review and Meta-analysis. *Pain Med*. 2020;21(10):2502-17.
32. Wong AY, Parent EC, Dhillon SS, Prasad N, Kawchuk GN. Do participants with low back pain who respond to spinal manipulative therapy differ biomechanically from nonresponders, untreated controls or asymptomatic controls? *Spine (Phila Pa 1976)*. 2015;40(17):1329-37.
33. Fritz JM, Koppenhaver SL, Kawchuk GN, Teyhen DS, Hebert JJ, Childs JD. Preliminary investigation of the mechanisms underlying the effects of manipulation: exploration of a multivariate model including spinal stiffness, multifidus recruitment, and clinical findings. *Spine*. 2011;36(21):1772-81.
34. Nim CG, Kawchuk GN, Schjøttz-Christensen B, O'Neill S. The effect on clinical outcomes when targeting spinal manipulation at stiffness or pain sensitivity: a randomized trial. *Scientific Reports*. 2020;10(1):14615.

35. Nim CG, O'Neill S, Geltoft AG, Jensen LK, Schjøttz-Christensen B, Kawchuk GN. A cross-sectional analysis of persistent low back pain, using correlations between lumbar stiffness, pressure pain threshold, and heat pain threshold. *Chiropr Man Therap*. 2021;29(1):34.
36. Price RC, Gandhi W, Nadeau C, Tarnavskiy R, Qu A, Fahey E, et al. Characterization of a novel capsaicin/heat ongoing pain model. *Eur J Pain*. 2018;22(2):370-84.
37. Fattori V, Hohmann MS, Rossaneis AC, Pinho-Ribeiro FA, Verri WA. Capsaicin: Current Understanding of Its Mechanisms and Therapy of Pain and Other Pre-Clinical and Clinical Uses. *Molecules*. 2016;21(7):844-77.
38. Quesada C, Kostenko A, Ho I, Leone C, Nochi Z, Stouffs A, et al. Human surrogate models of central sensitization: a critical review and practical guide. *Eur J Pain*. 2021;25:1389-428.
39. Ilie MA, Caruntu C, Tampa M, Georgescu SR, Matei C, Negrei C, et al. Capsaicin: Physicochemical properties, cutaneous reactions and potential applications in painful and inflammatory conditions. *Exp Ther Med*. 2019;18(2):916-25.
40. Mohammadian P, Gonsalves A, Tsai C, Hummel T, Carpenter T. Areas of capsaicin-induced secondary hyperalgesia and allodynia are reduced by a single chiropractic adjustment: a preliminary study. *J Manipulative Physiol Ther*. 2004;27(6):381-7.
41. Bromm B, Jahnke MT, Treede RD. Responses of human cutaneous afferents to CO₂ laser stimuli causing pain. *Experimental Brain Research*. 1984;55(1):158-66.
42. Plaghki L, Mouraux A. How do we selectively activate skin nociceptors with a high power infrared laser? Physiology and biophysics of laser stimulation. *Clinical Neurophysiology*. 2003;33(6):269-77.
43. Madden VJ, Catley MJ, Grabherr L, Mazzola F, Shohag M, Moseley GL. The effect of repeated laser stimuli to ink-marked skin on skin temperature-recommendations for a safe experimental protocol in humans. *PeerJ*. 2016;4:e1577.
44. Schaffler K, Nicolas LB, Borta A, Brand T, Reitmeir P, Roebeling R, et al. Investigation of the predictive validity of laser-EPs in normal, UVB-inflamed and capsaicin-irritated skin with four analgesic compounds in healthy volunteers. *British Journal of Clinical Pharmacology*. 2017;83(7):1424-35.
45. Lin RL, Douaud G, Filippini N, Okell TW, Stagg CJ, Tracey I. Structural Connectivity Variances Underlie Functional and Behavioral Changes During Pain Relief Induced by Neuromodulation. *Scientific Reports*. 2017;7:41603.
46. Segerdahl AR, Mezue M, Okell TW, Farrar JT, Tracey I. The dorsal posterior insula subserves a fundamental role in human pain. *Nature Neuroscience*. 2015;18(4):499-500.

47. Page I, Biner E, Descarreaux M. Vertebral Displacements and Muscle Activity During Manual Therapy: Distinct Behaviors Between Spinal Manipulation and Mobilization. *J Manipulative Physiol Ther.* 2018;41(9):753-61.
48. Herzog W. The biomechanics of spinal manipulation. *Journal of Bodywork and Movement Therapies.* 2010;14(3):280-6.
49. Triano JJ, Giuliano D, Kanga I, Starmer D, Brazeau J, Screaton CE, et al. Consistency and malleability of manipulation performance in experienced clinicians: a pre-post experimental design. *J Manipulative Physiol Ther.* 2015;38(6):407-15.
50. Pickar JG, Bolton PS. Spinal manipulative therapy and somatosensory activation. *Journal of Electromyography and Kinesiology.* 2012;22(5):785-94.
51. Downie AS, Vemulapad S, Bull PW. Quantifying the high-velocity, low-amplitude spinal manipulative thrust: a systematic review. *J Manipulative Physiol Ther.* 2010;33(7):542-53.
52. Picchiottino M, Honore M, Leboeuf-Yde C, Gagey O, Cottin F, Hallman DM. The effect of a single spinal manipulation on cardiovascular autonomic activity and the relationship to pressure pain threshold: a randomized, cross-over, sham-controlled trial. *Chiropr Man Therap.* 2020;28:7.
53. Chaibi A, Šaltytė Benth J, Bjørn Russell M. Validation of Placebo in a Manual Therapy Randomized Controlled Trial. *Scientific Reports.* 2015;5(1):11774.
54. Goffaux P, Redmond WJ, Rainville P, Marchand S. Descending analgesia--when the spine echoes what the brain expects. *Pain.* 2007;130(1-2):137-43.
55. Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods.* 2004;134:9-21.
56. Lenoir C, Plaghki L, Mouraux A, van den Broeke EN. Quickly responding C-fibre nociceptors contribute to heat hypersensitivity in the area of secondary hyperalgesia. *The Journal of Physiology.* 2018;596(18):4443-55.
57. Torta DM, Churyukanov MV, Plaghki L, Mouraux A. The effect of heterotopic noxious conditioning stimulation on A δ -, C- and A β -fibre brain responses in humans. *European Journal of Neuroscience.* 2015;42(9):2707-15.
58. van den Broeke EN, Mouraux A. Enhanced brain responses to C-fiber input in the area of secondary hyperalgesia induced by high-frequency electrical stimulation of the skin. *Journal of Neurophysiology.* 2014;112(9):2059-66.

59. Bragard D, Chen AC, Plaghki L. Direct isolation of ultra-late (C-fibre) evoked brain potentials by CO₂ laser stimulation of tiny cutaneous surface areas in man. *Neuroscience Letters*. 1996;209(2):81-4.
60. Hu L, Cai MM, Xiao P, Luo F, Iannetti GD. Human brain responses to concomitant stimulation of Adelta and C nociceptors. *The Journal of Neuroscience*. 2014;34(34):11439-51.
61. Jankovski A, Plaghki L, Mouraux A. Reliable EEG responses to the selective activation of C-fibre afferents using a temperature-controlled infrared laser stimulator in conjunction with an adaptive staircase algorithm. *Pain*. 2013;154(9):1578-87.
62. Perchet C, Godinho F, Mazza S, Frot M, Legrain V, Magnin M, et al. Evoked potentials to nociceptive stimuli delivered by CO₂ or Nd:YAP lasers. *Clinical Neurophysiology*. 2008;119(11):2615-22.
63. Cousineau D. Confidence intervals in within-subject designs: A simpler solution to Loftus and Masson's method. *Tutorials in Quantitative Methods for Psychology*. 2005;1(1):42-5.
64. O'Neill J, Brock C, Olesen AE, Andresen T, Nilsson M, Dickenson AH. Unravelling the mystery of capsaicin: a tool to understand and treat pain. *Pharmacol Rev*. 2012;64(4):939-71.
65. Schaffler K, Reitmeir P, Gschanes A, Eggenreich U. Comparison of the analgesic effects of a fixed-dose combination of orphenadrine and diclofenac (Neodolpasse) with its single active ingredients diclofenac and orphenadrine: a placebo-controlled study using laser-induced somatosensory-evoked potentials from capsaicin-induced hyperalgesic human skin. *Drugs in R&D*. 2005;6(4):189-99.
66. Hüllemann P, Watfeh R, Shao YQ, Nerdal A, Binder A, Baron R. Peripheral sensitization reduces laser-evoked potential habituation. *Clinical Neurophysiology*. 2015;45(6):457-67.
67. Tzabazis AZ, Klukinov M, Crottaz-Herbette S, Nemenov MI, Angst MS, Yeomans DC. Selective nociceptor activation in volunteers by infrared diode laser. *Molecular Pain*. 2011;7:18-.
68. Domnick C, Hauck M, Casey KL, Engel AK, Lorenz J. C-fiber-related EEG-oscillations induced by laser radiant heat stimulation of capsaicin-treated skin. *Journal of Pain Research*. 2009;2:49-56.
69. O'Neill S, Larsen JB, Nim C, Arendt-Nielsen L. Topographic mapping of pain sensitivity of the lower back - a comparison of healthy controls and patients with chronic non-specific low back pain. *Scandinavian Journal of Pain*. 2019;19(1):25-37.
70. O'Neill S, Manniche C, Graven-Nielsen T, Arendt-Nielsen L. Generalized deep-tissue hyperalgesia in patients with chronic low-back pain. *Eur J Pain*. 2007;11(4):415-20.

71. Ross GB, Mavor M, Brown SHM, Graham RB. The Effects of Experimentally Induced Low Back Pain on Spine Rotational Stiffness and Local Dynamic Stability. *Annals of Biomedical Engineering*. 2015;43(9):2120-30.
72. Pinto BL, Beaudette SM, Graham RB, Brown SHM. Experimentally induced neck pain causes a decrease in thoracic but not lumbar spine stability. *J Biomech*. 2019;90:78-83.
73. Baliki MN, Chialvo DR, Geha PY, Levy RM, Harden RN, Parrish TB, et al. Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. *The Journal of Neuroscience*. 2006;26(47):12165-73.
74. Aspinall SL, Jacques A, Leboeuf-Yde C, Etherington SJ, Walker BF. No difference in pressure pain threshold and temporal summation after lumbar spinal manipulation compared to sham: A randomised controlled trial in adults with low back pain. *Musculoskeletal Science & Practice*. 2019;43:18-25.
75. Haas M, Vavrek D, Peterson D, Polissar N, Neradilek MB. Dose-response and efficacy of spinal manipulation for care of chronic low back pain: a randomized controlled trial. *The Spine Journal*. 2014;14(7):1106-16.
76. Haas M, Bronfort G, Evans R, Schulz C, Vavrek D, Takaki L, et al. Dose-response and efficacy of spinal manipulation for care of cervicogenic headache: a dual-center randomized controlled trial. *The Spine Journal*. 2018;18(10):1741-54.
77. Teodorczyk-Injeyan JA, McGregor M, Triano JJ, Injeyan SH. Elevated Production of Nociceptive CC Chemokines and sE-Selectin in Patients With Low Back Pain and the Effects of Spinal Manipulation: A Nonrandomized Clinical Trial. *The Clinical Journal of Pain*. 2018;34(1):68-75.
78. Teodorczyk-Injeyan JA, Injeyan HS, Ruegg R. Spinal manipulative therapy reduces inflammatory cytokines but not substance P production in normal subjects. *J Manipulative Physiol Ther*. 2006;29(1):14-21.
79. Roy RA, Boucher JP, Comtois AS. Inflammatory response following a short-term course of chiropractic treatment in subjects with and without chronic low back pain. *Journal of Chiropractic Medicine*. 2010;9(3):107-14.
80. Gevers-Montoro C, Provencher B, Descarreaux M, Ortega de Mues A, Piché M. Neurophysiological mechanisms of chiropractic spinal manipulation for spine pain. *European Journal of Pain*. 2021;25(7):1429-48.
81. Provencher B, Northon S, Gevers Montoro C, O'Shaughnessy J, Piché M. Effects of chiropractic spinal manipulation on laser-evoked pain and brain activity. *The journal of Physiological Sciences*. 2021;71(1):20.

82. Navid MS, Lelic D, Niazi IK, Holt K, Mark EB, Drewes AM, et al. The effects of chiropractic spinal manipulation on central processing of tonic pain - a pilot study using standardized low-resolution brain electromagnetic tomography (sLORETA). *Scientific Reports*. 2019;9(1):6925.
83. Sparks C, Cleland JA, Elliott JM, Zagardo M, Liu WC. Using functional magnetic resonance imaging to determine if cerebral hemodynamic responses to pain change following thoracic spine thrust manipulation in healthy individuals. *The Journal of Orthopaedic and Sports Physical Therapy*. 2013;43(5):340-8.
84. Gay CW, Robinson ME, George SZ, Perlstein WM, Bishop MD. Immediate changes after manual therapy in resting-state functional connectivity as measured by functional magnetic resonance imaging in participants with induced low back pain. *Journal of Manipulative and Physiological Therapeutics*. 2014;37(9):614-27.
85. Sparks CL, Liu WC, Cleland JA, Kelly JP, Dyer SJ, Szetela KM, et al. Functional Magnetic Resonance Imaging of Cerebral Hemodynamic Responses to Pain Following Thoracic Thrust Manipulation in Individuals With Neck Pain: A Randomized Trial. *J Manipulative Physiol Ther*. 2017;40(9):625-34.
86. Isenburg K, Mawla I, Loggia ML, Ellingsen DM, Protsenko E, Kowalski MH, et al. Increased Salience Network Connectivity Following Manual Therapy is Associated with Reduced Pain in Chronic Low Back Pain Patients. *The Journal of Pain*. 2021;22(5):545-55.
87. Ellingsen DM, Napadow V, Protsenko E, Mawla I, Kowalski MH, Swensen D, et al. Brain Mechanisms of Anticipated Painful Movements and Their Modulation by Manual Therapy in Chronic Low Back Pain. *The Journal of Pain*. 2018;19(11):1352-65.
88. Meyer A-L, Amorim M-A, Schubert M, Schweinhardt P, Leboeuf-Yde C. Unravelling functional neurology: does spinal manipulation have an effect on the brain? - a systematic literature review. *Chiropractic & Manual Therapies*. 2019;27(1):60.
89. Pazzaglia C, Testani E, Giordano R, Padua L, Valeriani M. Expectation to feel more pain disrupts the habituation of laser-pain rating and laser-evoked potential amplitudes. *Neuroscience*. 2016;333:244-51.
90. Gyer G, Michael J, Inklebarger J, Tedla JS. Spinal manipulation therapy: Is it all about the brain? A current review of the neurophysiological effects of manipulation. *Journal of Integrative Medicine*. 2019;17(5):328-37.
91. Bialosky JE, Beneciuk JM, Bishop MD, Coronado RA, Penza CW, Simon CB, et al. Unraveling the Mechanisms of Manual Therapy: Modeling an Approach. *The Journal of Orthopaedic and Sports Physical Therapy*. 2018;48(1):8-18.

Chapitre 3: Étude 2 – C-Fiber-Related Brain Responses Evoked by Laser Heat Pulses Applied to the Back

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Provencher, B., & Piché, M. (2025). C-fiber-related brain responses evoked by laser heat pulses applied to the back. *The Journal of Physiological Sciences*, 75(2), 100018.
<https://doi.org/10.1016/j.jphys.2025.100018>

Contribution des auteurs selon la classification CRediT (*Contribution Roles Taxonomy*):

- Benjamin Provencher: conceptualisation, méthodologie, investigation, analyse formelle, validation, gestion des données et rédaction – version originale.
- Mathieu Piché: obtention du financement, administration du projet, ressources, conceptualisation, méthodologie, logiciel, investigation, analyse formelle, validation, gestion des données, rédaction – révision et édition, supervision.

Abstract

The aim of the present study was to examine C-fiber-related brain responses evoked by laser heat stimuli applied to the lumbar area, and to determine the stimulation protocol that produces the most reliable responses. Thirty healthy volunteers completed the study. Combinations of different stimuli (single pulses or trains of three pulses) with different pulse durations (7 or 14 ms) were used to compare C-fiber-related brain responses between protocols. The four protocols elicited comparable C-fiber-related brain responses to laser heat pulses. However, pulse trains of 7 ms pulses at 0.67 Hz elicited C-LEPs in the greatest proportion of participants (86.7%). C-LEPs occurred within a 500 ms to 1500 ms post-stimulus time window, consistent with the perception associated with C-fiber activation. These results provide novel data on C-fiber-related brain responses to painful stimuli and a reliable stimulation protocol for future studies on low back pain.

Introduction

Laser-evoked brain responses constitute an essential tool to investigate the nociceptive system, pain-related processes, and their regulation [1-7]. Laser heat pulses activate A δ and C fibers selectively [1, 8], avoiding the confound of and the interaction with touch-related activation of A β fibers. Nociceptive C fibers are of particular interest for the study of nociplastic pain. They are involved in windup and central sensitization and are thought to contribute to secondary hyperalgesia and allodynia [9-11].

The repeated activation of C-fiber afferents at relatively short intervals leads to windup and its perceptual correlate, temporal summation of pain [12-14], while the activation of C-fiber afferents caused by injuries contribute to central sensitization and chronic pain [10, 15-17]. Although windup and central sensitization represent distinct processes, both rely on C-fiber activity [9, 18, 19] and both are relevant to the investigation of acute and chronic pain mechanisms.

The measurement of brain responses related to C-fiber activation remains challenging [1-3, 8]. This may explain the wide variety of methods reported previously, including laser-evoked potentials (LEP) (see Table S1 in the supplementary material). The “first come first serve” hypothesis has been proposed, where “only the earliest of a series of somatosensory volleys elicits cerebral responses synchronous enough to yield EPs [evoked potentials]” [20]. This hypothesis is based on the observation that C-LEPs could be detected only if A δ fiber activation was limited by various procedures [21-26]. It is also supported by empirical evidence showing that brain activity related to A δ fiber activation is inhibited by preceding C-fiber-related responses [27]. However, the hypothesis was challenged by the demonstration of clear A δ -LEPs observable even when preceded by A β afferent volleys [28]. Despite this report, current studies on C-LEPs include procedures to limit the activation of A δ fibers [29-35]. These methods are not adapted to all research protocols and often lead to perceptual ratings below the pain threshold [33, 34, 36-40]. This is a major drawback for pain studies. It was proposed that C-LEPs induced by laser heat stimulation of the hand can be detected in most participants when using adapted stimulation parameters [41]. However, the results could not be replicated for back stimulation [5, 6]. In the present study, the lower back was favored over the hand dorsum to apply the results to future studies investigating low back pain.

The aim of the present study was to establish a protocol to investigate brain activity evoked by the activation of C fibers in the lumbar area. Based on previous studies (see Table S1 in the supplementary material), single or repeated laser pulses (3) were used, with a pulse duration of 7 or 14 ms. We hypothesized that laser pulse trains would elicit measurable C-fiber-related responses in a greater proportion of participants compared with single pulses. Moreover, we expected that laser pulse trains at 0.67 Hz would elicit an increase in the amplitude of C-fiber-related brain responses between the first and last train pulse.

Methods

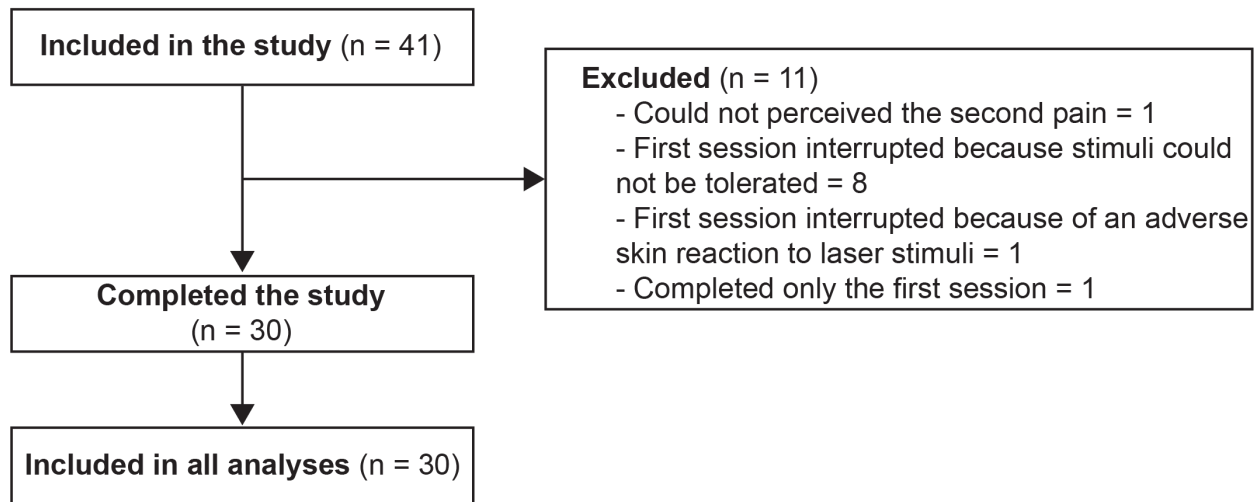
Sample size calculation

The sample size was determined using G*Power 3.1.9.7 software [42]. According to our hypothesis and experimental design, the sample size was established to detect a medium effect size ($\eta^2_p = 0.06$) for the interaction between the stimulus type (single pulse vs. trains) and stimulus duration (7 ms vs. 14 ms), with a power of 0.8 and an α of 0.05. The calculation resulted in a sample size of 34, which was rounded up to 40 participants to account for potential exclusions.

Participants

Healthy volunteers were recruited by advertisements on the campus of Université du Québec à Trois-Rivières and on social media. They were included if they were between 18 and 55 years old and in good general health. They were excluded if they reported acute or chronic pain, acute or chronic illness, psychiatric disorders or daily usage of recreational drugs, if they had an injury or surgery in the 3 months preceding the experiment, and if they took any pain medication or recreational drug within 48 h prior to the experimental session. They were also excluded if they presented a skin of type I on the Fitzpatrick scale [43], if they could not perceive the second pain evoked by laser stimuli, or presented an adverse skin reaction to laser stimulation. Forty-one healthy volunteers met the inclusion criteria and were included in the study. Eleven participants were excluded after inclusion, resulting in thirty participants that completed the study (14 women and 16 men; mean age $\pm$ SD: 30.9 $\pm$ 7.9 years). Participants that were excluded from the study ($n=11/41$) did not complete the experiment so their data could not be analyzed (see **Figure 3.1**). On these 11 participants, one could not perceive second pain, one presented an adverse skin reaction to the laser stimuli, eight could not tolerate the laser pulse trains, and one completed only one session. Among the thirty participants that were included, all data was of good quality and no participant was excluded during the analyses.

Figure 3.1 – Flow chart of participants included in the study and analyses



Forty-one healthy volunteers met the inclusion criteria and were included in the study. Eleven participants were excluded after inclusion, resulting in thirty participants that completed the study (14 women and 16 men; mean age $\pm$ SD: 30.9 ± 7.9 years). Participants that were excluded from the study ($n=11/41$) did not complete the experiment so their data could not be analyzed. On these 11 participants, one could not perceive second pain, one presented an adverse skin reaction to the laser stimuli, eight could not tolerate the laser pulse trains, and one completed only one session. Among the thirty participants that were included, all data was of good quality and no participant was excluded during the analyses.

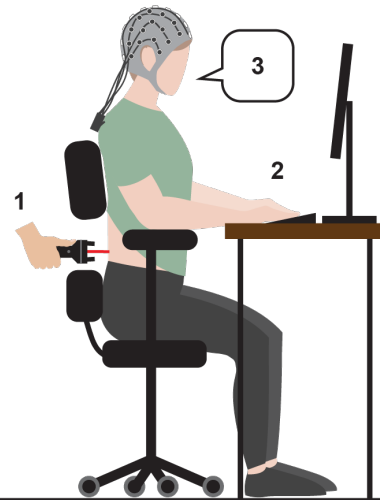
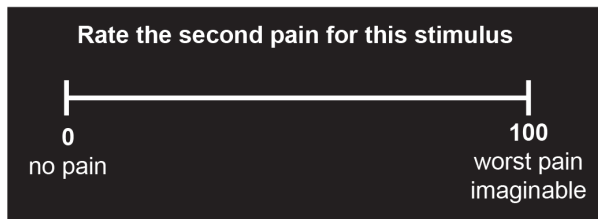
Experimental design and protocol

This study relies on a within-subject design to compare C-fiber responses between four stimulation protocols (single pulses vs. pulse trains of 7-ms or 14-ms duration). During the experiment, room temperature was kept constant at 24°C. All participants were seated on a regular desk chair. A 22 x 14 cm opening in the center of the backrest exposed the skin of the lower back for stimulation. The participant and experimenter were wearing safety glasses designed for a 1340 nm wavelength laser during the experiment. Participants were instructed to keep their eyes open, look at a fixation cross to minimize eye movement, and refrain movement as much as possible during the recordings.

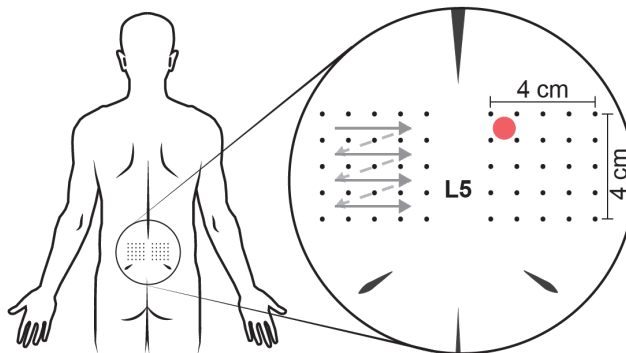
The experimental protocol is illustrated in **Figure 3.2**. Participants took part in two experimental sessions separated by approximately one week (mean $\pm$ SD: 8.3 ± 3.5 days). The two sessions were identical except for the laser pulse duration that was either 7 ms or 14 ms. The order of the sessions was counterbalanced between participants. Each session comprised two stimulation types: single pulses and pulse trains (three pulses at a frequency of 0.67 Hz). During each session, a total of 165 stimuli were delivered on either side of the L5 spinous process, including five blocks of 16 single-pulse stimuli ($n=80$), five blocks of 16 pulse-train stimuli ($n=80$) and five pre-train pulse (see **Figure 3.2C**). The number of stimuli was determined based on the results of a previous study indicating that 80 stimuli provide a good signal-to-noise ratio for C-LEPs [41]. In the present experiment, the 80 stimuli were grouped in blocks of 16 stimuli to limit habituation, based on results from two of our previous studies indicating that significant habituation of C-fiber responses occurred after 15-20 stimuli [5, 6]. The order of stimuli (single-pulse or pulse-train stimuli) was counterbalanced between participants and sessions. A pause followed each stimulation block to allow participants to move. The pause was not time-limited but lasted less than 2 minutes. Reaction times and pain ratings were measured as described below, during continuous electroencephalographic recording (EEG).

Figure 3.2 – Experimental protocol

- A) 1) Laser stimulus (single pulse or pulse train).
 2) Second pain detection indicated with the keyboard spacebar.
 3) Verbal rating of second pain prompted by the numerical pain rating scale (NRS).



B)



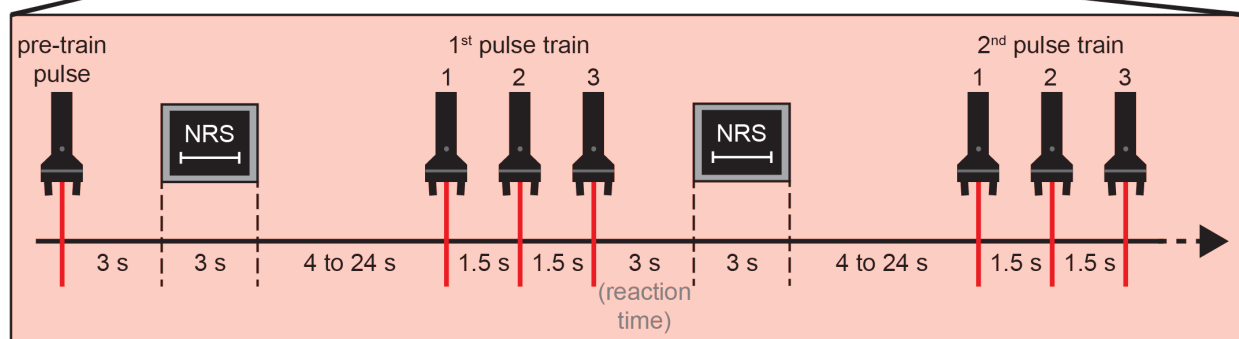
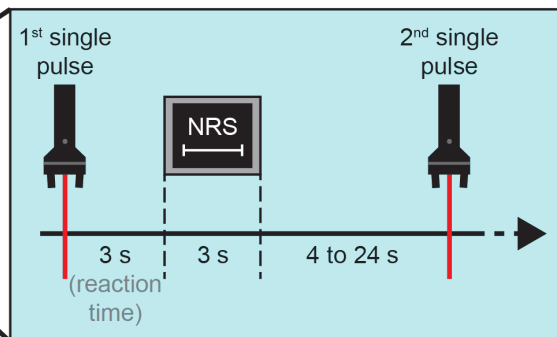
- movement of the laser beam within the stimulated area
 • laser beam (diameter = 9 mm)
 • black ink marks
 L5 tip of L5 spinous process

C)

Session 1: 7 ms pulse duration



Session 2: 14 ms pulse duration



Detailed representation of the experimental setup, stimulation procedures and protocol. A) The laser stimulus was delivered to the back area. Participants indicated the detection of second pain by pressing the spacebar. Reaction times were extracted to calculate the second pain perception occurrence. After each stimulus, participants were prompted to rate second pain with the display of a numerical pain rating scale. B) Illustration of skin landmarks (grid of ink marks) drawn around L5 vertebrae for the application of laser stimuli bilaterally. The 9 mm laser beam was carefully positioned at one of the 32 spots within this stimulation grid and on ink-free skin. The laser beam was moved to the next spot in the grid after each stimulus (single pulse, pre-train pulse, and pulse train) for safety purposes. It was moved sequentially from left to right and top to bottom. Within a pulse train however, the three pulses were delivered to the same spot to induce temporal summation, within safety limits. C) Stimulation protocol. Participants came to the laboratory for two experimental sessions. In both sessions, they received 5 series of stimuli, including 16 pulse trains preceded by one pre-train pulse for comparison, to assess temporal summation, and 16 single-pulse stimuli. One session comprised 7 ms stimuli while the other comprised 14 ms stimuli. Only one sequence is illustrated here, but the order of the sessions (7 ms or 14 ms) and the order of stimulus presentation (single pulse or pulse train) was counterbalanced between participants. Numbers (1, 2 and 3) represent the first, second and third pulse of the pulse trains. NRS: Numerical Rating Scale.

Pain ratings

Three seconds after each stimulus, participants were prompted to rate second pain verbally by a numerical scale (NRS) that appeared on the computer screen, where 0 indicated “no pain” and 100 indicated the “worse pain imaginable” [5]. To avoid contaminating the EEG signals, when the stimulus was a pulse train, participants were instructed to rate the third pulse only. As illustrated in **Figure 3.2C**, during the experiment, a pre-train pulse of the same stimulus intensity was delivered before each pulse train stimulation block. The rationale behind these pre-train pulses was to use their pain ratings to quantify the temporal summation of second pain induced

by pulse trains. They were only used for the pain rating analysis to confirm temporal summation of second pain.

Painful laser stimulation

Painful stimuli were produced by laser heat pulses generated by an infrared neodymium-doped yttrium aluminum perovskite laser (Nd:YAP, DEKA 1340, Electronical Engineering, Florence, Italy). Infrared laser stimuli have been shown to activate heat sensitive A δ and C fibers selectively, while avoiding the activation of A β fibers [8, 44]. The laser beam was transmitted through a 10 m optic fiber cable and was adjusted to a diameter of 9 mm ($\approx 63.6 \text{ mm}^2$ area), with a pulse duration of 7 or 14 ms. These pulse durations were selected after pilot testing. With these parameters, stimuli could be adjusted within a broad range of intensity (1.5 to 8.5 J) to induce pain perception that was tolerable and comparable between sessions for all participants. Similar pulse durations have been used to measure C-LEPs in previous studies, although parameters vary between experiments and laboratories (see **Table S1** in the supplementary material).

The interstimulus interval varied randomly from 10 to 30 s to limit predictability and habituation [45-47]. Pulse trains consisted of 3 pulses repeated at 0.67 Hz, which induced temporal summation of second pain [12, 13, 18] while allowing the detection of C-fiber-related brain responses for each pulse of the train. Indeed, C-LERP peaks have been measured within a 1500 ms window post-stimulus in previous studies [31, 36, 37, 41]. The maximal fluence used during the present study was 134 mJ/mm² for single pulses and 51 mJ/mm² for each pulse of the pulse trains. The laser was triggered using a stimulus presentation software (E-Prime2; Psychology Software Tools, Inc., Pittsburgh, PA, USA). To avoid stimulating the same area too frequently, 25 tiny ink marks were drawn on the skin with a marker (Staedtler triplus[®] fineliner 334, color: black, line width: 0.3 mm) to guide the experimenter. The marks were made within two 4 × 4 cm grids, one on each side of L5 spinous process. Stimulating blackened skin with a Nd:YAP laser results in higher temperature than stimulating unmarked skin, which increases the probability of reaching A δ fiber threshold [48]. Therefore, during the present experiment, the laser beam was aimed at

the space between the marks and it was moved sequentially to the next space in the grid after each stimulus (see **Figure 3.2**). The movement of the laser beam within the grids was kept the same across participants and sessions.

At the beginning of each session, pain thresholds and laser intensity evoking low to moderate pain were determined using a staircase procedure [6, 49]. This was done separately for each stimulus type (single pulse and pulse trains), because they induce pain of different intensity. Before pain threshold assessment, the experimenter explained the concept of second pain to the participant with visual support using a self-made figure. Participants were then instructed to focus on the second pain (the dull/hot/burning sensation in their back) and to report its intensity verbally after each stimulus, using a numerical rating scale ranging from 0 to 100, 0 indicating “no pain” and 100 “the worse pain imaginable.” Stimuli were delivered at an initial intensity of 1.5 J and stimulus intensity increased sequentially by 0.25 J increments until pain was reported (rating of 1/100 or higher). Then, the energy was increased sequentially again until a pain rating above 30/100 was reported. Participants were then familiarized with the selected intensity using three to five consecutive stimuli with an interstimulus interval varying between 5 and 10 s. If the intensity was deemed acceptable for the participant, the experiment continued. If the participant judged that the stimulus intensity produced pain that could not be tolerated for the duration of the experiment, stimulus intensity was decreased by 0.25 J and the familiarization procedure resumed until an acceptable stimulus intensity was reached. The average laser stimulation intensity was 5.7 ± 1.5 J (7 ms – single pulse), 5.5 ± 1.5 J (14 ms – single pulse), 2.2 ± 0.6 J (7 ms – pulse train) and 2.1 ± 0.5 J (14 ms – pulse train). The skin was visually monitored throughout the entire session. One participant presented an adverse skin reaction to laser stimuli. The experiment was stopped as soon as it was noticed, and the follow-up revealed that the skin healed completely within a few weeks. No other adverse event was observed by the experimenter or was reported by participants. After each session, the lumbar region was inspected. No swelling, redness, or other signs of inflammation or damage were noted.

Before the experiment, participants completed at least 10 practice trials (5 single pulses and 5 pulse trains) for familiarization with the procedures. During these trials, their reaction times were displayed on a screen and used to determine that participants understood the instructions and were able to perceive second pain. Participants were excluded from the study if they could not perceive the second pain, as assessed by the reaction times during the practice trials (latencies <650 ms, corresponding to A δ -fiber activation). This was necessary since the present study aimed to measure pain-related brain responses evoked by nociceptive C-fibers. Only one participant was excluded for this reason.

Reaction times

Participants were instructed to press the keyboard spacebar as soon as they perceived the second pain caused by a painful laser stimulus, as described previously [50]. When the stimulus was a pulse train, participants were instructed to press as soon as they perceived the second pain caused by the third pulse. Reaction times were recorded by the stimulus presentation software that triggered the laser (see above). Based on previous studies, reaction times greater than 650 ms were considered consistent with the perception of a C-fibers mediated sensation [30, 31, 33, 36-38, 51, 52].

Electroencephalographic recordings

EEG was recorded using a 64-channel BrainVision system with active Ag-AgCl electrodes mounted on an actiCAP, according to the International 10–20 system (Brain Products, Gilching, Germany). Electrodes were nose-referenced, and the ground was set at FPz [53-55]. Eye movements and blinks were recorded using electrooculography (EOG) with electrodes placed at the right suborbital ridge, and just lateral to the right external ocular canthus. Electrode impedance was kept below 20 k Ω . Signals were sampled at 1000 Hz and filtered using a 0.01–100 Hz band-pass filter.

Laser-evoked potentials

EEG signals were analyzed offline using MATLAB R2022a (MathWorks, Natick, MA, USA) and EEGLAB v2022.0 [56]. EEG signals were preprocessed using a standardized, automated, and open-source preprocessing pipeline for EEG data [57]. The preprocessing steps are briefly described here: 1- Downsampling the data from 1000 Hz to 500 Hz; 2- Re-referencing signals to the common average; 3- Automatic detection and spherical interpolation of channels of low quality using the outlier criterion $z > 3.29$ [58]; 4- Segmenting the data into “long” epochs (-2000 ms to 7000 ms) to get better independent component analysis (ICA) solution in the next steps; 5- High-pass filtering using a 0.5 Hz finite impulse response (FIR) filter; 6- First ICA using the built-in function Runica in EEGLAB; 7- Automatic detection and rejection of contaminated trials based on z -value detection (> 3.29) of independent components (ICs); 8- Second ICA; 9- Automatic detection and rejection of the ICs related to noise using the ICLabel plugin [59] with preset thresholds ($> 90\%$ for muscles and eyes, $> 95\%$ for heart, $> 75\%$ for line and channel noise); 10- Segmenting the data into suitable epochs for analysis (-500 ms to 1500 ms for single pulse conditions and -500 ms to 4500 ms for pulse train conditions); 11- Baseline correction (-500 ms to 0 ms)[31, 36, 37, 60]; 12- Low-pass filtering using a 30 Hz FIR filter. On average, 6.7 ± 1.8 channels were interpolated, 1.3 ± 0.9 epochs were rejected and $85.3 \pm 8.0\%$ of the variance remained after IC rejection.

After data preprocessing, average waveforms were computed for each participant and condition, and the positive slow wave evoked by laser stimuli was analyzed. The peak amplitude and latency of this positive slow wave were measured automatically using the max function within a specified time window on each average waveform. The peak was defined as the maximum value between 500 and 1450 ms with a maximum amplitude at Pz. This time window is based on previous studies measuring C-LEPs [29, 41, 61].

In addition, the proportion of participants presenting C-LEPs was calculated for each condition. These proportions were obtained by the two authors agreeing on the presence or absence of C-LEPs based on individual LEP waveforms and topographic maps.

Event-related spectral perturbation analyses

Event-related spectral perturbations (ERSP) were examined based on recent studies reporting that they present several advantages over LEPs to measure EEG activity that is not time-locked or is subject to latency jitters [2, 62]. In order to measure ERSP, EEG datasets were preprocessed using the same automated preprocessing pipeline as described above, with different values for filters (High-pass: 1 Hz; Low-pass: 100 Hz), baseline (-700 ms to -200 ms) and the final length of the epochs (-2000 ms to 2000 ms for single pulse conditions and -2000 ms to 5000 ms for pulse train conditions). Then, as in previous studies [6, 55], a Morlet wavelet convolution [63] was computed using the channel time–frequency options available in EEGLAB v.13.5.4b [56]. Four hundred or 1200 time points were generated (single pulse or pulse train conditions), and 100 linearly spaced frequencies were computed from 1 to 100 Hz. Variable cycles were used for low and high frequencies, with 3 cycles for lowest frequencies and up to 15 cycles for highest frequencies [56]. This variable number of cycles allows for the wavelet convolution method to provide a better frequency resolution at lower frequencies and a better temporal resolution at higher frequencies [64]. Time-frequency analyses were performed using time–frequency options available in EEGLAB which use Morlet wavelets. A Gaussian shape taper was used to taper wavelets to zero at both ends, and the length of the window used for time–frequency analysis was selected to avoid the contamination of the signal of interest by edge artifacts. ERSP data were computed in decibels relative to baseline for all electrodes separately. The time–frequency data of all trials were averaged for each participant and condition separately, resulting in 4 average time–frequency maps for each electrode. From these maps, the mean power was extracted from the Cz electrode in predetermined time $\times$ frequency regions of interests (ROIs) for each participant. Then, a mean ERSP value was then obtained for each participant and ROI by selecting and averaging the values with the 20% highest or lowest amplitude (for power increase or decrease relative to baseline).

Since the present study is the first to examine brain responses evoked by laser pulse trains, C-fiber conduction velocity (0.5 - 2 m/s)[65], visual inspection of the time-frequency maps, and results from previous studies [31, 41, 52] were used to define three ROIs at latencies

corresponding to C-fiber-related activity. ROI 1 included event-related synchronization (ERS) ranging between 2 and 5 Hz from 500 ms to 1200 ms [31, 41, 52]. Note that these frequencies are within the delta and theta range [66]. ROI 2 included event-related desynchronization (ERD) ranging between 7 Hz to 15 Hz from 1000 ms to 1500 ms [31, 52]. These frequencies are within the alpha range [66]. This ERD was reported to last longer, but the time window is limited to 1500 ms by the pulse train frequency in the present study. ROI 3 included the ERS ranging between 60 and 100 Hz from 500 ms to 1200 ms that was observed in the average time-frequency maps. These frequencies are within the gamma range [66].

Statistical analyses

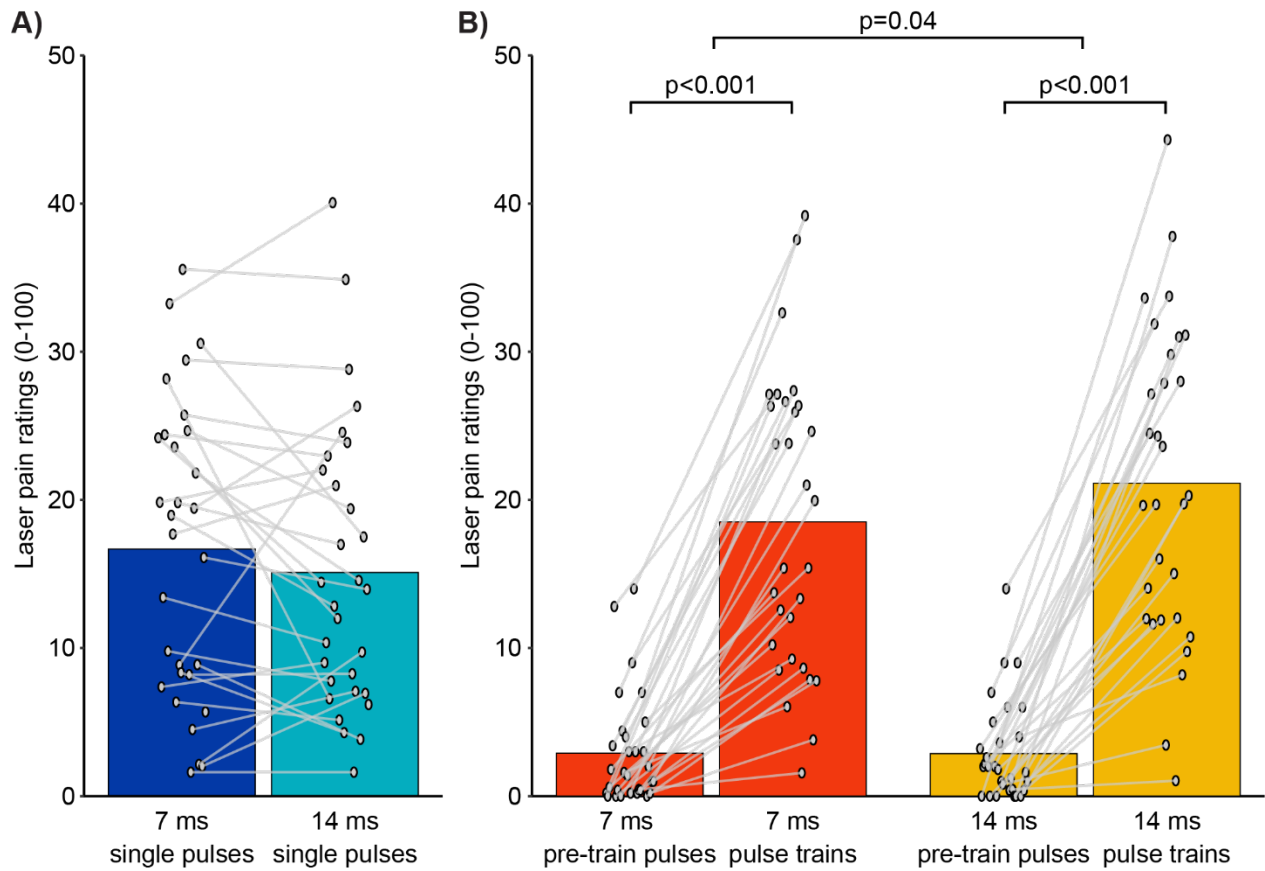
Statistical analyses were performed with IBM SPSS Statistics for Windows, Version 28.0 (Armonk, NY, USA: IBM Corp). All data are expressed as mean $\pm$ SD. Statistical significance threshold was set at $p \leq 0.05$. Data distribution was assessed for normality with the Kolmogorov-Smirnov test. Pain ratings and C-fiber-related brain responses were compared between the 7-ms and the 14-ms single-pulse conditions using paired sample t-tests. Reaction times were compared between the four conditions using Greenhouse-Geisser corrected repeated-measures ANOVA (2 pulse duration $\times$ 2 types of stimuli [single pulse or pulse train]). Temporal summation of second pain was assessed between the pulse train conditions using Greenhouse-Geisser corrected repeated-measures ANOVA (2 pulse durations $\times$ 2 types of stimuli [pre-train pulse or pulse train]). C-fiber-related brain responses induced by temporal summation were compared between the pulse train conditions using Greenhouse-Geisser corrected repeated-measures ANOVA (2 pulse durations $\times$ 3 pulses [pulse 1, 2 and 3 of each train]). Tuckey HSD tests were used to decompose significant effects. Effect sizes are reported based on partial eta-squared (η^2_p).

Results

Ratings of second pain

Ratings of the second pain were compared separately for single pulses and pulse trains. For single pulses, pain ratings were compared between the 7 ms and 14 ms conditions (see **Figure 3.3A**). The paired sample *t*-test revealed no significant difference between conditions ($t(29) = 1.5$, $p = 0.2$, $\eta^2_p = 0.05$), indicating that the pulse duration did not affect pain perception significantly. For pulse trains, pain ratings were compared between the pre-train pulses and the pulse trains for the 7 ms and 14 ms conditions using a two-way repeated-measures ANOVA (2 pulse durations $\times$ 2 types of stimuli [pre-train pulse or pulse train (pulse repetition)], see **Figure 3.3B**). Pain ratings were not significantly different between the 7 ms and the 14 ms conditions (main effect of pulse duration: $F(1,29) = 1.7$, $p = 0.2$, $\eta^2_p = 0.05$). Pain ratings were significantly greater for the pulse trains compared with the pre-train pulses (main effect of pulse repetition: $F(1,29) = 129.3$, $p < 0.001$, $\eta^2_p = 0.82$), and this effect was significantly different between the 7 ms and the 14 ms conditions (interaction between pulse duration and pulse repetition: $F(1,29) = 4.7$, $p = 0.04$, $\eta^2_p = 0.14$), where second pain produced by repeated pulses was significantly greater in the 14 ms condition compared with the 7 ms condition.

Figure 3.3 – Ratings of second pain and temporal summation of second pain



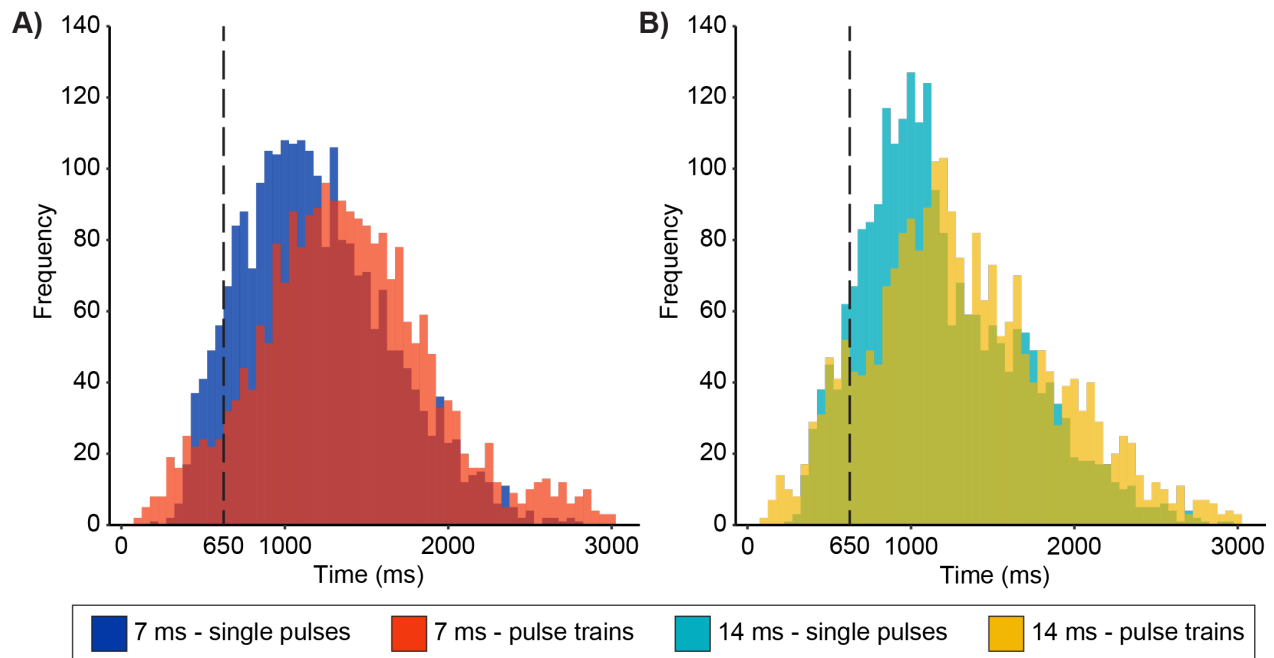
Data from each participant are represented by linked gray dots and the mean of these data points for each condition is represented by colored bars. A) For single pulses, pain ratings were not significantly different between the 7 ms and 14 ms conditions ($p = 0.23$). B) For pulse train stimuli, pain ratings were significantly greater compared with the pre-train pulses ($p < 0.001$), consistent with temporal summation of second pain. Moreover, this effect was significantly greater for the 14 ms compared with the 7 ms pulse duration ($p = 0.04$).

Reaction times

Frequency distributions of reaction times (all trials from all participants) for the 7 ms and 14 ms conditions are presented in **Figure 3.4A-B**, with an overlay of distributions for single pulses and pulse trains. A proportion of 89.6% of the reaction times were ultra-late (greater than 650 ms), consistent with nociceptive C-fiber activation. An additional 3.4% of the reaction times were missing (no button press), leaving only 7% of all trials with reaction times < 650 ms. The inclusion of these trials did not have a significant effect on LEP waveforms. Thus, all trials were included in the analysis. The mean reaction time for each condition was 1194 ± 447 ms (7 ms – single pulses), 1364 ± 534 ms (7 ms – pulse trains), 1183 ± 478 ms (14 ms – single pulses), and 1313 ± 563 ms (14 ms – pulse trains). These results are consistent with pain perception related to nociceptive C-fiber activation [33, 36, 37, 51].

Mean reaction times were compared between the 4 conditions using a two-way repeated-measures ANOVA (2 pulse durations $\times$ 2 types of stimuli [single pulse or pulse train (pulse repetition)]). The mean reaction times were not significantly different between the 7 ms and the 14 ms conditions (main effect of pulse duration: $F(1,29) = 0.3$, $p = 0.5$, $\eta^2_p = 0.01$). However, they were significantly longer for pulse trains compared with single pulses (main effect of pulse repetition: $F(1,29) = 12.0$, $p = 0.002$, $\eta^2_p = 0.29$). This effect was not significantly different between the 7 ms and the 14 ms conditions (interaction between pulse duration and pulse repetition: $F(1,29) = 0.02$, $p = 0.90$, $\eta^2_p = 0.01$).

Figure 3.4 – Frequency distribution histograms of trial-by-trial reaction times



Frequency distribution of trial-by-trial reaction times for each condition. The reaction times of trials on the right of the vertical dashed line were equal or greater than 650 ms (89.6% of trials). Reaction times were significantly longer for pulse trains compared with single pulses ($p = 0.002$). However, this effect was not significantly different between the 7 ms and the 14 ms conditions ($p = 0.90$).

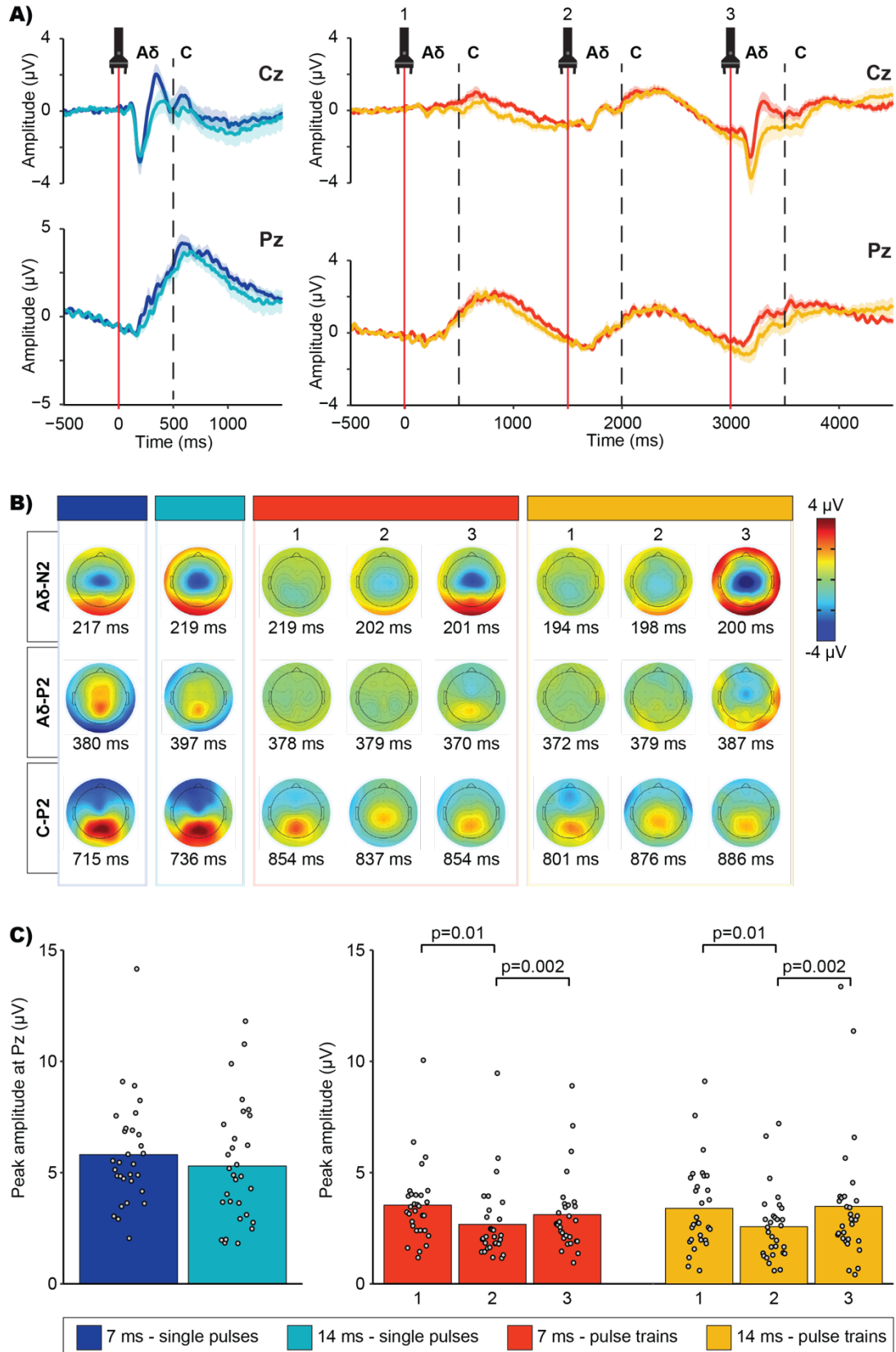
Laser-evoked potentials

C-LEPs were observed in 66.7% of the participants for the 7 ms and 14 ms single pulse conditions, in 86.7% of the participants for the 7 ms pulse train condition, and in 76.7% of the participants for the 14 ms pulse train condition. Average waveforms and topographic maps of the LEPs for each condition are presented in **Figure 3.5A-B**. A positive slow wave was observed between 500 ms and 1500 ms in every condition, corresponding to the range of C-fiber conduction velocity, and consistent with the reaction times and second pain perception reported above (see **Figure 3.4**). Trials with a reaction time <650 ms (7% of all trials) were first excluded to assess their influence on the brain responses. Their exclusion had no effect on the observed

responses. Therefore, all artifact-free trials were included in the EEG analyses, regardless of the reaction times.

The positive slow wave peak amplitude and latency were measured at the electrode showing maximal activity (Pz). Peak amplitude and latency are reported in **Table 3.1** and Figure **3.5C**. Peak amplitude and latency were not significantly different between the two single pulse conditions (amplitudes: $t(29) = 2.0$, $p = 0.16$, $\eta^2_p = 0.07$; latencies: $t(29) = 0.22$, $p = 0.6$, $\eta^2_p < 0.01$). For the pulse train conditions, peak amplitude and latency were compared between the 7 ms and 14 ms conditions and between the three pulses of the pulse trains with a two-way repeated-measures ANOVA (2 pulse durations $\times$ 3 pulses [pulse 1, 2 and 3 of each train (pulse repetition)]). Peak amplitude was not significantly different between the 7 ms and the 14 ms conditions (main effect of pulse duration t : $F(1,29) = 0.05$, $p = 0.8$, $\eta^2_p < 0.01$), but it was significantly different between the three pulses (main effect of pulse repetition: $F(2,58) = 5.1$, $p = 0.02$, $\eta^2_p = 0.15$). This repetition effect was not significantly different between the 7 ms and the 14 ms conditions (interaction between pulse duration and pulse repetition: $F(2,58) = 1.0$, $p = 0.4$, $\eta^2_p = 0.03$). For the 7 ms and 14 ms conditions combined (main effect of pulse repetition), the Tuckey HSD test revealed that the peak amplitude was significantly lower for the second pulse compared with the first pulse ($p = 0.01$) and third pulse ($p = 0.002$). No other significant effect was observed (all p 's > 0.05). Peak latency was not significantly different between the 7 ms and the 14 ms conditions (main effect of pulse duration: $F(1,29) = 0.04$, $p = 0.9$, $\eta^2_p < 0.01$), between the three pulses (main effect of pulse repetition: $F(1,29) = 0.5$, $p = 0.6$, $\eta^2_p = 0.02$), or between the 7 ms and the 14 ms conditions and the three pulses (interaction between pulse duration and pulse repetition: $F(2,58) = 1.8$, $p = 0.2$, $\eta^2_p = 0.06$).

Figure 3.5 – Average LEP waveforms, topographic maps and C-P2 peak amplitudes for each condition



A) Average LEP waveforms for each condition at Cz and Pz. The lightly colored areas above and below the LEP waveforms represent the standard error of the mean (SEM). Both A δ and C-fibers responses can be visualized at Cz. A vertical dashed line was added 500 ms after each pulse to mark the end of the A δ -fibers response. At Pz, a slow wave was observed between 500 ms and 1500 ms in every condition, corresponding to the range of C-fiber conduction velocity, and consistent with the reaction times. **B)** Average topographic maps of the A δ -N2, A δ -P2 and C-P2 components for each condition and each pulse of the pulse trains. **C)** Peak amplitudes of the C-P2 component for each condition. Data from each participant are represented by gray points and the average of these data points for each condition is represented by colored bars. Numbers 1, 2 and 3 represent the first, second and third pulse of the pulse trains. C-P2 peak amplitudes were not significantly different between the two single pulse conditions ($p = 0.16$). However, C-P2 peak amplitudes significantly decreased during the second pulses of the pulse trains, regardless of pulse duration ($p = 0.01$).

Table 3.1 – C-P2 peak amplitude (μ V) and latency (ms) for each condition (mean $\pm$ SD)

Stimulus type	Pulse duration	Pulse number	Amplitude	Latency
Single pulse	7 ms		5.8 $\pm$ 2.4	715.6 $\pm$ 203.9
	14 ms		5.3 $\pm$ 2.7	735.8 $\pm$ 206.3
Pulse train	7 ms	1	3.5 $\pm$ 1.7	854.3 $\pm$ 213.8
		2	2.7 $\pm$ 1.7	836.9 $\pm$ 197.5
		3	3.1 $\pm$ 1.7	854.1 $\pm$ 260.1
	14 ms	1	3.4 $\pm$ 1.9	800.8 $\pm$ 181.8
		2	2.6 $\pm$ 1.6	875.9 $\pm$ 216.8
		3	3.5 $\pm$ 2.8	886.4 $\pm$ 296.7

Event-related spectral perturbations

Event-related synchronization between 2 Hz and 5 Hz and from 500 ms to 1200 ms (ROI 1, delta-theta band oscillations)

ERS between 2 Hz and 5 Hz from 500 ms to 1200 ms was not significantly different between the 7 ms and 14 ms single pulse conditions ($t(29) = 0.05$, $p = 0.8$, $\eta^2_p < 0.01$; see **Figure 3.6 and 3.7** and **Table 3.2**). For pulse trains, the mean power was not significantly different between the 7 ms and the 14 ms conditions (main effect of pulse duration: $F(1,29) = 1.9$, $p = 0.2$, $\eta^2_p = 0.06$), but it was significantly different between the three pulses (main effect of pulse repetition: $F(2,58) = 5.0$, $p = 0.01$, $\eta^2_p = 0.16$) (see **Figure 3.6-3.8** and **Table 3.2**). This effect was not significantly different between the 7 ms and the 14 ms conditions (interaction between pulse duration and pulse repetition: $F(2,58) = 0.8$, $p = 0.4$, $\eta^2_p = 0.03$). For the 7 ms and 14 ms conditions combined (main effect of pulse repetition), the Tuckey HSD test revealed that ERS significantly decreased during the second pulse compared with the first pulse ($p = 0.005$), but not compared with the third pulse ($p = 0.6$).

Event-related desynchronization between 7 Hz and 15 Hz from 1000 ms to 1500 ms (ROI 2, alpha band oscillations)

ERD between 7 Hz and 15 Hz from 1000 to 1500 ms was not significantly different between the 7 ms and 14 ms single pulse conditions ($t(29) = 0.2$, $p = 0.7$, $\eta^2_p < 0.01$). For pulse trains, it was not significantly different between the 7 ms and the 14 ms conditions (main effect of pulse duration: $F(1,29) = 1.7$, $p = 0.2$, $\eta^2_p = 0.06$), but it was significantly different between the three pulses (main effect of pulse repetition: $F(2,58) = 56.8$, $p < 0.001$, $\eta^2_p = 0.66$). This effect was not significantly different between the 7 ms and the 14 ms conditions (interaction between pulse duration and pulse repetition: $F(2,58) = 0.6$, $p = 0.5$, $\eta^2_p = 0.02$). For the 7 ms and 14 ms conditions combined (main effect of pulse repetition), the Tuckey HSD test revealed that ERD was significantly greater between the first and second pulses ($p < 0.001$), between the second and third pulses ($p < 0.001$), and between the first and third pulses ($p < 0.001$).

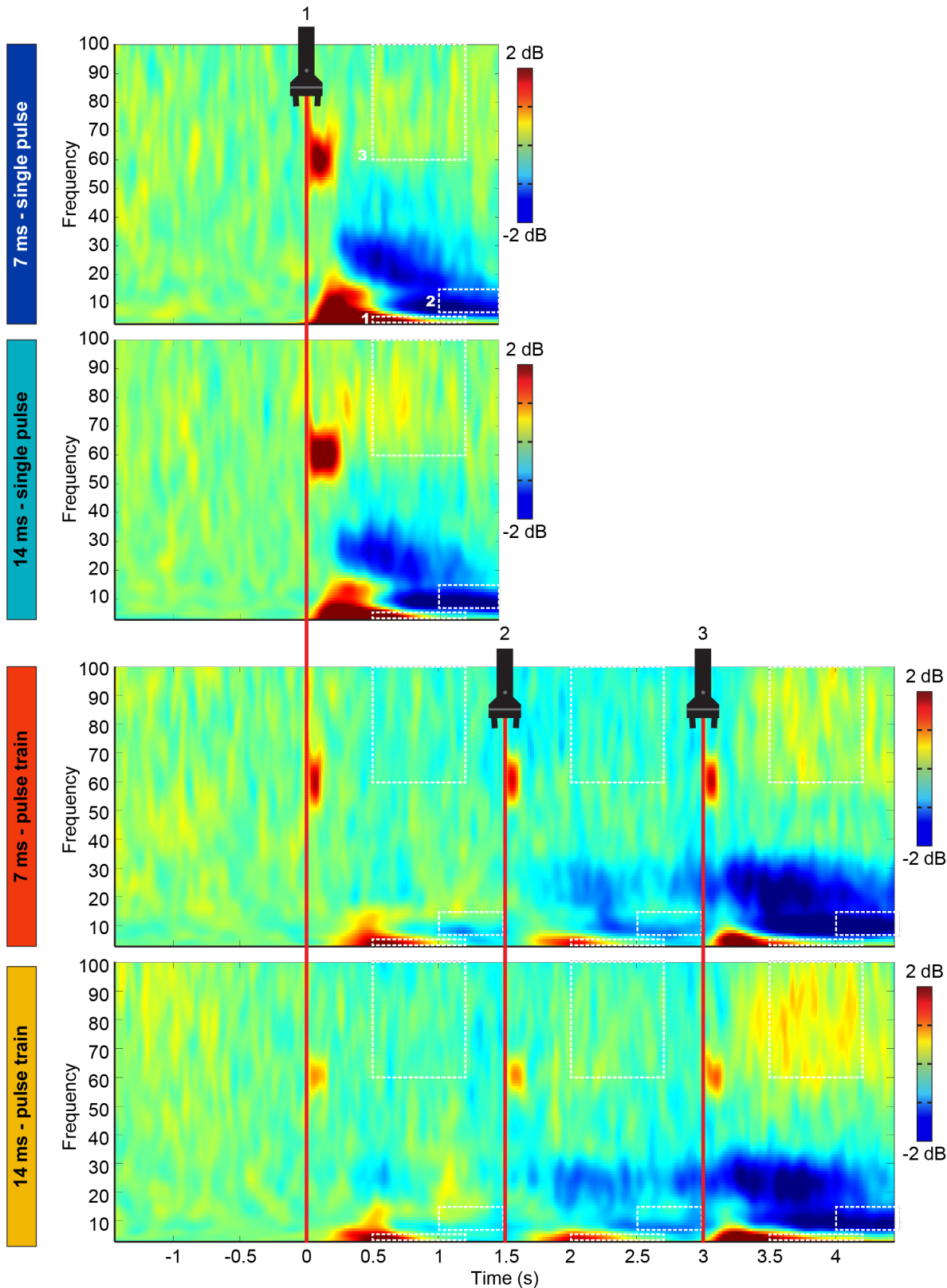
Event-related synchronization between 60 Hz and 100 Hz from 500 ms to 1200 ms (ROI 3, gamma band oscillations)

ERS between 60 Hz and 100 Hz from 500 ms to 1200 ms was not significantly different between the 7 ms and 14 ms single pulse conditions ($t(29) = 0.03$, $p = 0.9$, $\eta^2_p < 0.01$). For pulse trains, the mean power was significantly greater in the 14 ms compared with the 7 ms conditions (main effect of pulse duration: $F(1,29) = 4.6$, $p = 0.04$, $\eta^2_p = 0.14$). In addition, the mean power significantly increased with pulse repetition (main effect of pulse repetition: $F(2,58) = 11.6$, $p = 0.001$, $\eta^2_p = 0.29$). However, this effect was not significantly different between the 7 ms and the 14 ms conditions (interaction between pulse duration and pulse repetition: $F(2,58) = 2.2$, $p = 0.14$, $\eta^2_p = 0.07$). For the 7 ms and 14 ms conditions combined (main effect of pulse repetition), the Tuckey HSD tests revealed that ERS significantly increased from the first to the third pulse ($p = 0.003$), and from the second to the third pulse ($p = 0.008$), but not from the first to the second pulse ($p = 0.43$).

Table 3.2 – ERSP power (dB) for each condition and region of interest (ROI) (mean $\pm$ SD)

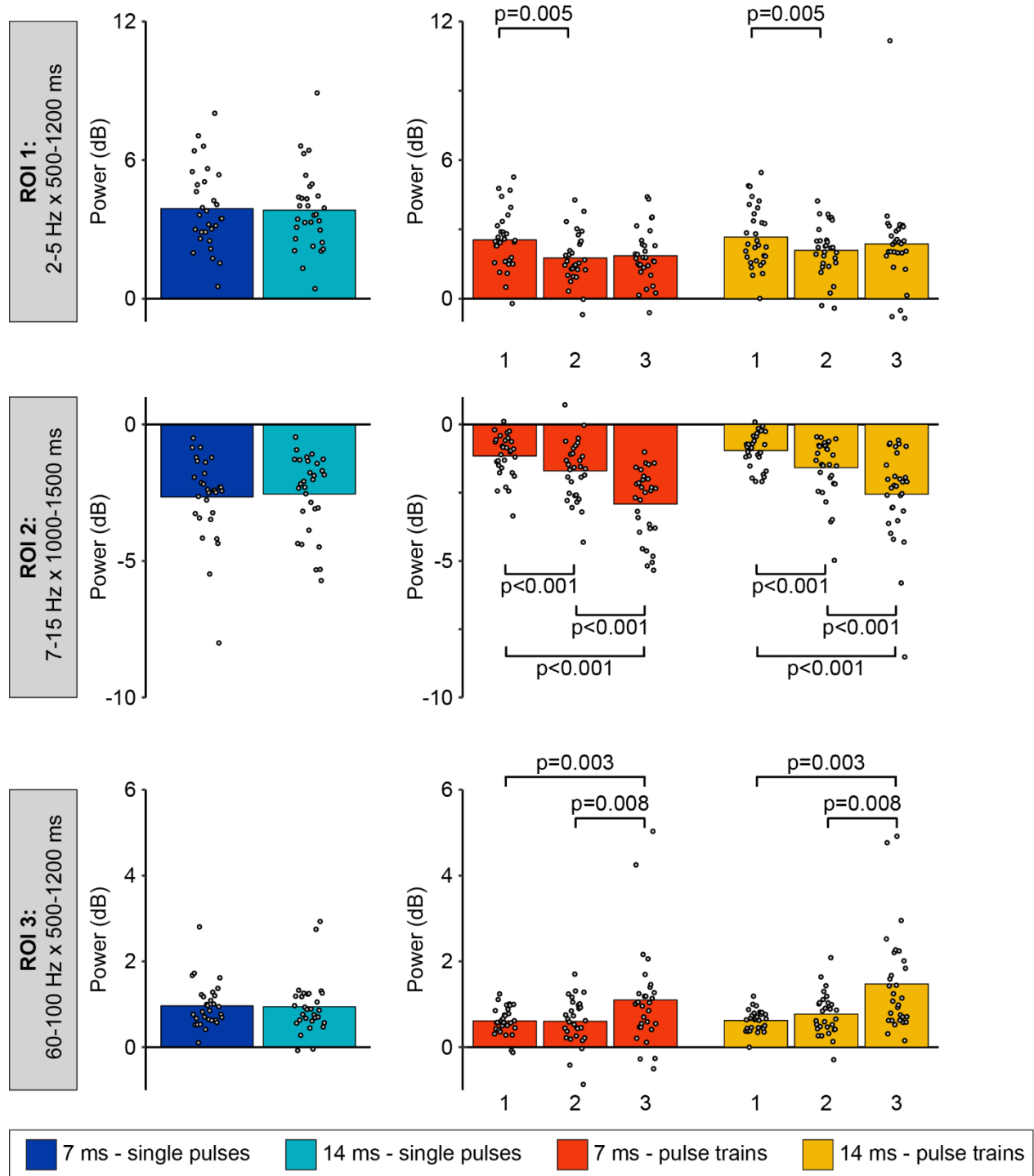
Stimulus type	Pulse duration	Pulse number	ROI 1	ROI 2	ROI 3
Single pulse	7 ms		3.9 ± 1.7	-2.7 ± 1.5	1.0 ± 0.5
	14 ms		3.8 ± 1.7	-2.6 ± 1.4	0.9 ± 0.6
Pulse train	7 ms	1	2.5 ± 1.3	-1.2 ± 0.8	0.6 ± 0.3
		2	1.8 ± 1.1	-1.7 ± 1.1	0.6 ± 0.5
		3	1.9 ± 1.2	-2.9 ± 1.3	1.1 ± 1.2
	14 ms	1	2.7 ± 1.3	-1.0 ± 0.6	0.6 ± 0.2
		2	2.1 ± 1.1	-1.6 ± 1.1	0.8 ± 0.5
		3	2.4 ± 2.0	-2.6 ± 1.7	1.5 ± 1.2

Figure 3.6 – Average time-frequency maps for each condition, time-locked to the onset of laser stimulation.



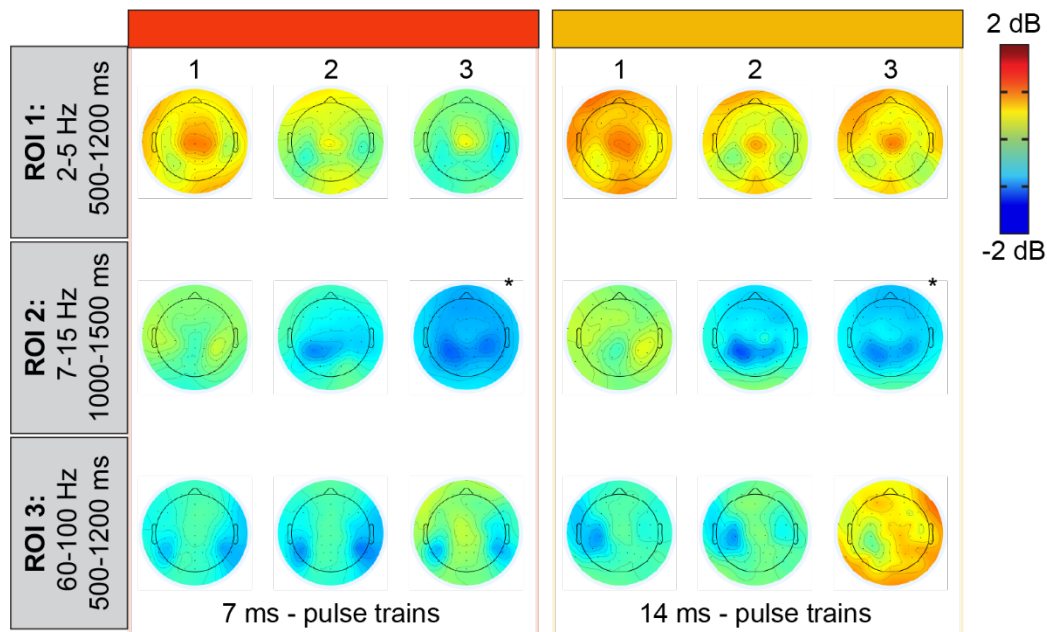
Average time-frequency maps for each condition in each of the three ROIs. Numbers (1, 2 and 3) represent the first, second and third pulse of the pulse trains. Conditions are indicated on the left with the colored rectangles. Regions of interest are highlighted by the dashed-line rectangles and labeled 1, 2 and 3. Note the desynchronization between 10 Hz and 30 Hz and the synchronization between 60 Hz and 100 Hz. See statistical comparisons in section 3.5 and Figure 8. Note the stimulation artifact as a power increase at 60 Hz directly after stimulus onset.

Figure 3.7 – Average ERSP values from the three regions of interest



Data from each participant are represented by gray dots and the average of these data points for each condition is represented by colored bars. Numbers (1, 2 and 3) represent the first, second and third pulse of the pulse trains. For all ROIs, the mean power was not significantly different between the 7 ms and 14 ms single pulse conditions ($p > 0.60$). For pulse trains in ROI 1, the mean power was not significantly different between the 7 ms and the 14 ms conditions ($p = 0.18$), but was significantly different between the three pulses ($p = 0.01$). This effect was not significantly different between the 7 ms and the 14 ms conditions ($p = 0.43$). For the 7 ms and 14 ms conditions combined (main effect of repetition), the Tuckey HSD test revealed that the mean power significantly decreased during the second pulse compared with the first pulse ($p = 0.005$), but not compared with the third pulse ($p = 0.56$). For pulse trains in ROI 2, mean power was not significantly different between the 7 ms and the 14 ms conditions ($p = 0.20$), but was significantly different between the three pulses ($p < 0.001$). This effect was not significantly different between the 7 ms and the 14 ms conditions ($p = 0.53$). For the 7 ms and 14 ms conditions combined (main effect of repetition), the Tuckey HSD test revealed that the desynchronization was significantly greater between the first and second pulses ($p < 0.001$), between the second and third pulses ($p < 0.001$), and between the first and third pulses ($p < 0.001$). For pulse trains in ROI 3, mean power was significantly greater in the 14 ms compared with the 17 ms conditions ($p = 0.04$). In addition, the mean power significantly increased with pulse repetition ($p = 0.001$). However, this effect was not significantly different between the 7 ms and the 14 ms conditions ($p = 0.14$). For the 7 ms and 14 ms conditions combined (main effect of repetition), the Tuckey HSD tests revealed that the mean power significantly increased from the first to the third pulse ($p = 0.003$), and from the second to the third pulse ($p = 0.008$), but not from the first to the second pulse ($p = 0.43$).

Figure 3.8 – Average topographic maps of the ERSP in the three regions of interest



*Average topographic maps of the time-frequency activity in each region of interest for the two pulse train conditions and each pulse of the trains. Numbers 1, 2 and 3 represent the first, second and third pulse of the pulse trains. * Scaling was adjusted from -5 dB to +5 dB for illustration purposes. See Figure 7 for statistics.*

Exploratory correlation analyses

To explore the association between perception and brain responses, exploratory correlation analyses were conducted with pain ratings and C-LEP peak amplitude, as well as the power of brain oscillations in each ROI. The results revealed no significant effect (all $p > 0.46$).

Discussion

The trains of 7 ms pulses elicited C-LEPs in the greatest proportion of participants (86.7 %). C-LEPs were observed as a positive slow wave between 500 ms and 1500 ms post-stimulus but did not show temporal summation. ERD (7-15 Hz) and ERS (60-100 Hz) increased with repeated pulses at 0.67 Hz, consistent with temporal summation of second pain and the underlying C-fiber-related processes. These results provide novel data on C-fiber-related brain responses to painful stimuli and an optimized stimulation protocol for future studies that will investigate nociceptive mechanisms related to the lumbar area.

Electrophysiological characteristics of C-fiber-related brain responses

In the present study, the C-LEPs were observed as a positive slow wave centered at Pz between 500 ms and 1500 ms post-stimulus. This is consistent with the time course of pain perception associated with C-fiber activation and with the conduction velocity of C-fibers [65, 67, 68]. It is also coherent with a previous magnetoencephalographic report that showed a laser-evoked C-fiber-related response observed as a slow wave within the same time window [25]. Other studies have reported C-LEPs as a biphasic potential comprising a negative deflection followed by a positive deflection between 350 ms and 2000 ms [29, 31, 36, 37, 41, 61, 69]. It is not clear if these C-LEPs and the positive slow wave observed in the present study reflect the same or distinct neural processes related to C fibers. The N2-P2 complex reported in previous studies may reflect the detection of the initial C-fiber afferent volley, while the slow wave in the present and previous studies [25] may reflect the perceptual processes underlying the characteristic slow and progressively increasing sensation of second pain, spanning over several hundreds of milliseconds. Accordingly, an earlier N2-P2 complex can be elicited by various salient non-nociceptive stimuli at a latency that corresponds to the detection of the stimulus [70]. In addition, most laser stimuli were perceived as non-painful or around pain threshold in studies that reported a C-fiber-related N2-P2 complex [26, 27, 33, 36, 37, 60, 61, 69, 71-73]. In contrast, laser stimuli evoked moderate pain when a slow wave was observed (current study and [25]). The response shape may thus vary with the number of activated C fiber afferents. However, in a few

studies that reported a N2-P2 complex, laser stimuli were also rated as painful [41, 52, 74], so this remains to be clarified in future studies.

Effect of stimulus repetition on C-fiber-related brain responses

Brain activity associated with second pain evoked by repeated stimuli was characterized in a previous functional magnetic resonance imaging (fMRI) study [75]. However, the temporal resolution of fMRI is insufficient to monitor the pulse-by-pulse responses and the progressive increase in response amplitude [75]. A few studies have used repeated laser stimuli to investigate temporal summation of second pain, but C-fiber-related brain responses were not measured [76-79]. In the present study, repeated laser stimuli increased the perception of second pain. Yet, the increase in C-LEPs amplitude expected after each pulse was not observed. This lack of temporal summation may result from the constant interstimulus interval between each pulse of the trains. Indeed, findings from previous studies indicate that LEP amplitude decreases significantly when temporal predictability is high [45-47]. This habituation could explain the significant decrease of the positive slow wave amplitude observed during the second pulse of the train. This decrease was followed by an increased response amplitude for the third pulse. This may reflect competing processes where the interplay between temporal summation and habituation results in a relatively small or no change in response amplitude.

In contrast, time-frequency analyses revealed a significant increase in ERD (7-15 Hz) and ERS (60-100 Hz) with pulse repetition. This effect was not observed for ERS between 2 Hz and 5 Hz from 500 ms to 1200 ms, which corresponds to the C-LEP in the frequency domain [31, 41, 52]. This is consistent with the lack of temporal summation observed for C-LEPs in the present study. The discrepancy between the C-LEPs and C-ERSPs may be explained by the latency jitter of C-fibers [41]. As reported in recent reviews, time-frequency analyses may be better suited to measure EEG activity that is not time-locked or subject to latency jitters [2, 62]. Altogether, this indicates that C-ERSPs are better suited for future investigation on the regulation of temporal summation of second pain.

Future directions

The present results indicate that a protocol of repeated laser heat pulses is the most suitable to detect C-fiber-related brain responses. Laser pulse trains produced distinct A δ -fiber and C-fiber responses and the C-fiber response was observable with no or a very small A δ -fiber response. However, although participants ignored the first pain sensation and reported the second pain sensation, we cannot completely rule out that the A δ -fiber response partially contributed to the C-fiber response and the reported temporal summation of pain. The skin temperature decreases progressively after Nd:YAP laser stimuli [48]. Although reaction times are consistent with the perception of second pain evoked by C fibers, the repeated application of laser heat pulses at a rate of 0.67 Hz may not allow sufficient heat dissipation. In this case, the temporal summation of pain may be caused by increased peripheral afferent activation in addition to wind-up in the dorsal horn of the spinal cord. In future studies, the use of a temperature-controlled feedback laser stimulator would prevent this potential confound.

Laser-evoked brain responses in the present study were produced by back stimulation. It is not clear if the present results apply to hand stimulation, which is the most common stimulation site for LEP studies. The distance between the peripheral afferents and the spinal cord, where windup and temporal summation occur, is longer for the hand and foot compared with the back. Previous studies using contact heat stimulation were designed to investigate the inhibition of temporal summation of second pain by spinal manipulation [80, 81]. In these studies, the lower limb was stimulated because the 3-second back stimuli did not allow distinguishing the second pain from the first pain. The present methods limit this issue because Nd:YAP laser heat pulses produce synchronized nociceptive afferent volleys [82]. Nevertheless, future studies should account for the stimulation site and potential perceptual differences, especially if the stimulation protocol involves repeated stimuli and different body regions.

In the present study, laser stimuli were used to investigate nociceptive processes associated with pain in the lumbar region and temporal summation processes. Although these processes are relevant to low back pain research [17], laser stimuli activate cutaneous A- δ and C fibers, which are less relevant to clinical low back pain than deep tissue nociceptors. However, mechanical stimuli that target deep tissues are not suited for the assessment of temporal

summation of C-fiber-related activity, an objective of the present study. Indeed, this requires the repeated application of a noxious stimuli at a relatively high frequency. Therefore, although clinical low back pain is generally driven by nociceptive afferents from deep tissues, cutaneous laser stimuli were the most appropriate for the present study. It should also be noted that laser-evoked potentials are relevant to assess the mechanisms of pain relief by clinical interventions [4, 7].

Conclusion

Pulse trains of three 7 ms pulses at 0.67 Hz elicited C-LEPs in the greatest proportion of participants (86.7 %), indicating that it is a suitable protocol to measure C-fiber-related brain responses to laser heat pulses applied to the back. These responses included C-LEPs presenting as a slow wave centered at Pz, in addition to ERD (7-15 Hz) and ERS (60-100 Hz), all within a 500 ms to 1500 ms post-stimulus time window, consistent the perception associated with C fiber activation. These results provide novel data on C-fiber-related brain responses to painful stimuli and an optimized stimulation protocol for future studies that will investigate nociceptive mechanisms related to lumbar pain.

Supplementary material

The Supplementary Material for this article can be found online at:

<https://www.sciencedirect.com/science/article/pii/S1880654625000733?via%3Dihub#sec0155>

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Funding statement

This project was funded by the Natural Science and Engineering Research Council of Canada (grant number: 06559), the Fondation Chiropratique du Québec, and the Canadian Foundation for Innovation (grant number: 33731). The contribution of Benjamin Provencher was supported by the Fondation Chiropratique du Québec, the Quebec Bio-Imaging Network and the Fonds de Recherche du Québec – Santé (FRQS).

Conflict of interest disclosure

The authors declare no competing interests and no relationship that may lead to any conflict of interest.

Ethics approval statement

All experimental procedures conformed to the standards set by the latest revision of the Declaration of Helsinki and the guidelines of the International Association for the Study of Pain. The protocol was approved by the Research Ethics Board of Université du Québec à Trois-Rivières and all participants gave written informed consent, acknowledging their right to withdraw from the experiment without prejudice, and received a compensation of \$50 for their travel expenses and commitment to the study.

References

1. Plaghki L, Mouraux A. EEG and laser stimulation as tools for pain research. *Current Opinion in Investigational Drugs*. 2005;6(1):58-64.
2. Verdugo RJ, Matamala JM, Inui K, Kakigi R, Valls-Solé J, Hansson P, et al. Review of techniques useful for the assessment of sensory small fiber neuropathies: Report from an IFCN expert group. *Clinical Neurophysiology*. 2022;136:13-38. doi: 10.1016/j.clinph.2022.01.002.
3. Garcia-Larrea L. Objective pain diagnostics: clinical neurophysiology. *Clinical Neurophysiology*. 2012;42(4):187-97. doi: 10.1016/j.neucli.2012.03.001.
4. Truini A, Panuccio G, Galeotti F, Maluccio MR, Sartucci F, Avoli M, Cruccu G. Laser-evoked potentials as a tool for assessing the efficacy of antinociceptive drugs. *European Journal of Pain*. 2010;14(2):222-5. doi: 10.1016/j.ejpain.2009.05.001.
5. Provencher B, Northon S, Piché M. Segmental Chiropractic Spinal Manipulation Does not Reduce Pain Amplification and the Associated Pain-Related Brain Activity in a Capsaicin-Heat Pain Model. *Frontiers in Pain Research*. 2021;2(86):733727. doi: 10.3389/fpain.2021.733727.
6. Provencher B, Northon S, Gevers Montoro C, O'Shaughnessy J, Piché M. Effects of chiropractic spinal manipulation on laser-evoked pain and brain activity. *The Journal of Physiological Sciences*. 2021;71(1):20-33. doi: 10.1186/s12576-021-00804-2.
7. Schaffler K, Reeh P, Duan WR, Best AE, Othman AA, Faltynek CR, et al. An oral TRPV1 antagonist attenuates laser radiant-heat-evoked potentials and pain ratings from UV(B)-inflamed and normal skin. *British Journal of Clinical Pharmacology*. 2013;75(2):404-14. doi: 10.1111/j.1365-2125.2012.04377.x.
8. Plaghki L, Mouraux A. How do we selectively activate skin nociceptors with a high power infrared laser? Physiology and biophysics of laser stimulation. *Clinical Neurophysiology*. 2003;33(6):269-77. doi: 10.1016/j.neucli.2003.10.003.
9. Woolf CJ. Windup and central sensitization are not equivalent. *Pain*. 1996;66(2):105-8. doi: 10.1097/00006396-199608000-00001.
10. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain*. 2011;152(3 Suppl):S2-15. doi: 10.1016/j.pain.2010.09.030.
11. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *The Journal of Pain*. 2009;10(9):895-926. doi: 10.1016/j.jpain.2009.06.012.

12. Price DD. Characteristics of second pain and flexion reflexes indicative of prolonged central summation. *Experimental Neurology*. 1972;37(2):371-87. doi: 10.1016/0014-4886(72)90081-7.
13. Price DD, Hu JW, Dubner R, Gracely RH. Peripheral suppression of first pain and central summation of second pain evoked by noxious heat pulses. *Pain*. 1977;3(1):57-68. doi: 10.1016/0304-3959(77)90035-5.
14. Price DD, Hayes RL, Ruda M, Dubner R. Neural representation of cutaneous aftersensations by spinothalamic tract neurons. *Federation Proceedings*. 1978;37(9):2237-9.
15. Harte SE, Harris RE, Clauw DJ. The neurobiology of central sensitization. *Journal of Applied Biobehavioral Research*. 2018;23(2):e12137. doi: 10.1111/jabr.12137.
16. Georgopoulos V, Akin-Akinyosoye K, Smith S, McWilliams DF, Hendrick P, Walsh DA. An observational study of centrally facilitated pain in individuals with chronic low back pain. *Pain Rep*. 2022;7(3):e1003. doi: 10.1097/pr9.0000000000001003.
17. McPhee ME, Vaegter HB, Graven-Nielsen T. Alterations in pronociceptive and antinociceptive mechanisms in patients with low back pain: a systematic review with meta-analysis. *Pain*. 2020;161(3):464-75. doi: 10.1097/j.pain.0000000000001737.
18. Herrero JF, Laird JM, Lopez-Garcia JA. Wind-up of spinal cord neurones and pain sensation: much ado about something? *Progress in Neurobiology*. 2000;61(2):169-203. doi: 10.1016/s0301-0082(99)00051-9.
19. Price DD, Staud R, Robinson ME, Mauderli AP, Cannon R, Vierck CJ. Enhanced temporal summation of second pain and its central modulation in fibromyalgia patients. *Pain*. 2002;99(1-2):49-59. doi: 10.1016/s0304-3959(02)00053-2.
20. Garcia-Larrea L. Somatosensory volleys and cortical evoked potentials: 'first come, first served'? *Pain*. 2004;112(1-2):5-7. doi: 10.1016/j.pain.2004.09.003.
21. Bromm B, Neitzel H, Tecklenburg A, Treede RD. Evoked cerebral potential correlates of C-fibre activity in man. *Neuroscience Letters*. 1983;43(1):109-14. doi: 10.1016/0304-3940(83)90137-4.
22. Magerl W, Ali Z, Ellrich J, Meyer RA, Treede RD. C- and A delta-fiber components of heat-evoked cerebral potentials in healthy human subjects. *Pain*. 1999;82(2):127-37. doi: 10.1016/s0304-3959(99)00061-5
23. Bragard D, Chen AC, Plaghki L. Direct isolation of ultra-late (C-fibre) evoked brain potentials by CO₂ laser stimulation of tiny cutaneous surface areas in man. *Neuroscience Letters*. 1996;209(2):81-4. doi: 10.1016/0304-3940(96)12604-5

24. Opsommer E, Weiss T, Plaghki L, Miltner WH. Dipole analysis of ultralate (C-fibres) evoked potentials after laser stimulation of tiny cutaneous surface areas in humans. *Neuroscience Letters*. 2001;298(1):41-4. doi: 10.1016/s0304-3940(00)01718-3
25. Ploner M, Gross J, Timmermann L, Schnitzler A. Cortical representation of first and second pain sensation in humans. *Proceedings of the National Academy of Sciences*. 2002;99(19):12444. doi: 10.1073/pnas.182272899.
26. Iannetti GD, Truini A, Romaniello A, Galeotti F, Rizzo C, Manfredi M, Cruccu G. Evidence of a Specific Spinal Pathway for the Sense of Warmth in Humans. *Journal of Neurophysiology*. 2003;89(1):562-70. doi: 10.1152/jn.00393.2002.
27. Truini A, Galeotti F, Cruccu G, Garcia-Larrea L. Inhibition of cortical responses to Adelta inputs by a preceding C-related response: testing the "first come, first served" hypothesis of cortical laser evoked potentials. *Pain*. 2007;131(3):341-7. doi: 10.1016/j.pain.2007.06.023.
28. Mouraux A, Plaghki L. Cortical interactions and integration of nociceptive and non-nociceptive somatosensory inputs in humans. *Neuroscience*. 2007;150(1):72-81. doi: 10.1016/j.neuroscience.2007.08.035.
29. Terhaar J, Viola FC, Franz M, Berger S, Bär K-J, Weiss T. Differential processing of laser stimuli by A δ and C fibres in major depression. *Pain*. 2011;152(8):1796-802. doi: 10.1016/j.pain.2011.03.027.
30. Churyukanov M, Plaghki L, Legrain V, Mouraux A. Thermal detection thresholds of A δ - and C-fibre afferents activated by brief CO₂ laser pulses applied onto the human hairy skin. *PLoS One*. 2012;7(4):e35817. doi: 10.1371/journal.pone.0035817.
31. Jankovski A, Plaghki L, Mouraux A. Reliable EEG responses to the selective activation of C-fibre afferents using a temperature-controlled infrared laser stimulator in conjunction with an adaptive staircase algorithm. *Pain*. 2013;154(9):1578-87. doi: 10.1016/j.pain.2013.04.032.
32. Naro A, Russo M, Leo A, Rifici C, Pollicino P, Bramanti P, Calabrò RS. Cortical Responsiveness to Nociceptive Stimuli in Patients with Chronic Disorders of Consciousness: Do C-Fiber Laser Evoked Potentials Have a Role? *PLoS One*. 2015;10(12):e0144713. doi: 10.1371/journal.pone.0144713.
33. Torta DM, Churyukanov MV, Plaghki L, Mouraux A. The effect of heterotopic noxious conditioning stimulation on A δ -, C- and A β -fibre brain responses in humans. *European Journal of Neuroscience*. 2015;42(9):2707-15. doi: 10.1111/ejn.13071.
34. Azevedo E, Silva A, Martins R, Andersen ML, Tufik S, Manzano GM. Activation of C-fiber nociceptors by low-power diode laser. *Arquivos de Neuro-Psiquiatria*. 2016;74(3):223-7. doi: 10.1590/0004-282X20160018.

35. Lefaucheur JP, Abbas SA, Lefaucheur-Ménard I, Rouie D, Tebbal D, Bismuth J, Nordine T. Small nerve fiber selectivity of laser and intraepidermal electrical stimulation: A comparative study between glabrous and hairy skin. *Clinical Neurophysiology*. 2021;51(4):357-74. doi: 10.1016/j.neucli.2021.06.004.
36. Lenoir C, Plaghki L, Mouraux A, van den Broeke EN. Quickly responding C-fibre nociceptors contribute to heat hypersensitivity in the area of secondary hyperalgesia. *The Journal of Physiology*. 2018;596(18):4443-55. doi: 10.1113/jp275977.
37. van den Broeke EN, Mouraux A. Enhanced brain responses to C-fiber input in the area of secondary hyperalgesia induced by high-frequency electrical stimulation of the skin. *Journal of Neurophysiology*. 2014;112(9):2059-66. doi: 10.1152/jn.00342.2014.
38. Mouraux A, Iannetti GD, Colon E, Nozaradan S, Legrain V, Plaghki L. Nociceptive Steady-State Evoked Potentials Elicited by Rapid Periodic Thermal Stimulation of Cutaneous Nociceptors. *The Journal of Neuroscience*. 2011;31(16):6079. doi: 10.1523/JNEUROSCI.3977-10.2011.
39. Qiu Y, Inui K, Wang X, Tran TD, Kakigi R. Conduction velocity of the spinothalamic tract in humans as assessed by CO₂ laser stimulation of C-fibers. *Neuroscience Letters*. 2001;311(3):181-4. doi: 10.1016/S0304-3940(01)02170-X.
40. Opsommer E, Masquelier E, Plaghki L. Determination of nerve conduction velocity of C-fibres in humans from thermal thresholds to contact heat (thermode) and from evoked brain potentials to radiant heat (CO₂ laser). *Clinical Neurophysiology*. 1999;29(5):411-22. doi: 10.1016/S0987-7053(00)87265-2.
41. Hu L, Cai MM, Xiao P, Luo F, Iannetti GD. Human brain responses to concomitant stimulation of Delta and C nociceptors. *The Journal of Neuroscience*. 2014;34(34):11439-51. doi: 10.1523/JNEUROSCI.1355-14.2014.
42. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*. 2007;39(2):175-91. doi: 10.3758/bf03193146.
43. Gupta V, Sharma VK. Skin typing: Fitzpatrick grading and others. *Clinics in Dermatology*. 2019;37(5):430-6. doi: 10.1016/j.clindermatol.2019.07.010.
44. Bromm B, Jahnke MT, Treede RD. Responses of human cutaneous afferents to CO₂ laser stimuli causing pain. *Experimental Brain Research*. 1984;55(1):158-66. doi: 10.1007/BF00240510.
45. Wang AL, Mouraux A, Liang M, Iannetti GD. Stimulus novelty, and not neural refractoriness, explains the repetition suppression of laser-evoked potentials. *Journal of Neurophysiology*. 2010;104(4):2116-24. doi: 10.1152/jn.01088.2009.

46. Ronga I, Valentini E, Mouraux A, Iannetti GD. Novelty is not enough: laser-evoked potentials are determined by stimulus saliency, not absolute novelty. *Journal of Neurophysiology*. 2013;109(3):692-701. doi: 10.1152/jn.00464.2012.
47. Iannetti GD, Hughes NP, Lee MC, Mouraux A. Determinants of laser-evoked EEG responses: pain perception or stimulus saliency? *Journal of Neurophysiology*. 2008;100(2):815-28. doi: 10.1152/jn.00097.2008.
48. Leandri M, Saturno M, Spadavecchia L, Iannetti GD, Cruccu G, Truini A. Measurement of skin temperature after infrared laser stimulation. *Clinical Neurophysiology*. 2006;36(4):207-18. doi: 10.1016/j.neucli.2006.08.004.
49. Northon S, Deldar Z, Piché M. Cortical interaction of bilateral inputs is similar for noxious and innocuous stimuli but leads to different perceptual effects. *Experimental Brain Research*. 2021;239(9):2803-19. doi: 10.1007/s00221-021-06175-9.
50. Bialosky JE, George SZ, Horn ME, Price DD, Staud R, Robinson ME. Spinal manipulative therapy-specific changes in pain sensitivity in individuals with low back pain (NCT01168999). *The Journal of Pain*. 2014;15(2):136-48. doi: 10.1016/j.jpain.2013.10.005.
51. Slimani H, Plaghki L, Ptito M, Kupers R. Pain hypersensitivity in congenital blindness is associated with faster central processing of C-fibre input. *European Journal of Pain*. 2016;20(9):1519-29. doi: 10.1002/ejp.876.
52. Mouraux A, Guérit JM, Plaghki L. Non-phase locked electroencephalogram (EEG) responses to CO₂ laser skin stimulations may reflect central interactions between A δ - and C-fibre afferent volleys. *Clinical Neurophysiology*. 2003;114(4):710-22. doi: 10.1016/S1388-2457(03)00027-0.
53. Northon S, Deldar Z, Piche M. Cortical interaction of bilateral inputs is similar for noxious and innocuous stimuli but leads to different perceptual effects. *Experimental brain research*. 2021;239(9):2803-19. doi: 10.1007/s00221-021-06175-9.
54. Northon S, Deldar Z, Piche M. Spinal and Cerebral Integration of Noxious Inputs in Left-handed Individuals. *Brain Topogr*. 2021;34(5):568-86. doi: 10.1007/s10548-021-00864-y.
55. Rustamov N, Northon S, Tessier J, Leblond H, Piché M. Integration of bilateral nociceptive inputs tunes spinal and cerebral responses. *Scientific Reports*. 2019;9(1):7143. doi: 10.1038/s41598-019-43567-y.
56. Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*. 2004;134:9-21. doi: 10.1016/j.jneumeth.2003.10.009.
57. Rodrigues J, Weiß M, Hewig J, Allen JJB. EPOS: EEG Processing Open-Source Scripts. *Frontiers in Neuroscience*. 2021;15:660449. doi: 10.3389/fnins.2021.660449.

58. Tabachnick BG, Fidell LS. Using multivariate statistics. 6th ed. Pearson Education; 2013.
59. Pion-Tonachini L, Kreutz-Delgado K, Makeig S. ICLabel: An automated electroencephalographic independent component classifier, dataset, and website. *NeuroImage*. 2019;198:181-97. doi: 10.1016/j.neuroimage.2019.05.026.
60. Hüllemann P, Shao YQ, Manthey G, Binder A, Baron R. Central habituation and distraction alter C-fibre-mediated laser-evoked potential amplitudes. *European Journal of Pain*. 2016;20(3):377-85. doi: 10.1002/ejp.735.
61. Mouraux A, Guerit JM, Plaghki L. Refractoriness cannot explain why C-fiber laser-evoked brain potentials are recorded only if concomitant Adelta-fiber activation is avoided. *Pain*. 2004;112(1-2):16-26. doi: 10.1016/j.pain.2004.05.024.
62. Morales S, Bowers ME. Time-frequency analysis methods and their application in developmental EEG data. *Developmental Cognitive Neuroscience*. 2022;54:101067. doi: 10.1016/j.dcn.2022.101067.
63. Mouraux A, Iannetti GD. Across-trial averaging of event-related EEG responses and beyond. *Magnetic Resonance Imaging*. 2008;26(7):1041-54. doi: 10.1016/j.mri.2008.01.011.
64. Cohen MX. Analyzing Neural Time Series Data: Theory and Practice. Issues in Clinical and Cognitive Neuropsychology. Cambridge, Massachusetts: The MIT Press; 2014.
65. Barrett KE, Barman SM, Brooks HL, Yuan JXJ. Ganong's Review of Medical Physiology. 26th ed. New York: McGraw-Hill Education; 2019.
66. Ploner M, Sorg C, Gross J. Brain Rhythms of Pain. *Trends in Cognitive Sciences*. 2017;21(2):100-10. doi: 10.1016/j.tics.2016.12.001.
67. Adriaensen H, Gybels J, Handwerker HO, Van Hees J. Response properties of thin myelinated (A-delta) fibers in human skin nerves. *Journal of Neurophysiology*. 1983;49(1):111-22. doi: 10.1152/jn.1983.49.1.111.
68. Van Hees J, Gybels J. C nociceptor activity in human nerve during painful and non painful skin stimulation. *Journal of Neurology, Neurosurgery, and Psychiatry*. 1981;44(7):600-7. doi: 10.1136/jnnp.44.7.600.
69. Ammendola E, Tancredi G, Ricci K, Falcicchio G, Valeriani M, de Tommaso M. Assessment of C Fibers Evoked Potentials in Healthy Subjects by Nd:YAP Laser. *Pain Research and Management*. 2022;2022:7737251. doi: 10.1155/2022/7737251.
70. Mouraux A, Iannetti GD. The search for pain biomarkers in the human brain. *Brain*. 2018;141(12):3290-307. doi: 10.1093/brain/awy281.

71. De Stefano G, Leone C, Di Pietro G, Esposito N, Falco P, Galosi E, et al. Unravelling the role of unmyelinated nerve fibres in trigeminal neuralgia with concomitant continuous pain. *Clinical Neurophysiology*. 2022;142:52-8. doi: 10.1016/j.clinph.2022.07.502.
72. Truini A, Gerardi MC, Di Stefano G, La Cesa S, Iannuccelli C, Pepe A, et al. Hyperexcitability in pain matrices in patients with fibromyalgia. *Clinical and Experimental Rheumatology*. 2015;33(1 Suppl 88):S68-72.
73. Cruccu G, Pennisi E, Truini A, Iannetti GD, Romaniello A, Le Pera D, et al. Unmyelinated trigeminal pathways as assessed by laser stimuli in humans. *Brain*. 2003;126(10):2246-56. doi: 10.1093/brain/awg227.
74. Opsommer E, Weiss T, Miltner WH, Plaghki L. Scalp topography of ultralate (C-fibres) evoked potentials following thulium YAG laser stimuli to tiny skin surface areas in humans. *Clinical Neurophysiology*. 2001;112(10):1868-74. doi: 10.1016/s1388-2457(01)00622-8.
75. Staud R, Craggs JG, Robinson ME, Perlstein WM, Price DD. Brain activity related to temporal summation of C-fiber evoked pain. *Pain*. 2007;129(1-2):130-42. doi: 10.1016/j.pain.2006.10.010.
76. Stancak A, Alghamdi J, Nurmikko TJ. Cortical activation changes during repeated laser stimulation: a magnetoencephalographic study. *PLoS One*. 2011;6(5):e19744. doi: 10.1371/journal.pone.0019744.
77. Ylloja S, Carlson S, Raij TT, Pertovaara A. Localization of touch versus heat pain in the human hand: a dissociative effect of temporal parameters on discriminative capacity and decision strategy. *Pain*. 2006;121(1-2):6-13. doi: 10.1016/j.pain.2005.11.014.
78. Nielsen J, Arendt-Nielsen L. The importance of stimulus configuration for temporal summation of first and second pain to repeated heat stimuli. *European Journal of Pain*. 1998;2(4):329-41. doi: 10.1016/s1090-3801(98)90031-3.
79. Svensson P, Beydoun A, Morrow TJ, Casey KL. Human intramuscular and cutaneous pain: psychophysical comparisons. *Experimental Brain Research*. 1997;114(2):390-2. doi: 10.1007/PL00005648.
80. Bialosky JE, Bishop MD, Price DD, Robinson ME, George SZ. The mechanisms of manual therapy in the treatment of musculoskeletal pain: a comprehensive model. *Manual Therapy*. 2009;14(5):531-8. doi: 10.1016/j.math.2008.09.001.
81. George SZ, Bishop MD, Bialosky JE, Zeppieri G, Jr., Robinson ME. Immediate effects of spinal manipulation on thermal pain sensitivity: an experimental study. *BMC Musculoskeletal Disorders*. 2006;7:68-78. doi: 10.1186/1471-2474-7-68.

82. Perchet C, Godinho F, Mazza S, Frot M, Legrain V, Magnin M, Garcia-Larrea L. Evoked potentials to nociceptive stimuli delivered by CO₂ or Nd:YAP lasers. *Clinical Neurophysiology*. 2008;119(11):2615-22. doi: 10.1016/j.clinph.2008.06.021.

Chapitre 4: Étude 3 – Widespread hyperalgesia is not associated with increased temporal summation of second pain and increased C-fiber-related brain responses in individuals with chronic primary low back pain.

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En préparation pour être soumis au journal *Psychophysiology*.

Contribution des auteurs selon la classification CRediT (*Contribution Roles Taxonomy*):

- Benjamin Provencher: conceptualisation, méthodologie, logiciel, investigation, analyse formelle, validation, gestion des données et rédaction – version originale.
- Gabriel parent : investigation, analyse formelle, validation
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Abstract

Chronic primary low back pain (CPLBP) is a nociplastic pain condition associated with mechanical hyperalgesia. Despite some discrepancies, increased temporal summation of second pain (TSSP) was reported in individuals with CPLBP. Although increased TSSP is thought to rely on C-fiber-related processes, this remains unclear. Therefore, the aim of this study is to examine whether individuals with CPLBP exhibit increased TSSP and C-fiber-related brain responses. Pressure pain thresholds (PPT), psychological factors, TSSP and C-fiber-related electroencephalographic responses to laser heat stimulation were measured in 30 individuals with CPLBP and 30 age- and sex-matched controls. In individuals with CPLBP, low back pain intensity and disability were low to moderate, with a mean pain duration of 13.4 years. Compared with controls, individuals with CPLBP showed significantly lower PPTs in the lumbar region ($p < .001$), lower limb ($p = .04$), and hand ($p = .02$), indicating widespread hyperalgesia. They also reported higher pain catastrophizing ($p = .03$), pain vigilance ($p = .001$), and depressive symptoms ($p = .03$). In contrast, groups were not significantly different for TSSP ($p = .75$), C-fiber-related evoked potentials ($p = .31$), and event-related spectral perturbations (all $p > .35$), even when controlling for group differences in stimulus intensity and psychological factors. These results indicate that individuals with CPLBP show clinical and psychological features consistent with nociplastic pain, although TSSP and C-fiber-related brain responses, as measured in this study, are not increased. This warrants future studies to examine whether increased TSSP and C-fiber responses may be observable in a subpopulation of individuals with CPLBP who show distinct clinical characteristics.

Introduction

Low back pain (LBP) is the leading cause of years lived with disability worldwide, and its burden is expected to increase in the next decades (GBD 2021 Diseases and Injuries Collaborators, 2024; GBD 2021 Forecasting Collaborators, 2024). Chronic primary pain, including chronic primary low back pain (CPLBP), is now recognized as a disease rather than a symptom of an underlying pathology (Nicholas et al., 2019; Treede et al., 2019; World Health Organisation (WHO), 2019). CPLBP is classified as a nociplastic pain condition, for which pain arises or persists due to altered nociceptive processing rather than tissue damage or nerve injury (Kaplan et al., 2024; World Health Organisation (WHO), 2019).

The low back pain phenotyping (BACPAP) consortium recommended classifying chronic LBP based on the dominant underlying pain mechanisms (Nijs et al., 2024). Accordingly, pain is classified as nociceptive, neuropathic, or nociplastic, depending on pain duration and distribution, signs of central sensitization, and the presence of comorbid symptoms (Nijs et al., 2024). Comorbid symptoms associated with chronic nociplastic pain include fatigue, sleep disturbance, increased sensitivity to sound, light, or odors, cognitive impairment, and depressive mood (Kaplan et al., 2024; Kosek et al., 2021). Notably, psychological factors central to the fear-avoidance model of pain, including anxiety, depressive symptoms, pain catastrophizing, and pain vigilance, have been shown to influence clinical pain intensity, pain-related disability, and mechanical hyperalgesia in individuals with chronic LBP (Aoyagi et al., 2019; Matheve et al., 2022; Meints et al., 2019; Rogers & Farris, 2022; Salas-González et al., 2025; Subramanian & Venkatesan, 2022; Vlaeyen et al., 2016). Moreover, meta-analyses have shown that compared with healthy controls, individuals with LBP, including chronic nociplastic LBP, exhibit impaired endogenous pain inhibition mechanisms, increased temporal summation of pain, widespread hyperalgesia, and other signs reflecting central sensitization (den Bandt et al., 2019; McPhee et al., 2020; Van Oosterwijck et al., 2025). Central sensitization refers to an increased responsiveness of nociceptive neurons in the central nervous system to normal or subthreshold afferent input, which translates into hyperalgesia (International Association for the Study of Pain, 2021; Woolf, 2011). It can be induced through sustained or repetitive nociceptive inputs from C-fibers (Li et al., 1999; Price et al., 1977). Although direct electrophysiological recording of central neurons is not

possible in experimental human studies, widespread hyperalgesia and increased temporal summation of pain may indicate central sensitization (Arendt-Nielsen et al., 2018).

The processing of nociceptive C-fiber inputs leads to second pain, a dull and diffuse sensation that follows the sharp, localized first pain induced by the processing of A δ -fiber inputs (Plaghki & Mouraux, 2005). Temporal summation of second pain (TSSP) induced by repeated heat stimuli is thought to result from temporal summation of C-fiber activity in the spinal cord (Price & Dubner, 1977; Price et al., 1977; Staud et al., 2007). This can be measured indirectly with brief laser heat pulses and electroencephalography (EEG) (Hu et al., 2014; Plaghki & Mouraux, 2005; Provencher & Piché, 2025).

A meta-analysis showed that TSSP is generally increased in individuals with acute or chronic LBP compared with healthy controls, although the effect size is small and it is not observable in every study (McPhee et al., 2020). However, this is based on behavioral assessment. The associated C-fiber-related activity has not been investigated to provide a neurophysiological marker of increased TSSP. Investigating TSSP in individuals with CPLBP using behavioral and neurophysiological measures could deepen our understanding of the condition and contribute to the refinement of the chronic LBP classification (Kaplan et al., 2024). Therefore, the main objective of the present study is to determine whether TSSP and the associated C-fiber-related brain responses are increased in individuals with CPLBP compared with age- and sex-matched healthy controls. We hypothesize that individuals with CPLBP will exhibit greater TSSP associated with increased amplitude of C-fiber-related brain responses compared with controls. In addition, we expect to observe widespread hyperalgesia and psychological distress, consistent with nociplastic pain.

Methods

Participants

Participants were recruited as part of a randomized controlled trial relying on a parallel design with four arms. It was designed to clarify the neurophysiological mechanisms underlying the therapeutic effects of spinal manipulative therapy for CPLBP (trial registration number NCT05986370). The fourth arm of the study comprised controls that were age- and sex-matched to individuals with CPLBP. Participants in this group did not receive any intervention. In the present study, only the data from the first experimental session are included. The results of the ongoing clinical study will be reported elsewhere.

Participants were recruited by advertisements on social media. Thirty individuals with CPLBP (18 women and 12 men; mean age $\pm$ SD: 41.7 ± 9.7 years) and thirty age- and sex-matched controls (18 women and 12 men; mean age $\pm$ SD: 42.1 ± 9.9 years) were included in the study. Among these 60 participants, all data was of good quality and no participant was excluded from any analysis. Participants with CPLBP were included if they were between 18 and 60 years old, had low back pain for at least 6 months with an average LBP intensity $\geq 3/10$ during the last 7 days. They were excluded following a thorough examination by a licensed chiropractor (BP), if a pathology responsible for their symptoms was identified (e.g.: fracture, spinal stenosis, herniated disc, neoplasia, infection, inflammatory arthritis, arthrosis or visceral conditions such as prostatitis, endometriosis, kidney stones, and aortic aneurism). They were also excluded if they had another chronic pain syndrome, a sensory or motor deficit in the lower limbs, presented contraindications to spinal manipulation or conditions that would normally require modifications to the therapy (history of spinal surgery, atherosclerosis of major blood vessels, vertebrobasilar insufficiency, aneurysms, osteoporosis (Bergmann & Peterson, 2011)) or if they received chiropractic care in the past 12 months. Controls were included if they matched the age (± 1 year) and sex of a participant with CPLBP. They were excluded if they reported acute or chronic pain, acute or chronic illness, weekly usage of pain medication, an injury or surgery in the 3 months preceding the experiment, and if they took any pain medication within 48 h prior to the experimental session. To minimize the risk of adverse events related to laser stimulation,

individuals with CPLBP and controls were also excluded if they presented a skin of type I on the Fitzpatrick scale (Gupta & Sharma, 2019).

Experimental design

This study relied on a cross-sectional design to assess differences between individuals with CPLBP and controls. All outcomes were measured by a member of the research team (GP) that was blind to the study hypotheses. The experimental protocol is presented in **Figure 4.1A**.

Pressure pain thresholds (PPTs)

PPTs were assessed at three different body locations, as illustrated in **Figure 4.1B**. 1) 2 cm lateral to the spinous process (bilaterally) of the most painful vertebra between L1 and S1, as a measure of primary hyperalgesia. The PPT values from both sides was averaged to get one PPT. 2) On the right lower limb in the dermatome corresponding to the level of the most painful vertebra. The rationale for this location is to provide a measure of secondary hyperalgesia. Specific test locations for L1 to S1 dermatomes were selected based on an evidence-based dermatome map (Lee et al., 2008). The test location for L1 dermatome was located 5 cm inferior to the right anterior superior iliac spine. The test location for L2 dermatome was located in the center of the right thigh, midway between the hip and the knee. The test location for L3 dermatome was located distally on the right thigh, just above the patella. The test location for L4 dermatome was located midway between the knee and the ankle, over the medial aspect of the calf muscles. The test location for L5 dermatome was located over the head of the second metatarsal bone of the right foot. The test location for S1 dermatome was located over the tuberosity of the 5th metatarsal bone of the right foot. 3) In the center of the right thenar eminence. This remote location was selected as a measure of widespread hyperalgesia. The right side was selected arbitrarily, since no side difference was expected.

PPTs were measured using a handheld digital algometer (Wagner Pain TestTM FPX, Greenwich, Connecticut, USA) and a standardized protocol (Mücke et al., 2021; Starkweather et al., 2016). The algometer was applied perpendicularly to the skin and the pressure increased at approximately 50 kPa/s until pain was reported by the participant. This procedure was repeated three times at the same test location with approximately 30 s between trials. The PPT was the average of the values obtained during these 3 trials. The same procedures were used for the three test locations (see **Figure 4.1B**). Excellent test-retest reliability was reported for PPTs assessed in the lower back and remote body areas in individuals with CPLBP (Paungmali et al., 2012).

Questionnaires

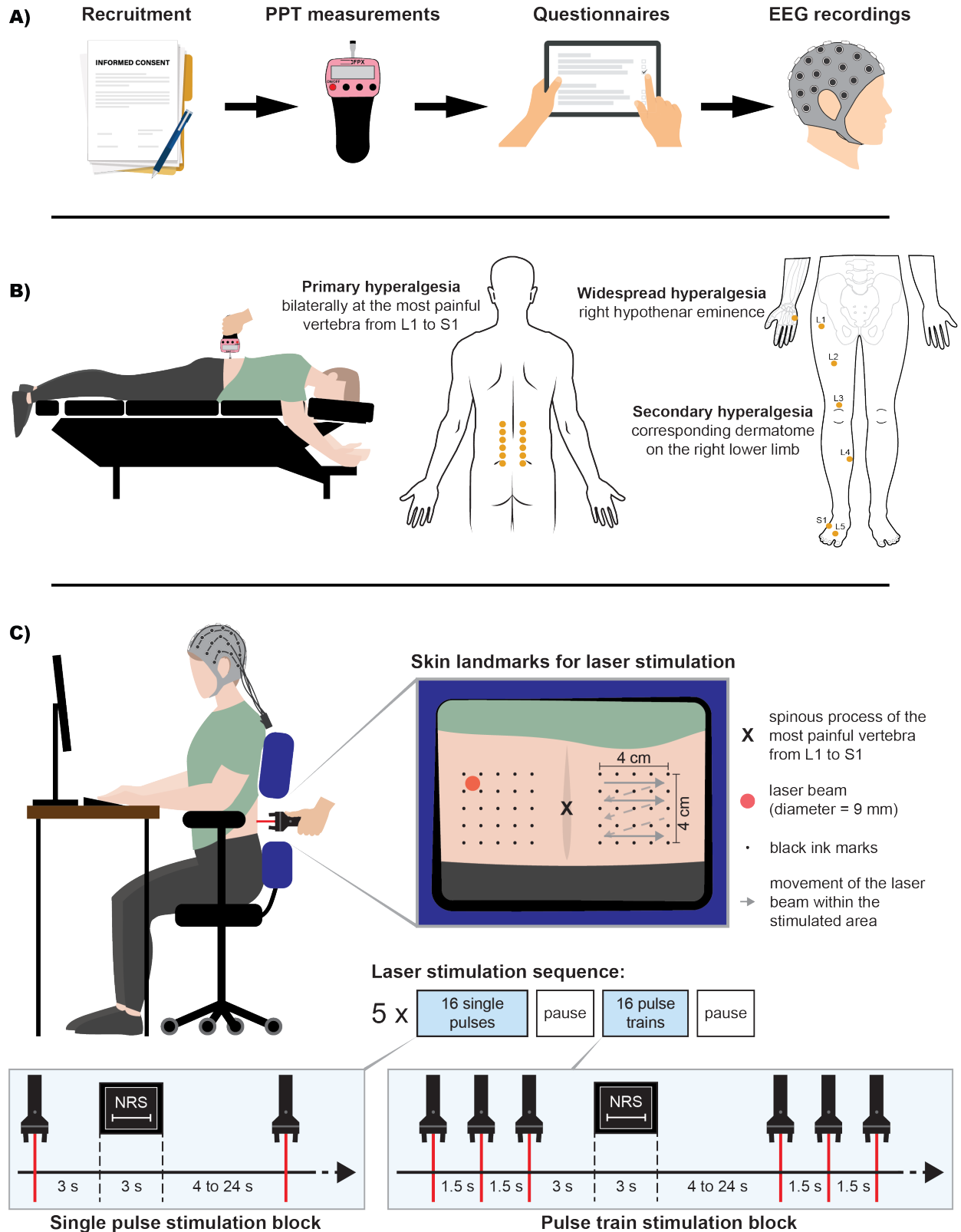
Pain catastrophizing and pain vigilance

Pain catastrophizing was measured with the French-Canadian version of the pain catastrophizing scale (PCS) (French et al., 2005), Cronbach α = 0.92, Spearman ρ = 0.88 (Wheeler et al., 2019). Pain hypervigilance was measured with a French adaptation of the pain vigilance and awareness questionnaire (PVAQ) (Desrochers et al., 2009; McCracken, 1997), Cronbach α = 0.86; test-retest reliability: r = 0.80 (McCracken, 1997). These two factors contribute to chronic pain and are part of the fear avoidance model of pain (Vlaeyen & Linton, 2000).

Depression and anxiety

Depression and anxiety are comorbidities of chronic LBP that may influence experimental and clinical pain (Bailes et al., 2021; Bener et al., 2013; Knezevic et al., 2021; Salas-González et al., 2025). Depressive symptoms were measured using the French-Canadian version of the Beck depression inventory (BDI) (Bourque & Beaudette, 1982). Anxiety was measured using the French-Canadian version of the state-trait anxiety inventory (STAI-Y) (Gauthier & Bouchard, 1993). Validity and reliability measures for these questionnaires are good to excellent (Cronbach α = 0.92 and 0.90, r = 0.61 and 0.31-0.86, respectively) (Bourque & Beaudette, 1982; Gauthier & Bouchard, 1993; Wang & Gorenstein, 2013).

Figure 4.1 – Experimental protocol



A) General steps followed during the experimental session. For controls, measurements were made at the same locations as in their age and sex-matched individuals with CPLBP. **B)** Illustration of how PPTs were measured as well as all the possible test locations to assess primary, secondary and widespread hyperalgesia. **C)** Detailed representation of the experimental setup, stimulation procedures and protocol. The laser stimulus was delivered to the back area within grids of ink marks drawn on each side of the most painful vertebra from L1 to S1. The 9 mm laser beam was carefully positioned on ink-free skin at one of the 32 spots within the stimulation grid. The laser beam was moved to the next spot in the grid after each stimulus (single pulse and pulse train) for safety purposes. It was moved sequentially from left to right and top to bottom. Within a pulse train however, the three pulses were delivered to the same spot to induce temporal summation. After each stimulus, participants were prompted to rate second pain with the display of a numerical pain rating scale. Participants received 5 series of stimuli, including 16 single pulse and 16 pulse trains stimuli delivered at the same laser intensity to assess temporal summation. PPT: pressure pain threshold, EEG: electroencephalography, NRS: Numerical Rating Scale.

Self-compassion

In the context of chronic pain, self-compassion may influence pain catastrophizing, depressive symptoms and anxiety (Emmerich et al., 2020). Therefore, self-compassion was evaluated in the present study using the French translation of the self-compassion scale (SCS) (Kotsou & Leys, 2016; Neff, 2003). The scale has excellent test-retest reliability (Cronbach α = 0.94) (Kotsou & Leys, 2016).

Sex and gender

Sex and a measure of gender roles (masculinity and femininity) were used to examine differences between males and females and to control for the influence of gender roles on the results. Sex was defined as the sex attributed at birth (male or female). Gender roles were assessed using the French version of the personal attributes questionnaire (PAQ). The PAQ has

good internal consistency (Cronbach α = 0.68 for femininity and 0.72 for masculinity) (K'Delant & Gana, 2009).

Temporal summation of second pain and C-fiber-related brain responses

Laser stimulation

The laser stimulation protocol is based on our previous study (Provencher & Piché, 2025) and is illustrated in **Figure 4.1C**. Painful stimuli were delivered using heat pulses generated by an infrared neodymium-doped yttrium aluminum perovskite laser (Nd:YAP, DEKA 1340, Electronical Engineering, Florence, Italy). A total of 160 stimuli were administered: 80 single pulses and 80 pulse trains, each train consisting of 3 pulses delivered at a frequency of 0.67 Hz. All stimuli had a pulse duration of 7 ms and were delivered at the same laser intensity. Stimuli were organized into five blocks of 16 trials, alternating between blocks of single pulses and pulse trains. Three seconds after each stimulus, a numerical rating scale (NRS) appeared on the screen, prompting participants to rate the second pain verbally on a scale from 0 (no pain) to 100 (worst pain imaginable). For pulse train stimuli, participants were instructed to rate the pain elicited by the last pulse of the train only.

At the beginning of each session, a member of the research team (BP) explained the concept of second pain to the participants. Participants were instructed to focus on the second pain (the dull/hot/burning sensation in their back) and to report its intensity verbally. Next, laser pain thresholds and laser intensity causing low to moderate pain were determined using a staircase procedure (Provencher et al., 2021; Provencher & Piché, 2025). Once this intensity was determined, it was kept constant for the rest of the experimental session

Temporal summation of second pain (TSSP)

The average pain rating for the 80 single laser pulses was subtracted from the average pain rating for the 80 laser pulse trains to estimate the amplitude of the TSSP for each participant. This measure reflects the amplification of spinal nociceptive transmission (Riley et al., 2019).

Electroencephalographic recording

Electroencephalography (EEG) was recorded using a 32-channel BrainVision system with active Ag-AgCl electrodes mounted on an actiCAP, according to the International 10–20 system (Brain Products, Gilching, Germany). Electrodes were nose-referenced and the ground was set at FPz. Signals were sampled at 500 Hz. Eye movements and blinks were recorded using electrooculography (EOG) with electrodes placed at the right sub and supraorbital ridges and just lateral to the external ocular canthi. Electrode impedance was kept below 20 k Ω . EEG activity was recorded continuously during all laser stimulation blocks.

Electroencephalographic analyses

EEG signals were analyzed offline using MATLAB R2024b (MathWorks, Natick, MA, USA) and EEGLAB v2024.2.1 (Delorme & Makeig, 2004). To analyze laser-evoked potentials (LEP), EEG signals were preprocessed using a standardized, automated, and open-source preprocessing pipeline for EEG data (Rodrigues et al., 2021). The preprocessing steps included: 1) Downsampling the data from 1000 Hz to 500 Hz; 2) Re-referencing signals to the common average; 3) Automatic detection and spherical interpolation of channels of low quality using the outlier criterion $z > 3.29$ (Tabachnick & Fidell, 2013); 4) Segmenting the data into “long” epochs (-2000 ms to 7000 ms) to get a better independent component analysis (ICA) solution in the next steps; 5) High-pass filtering using a 0.5 Hz finite impulse response (FIR) filter; 6) First ICA using the built-in function Runica in EEGLAB to identify trials with bad signal; 7) Automatic detection and rejection of contaminated trials based on z-value detection (> 3.29) of independent components (ICs); 8) Second ICA to identify artifact-driven components containing no relevant signal; 9) Automatic detection and rejection of the ICs related to noise using the ICLabel plugin (Pion-Tonachini et al., 2019) with preset thresholds ($> 90\%$ for muscles and eyes, $> 95\%$ for heart, $> 75\%$ for line and channel noise); 10) Segmenting the data into epochs for the analysis (-500 ms to 1500 ms for single pulse conditions and -500 ms to 4500 ms for pulse train conditions); 11) Baseline correction (-500 ms to 0 ms) (Hüllemann et al., 2016; Jankovski et al., 2013; Lenoir et al., 2018); 12) Low-pass filtering using a 30 Hz FIR filter. On average, 3.7 ± 1.3 channels were interpolated, 1.3 ± 1.5 epochs were rejected and $84.8 \pm 13.9\%$ of the variance remained after IC rejection. After this

preprocessing, average waveforms were computed for each participant and stimulus type, and the positive slow wave evoked by laser pulses was analyzed. The peak amplitude and latency of this positive slow wave were measured automatically using the max function within a specified time window on each average waveform (Provencher & Piché, 2025). The peak was defined as the maximum value between 500 and 1450 ms with a maximum amplitude at Pz (Provencher & Piché, 2025).

In order to measure event-related spectral perturbations (ERSP), EEG datasets were preprocessed using the same automated preprocessing pipeline as described above, with adapted parameters (High-pass: 1 Hz; Low-pass: 100 Hz), baseline (-700 ms to -200 ms) and the final length of the epochs (-2000 ms to 2000 ms for single pulse conditions and -2000 ms to 5000 ms for pulse train conditions). Then, as in previous studies (Provencher et al., 2021; Rustamov et al., 2019), a Morlet wavelet convolution (Mouraux & Iannetti, 2008) was computed using the channel time–frequency options available in EEGLAB (Delorme & Makeig, 2004). Four hundred or 1200 time points were generated (single pulse or pulse train stimuli), and 100 linearly spaced frequencies were computed from 1 to 100 Hz. Variable cycles were used for low and high frequencies, with 3 cycles for lowest frequencies and up to 15 cycles for highest frequencies (Delorme & Makeig, 2004). This variable number of cycles allows for the wavelet convolution method to provide a better frequency resolution at lower frequencies and a better temporal resolution at higher frequencies (Cohen, 2014). Time-frequency analyses were performed using time–frequency options available in EEGLAB which use Morlet wavelets. A Gaussian shape taper was used to taper wavelets to zero at both ends, and the length of the window used for time–frequency analysis was selected to avoid the contamination of the signal of interest by edge artifacts. ERSP data were computed in decibels relative to baseline for all electrodes separately. The time–frequency data of all trials were averaged for each participant and stimulus type separately, resulting in 2 average time–frequency maps for each electrode. From these maps, the mean power was extracted from the Cz electrode in predetermined time $\times$ frequency regions of interests (ROIs) for each participant (Provencher & Piché, 2025). A mean ERSP value was then obtained for each participant and ROI by selecting and averaging the values with the 20% highest or lowest amplitude (for power increase or decrease relative to baseline).

Clinical outcomes specific to individuals with chronic primary low back pain

Low back pain intensity

Participants were instructed to rate LBP intensity using a numeric rating scale (NRS) ranging from 0 (no pain) to 10 (worst pain imaginable) (Dworkin et al., 2005). As in the brief pain inventory (BPI) (Daut et al., 1983), they were instructed to rate their pain: 1) currently; 2) on average over the last 7 days; 3) at its worst over the last 7 days; 4) at its best over the last 7 days. A Cronbach α of 0.81 - 0.89, and a test-retest correlation of $r = 0.80$ have been reported for the BPI (Poquet & Lin, 2016).

Frequency and duration of low back pain

A modified version of the pain frequency-severity-duration scale was used (Salamon et al., 2014). Participants were instructed to answer these 3 questions: 1) Is the pain: recurrent (it comes in episodes) or continuous (it is always present); 2) How many days in the past week have you had low back pain? (0-7 days); 3) On average, how many hours per day does the pain last? (0; 1-4; 5-8; 9-12; 13-16; 17-20; 21-24 hours).

Disability related to low back pain

Self-reported LBP related disability was evaluated using the French-Canadian version of the Oswestry Disability Index (ODI) (Denis & Fortin, 2012). A Cronbach α of 0.88 and an excellent test-retest reliability (ICC = 0.92) were reported for this questionnaire (Denis & Fortin, 2012).

The Five Times Sit-to-Stand Test (FTSST) was used as a performance-based measure of physical function (Patel et al., 2021). Participants sitting on a supported chair were instructed to stand and sit again as fast as possible, five times in a row. Time was measured in seconds. The test was performed twice and the average time for the two trials is reported here. A Cronbach α of 0.73 and a test-retest correlation of $r = 0.99$ have been reported when this test was performed in individuals with CPLBP (Özüdoğru et al., 2022).

The Back Performance Scale (BPS) was used as a performance-based measure of physical function that is more specific to evaluate individuals afflicted with LBP. It includes daily activities, such as putting socks on or picking something on the floor (Strand et al., 2002). Participants received instructions and demonstrations, and their performance was scored as in a previous study (Strand et al., 2002). A Cronbach α of 0.73 has been reported for this scale (Strand et al., 2002)

Kinesiophobia

Pain-related fear was measured with a French adaptation of the Tampa scale for kinesiophobia (TSK) (Roelofs et al., 2007). This scale has an acceptable to excellent internal consistency (Cronbach α = 0.7-0.92) and a test-retest correlation of $r \geq 0.80$ (Liu et al., 2021).

Statistical analyses

Data were analyzed using the R Statistical language version 4.5.0 (R Core Team, 2025) on macOS Sequoia 15.5 and the packages tidyverse version 2.0.0 (Wickham et al., 2019), afex version 1.4.1 (Singmann et al., 2025), nlme version 3.1.168 (Pinheiro et al., 2025) and effectsize version 1.0.0 (Ben-Shachar et al., 2020). All results are expressed as mean $\pm$ standard deviation (SD). Statistical threshold was set at $p \leq 0.05$. Normality was assessed visually and with the Shapiro-Wilk test. Homogeneity of variance was assessed using Levene's test, and sphericity with Mauchly's test. Group differences were assessed using Welch's t-tests. TSSP was assessed between groups with a Greenhouse–Geisser corrected mixed ANOVA (2 groups $\times$ 2 types of stimuli [single pulse and pulse train]). C-fiber-related brain responses induced by temporal summation were compared between groups and laser pulses with Greenhouse–Geisser corrected mixed ANOVAs (2 groups $\times$ 3 pulses [train pulse 1, 2 and 3]). Effect sizes are reported based on partial eta-squared (η^2_p). Bonferroni corrected planned contrasts were used to decompose significant effects. General linear models were used to control potential confounding factors (main effects) and to examine if they moderated group differences (interactions).

Results

Characteristics of participants

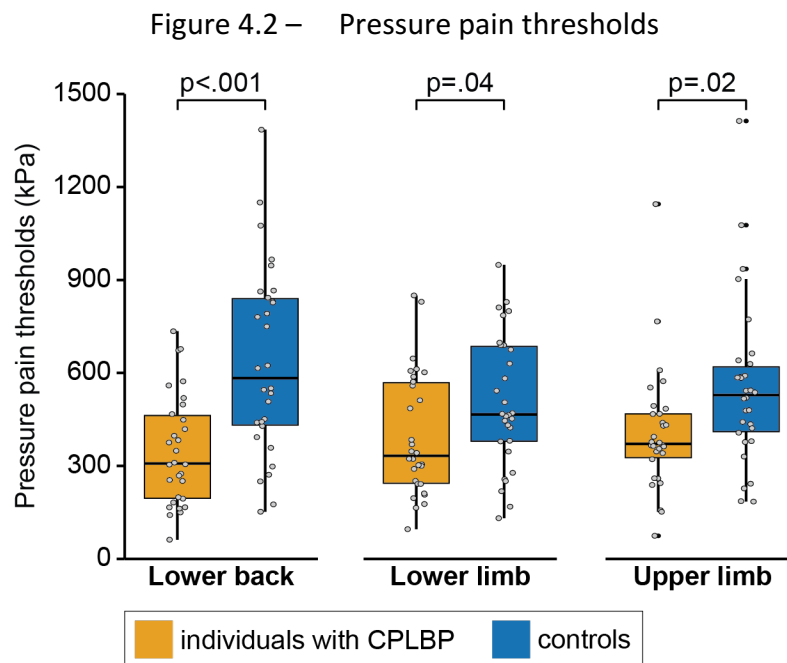
Characteristics of participants are reported in **Table 4.1**. Individuals with CPLBP were 41.7 ± 9.7 years old and had LBP for 13.4 ± 8.9 years. LBP intensity was low to moderate most days of the week, with low levels of disability. Compared with controls, individuals with CPLBP reported significantly higher pain catastrophizing (MD = 4.83, 95% CI [0.59, 9.08], $p = .03$, $\eta^2_p = .08$), pain vigilance (MD = 9.70, 95% CI [3.98, 15.42], $p = .001$, $\eta^2_p = .17$) and depressive symptoms (MD = 2.47, 95% CI [0.24, 4.69], $p = .03$, $\eta^2_p = .08$). However, groups were not significantly different for age (MD = 0.45, 95% CI [-5.12, 4.62], $p = .86$, $\eta^2_p = .001$), smoking status ($\chi^2(1, N = 60) = 2.2$, $p = .14$), systolic blood pressure (MD = 0.80, 95% CI [-5.38, 6.99], $p = .91$, $\eta^2_p = .002$), diastolic blood pressure (MD = 1.04, 95% CI [-3.67, 5.75], $p = .66$, $\eta^2_p = .005$), anxiety trait (MD = 1.73, 95% CI [-2.56, 6.03], $p = .42$, $\eta^2_p = .01$), self-compassion (MD = 3.13, 95% CI [-5.39, 11.66], $p = .46$, $\eta^2_p = .01$), femininity (MD = 0.10, 95% CI [-1.74, 1.94], $p = .91$, $\eta^2_p = 0$) and masculinity (MD = .60, 95% CI [-1.54, 2.74], $p = .58$, $\eta^2_p = .006$).

Table 4.1 – Characteristics of participants (mean $\pm$ SD)

Baseline characteristics	Individuals with CPLBP (n =30)	Controls (n = 30)
Female, n (%)	18 (60.0)	18 (60.0)
Male, n (%)	12 (40.0)	12 (40.0)
Age (years)	41.7 $\pm$ 9.7	42.1 $\pm$ 9.9
Smoking (Yes), n (%)	6 (20.0)	1 (3.3)
Systolic blood pressure (mm Hg)	126.1 $\pm$ 11.1	125.3 $\pm$ 10.6
Diastolic blood pressure (mm Hg)	81.9 $\pm$ 7.0	80.9 $\pm$ 8.9
Scores on questionnaires and tests		
Pain catastrophizing scale (0-52)	15.4 $\pm$ 8.5	10.5 $\pm$ 7.9
Pain vigilance and awareness questionnaire (0-80)	39.2 $\pm$ 11.6	29.5 $\pm$ 10.5
Beck Depression Inventory (0-63)	6.4 $\pm$ 4.3	3.9 $\pm$ 4.3
State-Trait Anxiety Inventory - Y2 (20-80)	34.7 $\pm$ 7.6	33.0 $\pm$ 9.0
Self-compassion scale (26-130)	92.8 $\pm$ 14	89.6 $\pm$ 18.6
Personal Attributes Questionnaire - Femininity (0-32)	25.2 $\pm$ 3.4	25.1 $\pm$ 3.7
Personal Attributes Questionnaire - Masculinity (0-32)	20.5 $\pm$ 3.1	19.9 $\pm$ 4.9
Oswestry disability index (0-100)	18.8 $\pm$ 5.2	
Tampa scale for kinesiophobia (17-68)	35.7 $\pm$ 7.3	
Five times sit-to-stand test (s)	7.8 $\pm$ 2	
Back performance scale (0-15)	3.6 $\pm$ 2.3	
Time with LBP (years)	13.4 $\pm$ 8.9	
LBP intensity (0-10)		
Currently	3.4 $\pm$ 2.1	
On average in the past week	4.1 $\pm$ 1.9	
Maximal in the past week	6.0 $\pm$ 2.0	
Minimal in the past week	1.9 $\pm$ 1.6	
LBP pattern, n (%)		
LBP described as recurrent	12 (40.0)	
LBP described as continuous	18 (60.0)	
Number of days with LBP in the past week	5.6 $\pm$ 2.1	
Average number of hours with LBP per day, n (%)		
1 to 4 hours	10 (33.3)	
5 to 8 hours	4 (13.3)	
9 to 12 hours	2 (6.7)	
13 to 16 hours	3 (10.0)	
17 to 20 hours	6 (20.0)	
21 to 24 hours	5 (16.7)	

Pressure pain thresholds

Mean PPT are presented in **Figure 4.2** and **Table 4.2**. Mean PPTs for the three body locations were significantly lower in individuals with CPLBP compared with controls (low back: MD =288.2, 95% CI [-417.5, -158.9], $p < .001$, $\eta^2_p = .30$; lower limb: MD = 109.2, 95% CI [-215.2, -3.2], $p = .04$, $\eta^2_p = .07$; right hand: MD = 147.2, 95% CI [-268.2, -26.1], $p = .02$, $\eta^2_p = .10$). This indicates that individuals with CPLBP showed widespread mechanical hyperalgesia.



Boxplot of the difference in PPTs between groups for each test location. Data from each participant are represented by gray dots. Average PPTs were significantly lower (increased pain sensitivity) in individuals with CPLBP compared with controls at the three test locations (all $p < .04$).

Table 4.2 – Average scores of each group during quantitative sensory testing (mean $\pm$ SD)

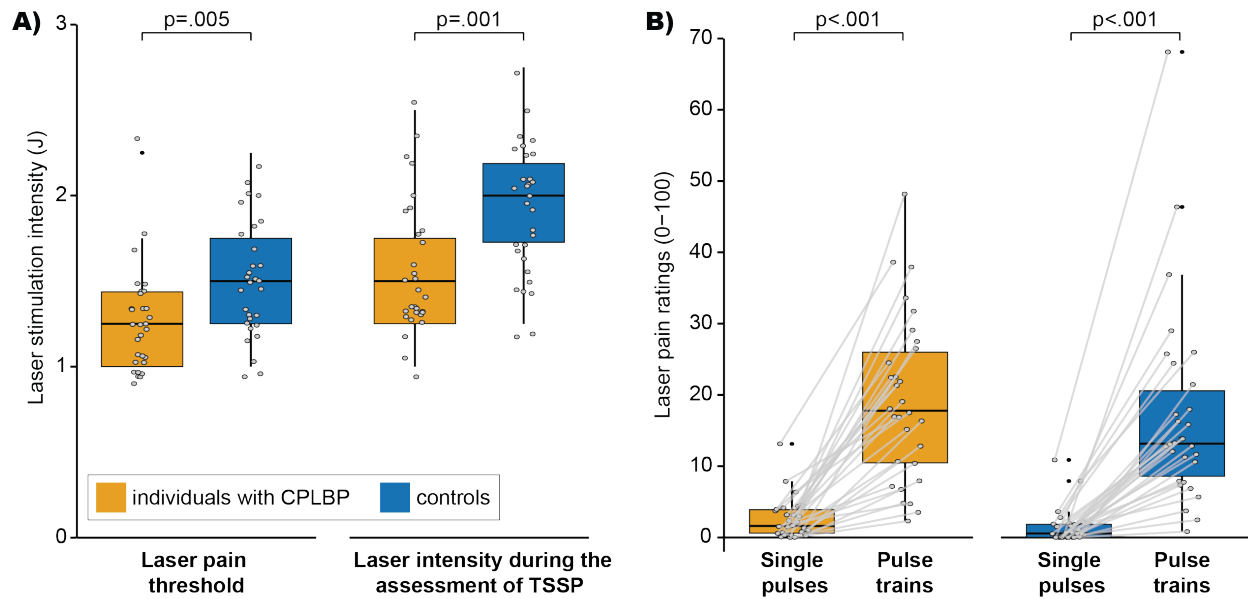
Outcome	Individuals with CPLBP	Controls
Pressure pain thresholds – lower back (kPa)	349 $\pm$ 177.8	637.1 $\pm$ 303.8
Pressure pain thresholds – right lower limb (kPa)	397.9 $\pm$ 197.4	507.1 $\pm$ 212.6
Pressure pain thresholds – right hand (kPa)	407.3 $\pm$ 199.1	554.5 $\pm$ 264.1
Laser pain thresholds – lower back (J)	1.3 $\pm$ 0.3	1.5 $\pm$ 0.3
Laser intensity used during TSSP assessment (J)	1.6 $\pm$ 0.4	1.9 $\pm$ 0.4
Temporal summation of second pain	16.6 $\pm$ 10.6	15.7 $\pm$ 12.5

Laser pain threshold and temporal summation of second pain

The mean laser intensities and TSSP values are presented in **Figure 4.3** and **Table 4.2**. The mean laser pain threshold measured in the lumbar area was significantly lower in individuals with CPLBP compared with controls (MD = 0.23, 95% CI [-.39, -.07], $p = .005$, $\eta^2_p = .13$). The mean intensity used for laser stimulation during the assessment of TSSP was also significantly lower in individuals with CPLBP compared with controls (MD = 0.36, 95% CI [-0.56, -0.16], $p = .001$, $\eta^2_p = .19$). This indicates that individuals with CPLBP showed thermal hyperalgesia in the lumbar area.

Figure 4.3B shows the mean laser-evoked pain ratings. Laser-evoked pain was compared between individuals with CPLBP and controls and between single pulse and pulse train stimuli using a mixed ANOVA. Laser-evoked pain was significantly greater for pulse train compared with single pulse stimuli (main effect of pulse repetition: $F_{1,58} = 116.3$, $p < .001$, $\eta^2_p = .67$, 95% CI: [.55, 1]), showing TSSP. However, this effect was not significantly different between groups (interaction: $F_{1,58} = 0.1$, $p = .75$, $\eta^2_p = .002$, 95% CI: [0, 1]).

Figure 4.3 – Laser intensities and temporal summation of second pain



A) Boxplots of the differences in laser pain threshold and laser intensity used during the assessment of TSSP between groups. Data from each participant are represented by gray dots. The average laser pain threshold was significantly lower (increased pain sensitivity) in individuals with CPLBP compared with controls ($p = .005$). The intensity used during the assessment of TSSP was also significantly lower in individuals with CPLBP ($p = .001$). **B)** Boxplots of the differences in laser pain ratings between group for each stimulus type. Laser pain ratings were significantly greater for pulse trains compared with single pulses ($p < .001$), consistent with temporal summation of second pain. However, this effect was not significantly different between groups ($p = .38$). Data from each participant are represented by linked gray dots.

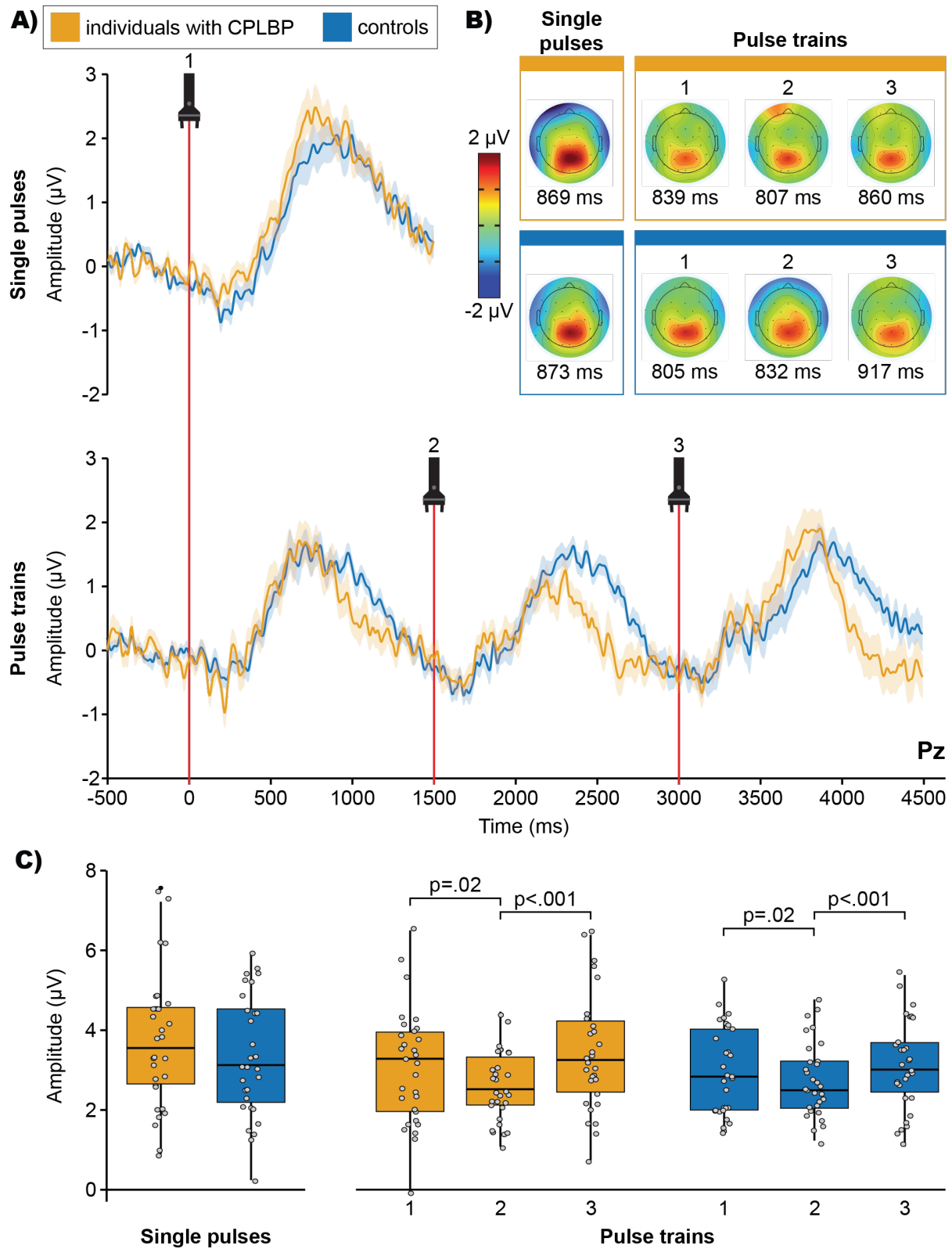
C-fiber-related brain responses

Laser-evoked potentials

Figure 4.4A–B illustrate the average laser-evoked potentials (LEPs) and the corresponding topographic maps. Peak amplitude and latency are summarized in **Table 4.3**, and the comparison of peak amplitude between groups and stimulus types is illustrated in **Figure 4.4C**. For single pulse stimuli, the mean C-fiber peak amplitude and latency were compared between groups using Welch's t-tests. Groups were not significantly different for peak amplitude (MD = 0.34, 95% CI [–0.49, 1.17], $p = .42$, $\eta^2_p = .01$) and peak latency (MD = 3.6 ms, 95% CI [–106.7, 99.5], $p = .94$, $\eta^2_p < 0.001$).

For pulse train stimuli, Greenhouse–Geisser corrected mixed ANOVAs were used to compare peak amplitude between groups (CPLBP vs controls) and pulses (first, second and third). Peak amplitude was significantly different between pulses (main effect: $F_{1.9,112.2} = 7.5$, $p = .001$, $\eta^2_p = .11$, 95% CI: [0.03, 1]), but this effect was not significantly different between groups (interaction: $F_{1.9,112.2} = 1.2$, $p = .31$, $\eta^2_p = .02$, 95% CI: [0, 1]). Bonferroni corrected planned contrasts revealed a significant increase in peak amplitude between the second and third pulse ($p < .001$), but not between the first and third pulse ($p = .13$). There was also a significant decrease in peak amplitude between the first and second pulse ($p = .02$). Peak latency was not significantly different between groups (main effect: $F_{1,58} = 0.2$, $p = .69$, $\eta^2_p = .003$, 95% CI: [0, 1]), between pulses (main effect: $F_{1.9,110.3} = 2.0$, $p = .14$, $\eta^2_p = .03$, 95% CI: [0, 1]) or between groups over pulses (interaction: $F_{1.9,110.3} = 0.7$, $p = .49$, $\eta^2_p = .01$, 95% CI: [0, 1]).

Figure 4.4 – Average LEP waveforms, topographic maps and C-P2 peak amplitudes for each group and stimulus type.



A) Average LEP waveforms for each group and stimulus type at Pz. Waveforms at Pz are presented since it was the electrode showing maximal activity in most participants, as demonstrated by the topographic maps. The lightly colored areas above and below the LEP waveforms represent the standard error of the mean (SEM). A slow wave was observed between 500 ms and 1500 ms, corresponding to the range of C-fiber conduction velocity. **B)** Average topographic maps of the C-P2 components for each group and each laser pulse (single pulse or pulse train). **C)** Boxplot of the peak amplitudes of the C-P2 component for each group and laser pulse. Data from each participant are represented by gray dots. Numbers 1, 2 and 3 represent the first, second and third pulse of the pulse trains. For both single pulse and pulse train stimuli, C-P2 peak amplitudes and latencies were not statistically significant difference between groups (all $p > 0.31$).

Table 4.3 – Average scores of each group for C-fibers-related brain responses (mean $\pm$ SD)

Outcome	Individuals with CPLBP	Controls
C-P2 peak (μ V) during single pulses	3.7 $\pm$ 1.7	3.3 $\pm$ 1.5
C-P2 latency (ms) during single pulses	869.2 $\pm$ 214.6	872.8 $\pm$ 182.7
C-P2 peak (μ V) during pulse 1 of pulse trains	3.1 $\pm$ 1.4	2.9 $\pm$ 1.1
C-P2 latency (ms) during pulse 1 of pulse trains	838.8 $\pm$ 256.3	804.8 $\pm$ 219.5
C-P2 peak (μ V) during pulse 2 of pulse trains	2.6 $\pm$ 0.9	2.7 $\pm$ 1
C-P2 latency (ms) during pulse 2 of pulse trains	806.9 $\pm$ 189.3	831.9 $\pm$ 175.3
C-P2 peak (μ V) during pulse 3 of pulse trains	3.4 $\pm$ 1.4	3.1 $\pm$ 1.1
C-P2 latency (ms) during pulse 3 of pulse trains	859.9 $\pm$ 274.9	917.2 $\pm$ 259.6
Power (dB) in ROI 1 during single pulses	2.5 $\pm$ 1.2	2.7 $\pm$ 1.5
Power (dB) in ROI 2 during single pulses	-1.2 $\pm$ 0.7	-1.2 $\pm$ 0.7
Power (dB) in ROI 3 during single pulses	1.1 $\pm$ 2.3	0.9 $\pm$ 1
Power (dB) in ROI 1 during pulse 1 of pulse trains	2 $\pm$ 1.4	2.7 $\pm$ 1.3
Power (dB) in ROI 2 during pulse 1 of pulse trains	-0.7 $\pm$ 0.6	-1.1 $\pm$ 0.6
Power (dB) in ROI 3 during pulse 1 of pulse trains	0.6 $\pm$ 1.2	0.6 $\pm$ 0.9
Power (dB) in ROI 1 during pulse 2 of pulse trains	2.1 $\pm$ 1.7	2.7 $\pm$ 1.7
Power (dB) in ROI 2 during pulse 2 of pulse trains	-1.2 $\pm$ 0.9	-1.6 $\pm$ 1
Power (dB) in ROI 3 during pulse 2 of pulse trains	1.2 $\pm$ 3.2	0.6 $\pm$ 1.1
Power (dB) in ROI 1 during pulse 3 of pulse trains	3 $\pm$ 1.9	3.8 $\pm$ 2
Power (dB) in ROI 2 during pulse 3 of pulse trains	-2.4 $\pm$ 1	-2.6 $\pm$ 1.3
Power (dB) in ROI 3 during pulse 3 of pulse trains	3.3 $\pm$ 5.1	2.2 $\pm$ 2.9

Event-related spectral perturbations

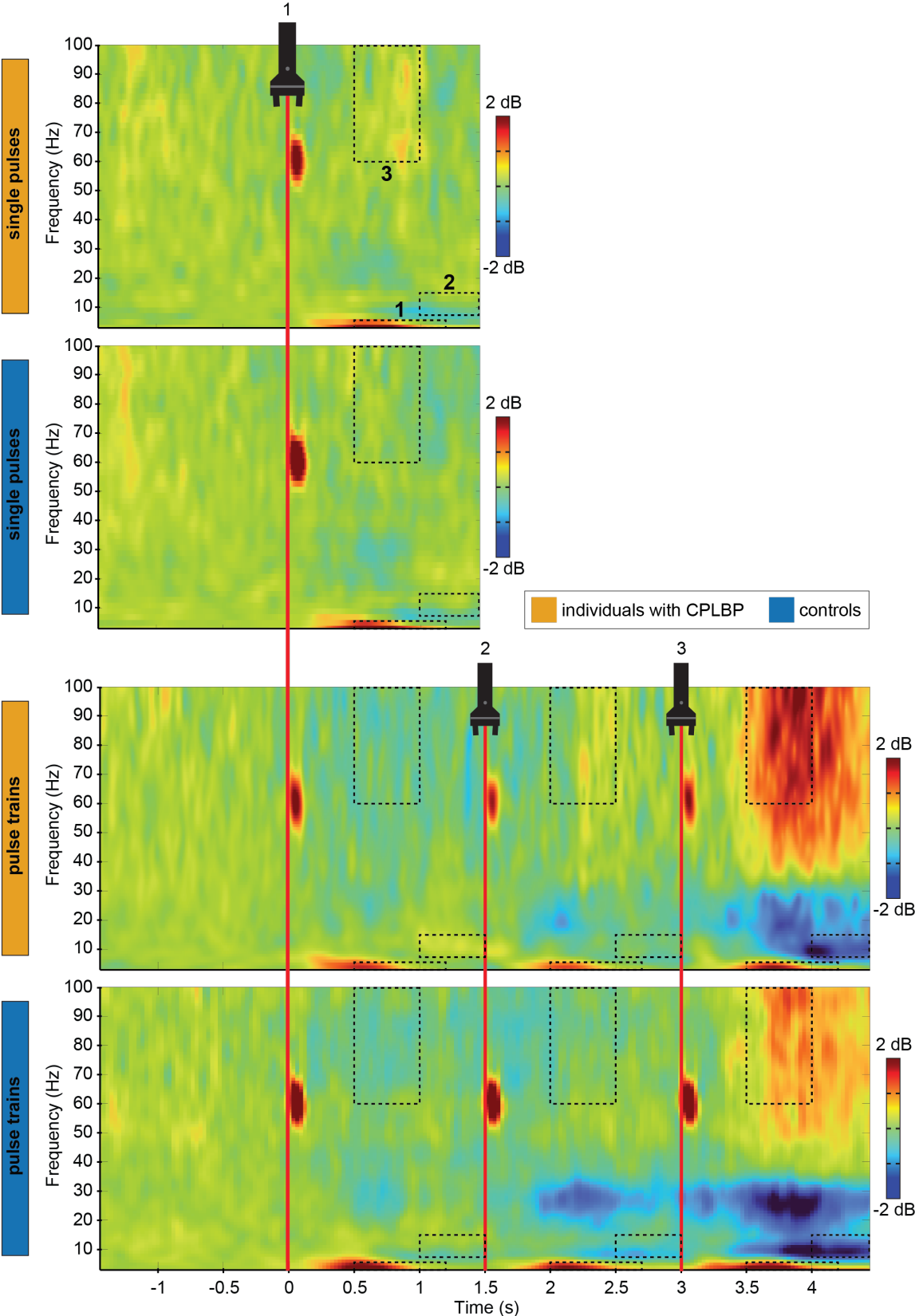
Figures 4.5 and 4.6 display the average time-frequency maps for each group and stimulus type and the topographic maps for each of the three ROI. The mean ERSP power within each ROI is shown in **Figure 4.7** and **Table 4.3**. For single pulse stimuli, group comparisons of ERSP power within each ROI were conducted using Welch's t-tests. No significant difference was observed between groups for any of the ROIs (all $p > .5$, $\eta^2_p < .008$).

For pulse train stimuli, ERSP power was compared between groups and pulses for each ROI using Greenhouse–Geisser corrected mixed ANOVAs. In ROI 1 (2-5 Hz $\times$ 500-1200 ms), power was significantly different between groups (main effect: $F_{1,58} = 4.1$, $p = .047$, $\eta^2_p = .07$, 95% CI: [.001, 1]) and pulses (main effect: $F_{1.9,110.1} = 15.4$, $p < .001$, $\eta^2_p = .21$, 95% CI: [.11, 1]), but not between groups and pulses (interaction: $F_{1.9,110.1} = 0.03$, $p = .96$, $\eta^2_p = .001$, 95% CI: [0, 1]). Bonferroni corrected planned contrasts revealed a significant increase in power from the first to the third pulse ($p < .001$) and from the second to the third pulse ($p < .001$), but not from the first to the second pulse ($p = .63$).

In ROI 2 (7-15 Hz $\times$ 1000-1500 ms), power was significantly different between pulses (main effect: $F_{1.6,93.1} = 101.2$, $p < .001$, $\eta^2_p = .64$, 95% CI: [.55, 1]), but not between groups (main effect: $F_{1,58} = 3.3$, $p = .08$, $\eta^2_p = .05$, 95% CI: [0, 1]) or groups over pulses (interaction: $F_{1.6,93.1} = 0.5$, $p = .50$, $\eta^2_p = .008$, 95% CI: [0, 1]). Bonferroni corrected planned contrasts showed a significant decrease in power from the first to the second pulse ($p = .001$), from the second to the third pulse ($p < .001$), and from the first to the third pulse ($p < .001$).

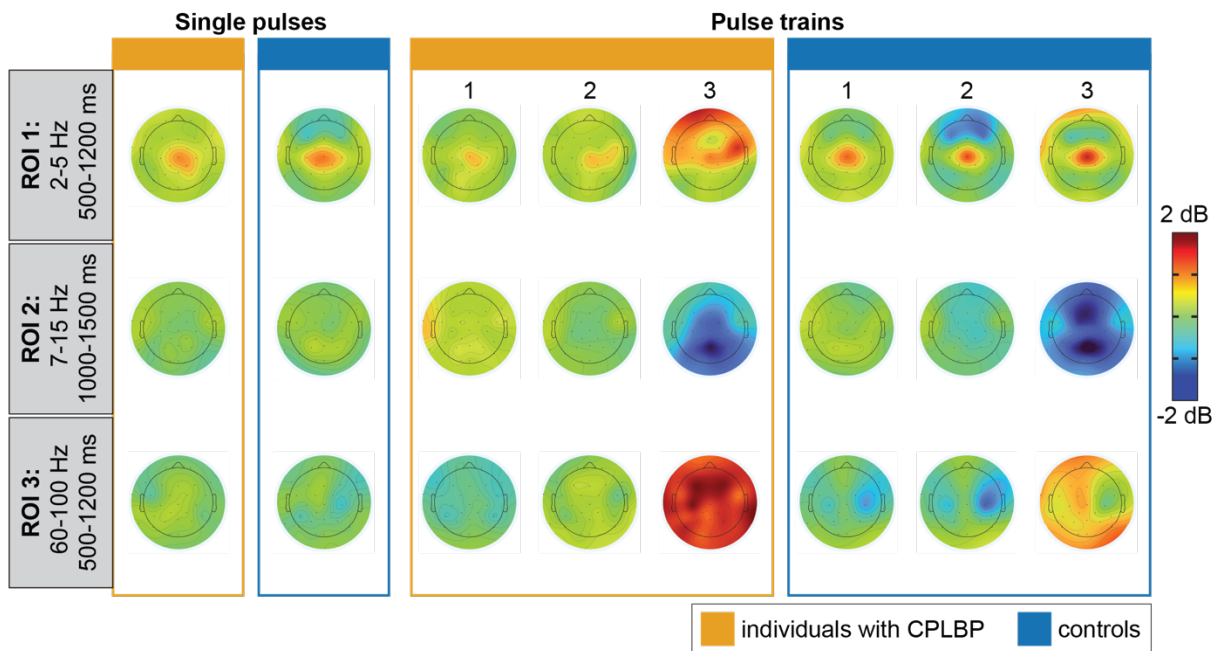
In ROI 3 (60-100 Hz $\times$ 500-1200 ms), power was significantly different between pulses (main effect: $F_{1.4,80.6} = 17.6$, $p < .001$, $\eta^2_p = .23$, 95% CI: [0, 1]), but not between groups (main effect: $F_{1,58} = 0.9$, $p = .33$, $\eta^2_p = .02$, 95% CI: [0, 1]) or between groups and pulses (interaction: $F_{1.4,80.6} = 1.0$, $p = .35$, $\eta^2_p = .02$, 95% CI: [0, 1]). Bonferroni corrected planned contrasts revealed a significant increase in power from the first to the third pulse ($p < .001$) and from the second to the third pulse ($p < .001$), but not from the first to the second pulse ($p = .26$). However, inspection of the average topographic maps suggests that this activity may reflect muscle artifacts rather than true event-related synchronization.

Figure 4.5 – Average time-frequency maps for each group and stimulus type



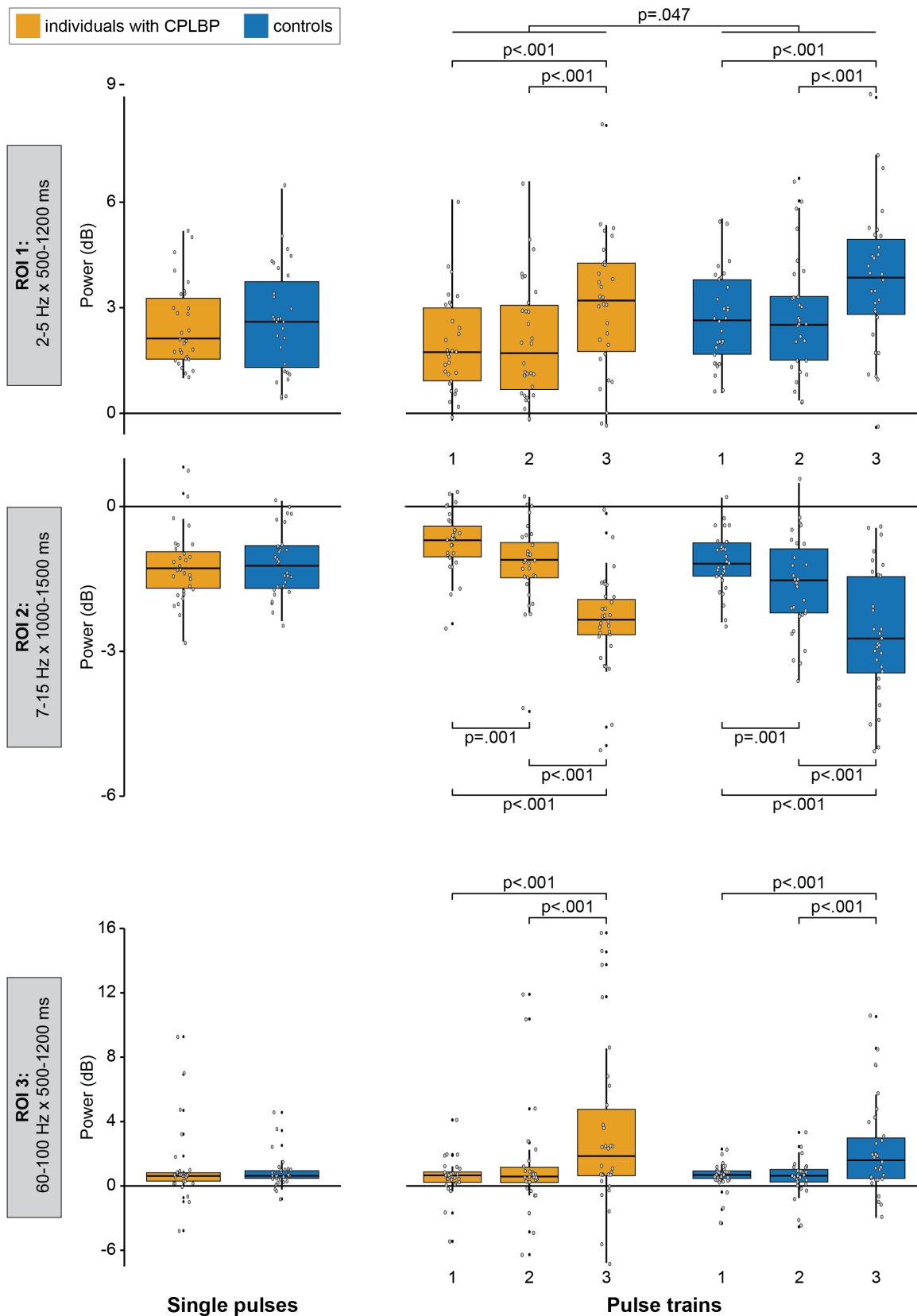
Average time-frequency maps for each group and stimulus type in each of the three ROIs. Numbers (1, 2 and 3) represent the first, second and third pulse of the pulse trains. ROIs are highlighted by the dashed line rectangles and labeled 1, 2 and 3. Note the desynchronization between 10 Hz and 30 Hz and the synchronization between 60 Hz and 100 Hz. See Figure 4.7 for detailed statistical comparisons. Note the stimulation artifact as a power increase at 60 Hz directly after stimulus onset.

Figure 4.6 – Average topographic maps of the ERSP in the three ROIs



Average topographic maps of the time-frequency activity in each ROI for each group and each laser pulse. Numbers 1, 2 and 3 represent the first, second and third pulse of the pulse trains. See Figure 4.7 for detailed statistical comparisons.

Figure 4.7 – ERSP values from the three regions of interest



Boxplot of the ERSP power for each group and laser pulse. Data from each participant are represented by gray dots. Numbers 1, 2 and 3 represent the first, second and third pulse of the pulse trains. For all ROIs, the mean power was not significantly different between groups during single pulses (all $p > 0.56$).

Confounding factors and moderators

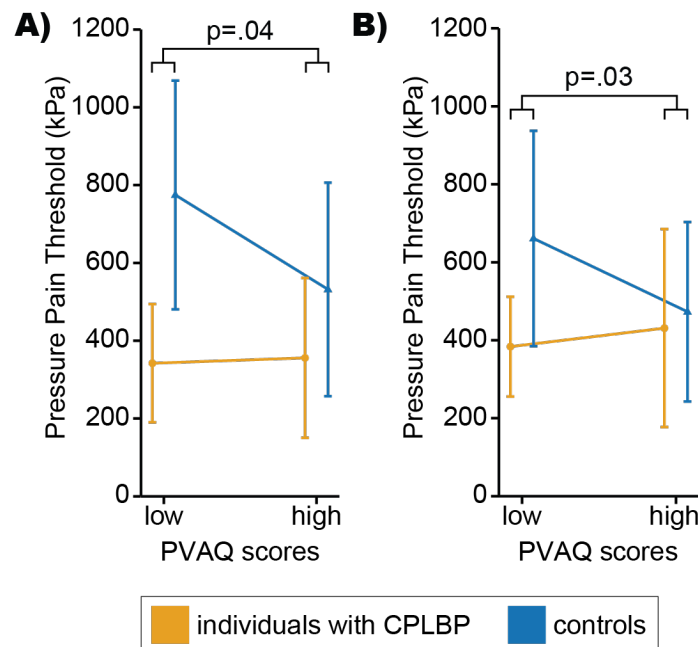
To control for the group difference in the laser intensity used for TSSP, the effects of group on TSSP and C-fiber-related brain responses were examined with laser intensity as a covariate in separate ANCOVAs. After controlling for laser intensity, TSSP and C-fiber-related brain responses were not significantly different between groups, (all $p > .08$).

To control for psychological factors, the effects of group on TSSP and C-fiber-related brain responses were examined with pain catastrophizing, pain vigilance, and depressive symptoms as covariates in separate ANCOVAs. After controlling for pain catastrophizing, pain vigilance, and depressive symptoms, TSSP and C-fiber-related brain responses were still not significantly different between groups (all $p > .26$).

For the group differences in PPTs and laser-pain thresholds, the confounding psychological factors were controlled for using separate ANCOVAs with pain catastrophizing, pain vigilance, and depressive symptoms as covariates. After controlling for these factors, PPTs in the lumbar region remained significantly lower in individuals with CPLBP compared with controls (all $p < .004$). In contrast, for PPTs on the right lower limb, groups were not significantly different after controlling for pain catastrophizing ($p = .07$), pain vigilance ($p = .07$) or depressive symptoms ($p = .3$). For PPTs on the right hand, individuals with CPLBP showed significantly lower values compared with controls after controlling for pain vigilance ($p = .006$), but not for pain catastrophizing ($p = .28$) or depressive symptoms ($p = .12$). For laser-pain thresholds, groups were not significantly different after controlling for pain catastrophizing ($p = .06$), pain vigilance ($p = .09$) or depressive symptoms ($p = .2$). This suggests that pain catastrophizing, pain vigilance, and depressive symptoms contribute to mechanical and thermal hyperalgesia in individuals with CPLBP.

To examine whether pain catastrophizing, pain vigilance, and depressive symptoms moderated mechanical and thermal hyperalgesia, they were included as continuous predictors in separate general linear models with the interaction term included in the model. Pain vigilance moderated the group difference in PPTs for the lumbar region ($F_{1,56} = 4.5$, $p = .04$, $\eta^2_p = .07$; see **Figure 4.8A**) and the right hand ($F_{1,56} = 5.2$, $p = .03$, $\eta^2_p = .08$; see **Figure 4.8B**). For both regions, controls that reported lower pain vigilance showed higher PPTs compared with those that reported higher pain vigilance, and this effect was not observed in individuals with CPLBP. No other significant interaction was observed between groups and pain catastrophizing, pain vigilance, or depressive symptoms for the lower limb PPTs and the laser-pain thresholds (all $p > 0.13$).

Figure 4.8 – Interaction between PVAQ scores and PPTs



*Significant interaction effects from the moderation analyses. **A)** Interaction between PVAQ scores and PPTs measured in the lower back. **B)** Interaction between PVAQ scores and PPTs measured in the right hand. In both locations, higher PVAQ scores are associated with lower PPTs in controls, but not in patients with CPLBP. Data points represent group means; error bars indicate SD.*

Discussion

The aim of the present study was to examine whether TSSP and C-fiber-related brain responses are increased in individuals with CPLBP. Consistent with the concept of nociplastic pain, individuals with CPLBP exhibited widespread hyperalgesia and higher pain catastrophizing, pain vigilance, and depressive symptoms. Despite these observations and contrary to our hypothesis, no significant group difference was observed for TSSP and C-fiber-related brain responses, even after controlling for confounding factors.

Widespread hyperalgesia and psychological distress

In line with findings from a recent meta-analysis and recent experimental studies (den Bandt et al., 2022; den Bandt et al., 2019; Gevers-Montoro et al., 2024), individuals with CPLBP in the present study showed lower PPTs in the low back, lower limb, and a remote body region (upper limb) compared with controls, indicating widespread mechanical hyperalgesia. The present results are also consistent with those of Aoyagi et al. (2019), who observed that individuals with chronic LBP that reported higher pain catastrophizing, depressive symptoms, and anxiety exhibited lower PPTs in the low back and on the hand (Aoyagi et al., 2019). Furthermore, the present study showed that psychological factors contributed differently to these alterations, depending on the body region. Mechanical hyperalgesia in the low back was not significantly moderated by pain catastrophizing, pain vigilance, or depressive symptoms. In contrast, hyperalgesia in pain-free regions (lower and upper limbs) was moderated significantly by all three psychological factors. This suggests that these psychological factors may preferentially contribute to widespread rather than primary mechanical hyperalgesia. This is consistent with findings by Meints et al. (2019) who reported that pain catastrophizing mediated group differences in lower-limb mechanical sensitivity, accounting for approximately 23% of the variance in mechanical sensitivity (Meints et al., 2019). Similarly, central sensitization symptoms measured with the Central Sensitization Inventory are associated with pain catastrophizing in individuals with chronic LBP (Huysmans et al., 2018). Taken together, these findings support the notion that pain

catastrophizing contributes to central sensitization and widespread hyperalgesia in CPLBP (Aoyagi et al., 2019; Meints et al., 2019).

Noteworthy, higher pain vigilance in controls was associated with increased mechanical sensitivity in the low back and on the hand in the present study. This indicates that the association between pain vigilance and mechanical sensitivity is present even without chronic pain. This suggests that individuals with higher pain vigilance may be predisposed to develop chronic pain. This interpretation is consistent with the fear-avoidance model of pain (Vlaeyen et al., 2016) and with findings from a longitudinal studies showing that higher pain vigilance predicts the transition from acute to chronic back pain (Zhang et al., 2025) and persistent postoperative pain (Horn-Hofmann et al., 2018). However, it should be noted that Baum et al. (2011) reported the opposite pattern in healthy participants, where higher pain vigilance was associated with lower pain sensitivity. This highlights the need to clarify how pain vigilance modulates pain sensitivity depending on the context (Baum et al., 2011).

Pressure pain thresholds at the lower limb were assessed within the dermatome corresponding to the most painful lumbar segment (Gevers-Montoro et al., 2024). This procedure was used to detect secondary hyperalgesia, based on the convergence of nociceptive inputs from the lower limb and the lumbar area on the spinal nociceptive neurons presumably affected by central sensitization (MacMahon et al., 2013). However, because hyperalgesia was observed on the upper limb, it is not possible to distinguish whether the lower PPTs on the lower limb result from secondary or widespread hyperalgesia. This does not exclude the sensitization of spinal nociceptive neurons, however, which may add to brain mechanisms that underlie widespread hyperalgesia.

In addition to widespread hyperalgesia, individuals with CPLBP reported higher pain catastrophizing, pain vigilance, and depressive symptoms compared with controls. This is consistent with the fear-avoidance model of pain (Vlaeyen et al., 2016; Vlaeyen & Linton, 2000) and a meta-analysis showing that pain catastrophizing, pain vigilance are moderately associated

with pain intensity and pain-related disability in several clinical pain populations (Rogers & Farris, 2022). However, unlike what is typically reported in the literature (Rogers & Farris, 2022), anxiety was not significantly different between groups in the present study. This discrepancy may be attributable to the heterogeneity of chronic LBP phenotypes (Hassan et al., 2023) and the low disability in the present sample. Specifically, individuals with CPLBP in the present study may have exhibited lower anxiety because their pain was not highly disabling. Consistent with this interpretation, previous studies have shown that baseline anxiety predicts subsequent disability in individuals with chronic LBP (Petrucci et al., 2025; Wang et al., 2023). Moreover, this pattern aligns with the findings of Aoyagi et al. (2019), in which a subgroup of individuals with chronic LBP and disability levels comparable to those in the present study (ODI: 19.24% vs. 18.8%) likewise exhibited low anxiety (Aoyagi et al., 2019). However, unlike the present sample, the subgroup with low anxiety did not show mechanical hyperalgesia (Aoyagi et al., 2019). This highlights the need for further research to understand the factors underlying heterogeneity in CPLBP, and to clarify the respective contribution of psychological and sensory mechanisms to chronic primary pain.

Lack of group difference in temporal summation and C-fiber-related brain responses

Contrary to our hypothesis, no significant group difference was observed for the TSSP and C-fiber–related brain responses, even after controlling for individual differences in laser intensity, pain catastrophizing, pain vigilance and depressive symptoms. This is consistent with the lack of group difference in TSSP. The hypothesis of the present study was based on a recent meta-analysis indicating that individuals with chronic LBP show greater TSSP compared with controls (McPhee et al., 2020). Notwithstanding, the magnitude of this difference was small (MD = 0.55, 95% CI [0.30, 0.81]). In addition, some of the studies included in this meta-analysis showed no significant difference in TSSP between individuals with chronic LBP and controls (Blumenstiel et al., 2011; Puta et al., 2013). Similar findings were reported in two other studies on relatively large samples (267 and 167 individuals with chronic LBP, respectively) (Meints et al., 2019; Petersen et

al., 2024) and in an exercise-induced experimental model of LBP (McPhee & Graven-Nielsen, 2019). Considering that various methods were used to assess TSSP in previous studies, the discrepancies are unlikely to be due to methodological issues. Further research is needed to clarify whether pain facilitation is more clearly increased in a subgroup of individuals with CPLBP that show distinct characteristics (Hassan et al., 2023), and whether TSSP is the most appropriate method to test pain facilitation in this population.

The assessment of experimental pain habituation may be a complementary method to examine signs of central sensitization in individuals with CPLBP. In an experimental study in healthy volunteers, pain habituation was reduced after heat-induced secondary hyperalgesia, a well-established model of central sensitization (Scheuren et al., 2020). Consistent with this, no difference in pain habituation to repeated heat stimulation or in contact-heat evoked potentials was observed between individuals with chronic pain and controls (De Schoenmacker et al., 2024). This study included 61 individuals with chronic LBP on a total of 164 individuals with various chronic pain syndromes. Further studies are needed reproduce these findings along with an assessment of TSSP. These complementary methods may shed light on the heterogeneity and presentation of central sensitization in individuals with CPLBP.

Conclusion

In summary, individuals with CPLBP showed widespread hyperalgesia and increased pain catastrophizing, pain vigilance, and depressive symptoms, consistent with nociplastic pain. However, TSSP and the associated C-fiber-related brain responses as measured in the present study were not significantly increased. This warrants future studies to examine whether increased TSSP and C-fiber responses may be observable in a subpopulation of individuals with CPLBP.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Funding statement

This work was supported by a grant from the Natural Science and Engineering Research Council of Canada (grant number: 06559), the Canadian Foundation for Innovation (grant number: 33731) and the Canadian Chiropractic Research Foundation. The contribution of Benjamin Provencher was supported by the Fonds de recherche du Québec – Santé (<https://doi.org/10.69777/313919>), the Fondation Chiropratique du Québec and the Réseau de Bio-Imagerie du Québec.

Conflicts of interest disclosure

The authors declare no competing interests and no relationship that may lead to any conflict of interest.

Ethics approval statement

All experimental procedures conformed to the standards set by the latest revision of the Declaration of Helsinki and the guidelines of the International Association for the Study of Pain. The protocol was approved by the Research Ethics Board of Université du Québec à Trois-Rivières and all participants gave written informed consent, acknowledging their right to withdraw from the study without prejudice. Participants with CPLBP received free chiropractic care. Controls received compensation of \$100 for their travel expenses and commitment.

CRediT statement

Benjamin Provencher: Conceptualization, Methodology, Software, Investigation, Formal analysis, Visualization, Validation, Data curation, Writing – original draft. **Gabriel Parent:** Methodology, Investigation, Validation, Formal analysis. **Mathieu Piché:** Funding acquisition, Conceptualization, Methodology, Software, Investigation, Formal analysis, Visualization, Validation, Supervision, Resources, Project administration, Data curation, Writing – review & editing.

Clinical trial registration

Trial registration number NCT05986370: <https://clinicaltrials.gov/study/NCT05986370>

References

- Aoyagi, K., He, J., Nicol, A. L., Clauw, D. J., Kluding, P. M., Jernigan, S., & Sharma, N. K. (2019). A Subgroup of Chronic Low Back Pain Patients With Central Sensitization. *Clin J Pain*, 35(11), 869-879. <https://doi.org/10.1097/ajp.0000000000000755>
- Arendt-Nielsen, L., Morlion, B., Perrot, S., Dahan, A., Dickenson, A., Kress, H. G., Wells, C., Bouhassira, D., & Drewes, A. M. (2018). Assessment and manifestation of central sensitisation across different chronic pain conditions. *Eur J Pain*, 22(2), 216-241. <https://doi.org/10.1002/ejp.1140>
- Bailes, A. H., Navlani, R., Koscumb, S., Malecky, A., Marroquin, O. C., Wasan, A. D., Gutstein, H. B., Delitto, A., Zigler, C., Vo, N., & Sowa, G. A. (2021). Use of healthcare resources in patients with low back pain and comorbid depression or anxiety. *Spine J*, 21(9), 1440-1449. <https://doi.org/10.1016/j.spinee.2021.03.031>
- Baum, C., Huber, C., Schneider, R., & Lautenbacher, S. (2011). Prediction of experimental pain sensitivity by attention to pain-related stimuli in healthy individuals. *Percept Mot Skills*, 112(3), 926-946. <https://doi.org/10.2466/02.09.22.Pms.112.3.926-946>
- Ben-Shachar, M., Lüdtke, D., & Makowski, D. (2020). effectsize: Estimation of Effect Size Indices and Standardized Parameters. *Journal of Open Source Software*, 5(56), 2815. <https://doi.org/10.21105/joss.02815>
- Bener, A., Verjee, M., Dafeeah, E. E., Falah, O., Al-Juhaishi, T., Schlogl, J., Sedeeq, A., & Khan, S. (2013). Psychological factors: anxiety, depression, and somatization symptoms in low back pain patients. *J Pain Res*, 6, 95-101. <https://doi.org/10.2147/jpr.S40740>
- Bergmann, T. F., & Peterson, D. H. (2011). *Chiropractic Technique Principles and Procedures* (Third ed.). Elsevier Mosby.
- Blumenstiel, K., Gerhardt, A., Rolke, R., Bieber, C., Tesarz, J., Friederich, H. C., Eich, W., & Treede, R. D. (2011). Quantitative sensory testing profiles in chronic back pain are distinct from those in fibromyalgia. *Clin J Pain*, 27(8), 682-690. <https://doi.org/10.1097/AJP.0b013e3182177654>
- Bourque, P., & Beaudette, D. (1982). Étude psychométrique du questionnaire de dépression de Beck auprès d'un échantillon d'étudiants universitaires francophones. [Psychometric study of the Beck Depression Inventory on a sample of French-speaking university students.]. *Canadian Journal of Behavioural Science / Revue canadienne des sciences du comportement*, 14, 211-218. <https://doi.org/10.1037/h0081254>
- Cohen, M. X. (2014). *Analyzing Neural Time Series Data: Theory and Practice*. The MIT Press.

- Daut, R. L., Cleeland, C. S., & Flanery, R. C. (1983). Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. *Pain*, 17(2), 197-210. [https://doi.org/10.1016/0304-3959\(83\)90143-4](https://doi.org/10.1016/0304-3959(83)90143-4)
- De Schoenmacker, I., Costa Marques, D., Scheuren, P. S., Lütolf, R., Gorrell, L. M., Mehli, S. C., Curt, A., Rosner, J., & Hubli, M. (2024). Novel neurophysiological evidence for preserved pain habituation across chronic pain conditions. *Clin Neurophysiol*, 166, 31-42. <https://doi.org/10.1016/j.clinph.2024.07.007>
- Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods*, 134, 9-21. <https://doi.org/10.1016/j.jneumeth.2003.10.009>
- den Bandt, H. L., Ickmans, K., Leemans, L., Nijs, J., & Voogt, L. (2022). Differences in Quantitative Sensory Testing Outcomes Between Patients With Low Back Pain in Primary Care and Pain-free Controls. *Clin J Pain*, 38(6), 381-387. <https://doi.org/10.1097/ajp.0000000000001038>
- den Bandt, H. L., Paulis, W. D., Beckwée, D., Ickmans, K., Nijs, J., & Voogt, L. (2019). Pain Mechanisms in Low Back Pain: A Systematic Review With Meta-analysis of Mechanical Quantitative Sensory Testing Outcomes in People With Nonspecific Low Back Pain. *J Orthop Sports Phys Ther*, 49(10), 698-715. <https://doi.org/10.2519/jospt.2019.8876>
- Denis, I., & Fortin, L. (2012). Development of a French-Canadian version of the Oswestry Disability Index: cross-cultural adaptation and validation. *Spine (Phila Pa 1976)*, 37(7), E439-444. <https://doi.org/10.1097/BRS.0b013e318233eaf9>
- Desrochers, G., Bergeron, S., Khalifé, S., Dupuis, M. J., & Jodoin, M. (2009). Fear avoidance and self-efficacy in relation to pain and sexual impairment in women with provoked vestibulodynia. *Clin J Pain*, 25(6), 520-527. <https://doi.org/10.1097/AJP.0b013e31819976e3>
- Dworkin, R. H., Turk, D. C., Farrar, J. T., Haythornthwaite, J. A., Jensen, M. P., Katz, N. P., Kerns, R. D., Stucki, G., Allen, R. R., Bellamy, N., Carr, D. B., Chandler, J., Cowan, P., Dionne, R., Galer, B. S., Hertz, S., Jadad, A. R., Kramer, L. D., Manning, D. C., . . . Witter, J. (2005). Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*, 113(1-2), 9-19. <https://doi.org/10.1016/j.pain.2004.09.012>
- Emmerich, A. C., Friehs, T., Crombez, G., & Glombiewski, J. A. (2020). Self-compassion predicting pain, depression and anger in people suffering from chronic pain: A prospective study. *Eur J Pain*, 24(10), 1902-1914. <https://doi.org/10.1002/ejp.1638>
- French, D. J., Noël, M., Vigneau, F., French, J. A., Cyr, C. P., & Evans, R. T. (2005). L'Échelle de dramatisation face à la douleur PCS-CF: Adaptation canadienne en langue française de l'échelle «Pain Catastrophizing Scale». [PCS-CF: A French-language, French-Canadian

- adaptation of the Pain Catastrophizing Scale.]. Canadian Journal of Behavioural Science / Revue canadienne des sciences du comportement, 37, 181-192. <https://doi.org/10.1037/h0087255>
- Gauthier, J., & Bouchard, S. (1993). Adaptation canadienne-française de la forme révisée du State-Trait Anxiety Inventory de Spielberger. [A French-Canadian adaptation of the revised version of Spielberger's State-Trait Anxiety Inventory.]. Canadian Journal of Behavioural Science / Revue canadienne des sciences du comportement, 25, 559-578. <https://doi.org/10.1037/h0078881>
- GBD 2021 Diseases and Injuries Collaborators. (2024). Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet, 403(10440), 2133-2161. [https://doi.org/10.1016/s0140-6736\(24\)00757-8](https://doi.org/10.1016/s0140-6736(24)00757-8)
- GBD 2021 Forecasting Collaborators. (2024). Burden of disease scenarios for 204 countries and territories, 2022-2050: a forecasting analysis for the Global Burden of Disease Study 2021. Lancet, 403(10440), 2204-2256. [https://doi.org/10.1016/s0140-6736\(24\)00685-8](https://doi.org/10.1016/s0140-6736(24)00685-8)
- Gevers-Montoro, C., Romero-Santiago, B., Medina-García, I., Larranaga-Arzamendi, B., Álvarez-Gálovich, L., Ortega-De Mues, A., & Piché, M. (2024). Reduction of Chronic Primary Low Back Pain by Spinal Manipulative Therapy is Accompanied by Decreases in Segmental Mechanical Hyperalgesia and Pain Catastrophizing: A Randomized Placebo-controlled Dual-blind Mixed Experimental Trial. J Pain, 25(8), 104500. <https://doi.org/10.1016/j.jpain.2024.02.014>
- Gupta, V., & Sharma, V. K. (2019). Skin typing: Fitzpatrick grading and others. Clinics in Dermatology, 37(5), 430-436. <https://doi.org/10.1016/j.clindermatol.2019.07.010>
- Hassan, S., Nesovic, K., Babineau, J., Furlan, A. D., Kumbhare, D., & Carlesso, L. C. (2023). Identifying chronic low back pain phenotypic domains and characteristics accounting for individual variation: a systematic review. Pain, 164(10), 2148-2190. <https://doi.org/10.1097/j.pain.0000000000002911>
- Horn-Hofmann, C., Scheel, J., Dimova, V., Parthum, A., Carbon, R., Griessinger, N., Sittl, R., & Lautenbacher, S. (2018). Prediction of persistent post-operative pain: Pain-specific psychological variables compared with acute post-operative pain and general psychological variables. Eur J Pain, 22(1), 191-202. <https://doi.org/10.1002/ejp.1115>
- Hu, L., Cai, M. M., Xiao, P., Luo, F., & Iannetti, G. D. (2014). Human brain responses to concomitant stimulation of Adelta and C nociceptors. J Neurosci, 34(34), 11439-11451. <https://doi.org/10.1523/JNEUROSCI.1355-14.2014>

- Hüllemann, P., Shao, Y. Q., Manthey, G., Binder, A., & Baron, R. (2016). Central habituation and distraction alter C-fibre-mediated laser-evoked potential amplitudes. *European Journal of Pain*, 20(3), 377-385. <https://doi.org/10.1002/ejp.735>
- Huysmans, E., Ickmans, K., Van Dyck, D., Nijs, J., Gidron, Y., Roussel, N., Polli, A., Moens, M., Goudman, L., & De Kooning, M. (2018). Association Between Symptoms of Central Sensitization and Cognitive Behavioral Factors in People With Chronic Nonspecific Low Back Pain: A Cross-sectional Study. *J Manipulative Physiol Ther*, 41(2), 92-101. <https://doi.org/10.1016/j.jmpt.2017.08.007>
- International Association for the Study of Pain. (2021). IASP Terminology. <https://www.iasp-pain.org/resources/terminology/>
- Jankovski, A., Plaghki, L., & Mouraux, A. (2013). Reliable EEG responses to the selective activation of C-fibre afferents using a temperature-controlled infrared laser stimulator in conjunction with an adaptive staircase algorithm. *Pain*, 154(9), 1578-1587. <https://doi.org/10.1016/j.pain.2013.04.032>
- K'Delant, P., & Gana, K. (2009). Analyse multitraits–multiméthodes des scores au Questionnaire d'attributs personnels (Personal attributes questionnaire [PAQ]) auprès d'un échantillon féminin. [A multitrait-multimethod analysis of scores on a French version of the Personal Attributes questionnaire (PAQ) among a female sample.]. *Psychologie Française*, 54(4), 323-336. <https://doi.org/10.1016/j.psfr.2009.06.002>
- Kaplan, C. M., Kelleher, E., Irani, A., Schrepf, A., Clauw, D. J., & Harte, S. E. (2024). Deciphering nociplastic pain: clinical features, risk factors and potential mechanisms. *Nat Rev Neurol*, 20(6), 347-363. <https://doi.org/10.1038/s41582-024-00966-8>
- Knezevic, N. N., Candido, K. D., Vlaeyen, J. W. S., Van Zundert, J., & Cohen, S. P. (2021). Low back pain. *Lancet*, 398(10294), 78-92. [https://doi.org/10.1016/s0140-6736\(21\)00733-9](https://doi.org/10.1016/s0140-6736(21)00733-9)
- Kosek, E., Clauw, D., Nijs, J., Baron, R., Gilron, I., Harris, R. E., Mico, J.-A., Rice, A. S. C., & Sterling, M. (2021). Chronic nociplastic pain affecting the musculoskeletal system: clinical criteria and grading system. *Pain*, 162(11), 2629-2634. <https://doi.org/10.1097/j.pain.0000000000002324>
- Kotsou, I., & Leys, C. (2016). Self-Compassion Scale (SCS): Psychometric Properties of The French Translation and Its Relations with Psychological Well-Being, Affect and Depression. *PLOS ONE*, 11(4), e0152880. <https://doi.org/10.1371/journal.pone.0152880>
- Lee, M. W., McPhee, R. W., & Stringer, M. D. (2008). An evidence-based approach to human dermatomes. *Clin Anat*, 21(5), 363-373. <https://doi.org/10.1002/ca.20636>

- Lenoir, C., Plaghki, L., Mouraux, A., & van den Broeke, E. N. (2018). Quickly responding C-fibre nociceptors contribute to heat hypersensitivity in the area of secondary hyperalgesia. *J Physiol*, 596(18), 4443-4455. <https://doi.org/10.1113/jp275977>
- Li, J., Simone, D. A., & Larson, A. A. (1999). Windup leads to characteristics of central sensitization. *Pain*, 79(1), 75-82. [https://doi.org/10.1016/s0304-3959\(98\)00154-7](https://doi.org/10.1016/s0304-3959(98)00154-7)
- Liu, H., Huang, L., Yang, Z., Li, H., Wang, Z., & Peng, L. (2021). Fear of Movement/(Re)Injury: An Update to Descriptive Review of the Related Measures. *Front Psychol*, 12, 696762. <https://doi.org/10.3389/fpsyg.2021.696762>
- MacMahon, S. B., Koltzenburg, M., Tracey, I., & Turk, D. C. (2013). *Wall and Melzack's textbook of pain* (6th ed. ed.). Saunders.
- Matheve, T., Janssens, L., Goossens, N., Danneels, L., Willems, T., Van Oosterwijck, J., & De Baets, L. (2022). The Relationship Between Pain-Related Psychological Factors and Maximal Physical Performance in Low Back Pain: A Systematic Review and Meta-Analysis. *J Pain*, 23(12), 2036-2051. <https://doi.org/10.1016/j.jpain.2022.08.001>
- McCracken, L. M. (1997). "Attention" to pain in persons with chronic pain: A behavioral approach. *Behavior Therapy*, 28(2), 271-284. [https://doi.org/10.1016/S0005-7894\(97\)80047-0](https://doi.org/10.1016/S0005-7894(97)80047-0)
- McPhee, M., & Graven-Nielsen, T. (2019). Alterations in Temporal Summation of Pain and Conditioned Pain Modulation Across an Episode of Experimental Exercise-Induced Low Back Pain. *J Pain*, 20(3), 264-276. <https://doi.org/10.1016/j.jpain.2018.08.010>
- McPhee, M. E., Vaegter, H. B., & Graven-Nielsen, T. (2020). Alterations in pronociceptive and antinociceptive mechanisms in patients with low back pain: a systematic review with meta-analysis. *Pain*, 161(3), 464-475. <https://doi.org/10.1097/j.pain.0000000000001737>
- Meints, S. M., Mawla, I., Napadow, V., Kong, J., Gerber, J., Chan, S. T., Wasan, A. D., Kaptchuk, T. J., McDonnell, C., Carriere, J., Rosen, B., Gollub, R. L., & Edwards, R. R. (2019). The relationship between catastrophizing and altered pain sensitivity in patients with chronic low-back pain. *Pain*, 160(4), 833-843. <https://doi.org/10.1097/j.pain.0000000000001461>
- Mouraux, A., & Iannetti, G. D. (2008). Across-trial averaging of event-related EEG responses and beyond. *Magn Reson Imaging*, 26(7), 1041-1054. <https://doi.org/10.1016/j.mri.2008.01.011>
- Mücke, M., Cuhls, H., Radbruch, L., Baron, R., Maier, C., Tölle, T., Treede, R. D., & Rolke, R. (2021). Quantitative sensory testing (QST). English version. *Schmerz*, 35(Suppl 3), 153-160. <https://doi.org/10.1007/s00482-015-0093-2> (Quantitative sensorische Testung (QST).)

- Neff, K. D. (2003). The development and validation of a scale to measure self-compassion. *Self and Identity*, 2, 223-250. <https://doi.org/10.1080/15298860309027>
- Nicholas, M., Vlaeyen, J. W. S., Rief, W., Barke, A., Aziz, Q., Benoliel, R., Cohen, M., Evers, S., Giamberardino, M. A., Goebel, A., Korwisi, B., Perrot, S., Svensson, P., Wang, S. J., & Treede, R. D. (2019). The IASP classification of chronic pain for ICD-11: chronic primary pain. *Pain*, 160(1), 28-37. <https://doi.org/10.1097/j.pain.0000000000001390>
- Nijs, J., Kosek, E., Chiarotto, A., Cook, C., Danneels, L. A., Fernández-de-las-Peñas, C., Hodges, P. W., Koes, B., Louw, A., Ostelo, R., Scholten-Peeters, G. G. M., Sterling, M., Alkassabi, O., Alsobayel, H., Beales, D., Bilika, P., Clark, J. R., De Baets, L., Demoulin, C., . . . George, S. Z. (2024). Nociceptive, neuropathic, or nociplastic low back pain? The low back pain phenotyping (BACPAP) consortium's international and multidisciplinary consensus recommendations. *The Lancet Rheumatology*, 6(3), e178-e188. [https://doi.org/10.1016/S2665-9913\(23\)00324-7](https://doi.org/10.1016/S2665-9913(23)00324-7)
- Özüdoğru, A., Canlı, M., Ceylan, İ., Kuzu, Ş., Alkan, H., & Karaçay, B. (2022). Five Times Sit-to-Stand Test in people with non-specific chronic low back pain-a cross-sectional test-retest reliability study. *Ir J Med Sci*. <https://doi.org/10.1007/s11845-022-03223-3>
- Patel, K. V., Amtmann, D., Jensen, M. P., Smith, S. M., Veasley, C., & Turk, D. C. (2021). Clinical outcome assessment in clinical trials of chronic pain treatments. *Pain reports*, 6(1), e784. <https://doi.org/10.1097/pr9.0000000000000784>
- Paungmali, A., Silitertpisan, P., Taneyhill, K., Pirunsan, U., & Uthaikhup, S. (2012). Intrarater reliability of pain intensity, tissue blood flow, thermal pain threshold, pressure pain threshold and lumbo-pelvic stability tests in subjects with low back pain. *Asian J Sports Med*, 3(1), 8-14. <https://doi.org/10.5812/asjism.34718>
- Petersen, K. K., O'Neill, S., Blichfeldt-Eckhardt, M. R., Nim, C., Arendt-Nielsen, L., & Vægter, H. B. (2024). Pain profiles and variability in temporal summation of pain and conditioned pain modulation in pain-free individuals and patients with low back pain, osteoarthritis, and fibromyalgia. *Eur J Pain*. <https://doi.org/10.1002/ejp.4741>
- Petrucci, G., Papalia, G. F., Ambrosio, L., Russo, F., Marchetti, A., De Marinis, M. G., Vadala, G., Papalia, R., & Denaro, V. (2025). The influence of psychological factors on postoperative clinical outcomes in patients undergoing lumbar spine surgery: a systematic review and meta-analysis. *Eur Spine J*, 34(4), 1409-1419. <https://doi.org/10.1007/s00586-025-08733-z>
- Pinheiro, J., Bates, D., DebRoy, S., Sarkar, D., & R Core Team. (2025). nlme: Linear and Nonlinear Mixed Effects Models. <https://CRAN.R-project.org/package=nlme>

- Pion-Tonachini, L., Kreutz-Delgado, K., & Makeig, S. (2019). ICLabel: An automated electroencephalographic independent component classifier, dataset, and website. *Neuroimage*, 198, 181-197. <https://doi.org/10.1016/j.neuroimage.2019.05.026>
- Plaghki, L., & Mouraux, A. (2005). EEG and laser stimulation as tools for pain research. *Current Opinion in Investigational Drugs*, 6(1), 58-64. <https://www.ncbi.nlm.nih.gov/pubmed/15675604>
- Poquet, N., & Lin, C. (2016). The Brief Pain Inventory (BPI). *Journal of Physiotherapy*, 62(1), 52. <https://doi.org/10.1016/j.jphys.2015.07.001>
- Price, D. D., & Dubner, R. (1977). Mechanisms of first and second pain in the peripheral and central nervous systems. *J Invest Dermatol*, 69(1), 167-171. <https://doi.org/10.1111/1523-1747.ep12497942>
- Price, D. D., Hu, J. W., Dubner, R., & Gracely, R. H. (1977). Peripheral suppression of first pain and central summation of second pain evoked by noxious heat pulses. *Pain*, 3(1), 57-68. [https://doi.org/10.1016/0304-3959\(77\)90035-5](https://doi.org/10.1016/0304-3959(77)90035-5)
- Provencher, B., Northon, S., Gevers Montoro, C., O'Shaughnessy, J., & Piché, M. (2021). Effects of chiropractic spinal manipulation on laser-evoked pain and brain activity. *The Journal of Physiological Sciences*, 71(1), 20-33. <https://doi.org/10.1186/s12576-021-00804-2>
- Provencher, B., & Piché, M. (2025). C-fiber-related brain responses evoked by laser heat pulses applied to the back. *The Journal of Physiological Sciences*, 75(2), 100018. <https://doi.org/10.1016/j.jphyss.2025.100018>
- Putz, C., Schulz, B., Schoeler, S., Magerl, W., Gabriel, B., Gabriel, H. H., Miltner, W. H., & Weiss, T. (2013). Somatosensory abnormalities for painful and innocuous stimuli at the back and at a site distinct from the region of pain in chronic back pain patients. *PLOS ONE*, 8(3), e58885. <https://doi.org/10.1371/journal.pone.0058885>
- R Core Team. (2025). R: A Language and Environment for Statistical Computing. In R Foundation for Statistical Computing. <https://www.R-project.org/>
- Riley, J. L., 3rd, Cruz-Almeida, Y., Staud, R., & Fillingim, R. B. (2019). Effects of manipulating the interstimulus interval on heat-evoked temporal summation of second pain across the age span. *Pain*, 160(1), 95-101. <https://doi.org/10.1097/j.pain.0000000000001382>
- Rodrigues, J., Weiß, M., Hewig, J., & Allen, J. J. B. (2021). EPOS: EEG Processing Open-Source Scripts. *Frontiers in Neuroscience*, 15, 660449. <https://doi.org/10.3389/fnins.2021.660449>

- Roelofs, J., Sluiter, J. K., Frings-Dresen, M. H., Goossens, M., Thibault, P., Boersma, K., & Vlaeyen, J. W. (2007). Fear of movement and (re)injury in chronic musculoskeletal pain: Evidence for an invariant two-factor model of the Tampa Scale for Kinesiophobia across pain diagnoses and Dutch, Swedish, and Canadian samples. *Pain*, 131(1-2), 181-190. <https://doi.org/10.1016/j.pain.2007.01.008>
- Rogers, A. H., & Farris, S. G. (2022). A meta-analysis of the associations of elements of the fear-avoidance model of chronic pain with negative affect, depression, anxiety, pain-related disability and pain intensity. *Eur J Pain*, 26(8), 1611-1635. <https://doi.org/10.1002/ejp.1994>
- Rustamov, N., Northon, S., Tessier, J., Leblond, H., & Piché, M. (2019). Integration of bilateral nociceptive inputs tunes spinal and cerebral responses. *Sci Rep*, 9(1), 7143. <https://doi.org/10.1038/s41598-019-43567-y>
- Salamon, K. S., Davies, W. H., Fuentes, M. R., Weisman, S. J., & Hainsworth, K. R. (2014). The pain frequency-severity-duration scale as a measure of pain: preliminary validation in a pediatric chronic pain sample. *Pain Res Treat*, 2014, 653592. <https://doi.org/10.1155/2014/653592>
- Salas-González, J., Heredia-Rizo, A. M., Fricke-Comellas, H., Chimenti, R. L., & Casuso-Holgado, M. J. (2025). Patterns of pain perception in individuals with anxiety or depressive disorders: A systematic review and meta-analysis of experimental pain research. *J Pain*, 35, 105530. <https://doi.org/10.1016/j.jpain.2025.105530>
- Scheuren, P. S., Rosner, J., Curt, A., & Hubli, M. (2020). Pain-autonomic interaction: A surrogate marker of central sensitization. *Eur J Pain*, 24(10), 2015-2026. <https://doi.org/10.1002/ejp.1645>
- Singmann, H., Bolker, B., Westfall, J., Aust, F., & Ben-Shachar, M. S. (2025). afex: Analysis of Factorial Experiments. <https://CRAN.R-project.org/package=afex>
- Starkweather, A. R., Heineman, A., Storey, S., Rubia, G., Lyon, D. E., Greenspan, J., & Dorsey, S. G. (2016). Methods to measure peripheral and central sensitization using quantitative sensory testing: A focus on individuals with low back pain. *Appl Nurs Res*, 29, 237-241. <https://doi.org/10.1016/j.apnr.2015.03.013>
- Staud, R., Robinson, M. E., & Price, D. D. (2007). Temporal summation of second pain and its maintenance are useful for characterizing widespread central sensitization of fibromyalgia patients. *J Pain*, 8(11), 893-901. <https://doi.org/10.1016/j.jpain.2007.06.006>
- Strand, L. I., Moe-Nilssen, R., & Ljunggren, A. E. (2002). Back Performance Scale for the assessment of mobility-related activities in people with back pain. *Phys Ther*, 82(12), 1213-1223.

- Subramanian, M., & Venkatesan, P. (2022). The predictors for altered central pain modulation in individuals with nonspecific chronic low back pain: A systematic review. *Pain Pract*, 22(2), 276-284. <https://doi.org/10.1111/papr.13081>
- Tabachnick, B. G., & Fidell, L. S. (2013). *Using multivariate statistics* (6th ed ed.). Pearson Education.
- Treede, R. D., Rief, W., Barke, A., Aziz, Q., Bennett, M. I., Benoliel, R., Cohen, M., Evers, S., Finnerup, N. B., First, M. B., Giamberardino, M. A., Kaasa, S., Korwisi, B., Kosek, E., Lavand'homme, P., Nicholas, M., Perrot, S., Scholz, J., Schug, S., . . . Wang, S. J. (2019). Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). *Pain*, 160(1), 19-27. <https://doi.org/10.1097/j.pain.0000000000001384>
- Van Oosterwijck, S., Billens, A., Cnockaert, E., Danneels, L., Mertens, T., Dhondt, E., & Van Oosterwijck, J. (2025). Spinal hyperexcitability in patients with chronic musculoskeletal pain or headache as evidenced by alterations in the nociceptive withdrawal reflex: a systematic review and meta-analysis. *Pain*, 166(5), 1002-1029. <https://doi.org/10.1097/j.pain.0000000000003436>
- Vlaeyen, J. W. S., Crombez, G., & Linton, S. J. (2016). The fear-avoidance model of pain. *Pain*, 157(8), 1588-1589. <https://doi.org/10.1097/j.pain.0000000000000574>
- Vlaeyen, J. W. S., & Linton, S. J. (2000). Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. *Pain*, 85(3), 317-332. [https://doi.org/10.1016/S0304-3959\(99\)00242-0](https://doi.org/10.1016/S0304-3959(99)00242-0)
- Wang, L. Y., Fu, T. S., Tsia, M. C., & Hung, C. I. (2023). The associations of depression, anxiety, and insomnia at baseline with disability at a five-year follow-up point among outpatients with chronic low back pain: a prospective cohort study. *BMC Musculoskelet Disord*, 24(1), 565. <https://doi.org/10.1186/s12891-023-06682-6>
- Wang, Y. P., & Gorenstein, C. (2013). Psychometric properties of the Beck Depression Inventory-II: a comprehensive review. *Braz J Psychiatry*, 35(4), 416-431. <https://doi.org/10.1590/1516-4446-2012-1048>
- Wheeler, C. H. B., Williams, A. C. C., & Morley, S. J. (2019). Meta-analysis of the psychometric properties of the Pain Catastrophizing Scale and associations with participant characteristics. *Pain*, 160(9), 1946-1953. <https://doi.org/10.1097/j.pain.0000000000001494>
- Wickham, H., Averick, M., Bryan, J., Chang, W., D'Agostino McGowan, L., François, R., Grolemond, G., Hayes, A., Henry, L., Hester, J., Kuhn, M., Lin Pedersen, T., Miller, E., Milton Bache, S., Müller, K., Ooms, J., Robinson, D., Seidel, D., Spinu, V., . . . Yutani, H. (2019). Welcome to

the Tidyverse. Journal of Open Source Software, 4(43), 1686.
<https://doi.org/10.21105/joss.01686>

Woolf, C. J. (2011). Central sensitization: implications for the diagnosis and treatment of pain. Pain, 152(3 Suppl), S2-15. <https://doi.org/10.1016/j.pain.2010.09.030>

World Health Organisation (WHO). (2019). International Classification of Diseases, Eleventh Revision (ICD-11). <https://icd.who.int/browse/2025-01/mms/en>

Zhang, W., Löffler, M., Usai, K., Mišić, M., Nees, F., & Flor, H. (2025). Hypervigilance to Pain May Predict the Transition from Subacute to Chronic Back Pain: A Longitudinal Observational Study. J Pain Res, 18, 3141-3158. <https://doi.org/10.2147/jpr.S512911>

Chapitre 5: Étude 4 – Pain relief by spinal manipulative therapy increases with the number of sessions and is greater when applied to all regions of the spine: an explanatory randomized controlled trial in individuals with chronic primary low back pain

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En préparation pour être soumis au journal *Neuroscience*.

Contribution des auteurs selon la classification CRediT (*Contribution Roles Taxonomy*):

- Benjamin Provencher: conceptualisation, méthodologie, logiciel, investigation, analyse formelle, validation, gestion des données et rédaction – version originale.
- Gabriel parent : investigation, analyse formelle, validation
- Mathieu Piché: obtention du financement, administration du projet, ressources, conceptualisation, méthodologie, logiciel, investigation, analyse formelle, validation, gestion des données, rédaction – révision et édition, supervision.

Abstract

Spinal manipulative therapy (SMT) is recommended for the management of chronic primary low back pain (CPLBP). Notwithstanding, the neurophysiological mechanisms underlying its clinical benefits are poorly understood. The aim of this randomized controlled trial (NCT05986370) is to examine whether SMT relieves pain through the inhibition of C-fibers related processes. Forty-nine individuals with CPLBP were recruited to participate in 36 sessions. They were randomly assigned to one of the three groups: SMT applied globally to all regions of the spine (SMT-G); SMT applied to the lumbar region only (SMT-L); control intervention. LBP intensity, temporal summation of second pain (TSSP) and C-fibers related brain responses were measured at baseline, one month, and three months. The results indicate that SMT-G produced greater pain relief compared with SMT-L and control, after one month of intervention ($p=.005$). From one to three months, pain relief increased ($p<.001$), but this effect was not significantly different between groups ($p=.91$). However, the proportion of individuals that achieved minimal clinically important difference at three months was greater in the SMT-G group. Between one and three months, SMT (G and L) also reduced the temporal summation of C-fibers related brain oscillations (2–5 Hz) ($p=.005$). These results indicate that pain relief by SMT is greater when applied to all regions of the spine (SMT-G) and that part of this effect may rely on the inhibition of C-fibers related brain responses. However, pain relief between one and three months likely relies on non-specific effects, including those produced by contextual factors.

Introduction

Low back pain (LBP) is the leading cause of disability worldwide and is a significant socioeconomic burden, particularly among working-age adults (GBD 2021 Diseases and Injuries Collaborators, 2024; Zhang et al., 2025). LBP is influenced by biological (e.g., sex), psychological (e.g., pain catastrophizing, pain vigilance), and social (e.g., gender) factors that shape the pain experience (Nicholas, 2022; Osborne & Davis, 2022; Rogers & Farris, 2022). The current international and multidisciplinary consensus recommends that chronic LBP be categorized as nociceptive, neuropathic, or nociplastic (Nijs et al., 2024), with the objective of developing personalized interventions based on the mechanisms underlying pain. For example, nociplastic LBP, referred to as chronic primary low back pain (CPLBP) (Kosek et al., 2021; Nijs et al., 2024; World Health Organisation (WHO), 2019), may respond better to interventions that target central sensitization (Nijs et al., 2024). Accordingly, individuals with pain at multiple sites, a feature of CPLBP (Kosek et al., 2021), showed a better response to duloxetine and imipramine compared with a placebo (Alev et al., 2017; Schliessbach et al., 2018). Spinal manipulative therapy (SMT) may have similar anti-hyperalgesic effects (Bialosky et al., 2014; Bishop et al., 2011; George et al., 2006; Randall et al., 2017), but this remains to be clarified.

SMT is among the interventions recommended in evidence-based clinical practice guidelines for the management of LBP, including the World Health Organization guidelines for CPLBP (World Health Organization, 2023; Zaina et al., 2023). For individuals with chronic LBP syndromes, exercise and SMT may be the only primary care interventions for which the benefits may outweigh the risks (Kirkwood et al., 2021; Kolber et al., 2021). Yet, the effectiveness of SMT is modest, where less than 55 % of individuals with chronic LBP achieve clinically meaningful pain relief (Kirkwood et al., 2021; Korownyk et al., 2022). However, the effects may be greater in carefully selected individuals with CPLBP (Nijs et al., 2024). In addition, SMT may be adapted to improve effectiveness. In previous studies, a linear relationship was reported between the number of SMT sessions (dosage) and the improvement of clinical outcomes (Haas et al., 2018; Haas et al., 2004; Haas et al., 2014), but the optimal dosage and frequency of sessions that provide

optimal pain relief remain to be determined. The area of SMT application, restricted to the painful area or extended to all regions of the spine, may also influence effectiveness (Nim, Downie, et al., 2021). A recent systematic review showed no measurable difference in the improvement of clinical outcomes when SMT was applied to the symptomatic region of the spine compared with a non-symptomatic region (Nim, Downie, et al., 2021). This may reflect non-specific effects (Gevers-Montoro, Provencher, Descarreaux, et al., 2021; Sean et al., 2024). Alternatively, it may reflect the effects of distinct mechanisms (Gevers-Montoro, Provencher, Descarreaux, et al., 2021), in which case SMT applied to all regions of the spine may produce additive pain relief, but this remains to be investigated.

Spinal manipulation was shown to decrease pain by inhibiting processes related to C-fibers activity and central sensitization, including temporal summation of second pain (TSSP) (Bialosky et al., 2014; Bishop et al., 2011; George et al., 2006; Randoll et al., 2017) and secondary hyperalgesia (Gevers-Montoro, Provencher, Northon, et al., 2021; Mohammadian et al., 2004). However, these effects have been demonstrated using psychophysical methods, primarily in asymptomatic individuals, and immediately after spinal manipulation (Bishop et al., 2011; George et al., 2006; Gevers-Montoro, Provencher, Northon, et al., 2021; Mohammadian et al., 2004; Randoll et al., 2017). The clinical relevance of these findings in individuals with CPLBP remains to be shown, and neurophysiological methods are needed to confirm the underlying mechanisms.

The objective of the present study was to examine the efficacy of SMT to reduce CPLBP and the underlying neurophysiological mechanisms. We hypothesized that 1) SMT will produce a greater reduction in LBP intensity compared with a control intervention; 2) SMT applied globally (to all regions of the spine) will lead to a greater reduction in LBP intensity compared with SMT applied to the lumbar region; 3) LBP intensity will decrease progressively over time (Haas et al., 2018; Haas et al., 2014), where more sessions produce greater effects over three months; 4) The reduction of LBP intensity by SMT will be accompanied by decreased temporal summation of second pain, decreased temporal summation of C-fibers related brain responses, and decreased

mechanical sensitivity (Bialosky et al., 2009; Bialosky et al., 2014; Gevers-Montoro, Provencher, Northon, et al., 2021; Provencher, Northon, Gevers Montoro, et al., 2021; Randoll et al., 2017). Because pain is modulated by pain-related psychological factors (Emmerich et al., 2020; Rogers & Farris, 2022; Ryum & Stiles, 2023; Salas-González et al., 2025; Wood et al., 2023), we also hypothesize that pain-related psychological factors will moderate the effect of SMT on LBP intensity.

Experimental procedures

Ethics approval

All experimental procedures conformed to the standards set by the latest revision of the Declaration of Helsinki and the guidelines of the International Association for the Study of Pain. The protocol was approved by the Research Ethics Board of Université du Québec à Trois-Rivières and all participants gave written informed consent, acknowledging their right to withdraw from the study without prejudice. For all participants, the 36 intervention sessions were offered at no cost. After the final outcome assessment, participants also received an educational booklet containing information on physical activity, sleep hygiene, and additional resources to help manage or prevent future episodes of LBP.

Sample size calculation

This study was registered as an explanatory randomized controlled trial (RCT) (trial registration number NCT05986370: <https://clinicaltrials.gov/study/NCT05986370>). The sample size was determined using G*Power 3.1 based on the effect size reported in our previous study (Gevers-Montoro et al., 2024), for a mixed ANOVA with three groups and three time points. With an α level of .05, 80 % power, and a η^2_p of .024 for greater pain relief in one group compared with others, the required sample size was 84 participants (3 groups of 28 participants) with a 1:1 M:F

ratio. Due to limited resources, the sample size had to be reduced to 49 participants. Based on the initial sample size calculation, this leads to a minimum detectable effect size of $\eta^2_p = .07$ instead of $\eta^2_p = .024$. As reported in the results section below, the effect size was much larger than expected ($\eta^2_p = .16$), so the revised sample is appropriate to test all hypotheses, as planned.

Participants

Sixty-seven participants were recruited between October 2023 and January 2025 by advertisements on social media. Individuals with CPLBP were included if they were between 18 and 60 years old, had low back pain for at least 6 months with an average LBP intensity $\geq 3/10$ during the last 7 days. They were excluded following a thorough examination by a licensed chiropractor involved in this study (BP), if a pathology responsible for their symptoms was identified (e.g.: fracture, spinal stenosis, herniated disc, neoplasia, infection, inflammatory arthritis, arthrosis or visceral conditions such as prostatitis, endometriosis, kidney stones, and aortic aneurism). They were also excluded if they had another chronic pain syndrome, a sensory or motor deficit in the lower limbs, presented contraindications to spinal manipulation or conditions that would normally require modifications of the therapy (history of spinal surgery, atherosclerosis of major blood vessels, vertebrobasilar insufficiency, aneurysms, osteoporosis (Bergmann & Peterson, 2011)), if they received disability compensation for their LBP or chiropractic care in the past 12 months. To minimize the risk of adverse events related to laser stimulation, participants were also excluded if they presented a skin of type I on the Fitzpatrick scale (Gupta & Sharma, 2019). A group of healthy volunteers was also recruited for the comparison of baseline values. These results are reported elsewhere.

Experimental design

The study relies on a parallel design with three groups of individuals with CPLBP. The primary outcomes are LBP intensity and temporal summation of second pain (TSSP). The secondary outcomes are detailed below. They include clinical measures, questionnaires, quantitative sensory testing (QST), and neurophysiological measures. Primary and secondary

outcomes were assessed at baseline and at primary endpoints, i.e. the end of the first and third months of the interventions (after 12 and 36 sessions). Follow up on LBP intensity, frequency and disability were conducted via online questionnaires at secondary time points, three, six and nine months after the end of the interventions (six, nine and twelve months after the beginning of the intervention). The timeline is illustrated in **Figure 5.1A**.

Randomization, group allocation and concealment

Participants were randomized to one of the three groups: 1) SMT applied globally (SMT-G) to dysfunctional spinal segments identified during physical examination in any spinal region (Triano et al., 2013); 2) SMT applied in the lumbar region (SMT-L) to dysfunctional spinal segments; 3) Control intervention.

A randomization sequence was generated by an investigator not involved in data collection to obtain a balanced randomization sequence assigning participants to the SMT-G, SMT-L or control intervention groups in a 1:1:1 ratio (MATLAB version 9.13.0, R2022b; The MathWorks Inc, Natick, Massachusetts, USA).

The investigator who generated the allocation sequence wrote down the group allocation on a folded piece of paper that was put in a sealed envelope identified with the participants' ID. Group allocation was concealed from participants and investigators, except for the experimenter that provided the interventions, who opened the corresponding envelope just before delivering the intervention on the day of the first session. The experimenter who collected most of the data, with the exception of adverse events and co-interventions, was blind to group allocation throughout the study.

The efficacy of blinding was assessed following the evaluation of the outcomes at 3 months. For two participants who indicated that they would like to withdraw after the first primary endpoint (1 month), blinding was assessed at that time. Participants were asked whether they believed they had received a real chiropractic intervention for back pain (Yes/No). They were also instructed to rate their certainty about having received a real chiropractic intervention rather

than a control intervention, using a scale from 0 (“absolutely uncertain”) to 10 (“absolutely certain”) (Chaibi et al., 2015; Gevers-Montoro et al., 2024).

Interventions

The description of interventions follows the TIDieR-Placebo/CoPPS reporting checklist (Hohenschurz-Schmidt et al., 2023). All interventions were delivered by one licensed chiropractor. All sessions took place in designated rooms at the Université du Québec à Trois-Rivières, using the same equipment, under the same environmental conditions. Interventions were delivered in 36 sessions over 3 months, 3 times per week.

Test intervention (spinal manipulative therapy)

Rationale

SMT is recommended by several clinical practice guidelines on the management of LBP (Corp et al., 2021; Zaina et al., 2023). Few trials have investigated the ideal dose and frequency of SMT (Pasquier et al., 2019). A linear trend between the number of SMT sessions and the clinical outcomes was reported for individuals with chronic musculoskeletal pain (Haas et al., 2018; Haas et al., 2014). In individuals with CPLBP, a frequency of 3 to 4 sessions per week yielded better results compared with 1 or 2 sessions per week (Haas et al., 2004).

Procedures

High-velocity, low amplitude spinal manipulations were performed using the diversified technique (Bergmann & Peterson, 2011). For each session, a minimum of two spinal manipulations was performed, one on each side of the most painful lumbar vertebra, identified during physical examination at baseline. Manipulations in the lumbar region could include sacroiliac joints. If clinically indicated, spinal manipulations were performed at other dysfunctional spinal segments in the lumbar region (SMT-L group) or in any region (SMT-G). When

necessary, the manipulation was performed a second time (17% of the manipulations). During the spinal manipulation, the participant laid prone, supine or in lateral decubitus, depending on the type of the manipulation, and was instructed to inhale and exhale fully before each thrust.

Tailoring

To maximize ecological validity, the vertebral segments to be manipulated (other than the most painful lumbar vertebra) were determined during a clinical examination at the beginning of each session. Dysfunctional vertebral joints were identified as painful upon palpation, with differences in the texture of soft tissue, asymmetry in bony or muscle landmarks, or with restriction of the segmental movement (Bergmann & Peterson, 2011; Triano et al., 2013). Every month (after 12 sessions), participants underwent a physical reevaluation to monitor their progress.

Control intervention

Rationale

The control intervention was designed to be structurally equivalent to SMT (Machado et al., 2008; Puhl et al., 2017). The same body regions were attended with an equivalent amount of physical contact. The control intervention also matched SMT in terms of session number, frequency, and duration. Importantly, the same experimenter (BP) delivered SMT and the control intervention to limit variability. While the control intervention did not activate deep high-threshold mechanoreceptors, it retained all other components of SMT that may elicit a placebo response, including therapeutic alliance, therapeutic environment, physical touch, and expectations (Sherriff et al., 2022). Also, prior to randomization, participants were informed that the trial was comparing the mechanisms of two equally effective interventions for CPLBP, one involving the audible pop typically associated with spinal manipulations, and one without.

Procedures

Three maneuvers were used interchangeably during each session to enhance blinding and maintain protocol adherence. A control maneuver was designed for each of the three positions that may be used during SMT. During these three maneuvers, participants were periodically instructed to inhale and exhale fully:

1) With the participants lying prone, 3 to 8 light and brief manual contacts (≈ 20 N for 5 s) were applied over some of their spinous processes. Similar mechanical stimuli did not modulate experimental back pain in previous studies (Provencher, Northon, Gevers Montoro, et al., 2021; Randoll et al., 2017). After these manual contacts, sections of the intervention table were slightly raised or lowered by ≈ 5 cm and legs were crossed at the ankles during approximately 30 s before the next maneuvers.

2) With the participants lying supine, their lower limbs position was changed once or twice (e.g. knees bent, and hips internally or externally rotated. Each position was maintained during ≈ 30 s.

3) With participants lying in lateral decubitus, 3 to 6 impulses at the lowest setting of the Activator V instrument (Activator Methods Int. Ltd., Phoenix, Arizona, USA) were applied over the gluteus medius, and laterally to the erector spinae muscles on one side of their body. The lowest setting of the Activator V generates a mean peak force of 26-41 N when delivered in vivo (Reed et al., 2023).

Tailoring

The vertebral segments to be manipulated were determined during a clinical examination at the beginning of each session. The brief manual contacts during the first maneuver of the control intervention targeted all these segments to enhance blinding. The other two maneuvers were not directed at any specific joint. Nonetheless, participants were asked whether the positioning exacerbated their LBP. If so, positioning was adapted to limit pain. Every month (after 12 sessions), participants underwent a physical reevaluation to monitor their progress.

Strategies to maintain adherence to the intervention

Participants were requested to attend sessions three times per week. To maintain adherence, they were free to choose the days that suited their schedule. If possible, the three sessions were spaced evenly. A schedule was established at the beginning of each month. Regular appointment reminders were sent by phone and text messages to avoid missed appointments. Following the first primary endpoint (one month), participants were allowed up to two weeks of absence, after which the intervention resumed. Adherence was defined as the number of intervention sessions completed by participants relative to the 36 sessions planned, as commonly reported in non-pharmacological RCTs (Giovanazzi et al., 2022).

Assessment of outcome measures

Adverse events (AEs) and co-interventions were documented by the licensed chiropractor (BP) at the beginning of each session. All other patient-reported outcome measures were collected via online questionnaires or by the research assistant (GP), who was blind to group allocation and study hypotheses. Primary and secondary outcomes were measured at baseline and at two primary endpoints: after 12 and 36 sessions. Given that each assessment required approximately three hours, scheduling was flexible to limit dropouts. Thus, the second assessment was conducted between the 10th and 15th sessions, and the final assessment between the 31st and 36th sessions. Follow-up outcomes (at secondary endpoints) were all assessed using online questionnaires.

Primary outcome measures

Low back pain intensity

Participants were instructed to rate the intensity of their LBP using a numeric rating scale (NRS) ranging from 0 (no pain) to 10 (worst pain imaginable) (Dworkin et al., 2005). As in the brief pain inventory (BPI) (Daut et al., 1983), they were instructed to rate their pain: 1) currently; 2) on average over the last 7 days; 3) at its worst over the last 7 days; 4) at its best over the last 7 days.

A Cronbach α of .81 - .89, and a test-retest correlation of $r = .80$ have been reported for the BPI (Poquet & Lin, 2016). Only the LBP intensity “at its worst” values are presented, as these are considered the most meaningful indicators of pain for both patients and clinicians (Stone et al., 2021). LBP intensity was measured at baseline and at all primary and secondary endpoints.

Temporal summation of second pain

The laser stimulation protocol used to assess temporal summation of second pain (TSSP) is illustrated in **Figure 5.1C**. The average pain rating for the 80 single pulses was subtracted from the average pain rating for the 80 pulse trains to estimate the TSSP intensity for each participant at baseline and at both primary endpoints. TSSP reflects the amplification of spinal nociceptive transmission (Rachael L. Bosma et al., 2015; Herrero et al., 2000).

Secondary outcome measures

Clinical outcomes

Frequency and duration of low back pain

A modified version of the pain frequency-severity-duration scale was used (Salamon et al., 2014). Participants were instructed to answer these 3 questions: 1) Is the pain: recurrent (it comes in episodes) or continuous (it is always present); 2) How many days in the past week have you had low back pain? (0-7 days); 3) On average, how many hours per day does the pain last? (0; 1-4; 5-8; 9-12; 13-16; 17-20; 21-24 hours). LBP frequency and duration were measured at baseline and then once a week for the next 12 weeks. LBP frequency and duration were also measured at all secondary endpoints.

Global impression of change

Once a month, after each multiple of 12 sessions, participants were instructed to give their global impression of change on a scale from -100 to 100 (-100 = very much worse, 0 = no change, 100 = very much improved) (Cormier et al., 2016; Dworkin et al., 2005).

Disability related to low back pain

Self-reported LBP-related disability was evaluated using the validated French-Canadian version of the Oswestry Disability Index (ODI) (Denis & Fortin, 2012). A Cronbach α of 0.88 and an excellent test–retest reliability (ICC = .92) were reported for this questionnaire (Denis & Fortin, 2012). Self-reported LBP-related disability was measured at baseline and at all primary and secondary endpoints.

The Five Times Sit-to-Stand Test (FTSST) was used as a performance-based measure of physical function (Patel et al., 2021). Participants were seated on a chair with back support and were instructed to stand up and sit down again as quickly as possible, five consecutive times. Time was measured in seconds. The test was performed twice, and performance is reported as the average time for the two trials. A Cronbach α of .73 and a test-retest correlation of $r = .99$ have been reported when this test was performed in individuals with CPLBP (Özüdoğru et al., 2022). FTSST was measured at baseline and at both primary endpoints.

The Back Performance Scale (BPS) was used as a performance-based measure of physical function that is more specific to individuals afflicted with LBP. It includes daily activities such as putting on socks or picking up an object from the floor (Strand et al., 2002). In addition to the instructions, a demonstration was provided to the participants. The performance is reported as in a previous study (Strand et al., 2002). A Cronbach α of .73 has been reported for this scale (Strand et al., 2002). BPS was measured at baseline and at both primary endpoints.

Co-interventions

Participants were informed that they could seek care for their LBP outside the study at any time, as needed. Based on recent Canadian practice guidelines for chronic LBP (Kirkwood et al., 2021; Korownyk et al., 2022), exercise and oral nonsteroidal anti-inflammatory drugs (NSAIDs) were recommended as first-line alternatives to the interventions provided in the study. Participants were free to receive other interventions but were asked to report them. Co-interventions were documented at the beginning of each session. After the questions on AEs, three other questions were asked: 1) Have you used or received any other intervention for low back pain or another healthcare problem since your last visit? (yes / no) 2) If so, please specify the nature, number and dose of the intervention. Co-interventions for LBP were also documented at all secondary endpoints.

Adverse events

Participants were informed of the risk of AEs and the importance of communicating any unpleasant or abnormal sensation occurring in the hours or days following a treatment session. Moreover, at the beginning of each session, before performing the intervention, participants were asked the following questions: 1) Did you have any side effect following the last session? If so, please describe what happened. 2) How long did it last? The number, nature and severity of AEs was then documented (Funabashi et al., 2022). Mild AEs were defined as transient/reversible reactions (≤ 48 h) that did not require further intervention. Moderate AEs were defined as reactions that lasted more than 48 hours or that required another intervention, such as taking pain medication. Severe AEs were defined as reactions that required hospital admission, life threatening or causing long-lasting disability.

Expectations of pain relief

Expectations of pain relief are known to predict outcomes (Cormier et al., 2016). Therefore, they were measured at baseline and after one month (first primary endpoint).

Participants were instructed to rate their expectations of pain relief on a scale from 0 to 100, 0 being “no relief” and 100 being “complete relief” (Cormier et al., 2016).

Contextual factors

Contextual factors may influence the outcomes of clinical interventions (Rossetтини et al., 2018). For example, therapeutic alliance has been shown to predict the outcomes of manual therapy in individuals with LBP (Bishop et al., 2021). Thus, contextual factors were measured using a French adaptation of the healing encounters and attitudes lists (HEAL) (Greco et al., 2016). This scale has an acceptable to excellent internal consistency (Cronbach α of .74-.93) and test-retest correlations of $r = .71-.96$ have been reported for the English and German versions of the questionnaire (Gerger et al., 2019; Greco et al., 2016). HEAL items assessing positive outlook and attitudes toward complementary and alternative medicine were measured at baseline and both primary endpoints; treatment expectancy at baseline and the first primary endpoint; and patient-provider connection and healthcare environment at both primary endpoints.

Pain catastrophizing, kinesiophobia and pain vigilance

The main elements that contribute to the pain experience according to the fear avoidance model of pain (Vlaeyen & Linton, 2000) were measured in this study. Pain catastrophizing was measured with the French-Canadian version of the pain catastrophizing scale (PCS) (French et al., 2005). This scale has an excellent internal consistency (Cronbach $\alpha = .92$) and a test-retest reliability of .88 [95% CI = .83-.93] (Wheeler et al., 2019). Pain-related fear was measured with a French adaptation of the Tampa scale for kinesiophobia (TSK) (Roelofs et al., 2007). This scale has an acceptable to excellent internal consistency (Cronbach $\alpha = .7-.92$) and a test-retest correlation of $r \geq .80$ (Liu et al., 2021). Pain vigilance was measured with a French adaptation of the pain vigilance and awareness questionnaire (PVAQ) (Desrochers et al., 2009; McCracken, 1997). This scale has an excellent internal consistency (Cronbach $\alpha = 0.86$) and a test-retest correlation of $r = 0.80$ (McCracken, 1997). PCS, TSK and PVAQ were measured at baseline and at both primary endpoints.

Depressive symptoms and anxiety

Depressive symptoms and anxiety are common comorbidities that may influence the pain experience in individuals with chronic LBP (Knezevic et al., 2021). Depressive symptoms were measured using the validated French-Canadian version of the Beck Depression Inventory (BDI) (Bourque & Beaudette, 1982). Anxiety was measured using the validated French-Canadian version of the State-Trait Anxiety Inventory (STAI-Y) (Gauthier & Bouchard, 1993). Both scales have an excellent internal consistency (Cronbach α = .92 and .90, respectively) and test-retest correlations of r = .61 and .31-.86, respectively (Bourque & Beaudette, 1982; Gauthier & Bouchard, 1993; Wang & Gorenstein, 2013). The BDI and the STAI-Y were measured at baseline and at both primary endpoints.

Self-compassion

Self-compassion has been shown to predict pain and depressive symptoms in individuals with chronic pain (Emmerich et al., 2020). Self-compassion was measured with the validated French version of the Self-Compassion Scale (SCS). This scale has an excellent internal consistency (Cronbach α = .94) (Kotsou & Leys, 2016).

Sex and gender

Sex was determined by participants as the sex assigned at birth (male or female). Gender was assessed using the validated French version of the personal attributes questionnaire (PAQ). This scale has an acceptable internal consistency (Cronbach α = .68 for femininity and .72 for masculinity) (K'Delant & Gana, 2009). Sex and gender roles were assessed to examine their influence on the results, as recommended by the Canadian Institutes of Health Research.

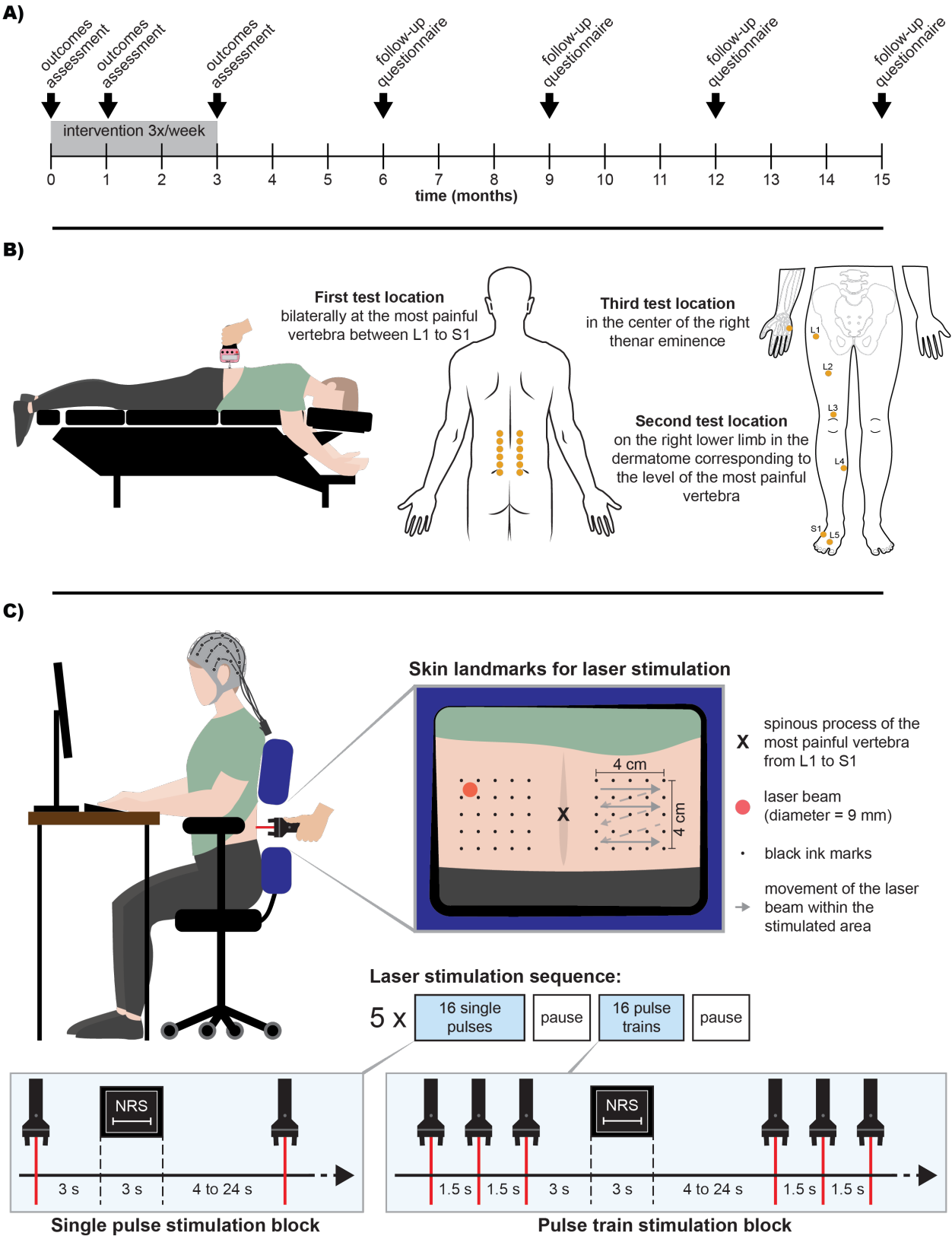
Quantitative sensory testing

Pressure pain thresholds

PPTs were tested on three different body locations, as illustrated in **Figure 5.1B**. 1) Bilaterally, 2 cm lateral to the spinous process of the most painful vertebra between L1 and S1, as a measure of primary hyperalgesia. 2) On the right lower limb in the dermatome corresponding to the level of the most painful vertebra. The rationale for this location is to assess secondary hyperalgesia. Specific test locations for L1 to S1 dermatomes were determined based on an evidence-based dermatome map (Lee et al., 2008). The test location for the L1 dermatome was located 5 cm inferior to the right anterior superior iliac spine. The test location for the L2 dermatome was located in the center of the right thigh, midway between the hip and the knee. The test location for the L3 dermatome was located on the right thigh, just above the patella. The test location for the L4 dermatome was located midway between the knee and the ankle, over the medial aspect of the calf muscles. The test location for the L5 dermatome was located over the head of the second metatarsal bone of the right foot. The test location for the S1 dermatome was located over the tuberosity of the 5th metatarsal bone on the right foot. 3) In the center of the right thenar eminence. This remote location was selected as a measure of widespread hyperalgesia. The right side was selected arbitrarily since no side difference was expected.

Pressure pain thresholds (PPTs) were measured using a handheld digital algometer (Wagner Pain TestTM FPX, Greenwich, Connecticut, USA) and a standardized protocol (Mücke et al., Quantitative sensorische Testung (QST)./2021; Starkweather et al., 2016). The algometer was applied perpendicularly to the skin of the first test location and the pressure increased at approximately 50 kPa/s until pain was reported. This procedure was repeated three times at the same test location with 60 s between trials. The PPT reported in this study is the average of the values obtained during the three trials. The same procedures were repeated at the two other test locations. Excellent test-retest reliability was reported for PPTs assessed in the lower back and remote body areas in individuals with CPLBP (Paungmali et al., 2012). PPTs were measured at baseline and at both primary endpoints.

Figure 5.1 – Experimental protocol



A) Timeline of the assessment of outcome measures. **B)** Illustration of how PPTs were measured as well as all the possible test locations. **C)** Detailed representation of the experimental setup, stimulation procedures and protocol. The laser stimulus was delivered to the back area within grids of ink marks drawn on each side of the most painful vertebra from L1 to S1. The 9 mm laser beam was carefully positioned on ink-free skin at one of the 32 spots within the stimulation grid. The laser beam was moved to the next spot in the grid after each stimulus (single pulse and pulse train) for safety purposes. It was moved sequentially from left to right and top to bottom. Within a pulse train however, the three pulses were delivered to the same spot to induce temporal summation. After each stimulus, participants were prompted to rate second pain with the display of a numerical pain rating scale. Participants received 5 series of stimuli, including 16 single pulse and 16 pulse trains stimuli delivered at the same laser intensity to assess temporal summation. PPT: pressure pain threshold, EEG: electroencephalography, NRS: Numerical Rating Scale.

C-fiber-related brain responses

Laser stimulation

The laser stimulation protocol is illustrated in Figure 5.1C. Painful stimuli were produced by laser heat pulses generated by an infrared neodymium-doped yttrium aluminum perovskite laser (Nd:YAP, DEKA 1340, Electronical Engineering, Florence, Italy). The laser stimulation protocol was as reported in our previous study with a pulse duration of 7 ms (Provencher & Piché, 2025).

A total of 160 stimuli, 80 pulse trains (3 pulses delivered at 0.67 Hz) and 80 single pulses, will be delivered. Stimuli will be divided into 5 blocks of 16. Blocks of single pulses and pulse trains were delivered alternately. Three seconds after each stimulus, participants were prompted by a numerical scale (NRS) appearing on the screen to rate the second pain for this stimulus verbally, from 0 to 100, 0 indicating “no pain” and 100 the “worse pain imaginable”. Participants were instructed to only rate the last pulse of the train when the stimulus was a pulse train.

At the beginning of each session, an investigator explained the concept of second pain to the participant using a self-made figure for visual support. Participants were instructed to focus on the second pain (the dull/hot/burning sensation in their back) and to report its intensity verbally. Next, laser pain thresholds and laser intensity causing low to moderate pain were determined using a staircase procedure described elsewhere (Provencher, Northon, & Piché, 2021; Provencher & Piché, 2025). Once this intensity was determined, it was kept constant for the rest of this assessment.

Electroencephalographic recording

Electroencephalography (EEG) was recorded using a 32-channel BrainVision system with active Ag-AgCl electrodes mounted on an actiCAP, according to the International 10–20 system (Brain Products, Gilching, Germany) and as reported in our previous study (Provencher & Piché, 2025). Opened eyes resting state EEG was recorded for 5 min prior to laser stimuli for exploratory EEG analyses, which are not presented here. Evoked EEG activity was recorded continuously during the five laser stimulation blocks. EEG was recorded at baseline and at both primary endpoints.

Electroencephalographic analyses

EEG signals were analyzed offline using MATLAB R2024b (MathWorks, Natick, MA, USA) and EEGLAB v2024.2.1 (Delorme & Makeig, 2004), following the procedures described in our previous study (Provencher & Piché, 2025). To analyze laser-evoked potentials (LEP), EEG signals were preprocessed using a standardized, automated, and open-source preprocessing pipeline for EEG data (Rodrigues et al., 2021). The preprocessing steps are briefly described here: 1- Downsampling the data from 1000 Hz to 500 Hz; 2- Re-referencing signals to the common average; 3- Automatic detection and spherical interpolation of channels of low quality using the outlier criterion $z > 3.29$ (Tabachnick & Fidell, 2013); 4- Segmenting the data into “long” epochs (-2000 ms to 7000 ms) to get a better independent component analysis (ICA) solution in the next steps; 5- High-pass filtering using a 0.5 Hz finite impulse response (FIR) filter; 6- First ICA using the

built-in function Runica in EEGLAB to identify trials with bad signal; 7- Automatic detection and rejection of contaminated trials based on z-value detection (> 3.29) of independent components (ICs); 8- Second ICA to identify artifact-driven components containing no relevant signal; 9- Automatic detection and rejection of the ICs related to noise using the ICLabel plugin (Pion-Tonachini et al., 2019) with preset thresholds ($> 90\%$ for muscles and eyes, $> 95\%$ for heart, $> 75\%$ for line and channel noise); 10- Segmenting the data into suitable epochs for analysis (-500 ms to 1500 ms for single pulse conditions and -500 ms to 4500 ms for pulse train conditions); 11- Baseline correction (-500 ms to 0 ms) (Hüllemann et al., 2016; Jankovski et al., 2013; Lenoir et al., 2018); 12- Low-pass filtering using a 30 Hz FIR filter. On average, 3.6 ± 1.3 channels were interpolated, 2.3 ± 5.8 epochs were rejected and $85.0 \pm 14.7\%$ of the variance remained after IC rejection. After data preprocessing, average waveforms were computed for each participant and time point, and the positive slow wave evoked by laser stimuli was analyzed. The peak amplitude and latency of this positive slow wave were measured automatically using the max function within a specified time window on each average waveform. The peak was defined as the maximum value between 500 and 1450 ms with a maximum amplitude at Pz (Provencher & Piché, 2025).

In order to measure event-related spectral perturbations (ERSP), EEG datasets were preprocessed using the same automated preprocessing pipeline as described above, with different values for filters (High-pass: 1 Hz; Low-pass: 100 Hz), baseline (-700 ms to -200 ms) and the final length of the epochs (-2000 ms to 2000 ms for single pulse conditions and -2000 ms to 5000 ms for pulse train conditions). Then, as in previous studies (Provencher, Northon, Gevers Montoro, et al., 2021; Rustamov et al., 2019), a Morlet wavelet convolution (Mouraux & Iannetti, 2008) was computed using the channel time–frequency options available in EEGLAB (Delorme & Makeig, 2004). Four hundred or 1200 time points were generated (single pulse or pulse train stimuli), and 100 linearly spaced frequencies were computed from 1 to 100 Hz. Variable cycles were used for low and high frequencies, with 3 cycles for lowest frequencies and up to 15 cycles for highest frequencies (Delorme & Makeig, 2004). This variable number of cycles allows for the wavelet convolution method to provide a better frequency resolution at lower frequencies and a better temporal resolution at higher frequencies (Cohen, 2014). Time-frequency analyses were performed using time–frequency options available in EEGLAB which use Morlet wavelets. A

Gaussian shape taper was used to taper wavelets to zero at both ends, and the length of the window used for time-frequency analysis was selected to avoid contamination of the signal of interest by edge artifacts. ERSP data were computed in decibels relative to baseline for all electrodes separately. The time–frequency data of all trials were averaged for each participant and time point separately, resulting in 3 average time–frequency maps for each electrode and participant. From these maps, the mean power was extracted from the Cz electrode in predetermined time × frequency regions of interests (ROIs) for each participant and time point (Provencher & Piché, 2025). At each time point, a mean ERSP value was then obtained for each participant and ROI by selecting and averaging the values with the 20% highest or lowest amplitude (for power increase or decrease relative to baseline).

Statistical analyses

Data were analyzed using the R Statistical language version 4.5.0 (R Core Team, 2025) on macOS Sequoia 15.5 and the packages tidyverse version 2.0.0 (Wickham et al., 2019), afex version 1.4.1 (Singmann et al., 2025), nlme version 3.1.168 (Pinheiro et al., 2025) and effectsize version 1.0.0 (Ben-Shachar et al., 2020). All results are expressed as mean ± standard deviation (SD). For within-subject effects, SD values were corrected to remove between-subject variability (Loftus & Masson, 1994). The statistical threshold was set at $p \leq 0.05$. Normality was assessed visually and with the Shapiro-Wilk test. Homogeneity of variance was assessed using Levene’s test, and sphericity with the Mauchly’s test. Effect sizes are reported based on partial eta-squared (η^2_p).

Primary analysis

Primary and secondary outcome measures were analyzed using Greenhouse-Geisser corrected mixed ANOVAs (3 groups × 3 time points [baseline, month 1 and month 3]). Significant effects were decomposed using the following orthogonal contrasts for groups: 1) Control vs SMT-G and SMT-L; 2) SMT-G vs SMT-L, and for time: 1) baseline vs month 1 and month 3; 2) month 1 vs month 3. To control for potential confounding effects, changes in primary outcomes and C-

fiber–related brain responses at 1 and 3 months were compared between groups using separate ANCOVAs, in which secondary outcomes that changed significantly over time were entered individually as continuous covariates (i.e., change scores).

Secondary analysis

LBP intensity, frequency, and associated disability were analyzed using 3×6 mixed ANOVAs, including 3 groups and 6 time points (baseline and 3-, 6-, 9-, 12, 15-months post randomization). Significant effects were decomposed using Bonferroni corrected planned contrasts.

Missing data

Missing data and their causes were documented and reported separately for each group. Both per-protocol and intention-to-treat analyses were performed using the last observation carried forward for missing primary endpoint measurements, which yielded equivalent results and conclusions. In this context, the per-protocol analysis was equivalent to a complete case analysis. Overall, 9.9% of data were missing. Little’s MCAR (Missing Completely At Random) test indicated that the data were missing completely at random ($\chi^2 = 3.2$, $p = 0.37$). Given the low proportion of missing data and the MCAR assumption, complete case analysis was deemed appropriate to minimize potential biases associated with imputation (Jakobsen et al., 2017; Medcalf et al., 2024). Therefore, only the per-protocol results are presented for clarity.

Minimal clinically important difference

According to recent recommendations (Sedaghat, 2019), both anchor-based and distribution-based approaches were used to calculate and report the minimal clinically important difference (MCID), since different approaches can lead to different threshold values (Franceschini et al., 2023). All methods are described in detail elsewhere (Franceschini et al., 2023).

Results

Participants

Between October 2023 and January 2025, following the enrollment process, 49 individuals with CPLBP (24 women and 25 men) were included in the study and randomized to receive one of the three interventions (see **Figure 5.2**). Sample characteristics are presented in **Table 5.1**. At baseline, groups were not significantly different for sex, gender roles, age, duration of LBP, neck pain, upper back pain, history of chiropractic care, expectations of pain relief, smoking status, systolic or diastolic blood pressure (all $p > 0.26$; see **Table 5.1**). Also, groups were not significantly different for the coprimary outcome measures (LBP intensity and TSSP) and secondary outcome measures (LBP frequency, ODI, FTSST, BPS, PCS, TSK, BDI, STAI-Y2, SCS, PPT in the lower and upper limbs, laser stimulation intensity used to assess TSSP, temporal summation of C-P2 peak amplitude and temporal summation of the ERSP power within ROI2) (all $p > .20$), with the exception of pain vigilance, PPT in the lower back and temporal summation of the ERSP power within ROI1, indicating that randomization was generally successful. Participants in the control intervention group reported higher pain vigilance compared with the SMT-G group ($p = .03$), but not the SMT-L group ($p = .33$). Participants in the SMT-L group showed lower PPT in the lower back compared with the SMT-G group ($p = .008$) and the control intervention group ($p = .03$). Moreover, participants in the SMT-G group showed higher temporal summation of the ERSP power within ROI1 compared to the control intervention group ($p = .03$), but not the SMT-L group ($p = .17$).

Among the 49 participants, 43 (22 women and 21 men) adhered to the protocol, completed all outcome assessment sessions (baseline, one and three months), and were included in all analyses presented in this report. Four participants discontinued the intervention due to time constraints, after completing 2, 3, 7, and 11 sessions, respectively. One participant withdrew after 17 sessions because he was not satisfied with the clinical progress. Another participant withdrew after 26 sessions and could not be reached. Among the 43 participants included in the analyses, 38 attended all 36 intervention sessions. The remaining five attended 31, 31, 33, 34, and 35 sessions, respectively, due to time constraints, but completed all outcome assessments.

For these participants, the final assessment was conducted on the day of their last intervention session. Based on the number of sessions attended relative to the 36 planned sessions, adherence was 90.6% among the 49 randomized participants and 97.7% among the 43 participants included in the analyses.

Figure 5.2 – Flow diagram of the progress through the phases of the study based on the CONSORT Statement

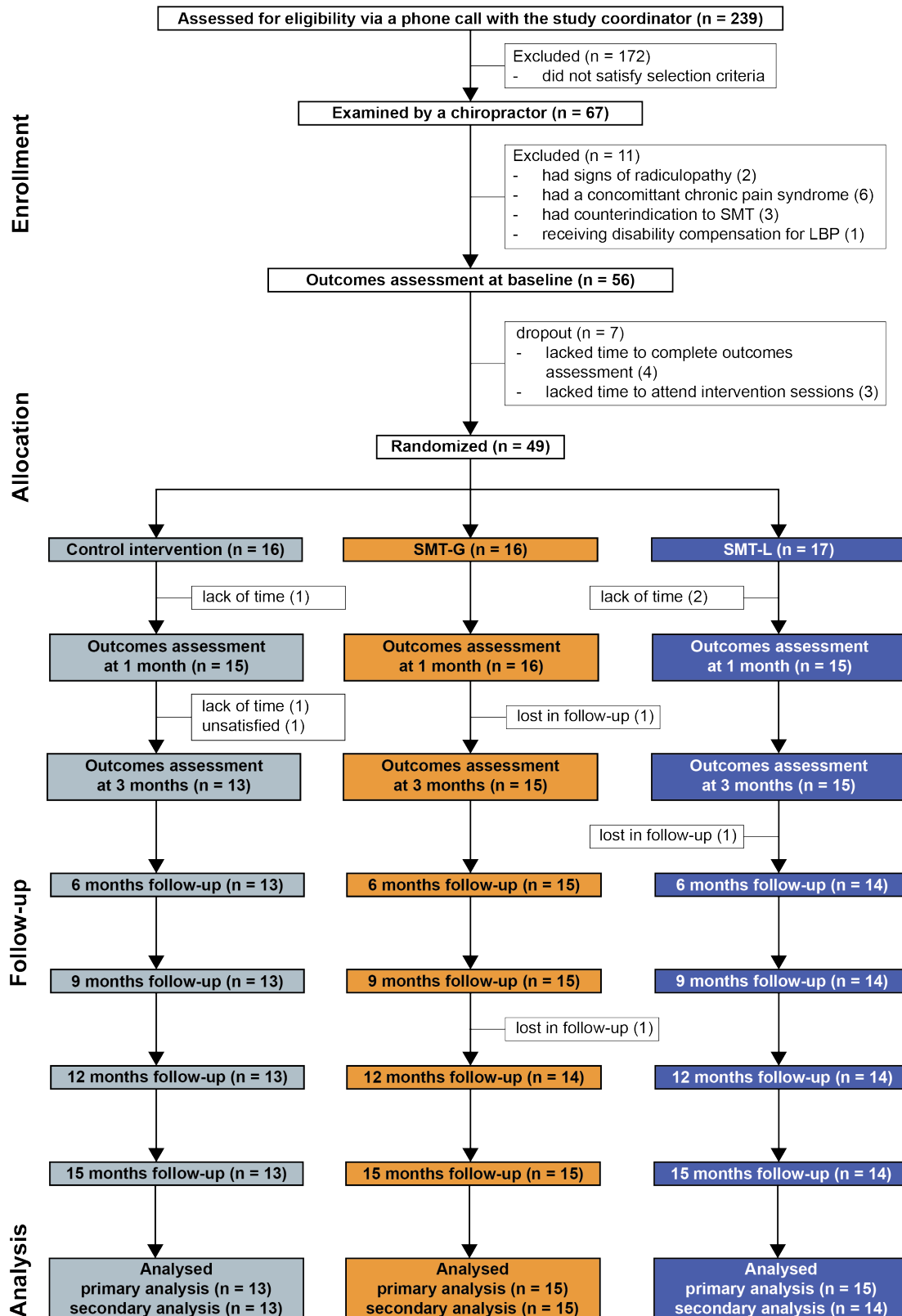


Table 5.1 – Baseline demographic and clinical characteristics for each group (mean ± SD)

Baseline characteristics	Control intervention (n =16)	SMT-G (n = 16)	SMT-L (n = 17)
Sex – female, n (%)	8 (50)	8 (50)	8 (47.1)
Sex – male, n (%)	8 (50)	8 (50)	9 (52.9)
Gender roles (0-32)			
Personal Attributes Questionnaire – Femininity	24.5 ± 3.3	24.2 ± 3.3	23.7 ± 4.1
Personal Attributes Questionnaire – Masculinity	20.9 ± 4.2	19.6 ± 3.8	21.3 ± 3.1
Age (years)	46.6 ± 11.6	43.9 ± 8.9	44.3 ± 7.9
Time with LBP (years)	12.2 ± 9.0	14.0 ± 8.1	16.0 ± 10.9
Reported concomitant neck pain, n (%)	9 (56.2)	8 (50)	9 (52.9)
Reported concomitant upper back pain, n (%)	5 (31.2)	8 (50)	4 (23.5)
History of chiropractic care (Yes), n (%)	13 (81.2)	13 (81.2)	14 (82.4)
Time since the last treatment (years)	12.7 ± 12.2	9.1 ± 8.4	6.9 ± 5.3
Expectations of pain relief (0-100)	71.9 ± 13.5	71.6 ± 21.2	65.9 ± 19.6
Smoking (Yes), n (%)	4 (25.0)	3 (18.8)	3 (17.6)
Systolic blood pressure (mm Hg)	126.4 ± 7.5	126.9 ± 12.9	126.4 ± 14.5
Diastolic blood pressure (mm Hg)	83.6 ± 5.0	82.3 ± 9.5	81.1 ± 8.9
Primary outcomes			
LBP intensity (0-10)	6.0 ± 2.0	6.5 ± 1.5	5.6 ± 1.9
TSSP (0-100)	17.0 ± 13.4	22.3 ± 13.7	22.8 ± 17.9
Secondary outcomes			
Number of days with LBP in the past week	5.2 ± 2.1	5.9 ± 1.8	5.8 ± 1.9
Oswestry disability index (0-50)	9.1 ± 3.9	9.0 ± 2.9	9.4 ± 2.3
Five times sit-to-stand test (s)	7.2 ± 2.1	7.1 ± 1.3	7.8 ± 2.3
Back performance scale (0-15)	3.2 ± 2.0	3.3 ± 2.8	2.8 ± 2.7
Pain catastrophizing scale (0-52)	13.7 ± 7.0	12.0 ± 8.1	16.2 ± 9.8
Pain vigilance and awareness questionnaire (0-80)	43.7 ± 12.5	34.1 ± 8.3	38.0 ± 8.9
Tampa scale for kinesiophobia (17-68)	34.1 ± 8.2	32.4 ± 5.5	36.8 ± 7.3
Beck Depression Inventory (0-63)	7.3 ± 4.0	6.5 ± 5.2	5.9 ± 4.3
State-Trait Anxiety Inventory - Y2 (20-80)	36.1 ± 6.7	34.4 ± 7.6	33.7 ± 7.7
Self-compassion scale (26-130)	92.1 ± 18.1	92.3 ± 15.0	93.2 ± 9.4
Pressure pain threshold – lower back (kPa)	424.9 ± 220.7	452.3 ± 173.0	260.6 ± 114.5
Pressure pain threshold – lower limb (kPa)	432.1 ± 247.2	397.2 ± 151.1	335.5 ± 144.9
Pressure pain threshold – upper limb (kPa)	464.9 ± 264.7	415.6 ± 122.8	315.8 ± 124.7
Laser stimulation intensity (J)	1.6 ± 0.4	1.5 ± 0.4	1.4 ± 0.4
Temporal summation of C-P2 peak amplitude (uV)	0.3 ± 1.6	0.5 ± 1.1	0.3 ± 1.5
Temporal summation of ERSP power in ROI1 (dB)	0.3 ± 1.6	2.2 ± 2.8	0.8 ± 1.3
Temporal summation of ERSP power in ROI2 (dB)	-1.6 ± 0.8	-1.1 ± 1.3	-1.4 ± 0.8

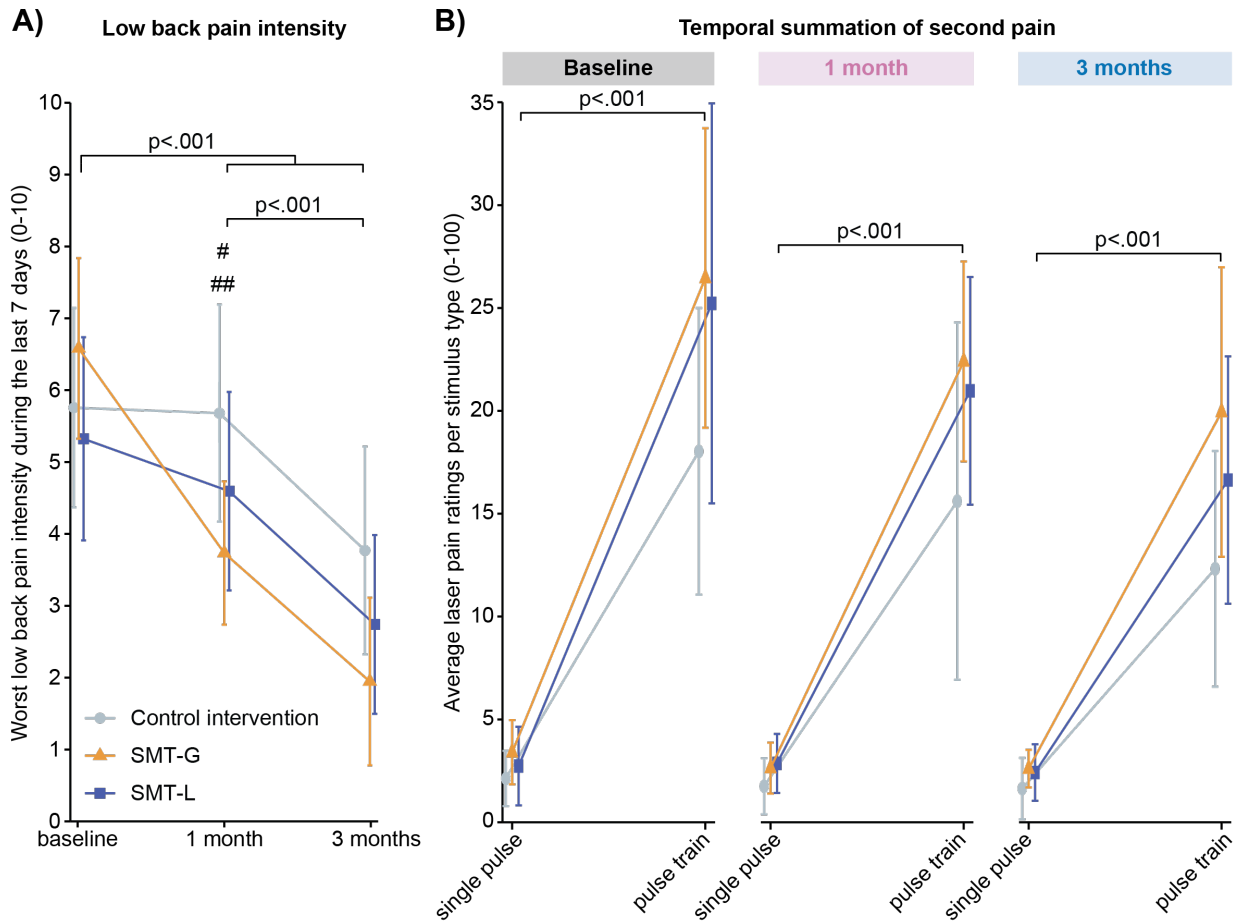
Primary outcomes

LBP intensity

After 3 months, the mean change in LBP intensity was -4.7, 95% confidence interval (CI) [-5.9, -3.4] for the SMT-G group, -2.6, 95% CI [-3.9, -1.3] for the SMT-L group, and -2.0 95% CI [-3.5, -0.5] for the control intervention group. The LBP intensity was compared between groups over time using a mixed ANOVA (**Figure 5.3A**). LBP intensity was not significantly different between groups (main effect: $F_{2, 40} = 1.45$, $p = .25$; $\eta^2_p = .07$, 95% CI: [0, 1]). However, LBP intensity decreased significantly over time (main effect: $F_{2.0, 79.7} = 39.47$, $p < .001$; $\eta^2_p = .50$, 95% CI: [.37, 1]) and this effect was significantly different between groups (interaction: $F_{4.0, 79.7} = 3.73$, $p = .008$, $\eta^2_p = .16$, 95% CI: [.03, 1]). Orthogonal planned contrasts revealed that the decrease in LBP intensity from baseline to the two primary endpoints was significantly greater for the two SMT groups compared with the control intervention group ($p = .01$). In addition, the decrease in LBP intensity in the SMT-G group was significantly greater compared with the SMT-L group over the same period ($p = .005$). Moreover, LBP intensity decreased significantly between 1 and 3 months ($p < .001$), but this effect was not significantly different between the two SMT groups and the control group ($p = .91$), or between the SMT-G and SMT-L groups ($p = .94$) (see **Figure 5.3A**). These results indicate that SMT-G provided greater pain relief during the first month of the intervention, after which LBP intensity continued to decline regardless of group allocation.

The MCID was calculated using four different methods. The resulting threshold values and corresponding proportions of participants who met these thresholds are presented in **Table 5.2**. As expected, the MCID estimates varied substantially across methods (Franceschini et al., 2023). Nevertheless, regardless of the method, the SMT-G group showed a greater proportion of participants reaching the MCID threshold after three months (46.7%, 80.0%, 93.3%, and 100%) compared with the SMT-L group (13.3%, 20.0%, 66.7%, and 93.3%) and the control group (15.4%, 15.4%, 61.5%, and 84.6%). Similar findings were observed for the other time points (see **Table 5.2**). These findings indicate that although the average pain relief was not significantly different between groups after three months, more participants showed clinically significant pain relief in the SMT-G group.

Figure 5.3 – Changes in primary outcomes between groups over time



A) Average LBP intensity for each group and time point. LBP intensity decreased significantly over time ($p < .001$) and this effect was significantly different between groups ($p = .008$). Orthogonal planned contrasts revealed that the decrease in LBP intensity from baseline to the two primary endpoints was significantly greater for the two SMT groups compared with the control intervention group (#: $p = .01$). In addition, the decrease in LBP intensity in the SMT-G group was significantly greater compared with the SMT-L group over the same time period (##: $p = .005$). Moreover, LBP intensity decreased significantly between 1 and 3 months ($p < .001$), but this effect was not significantly different between the two SMT groups and the control group ($p = .91$), or between the SMT-G and SMT-L groups ($p = .94$). **B)** Average pain ratings for each stimulus type, group, and time point. Across all time points, pain ratings elicited by pulse train stimuli were significantly higher than those elicited by single pulses ($p < .001$), confirming that repeated laser stimulation induced TSSP. TSSP values were calculated by subtracting single pulse ratings from

pulse train ratings. TSSP decreased significantly over time ($p = .003$). However, this effect was not significantly different between groups ($p = .95$). Orthogonal planned contrasts revealed that TSSP significantly decreased from baseline to the two primary endpoints combined (one and three months) ($p = .002$), but not between one and three months ($p = .08$). Error bars represent the corrected SD. TSSP: temporal summation of second pain.

Table 5.2 – Participants achieving the minimal clinically important difference (MCID) in low back pain intensity during the intervention period, n (%)

1 month (after 12 sessions)				
Methods	MCID	Control intervention (n =13)	SMT-G (n = 15)	SMT-L (n = 15)
Distribution-Based Methods				
MCID = 0.5 x SD of the Δ scores	1.3	4 (30.8)	12 (80.0)	8 (53.3)
MCID based on the medium effect size	0.2	9 (69.2)	14 (93.3)	11 (73.3)
Anchor-Based Methods				
95% limits of lower agreement	1.4	4 (30.8)	12 (80.0)	8 (53.3)
Within-patients score change	2.4	2 (15.4)	10 (66.7)	2 (13.3)
3 months (after 36 sessions)				
Methods	MCID	Control intervention (n =13)	SMT-G (n = 15)	SMT-L (n = 15)
Distribution-Based Methods				
MCID = 0.5 x SD of the Δ scores	1.3	8 (61.5)	14 (93.3)	10 (66.7)
MCID based on the medium effect size	0.5	11 (84.6)	15 (100)	14 (93.3)
Anchor-Based Methods				
95% limits of lower agreement	4.4	2 (15.4)	7 (46.7)	2 (13.3)
Within-patients score change	3.6	2 (15.4)	12 (80.0)	3 (20.0)

TSSP

From baseline to 3 months, the mean change in TSSP was -5.7, 95% CI [-12.9, 1.5] for the SMT-G group, -8.3, 95% CI [-16.4, -0.1] for the SMT-L group, and -5.2, 95% CI [-9.9, -0.5] for the control intervention group. TSSP was compared between groups over time using a mixed ANOVA (**Figure 5.3B**). TSSP was not significantly different between groups (main effect: $F_{2, 40} = 1.83$, $p = .17$, $\eta^2_p = .08$, 95% CI [.03, 1]) but decreased significantly over time (main effect: $F_{1.8, 73.6} = 6.5$, $p = .003$, $\eta^2_p = .14$, 95% CI [.03, 1]). However, this effect was not significantly different between groups (interaction: $F_{3.7, 73.6} = 0.16$, $p = .95$, $\eta^2_p = .008$, 95% CI [0, 1]), indicating that TSSP was not reduced significantly in the SMT groups compared with the control intervention group. For the significant reduction of TSSP over time, orthogonal planned contrasts revealed that TSSP significantly decreased from baseline to the two primary endpoints combined (1 and 3 months) ($p = .002$), but not between the two primary endpoints ($p = .08$).

Secondary outcomes

LBP frequency

Results from the secondary clinical outcomes are presented in **Figure 5.4**. From baseline to 3 months, the mean change in LBP frequency (days per week) was -3.1, 95% CI [-4.6, -1.5] for the SMT-G group, -2.1, 95% CI [-3.6, -0.7] for the SMT-L group, and -1.4, 95% CI [-2.7, -0.04] for the control intervention group. These changes were compared between groups using a mixed ANOVA (**Figure 5.4A**). LBP frequency was not significantly different between groups (main effect: $F_{2, 40} = 0.45$, $p = .64$, $\eta^2_p = .02$, 95% CI [0, 1]) but decreased significantly over time (main effect: $F_{1.8, 70.5} = 20.7$, $p < .001$, $\eta^2_p = .34$, 95% CI [.20, 1]). However, this effect was not significantly different between groups (interaction: $F_{3.5, 70.5} = 1.3$, $p = .23$, $\eta^2_p = .06$, 95% CI [0, 1]), indicating that LBP frequency was not reduced significantly in the SMT groups compared with the control intervention group. For the significant reduction over time, orthogonal planned contrasts revealed that LBP frequency decreased significantly from baseline to the two other time points combined ($p < .001$), as well as from 1 to 3 months ($p < .001$).

Global impression of change

From the first to the second primary endpoint, the global impression of change increased by 28.0, 95% CI [18.3, 37.7] for the SMT-G group, and by 33.7, 95% CI [22.7, 44.8] for the SMT-L group, and by 38.7, 95% CI [26.2, 51.1] for the control intervention group. The efficacy of SMT was assessed using a mixed ANOVA comparing global impression of change between groups over time (**Figure 5.4B**). Global impression of change was not significantly different between groups (main effect: $F_{2, 40} = 0.63$, $p = .44$, $\eta^2_p = .03$, 95% CI [0, 1]) but increased significantly over time (main effect: $F_{1.9, 74.8} = 65.91$, $p < .001$, $\eta^2_p = .62$, 95% CI [.51, 1]). However, this effect was not significantly different between groups (interaction: $F_{3.7, 74.8} = 0.55$, $p = .69$, $\eta^2_p = .03$, 95% CI [0, 1]). Moreover, orthogonal planned contrasts showed that global impression of change significantly increased from 1 month to the two other time points combined ($p < .001$), and from 2 to 3 months ($p = .001$), suggesting that participants generally improved with additional sessions, regardless of group allocation.

LBP related disability

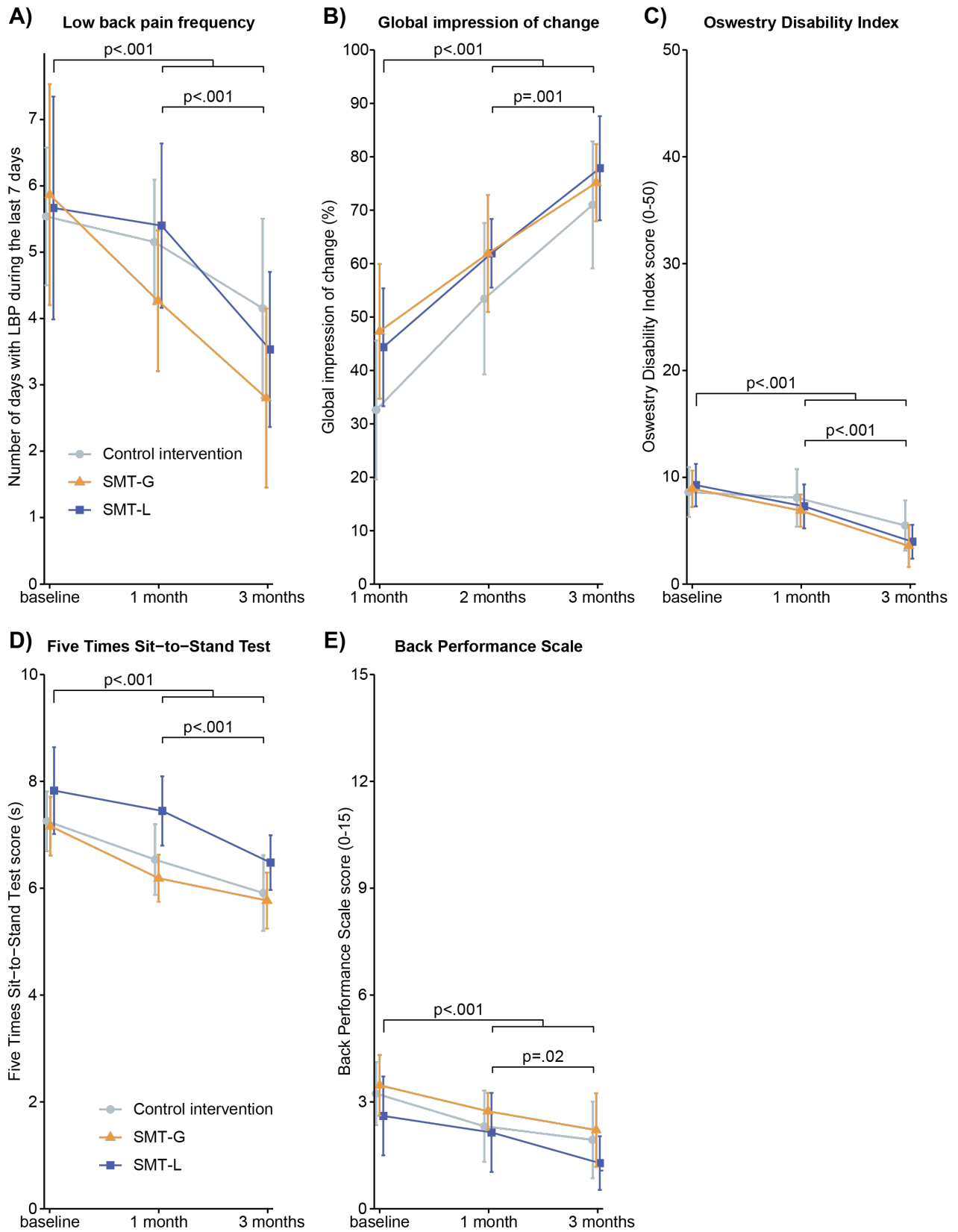
Results from LBP related disability outcomes are presented in **Figure 5.4C-5.4E**. From baseline to the second primary endpoint, the mean reduction in ODI scores was -5.4, 95% CI [-7.3, -3.5] for the SMT-G group, -5.3, 95% CI [-7.0, -3.7] for the SMT-L group, and -3.2, 95% CI [-5.5, -0.8] for the control intervention group. The efficacy of SMT was assessed using a mixed ANOVA comparing ODI scores between groups over time (**Figure 5.4C**). ODI scores were not significantly different between groups (main effect: $F_{2, 40} = 0.40$, $p = .67$, $\eta^2_p = .02$, 95% CI [0, 1]) but they decreased significantly over time (main effect: $F_{2.0, 79.4} = 37.91$, $p < .001$, $\eta^2_p = .49$, 95% CI [.35, 1]). However, this effect was not significantly different between groups (interaction: $F_{4.0, 79.4} = 0.92$, $p = .46$, $\eta^2_p = .04$, 95% CI [0, 1]).

In addition, from baseline to the second primary endpoint, the mean reduction in FTSST scores was -1.4 s, 95% CI [-1.9, -0.9] for the SMT-G group, -1.4 s, 95% CI [-2.0, -0.7] for the SMT-L group, and -1.4 s, 95% CI [-2.0, -0.7] for the control intervention group. The efficacy of SMT was assessed using a mixed ANOVA comparing FTSST scores between groups over time (**Figure 5.4D**). FTSST scores were not significantly different between groups (main effect: $F_{2, 40} = 1.19$, $p = .32$, $\eta^2_p = .06$, 95% CI [0, 1]) but they decreased significantly over time (main effect: $F_{2.0, 78.1} = 35.65$, p

$< .001$, $\eta^2_p = .47$, 95% CI [.34, 1]). However, this effect was not significantly different between groups (interaction: $F_{3.9, 78.1} = 0.75$, $p = .56$, $\eta^2_p = .04$, 95% CI [0, 1]).

Similarly, from baseline to the second primary endpoint, the mean reduction in BPS scores was -1.3, 95% CI [-2.3, -0.3] for the SMT-G group, -1.3, 95% CI [-2.2, -0.5] for the SMT-L group, and -1.3, 95% CI [-2.3, -0.3] for the control intervention group. The efficacy of SMT was assessed using a mixed ANOVA comparing BPS scores between groups over time (**Figure 5.4E**). BPS scores were not significantly different between groups (main effect: $F_{2, 40} = 0.64$, $p = .53$, $\eta^2_p = .03$, 95% CI [0, 1]) but they decreased significantly over time (main effect: $F_{2.0, 79.6} = 13.52$, $p < .001$, $\eta^2_p = .25$, 95% CI [.12, 1]). However, this effect was not significantly different between groups (interaction: $F_{4.0, 79.6} = 0.20$, $p = .94$, $\eta^2_p = .01$, 95% CI [0, 1]).

Figure 5.4 – Changes in secondary clinical outcomes between groups over time



A) Average low back pain frequency. **B)** Average global impression of change. **C)** Average Oswestry Disability Index scores. **D)** Average times to perform the five times sit-to-stand test. **E)** Average back performance scale scores. These outcomes were not significantly different between groups (all $p > .32$) but they improved significantly over time (all $p < .001$). However, this effect was not significantly different between groups (all $p > .23$). For the significant improvement over time, orthogonal planned contrasts revealed that these secondary outcomes improved significantly from the first to the two other time points combined (all $p < .001$), as well as from the second to the third time point (all $p < .02$). Values represent average scores for each group and time point and error bars represent the corrected SD.

Orthogonal planned contrasts to decompose the significant main effect of time revealed that ODI, FTSST and BPS scores significantly decreased from baseline to the two other time points combined (all $p < .001$), as well as from 1 to 3 months (all $p < .02$), suggesting a progressive reduction of disability with additional sessions, regardless of the intervention groups.

Co-interventions and adverse events

A timeline of co-interventions and adverse events by participants is presented in **Figure 5.5**. The proportions of sessions for which participants reported using a concomitant intervention for pain relief, either for LBP or for pain in other body regions, as well as the proportions of sessions with reported AEs, are presented in **Table 5.3**. The Chi-Square test revealed that the proportion of sessions for which participants reported the use of a co-intervention for LBP was significantly different between groups ($\chi^2(2, N = 49) = 123.4, p < .001$). In the SMT-G group, the use of a co-intervention for LBP was reported for 3.0% of the sessions, while it was reported for 13.2% and 26.6% of the sessions for SMT-L and the control intervention groups, respectively. In contrast, the use of a co-intervention for pain in other body areas was not significantly different between groups ($\chi^2(2, N = 49) = 2.4, p = .30$). Oral NSAIDs were the most frequently reported co-intervention (see Table 3).

Considering these findings, it is possible that co-interventions contributed to pain relief during the interventions, particularly for the control intervention and SMT-L. Greater use of co-interventions in these groups may have inflated pain relief, hiding specific effects of SMT or greater pain relief by SMT-G compared with SMT-L. To examine these possibilities, changes in LBP intensity at 1 month and at 3 months were compared between groups using ANCOVAs, with the number of sessions for which co-interventions were reported as covariate.

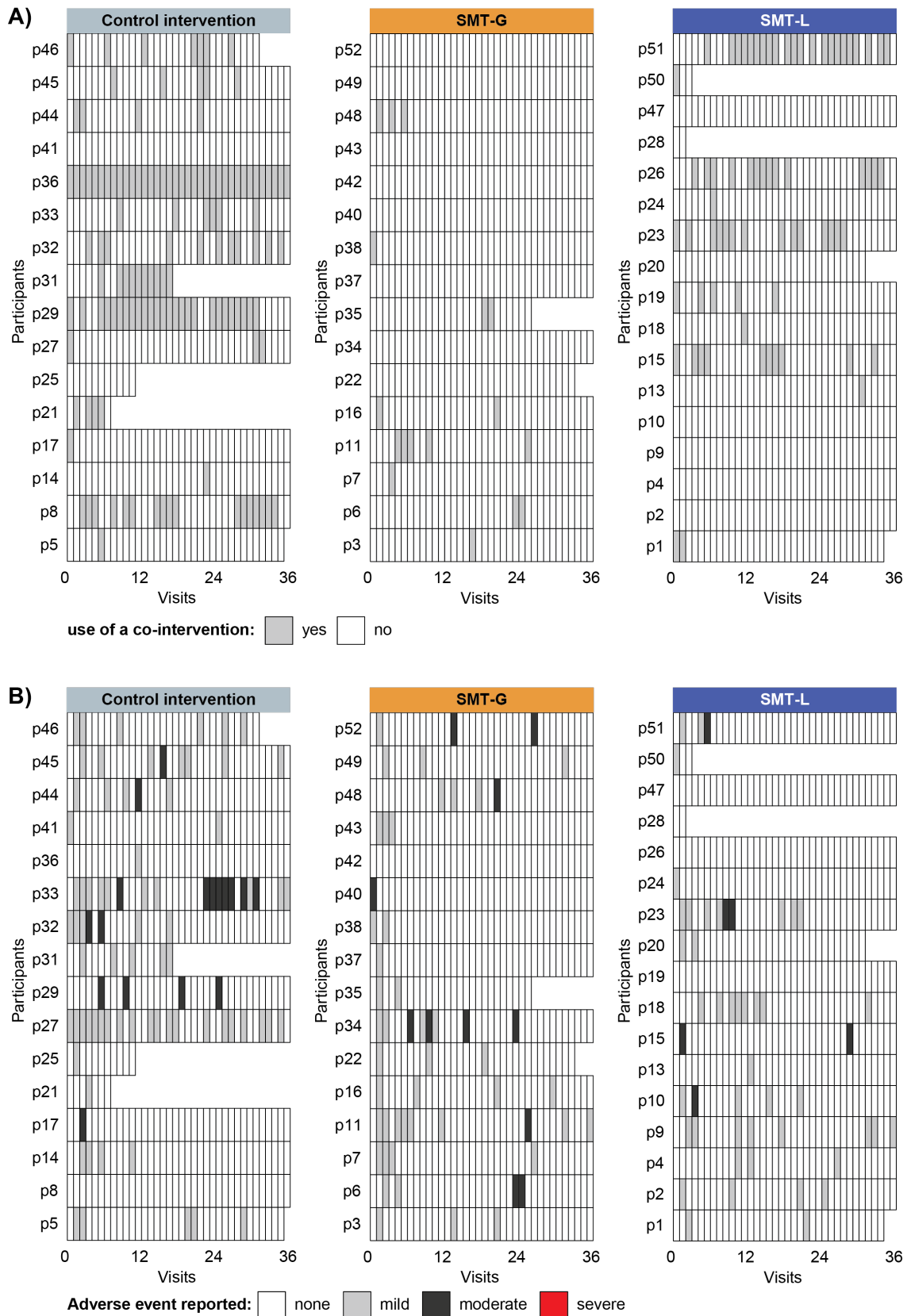
For changes in LBP intensity at 1 month, groups were significantly different after controlling for co-interventions ($F_{2, 39} = 3.28$, $p = .048$, $\eta^2_p = .14$, 95% CI [0, 1]). Orthogonal planned contrasts revealed that pain relief in the two SMT groups was not significantly greater compared with the control intervention group ($p = .14$), but SMT-G produced greater effects compared with SMT-L ($p = .04$). For changes in LBP intensity at 3 months, groups were significantly different after controlling for co-interventions ($F_{2, 39} = 3.25$, $p = .050$, $\eta^2_p = .14$, 95% CI [0, 1]). Orthogonal planned contrasts revealed that pain relief in the two SMT groups was not significantly greater compared with the control intervention group ($p = .14$), but SMT-G produced greater effects compared with SMT-L ($p = .04$). This shows that the specific effects of SMT-G are independent of co-interventions and that they persist over three months.

Similarly, it is possible that co-interventions confounded different changes between groups. To examine these possibilities, changes in TSSP at one month and at three months were compared between groups using ANCOVAs, with the number of sessions for which co-interventions were reported as covariate. For changes in TSSP at 1 month, groups were not significantly different after controlling for co-interventions ($F_{2, 39} = 0.09$, $p = .91$, $\eta^2_p = .005$, 95% CI [0, 1]). Similarly, for changes in TSSP at 3 months, groups were not significantly different after controlling for co-interventions ($F_{2, 39} = 0.29$, $p = .75$, $\eta^2_p = .01$, 95% CI [0, 1]).

Besides, the Chi-Square test revealed that the proportion of sessions for which participants reported AEs was significantly different between groups ($\chi^2(2, N = 49) = 22.75$, $p < .001$). In the SMT-G group, AEs occurred for 9.6% of the sessions, while they occurred for 9.1% and 17.7% of the sessions for SMT-L and the control intervention groups, respectively. The

majority of AEs were mild (82.2 %), with moderate AEs accounting for the remaining 17.8 %. No severe adverse event was reported during this study, and AE severity was not significantly different between groups ($\chi^2(2, N = 49) = 1.41, p = .49$).

Figure 5.5 – Timeline of co-intervention use and adverse event reports by participants



A) Co-intervention use over time for each participant. The proportion of sessions for which participants reported the use of a co-intervention for LBP was significantly different between groups ($p < .001$). **B)** Occurrence and severity of adverse events reported over time for each participant. The proportion of sessions for which participants reported AEs was significantly different between groups ($p < .001$). Blank rows indicate when participants discontinued the intervention.

Table 5.3 – Number of sessions, co-interventions and adverse events for each group, n(%)

	Control intervention (n =16)	SMT-G (n = 16)	SMT-L (n = 17)
Total number of sessions provided	497	563	538
Co-interventions for low back pain	132 (26.6)	17 (3.0)	71 (13.2)
Interventions for pain elsewhere	41 (8.2)	41 (7.3)	53 (9.9)
Type of co-interventions			
oral NSAIDs	106 (61.3)	37 (63.8)	34 (27.4)
topical cream	4 (2.3)	2 (3.4)	8 (6.5)
opioids	36 (20.8)	0 (0)	0 (0)
other medication	17 (9.8)	1 (1.7)	1 (0.8)
massage	3 (1.7)	3 (5.2)	23 (18.5)
physical therapy	0 (0)	13 (22.4)	19 (15.3)
therapeutic exercises	2 (1.2)	0 (0)	2 (1.6)
heat or cold	2 (1.2)	2 (3.4)	23 (18.5)
SMT (outside of group assignment)	0 (0)	-	14 (11.3)
other co-intervention	3 (1.7)	0 (0)	0 (0)
Total number of adverse events	88 (17.7)	54 (9.6)	49 (9.1)
mild adverse events	71 (80.7)	43 (79.6)	43 (87.8)
moderate adverse events	17 (19.3)	11 (20.4)	6 (12.2)
severe adverse events	0 (0)	0 (0)	0 (0)

Success of blinding

A total of 45 participants (15 per group) completed the blinding success assessment. All participants (100 %) in the two SMT groups and 11 out of 15 (73.3 %) in the control intervention group believed they received a real chiropractic intervention for LBP. This distribution differed significantly between groups, $\chi^2(2, N = 45) = 8.78, p = .01$. Among those who believed they had received a real chiropractic intervention, the average certainty score was 9.1, 95% CI [8.5, 9.7] in the SMT-G group, 8.8, 95% CI [8.1, 9.5] in the SMT-L group, and 8.0, 95% CI [6.7, 9.3] in the control group. These certainty scores did not differ significantly between groups, $F(2, 38) = 1.85, p = .17, \eta^2_p = .09, 95\% \text{ CI } [0, 1]$. In contrast, the four participants in the control group who believed that they had received a placebo intervention reported a much lower average certainty score of 2.2 (95% CI [-0.5, 5.0]). Overall, the majority of participants (91%), including most participants in the control group (73.3%), believed that they received a real chiropractic intervention. This indicates that the blinding procedure was successful.

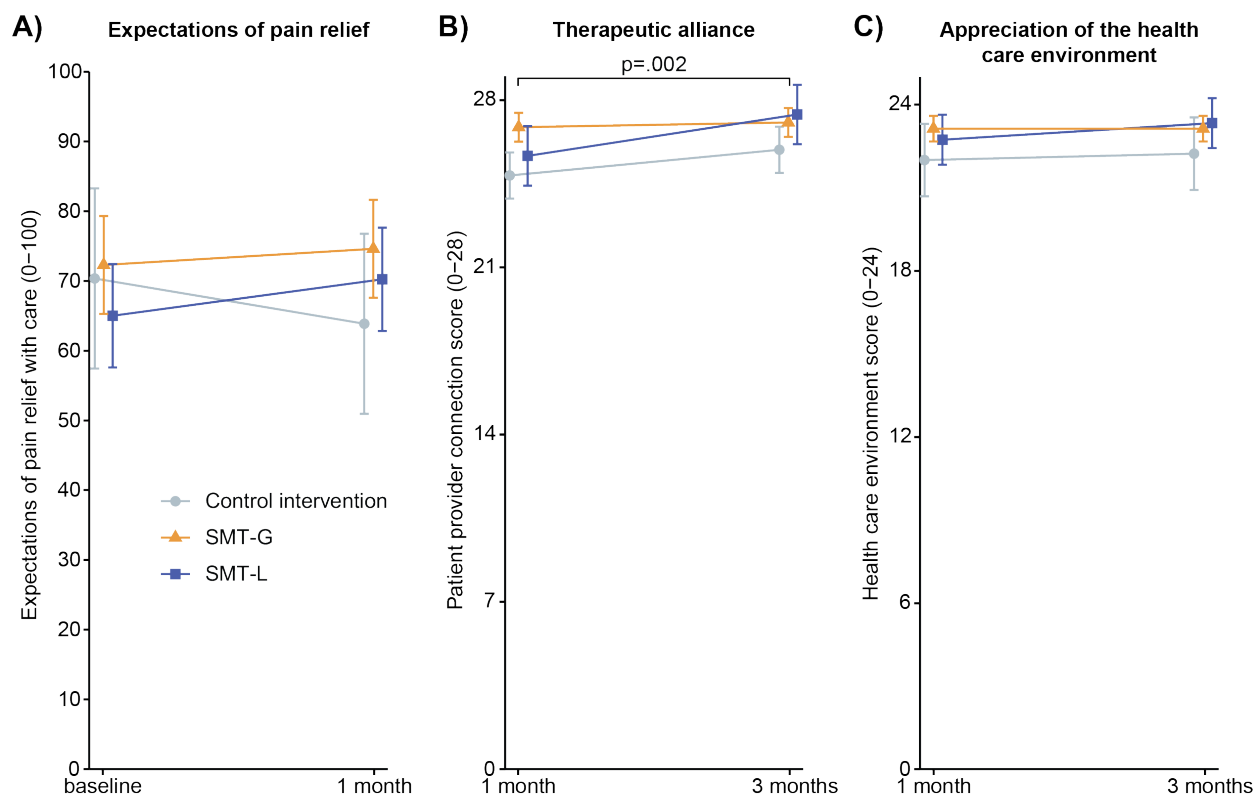
Expectations and contextual factors

Expectations of pain relief were compared between groups over time using a mixed ANOVA (**Figure 5.6A**). Expectations were not significantly different between groups (main effect: $F_{2,40} = 0.53, p = .59, \eta^2_p = .03, 95\% \text{ CI } [0, 1]$), over time (main effect: $F_{1,40} = 0.02, p = .90, \eta^2_p < .001, 95\% \text{ CI } [0, 1]$), or between groups over time (interaction: $F_{2,40} = 1.47, p = .25, \eta^2_p = .07, 95\% \text{ CI } [0, 1]$).

Patient-provider connection scores (Section 1 of the HEAL questionnaire) were compared between groups over time using a mixed ANOVA (**Figure 5.6B**). Therapeutic alliance was not significantly different between groups (main effect: $F_{2,40} = 2.07, p = .14, \eta^2_p = .09, 95\% \text{ CI } [0, 1]$) but increased significantly over time (main effect: $F_{1,40} = 11.32, p = .002, \eta^2_p = .22, 95\% \text{ CI } [.06, 1]$). However, this effect was not significantly different between groups (interaction: $F_{2,40} = 2.33, p = .11, \eta^2_p = .10, 95\% \text{ CI } [0, 1]$). This suggests that the therapeutic alliance strengthened over the course of the intervention in every group.

The health care environment scores (section 2 of the HEAL questionnaire) were also compared between groups over time using a mixed ANOVA (**Figure 5.6C**). These scores were not significantly different between groups (main effect: $F_{2, 40} = 1.84$, $p = .17$, $\eta^2_p = .08$, 95% CI [0, 1]), over time (main effect: $F_{1, 40} = 0.94$, $p = .34$, $\eta^2_p = .02$, 95% CI [0, 1]), or between groups over time (interaction: $F_{2, 40} = 0.39$, $p = .68$, $\eta^2_p = .02$, 95% CI [0, 1]). These findings indicate that expectations and contextual factors were comparable between groups.

Figure 5.6 – Changes in expectations and contextual factors between groups over time



A) Average expectations of pain relief with care for each group. No significant difference in expectations was observed between groups ($p = .59$), over time ($p = .90$), or between groups over time ($p = .25$). **B)** Average patient-provider connection scores for each group (section 1 of the HEAL questionnaire). Therapeutic alliance was not significantly different between groups ($p = .14$) but increased significantly over time ($p = .002$). However, this effect was not significantly different between groups ($p = .11$). **C)** Average healthcare environment scores for each group (section 2 of the HEAL questionnaire). No significant difference in the appreciation of the healthcare

environment was observed between groups ($p = .17$), over time ($p = .34$), or between groups over time ($p = .68$). Error bars represent the corrected SD.

Pain catastrophizing

Results from questionnaire outcomes are presented in **Figure 5.7**. From baseline to the second primary endpoint, the mean reduction in PCS scores was -6.3, 95% CI [-11.0, -1.7] for the SMT-G group, -9.3, 95% CI [-1.9, -5.4] for the SMT-L group, and -8.6, 95% CI [-13.1, -4.1] for the control intervention group. Pain catastrophizing was compared between groups over time using a mixed ANOVA (**Figure 5.7A**). PCS scores were not significantly different between groups (main effect: $F_{2, 40} = 1.99$, $p = .15$, $\eta^2_p = .09$, 95% CI [0, 1]) but they decreased significantly over time (main effect: $F_{1.8, 73.8} = 22.51$, $p < .001$, $\eta^2_p = .36$, 95% CI [.22, 1]). However, this effect was not significantly different between groups (interaction: $F_{3.7, 73.8} = 0.54$, $p = .70$, $\eta^2_p = .03$, 95% CI [0, 1]).

Pain vigilance

From baseline to the second primary endpoint, the mean reduction in PVAQ scores was -4.9, 95% CI [-8.5, -1.3] for the SMT-G group, -5.4, 95% CI [-9.8, -1.0] for the SMT-L group, and -8.2, 95% CI [-16.4, 0.1] for the control intervention group. Pain vigilance was compared between groups over time using a mixed ANOVA (**Figure 5.7B**). PVAQ scores were significantly different between groups (main effect: $F_{2, 40} = 4.20$, $p = .02$, $\eta^2_p = .17$, 95% CI [.02, 1]) and time (main effect: $F_{1.8, 70.9} = 11.63$, $p < .001$, $\eta^2_p = .23$, 95% CI [.1, 1]). However, pain vigilance was not significantly different between groups over time (interaction: $F_{3.5, 70.9} = 0.49$, $p = .72$, $\eta^2_p = .02$, 95% CI [0, 1]).

Kinesiophobia

From baseline to the second primary endpoint, the mean reduction in TSK scores was -1.4, 95% CI [-3.1, 0.3] for the SMT-G group, -3.8, 95% CI [-7.5, -0.1] for the SMT-L group, and -3.9, 95% CI [-8.1, 0.2] for the control intervention group. Kinesiophobia was compared between groups over time using a mixed ANOVA (**Figure 5.7C**). TSK scores were not significantly different between

groups (main effect: $F_{2, 40} = 1.24$, $p = .30$, $\eta^2_p = .06$, 95% CI [0, 1]), but they decreased significantly over time (main effect: $F_{1.5, 61.7} = 9.06$, $p = .001$, $\eta^2_p = .19$, 95% CI [.06, 1]). However, this effect was not significantly different between groups (interaction: $F_{3.7, 73.8} = 0.54$, $p = .70$, $\eta^2_p = .03$, 95% CI [0, 1]).

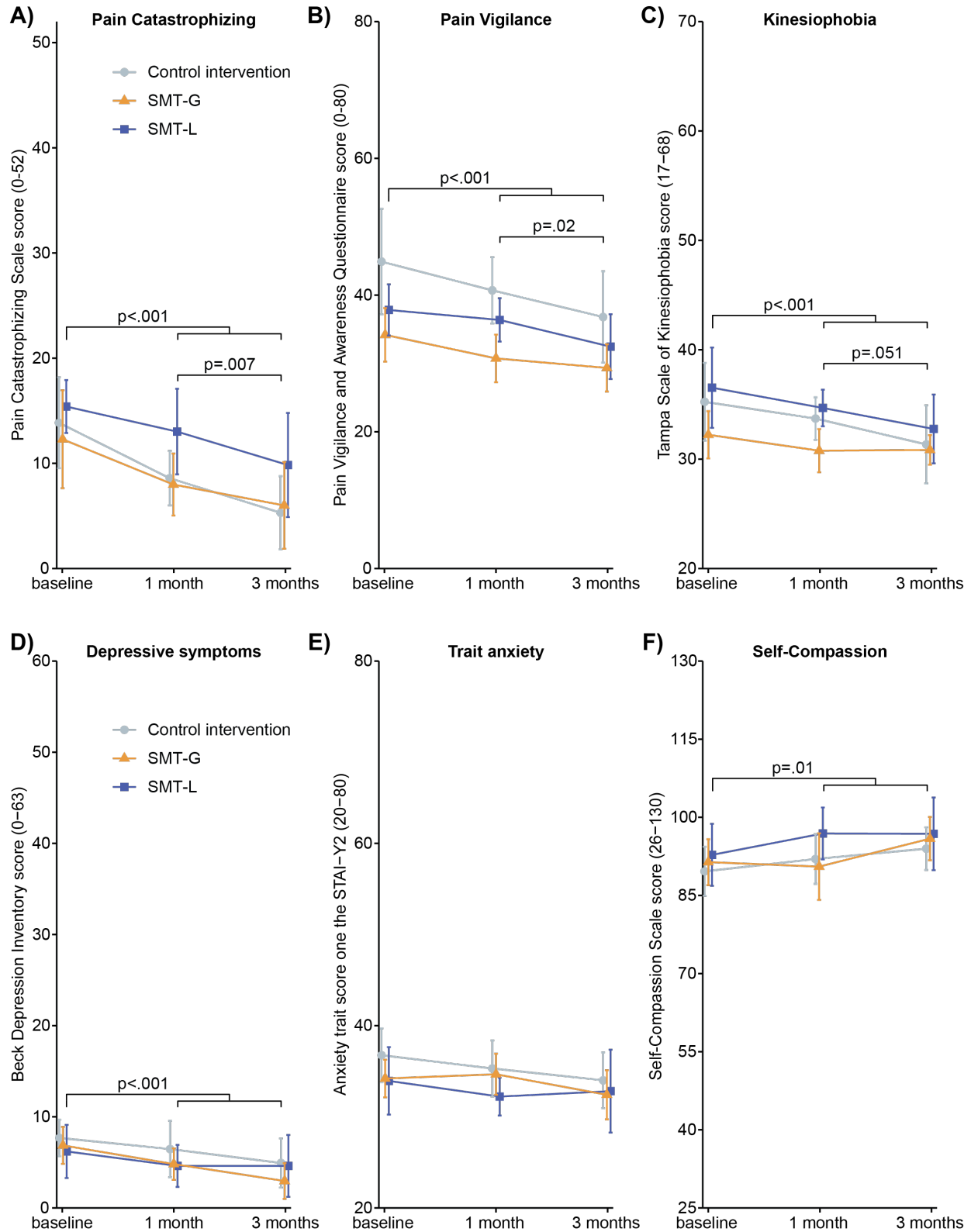
Depressive symptoms

From baseline to the second primary endpoint, the mean reduction in BDI scores was -3.9, 95% CI [-5.9, -1.9] for the SMT-G group, -1.6, 95% CI [-4.9, 1.7] for the SMT-L group, and -2.8, 95% CI [-5.0, -0.6] for the control intervention group. Depressive symptoms were compared between groups over time using a mixed ANOVA (**Figure 5.7D**). BDI scores were not significantly different between groups (main effect: $F_{2, 40} = 0.64$, $p = .53$, $\eta^2_p = .03$, 95% CI [0, 1]) but they decreased significantly over time (main effect: $F_{1.9, 77.1} = 8.61$, $p < .001$, $\eta^2_p = .18$, 95% CI [.06, 1]). However, this effect was not significantly different between groups (interaction: $F_{3.9, 77.1} = 0.65$, $p = .62$, $\eta^2_p = .03$, 95% CI [0, 1]).

Trait Anxiety

From baseline to the second primary endpoint, the mean reduction in STAI-Y2 scores was -1.8, 95% CI [-4.2, 0.6] for the SMT-G group, -1.1, 95% CI [-5.6, 3.3] for the SMT-L group, and -2.8, 95% CI [-5.9, 0.4] for the control intervention group. Anxiety was compared between groups over time using a mixed ANOVA (**Figure 5.7E**). STAI-Y2 scores were not significantly different between groups (main effect: $F_{2, 40} = 0.35$, $p = .70$, $\eta^2_p = .02$, 95% CI [0, 1]), over time (main effect: $F_{1.7, 68.6} = 2.76$, $p = .08$, $\eta^2_p = .07$, 95% CI [0, 1]), or between groups over time (interaction: $F_{3.4, 68.6} = 0.74$, $p = .55$, $\eta^2_p = .04$, 95% CI [0, 1]), indicating that anxiety was stable throughout the study period for the three groups.

Figure 5.7 – Changes in psychological factors between groups over time



A) Pain Catastrophizing Scale (PCS). PCS scores were not significantly different between groups ($p = .15$) but they decreased significantly over time ($p < .001$). However, this effect was not significantly different between groups ($p = .70$). **B) Pain Vigilance and Awareness Questionnaire (PVAQ).** PVAQ scores were significantly different between groups ($p = .02$) and time ($p < .001$). However, pain vigilance was not significantly different between groups over time ($p = .72$). **C) Tampa Scale of Kinesiophobia (TSK).** TSK scores were not significantly different between groups ($p = .30$), but they decreased significantly over time ($p = .001$). However, this effect was not significantly different between groups ($p = .70$). **D) Beck Depression Inventory (BDI).** BDI scores were not significantly different between groups ($p = .53$) but they decreased significantly over time ($p < .001$). However, this effect was not significantly different between groups ($p = .62$). **E) Trait subscale of the State-Trait Anxiety Inventory (STAI-Y2).** STAI-Y2 scores were not significantly different between groups ($p = .70$), over time ($p = .08$), or between groups over time ($p = .55$). **F) Self-Compassion Scale (SCS).** SCS scores were not significantly different between groups ($p = .79$) but they increased significantly over time ($p = .01$). However, this effect was not significantly different between groups ($p = .51$). For pain catastrophizing, pain vigilance, and kinesiophobia, orthogonal planned contrasts revealed significant decreases from baseline to the two other time points combined (PCS: $p < .001$, PVAQ: $p < .001$, and TSK: $p < .001$), and additional reductions from 1 to 3 months (PCS: $p = .007$, PVAQ: $p = .02$, and TSK: $p = .051$). In contrast, BDI scores decreased significantly from baseline to the two other time points combined (all $p < .001$), but not from 1 to 3 months ($p = .09$). Similarly, SCS scores increased significantly from baseline to the two other time points combined ($p = .01$), but not from 1 to 3 months ($p = .09$). Values represent average scores for each group and time point. Error bars indicate corrected SD.

Self-compassion

From baseline to the second primary endpoint, the mean increase in SCS scores was 4.5, 95% CI [1.3, 7.7] for the SMT-G group, 4.1, 95% CI [-2.6, 10.7] for the SMT-L group, and 4.4, 95% CI [-0.1, 8.9] for the control intervention group. Changes in self-compassion were assessed using a mixed ANOVA comparing SCS scores between groups over time (**Figure 5.7F**). SCS scores were not significantly different between groups (main effect: $F_{2, 40} = 0.24$, $p = .79$, $\eta^2_p = .01$, 95% CI [0,

1]) but they increased significantly over time (main effect: $F_{2.0, 79.5} = 4.74$, $p = .01$, $\eta^2_p = .11$, 95% CI [.02, 1]). However, this effect was not significantly different between groups (interaction: $F_{3.9, 79.5} = 0.83$, $p = .51$, $\eta^2_p = .04$, 95% CI [0, 1]).

For pain catastrophizing, pain vigilance, and kinesiophobia, orthogonal planned contrasts revealed significant decreases from baseline to the two other time points combined (PCS: $p < .001$, PVAQ: $p < .001$, and TSK: $p < .001$), and additional reductions from 1 to 3 months (PCS: $p = .007$, PVAQ: $p = .02$, and TSK: $p = .051$). These findings indicate a progressive and sustained attenuation of pain catastrophizing, pain vigilance, and kinesiophobia until the end of the intervention, regardless of the intervention group. In contrast, BDI scores decreased significantly from baseline to the two other time points combined (all $p < .001$), but not from 1 to 3 months ($p = .09$). Similarly, SCS scores increased significantly from baseline to the two other time points combined ($p = .01$), but not from 1 to 3 months ($p = .09$). These findings indicate that BDI and SCS scores improved primarily during the first month of care, regardless of the intervention group.

Quantitative sensory testing

The QST outcomes are presented in **Figure 5.8**. From baseline to the second primary endpoint, the mean change in mechanical pain sensitivity (PPT) in the lower back was -14.4 kPa, 95% CI [-100.5, 71.7] for the SMT-G group, 46.4 kPa, 95% CI [-27.6, 120.5] for the SMT-L group, and -69.5 kPa, 95% CI [-164.4, 24.4] for the control intervention group. The efficacy of SMT to reduce mechanical pain sensitivity was assessed using a mixed ANOVA to compare PPTs between groups over time (**Figure 5.8A**). PPTs were not significantly different between groups (main effect: $F_{2, 40} = 3.08$, $p = .06$, $\eta^2_p = .13$, 95% CI [0, 1]), over time (main effect: $F_{2.0, 79.7} = 0.35$, $p = .70$, $\eta^2_p = .009$, 95% CI [0, 1]), or between groups over time (interaction: $F_{3.4, 79.7} = 1.16$, $p = .34$, $\eta^2_p = .06$, 95% CI [0, 1]). This indicates that mechanical pain sensitivity in the lower back remained stable throughout the study period for the three groups.

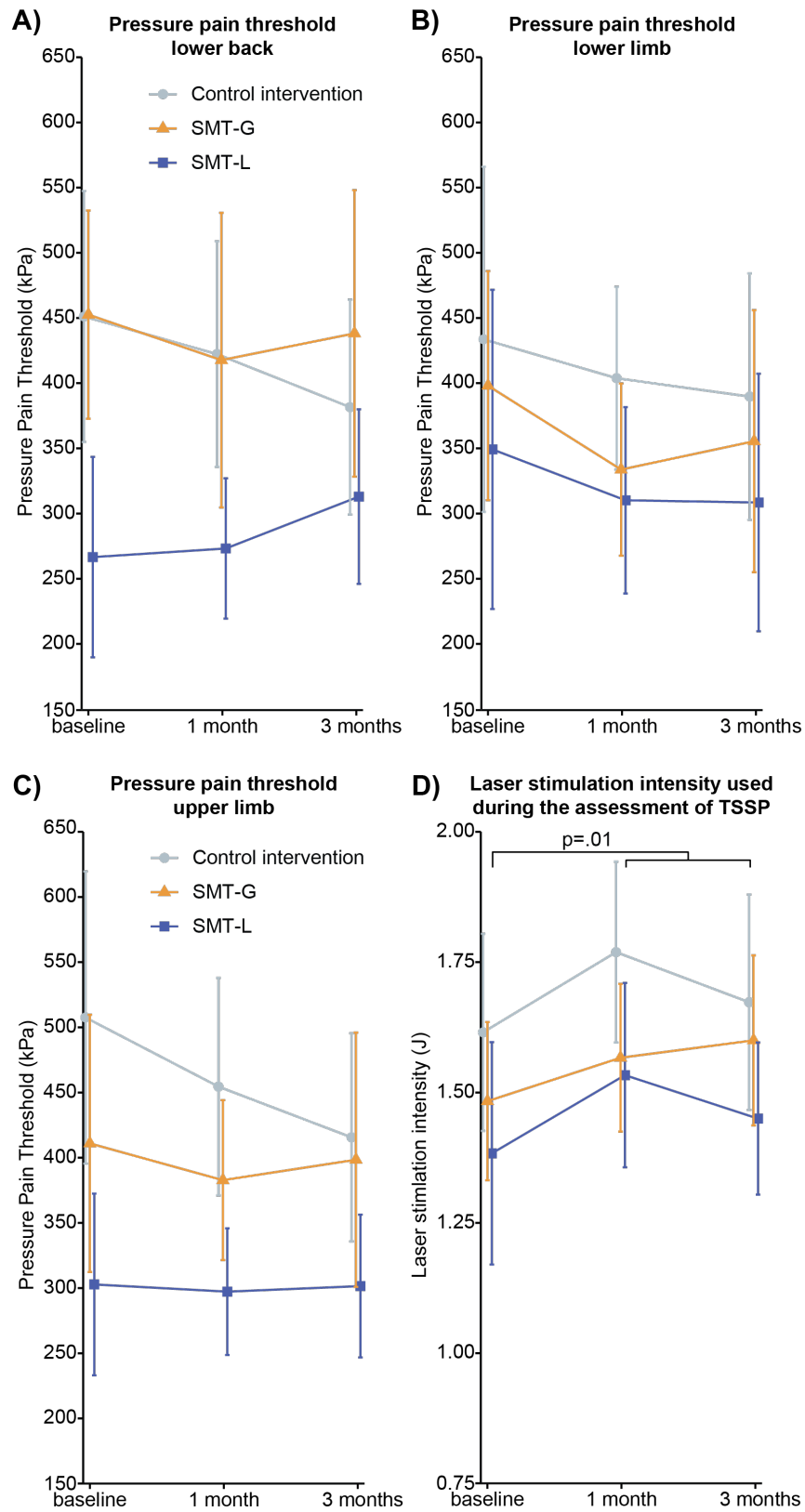
From baseline to the second primary endpoint, the mean change in mechanical pain sensitivity (PPT) in the right lower limb was -42.6 kPa, 95% CI [-140.6, 55.4] for the SMT-G group, -40.7 kPa, 95% CI [-157.4, 76.0] for the SMT-L group, and -44.0 kPa, 95% CI [-176.3, 88.4] for the

control intervention group. The efficacy of SMT to reduce mechanical sensitivity was assessed using a mixed ANOVA comparing PPTs between groups over time (**Figure 5.8B**). PPTs were not significantly different between groups (main effect: $F_{2, 40} = 0.89$, $p = .41$, $\eta^2_p = .04$, 95% CI [0, 1]), over time (main effect: $F_{1.6, 62.5} = 1.95$, $p = .16$, $\eta^2_p = .05$, 95% CI [0, 1]), or between groups over time (interaction: $F_{3.1, 62.5} = 0.11$, $p = .96$, $\eta^2_p = .006$, 95% CI [0, 1]). This indicates that mechanical pain sensitivity in the right lower limb remained stable throughout the study period for all groups.

From baseline to the second primary endpoint, the mean change in mechanical pain sensitivity (PPT) in the right hand was -12.5 kPa, 95% CI [-115.8, 90.7] for the SMT-G group, -1.3 kPa, 95% CI [-65.3, 62.7] for the SMT-L group, and -92.0 kPa, 95% CI [-198.2, 14.3] for the control intervention group. The efficacy of SMT to reduce mechanical pain sensitivity was assessed using a mixed ANOVA to compare PPTs between groups over time (**Figure 5.8C**). PPTs were not significantly different between groups (main effect: $F_{2, 40} = 2.24$, $p = .12$, $\eta^2_p = .10$, 95% CI [0, 1]), over time (main effect: $F_{1.7, 68.2} = 1.56$, $p = .22$, $\eta^2_p = .04$, 95% CI [0, 1]), or between groups over time (interaction: $F_{3.4, 68.2} = 0.90$, $p = .46$, $\eta^2_p = .04$, 95% CI [0, 1]), suggesting that mechanical pain sensitivity in the right hand remained stable throughout the study period for all groups.

Regarding thermal sensitivity, from baseline to the second primary endpoint, the mean change in laser stimulation intensity used to assess TSSP was 0.1 J, 95% CI [0.0, 0.3] for the SMT-G group, 0.1 J, 95% CI [-0.1, 0.2] for the SMT-L group, and 0.1 J, 95% CI [-0.2, 0.3] for the control intervention group. The laser stimulation intensity was compared between groups over time using a mixed ANOVA (**Figure 5.8D**). Laser stimulation intensity was not significantly different between groups (main effect: $F_{2, 40} = 1.73$, $p = .19$, $\eta^2_p = .08$, 95% CI [0, 1]) but significantly increased over time (main effect: $F_{2.0, 78.3} = 3.99$, $p = .02$, $\eta^2_p = .09$, 95% CI [.008, 1]). However, this effect was not significantly different between groups (interaction: $F_{3.9, 78.3} = 0.42$, $p = .80$, $\eta^2_p = .02$, 95% CI [0, 1]). Orthogonal planned contrasts revealed that laser stimulation intensity significantly increased from baseline to the two other time points combined ($p = .01$) but not from 1 to 3 months ($p = .29$), indicating that the change occurred during the first month of the intervention.

Figure 5.8 – Changes in quantitative sensory testing outcomes between groups over time



A) Average pressure pain thresholds (PPTs) at the lower back test location. **B)** Average PPTs at the right lower limb test location. **C)** Average PPTs at the right-hand test location. Across all test locations, no significant difference in PPTs was observed between groups (all $p > .06$), over time (all $p > .16$), or between groups over time (all $p > .34$). **D)** Average laser stimulation intensity used during the assessment of TSSP. Laser stimulation intensity was not significantly different between groups ($p = .19$) but significantly increased over time ($p = .02$). However, this effect was not significantly different between groups ($p = .80$). Orthogonal planned contrasts revealed that laser stimulation intensity significantly increased from baseline to the two other time points combined ($p = .01$) but not from 1 to 3 months ($p = .29$). Values represent average scores for each group and time point and error bars represent the corrected SD. TSSP: temporal summation of second pain.

C-fibers related brain responses

C-fibers related LEPs and ERSPs can be visualized in **Figures 5.9 and 5.10** respectively. The quantification of the amplitude of these responses is presented in **Figure 5.11** as well as **Tables 5.4 and 5.5**. As for TSSP, C-fibers related brain responses were compared between groups by subtracting the average value of the first pulse of the trains from the average value of the third pulse to estimate the intensity of the temporal summation for each participant and time point. From baseline to the second primary endpoint, the mean change in temporal summation of C-P2 peak amplitude was 0.0 μV , 95% CI [-1.0, 1.0] for the SMT-G group, -0.6 μV , 95% CI [-1.5, 0.3] for the SMT-L group, and -0.5 μV , 95% CI [-1.6, 0.7] for the control intervention group. The efficacy of SMT to modulate the C-LEPs was assessed using a mixed ANOVA to compare the temporal summation of C-P2 peak amplitude between groups over time (**Figure 5.11A**). C-P2 peak amplitude was not significantly different between groups (main effect: $F_{2,40} = 0.29$, $p = .74$, $\eta^2_p = .02$, 95% CI [0, 1]) but decreased significantly over time (main effect: $F_{2,0,78.4} = 3.83$, $p = .03$, $\eta^2_p = .09$, 95% CI [.006, 1]). However, this effect was not significantly different between groups (interaction: $F_{3,9,78.4} = 0.90$, $p = .47$, $\eta^2_p = .04$, 95% CI [0, 1]). This suggests that SMT did not reduce C-P2 peak amplitude significantly more than the control intervention. Moreover, orthogonal planned contrasts showed that temporal summation of C-P2 peak amplitude decreased

significantly from baseline to the two other time points combined ($p = .023$), but not from 1 to 3 months ($p = .13$), indicating that the change occurred during the first month of the intervention.

From baseline to the second primary endpoint, the mean change in temporal summation of the ERSP power within ROI1 (2-5 Hz $\times$ 500-1200 ms) was -0.8 dB, 95% CI [-2.0, 0.5], in the SMT-G group, -0.8 dB, 95% CI [-1.6, 0.0], in the SMT-L group, and 2.0 dB, 95% CI [-0.1, 4.1], in the control intervention group. The efficacy of SMT in modulating ERSP power in ROI1 was assessed using a mixed ANOVA comparing the temporal summation of the ERSP power between groups over time (**Figure 5.11B**). ERSP power was not significantly different between groups (main effect: $F_{2,40} = 0.34$, $p = .71$, $\eta^2_p = .02$, 95% CI [0, 1]), or over time (main effect: $F_{1.8,73.6} = 0.22$, $p = .79$, $\eta^2_p = .005$, 95% CI [0, 1]). However, it was significantly different between groups over time (interaction: $F_{3.7,73.6} = 4.58$, $p = .003$, $\eta^2_p = .19$, 95% CI [0.05, 1]). Orthogonal planned contrasts revealed that the decrease in temporal summation of ERSP power from baseline to the two primary endpoints was significantly greater for the two SMT groups compared with the control intervention group ($p = .04$), but this effect was not significantly different between the SMT-G and SMT-L groups during the same period ($p = .24$). Moreover, from one month to three months, the decrease in temporal summation of ERSP power was significantly greater for the two SMT groups compared with the control intervention group ($p = .005$). In addition, this effect was significantly greater in the SMT-L group compared with the SMT-G group during the same period ($p = .04$). This indicates that SMT (G and L) decreased the temporal summation of ERSP power within ROI1 mostly after one month of intervention.

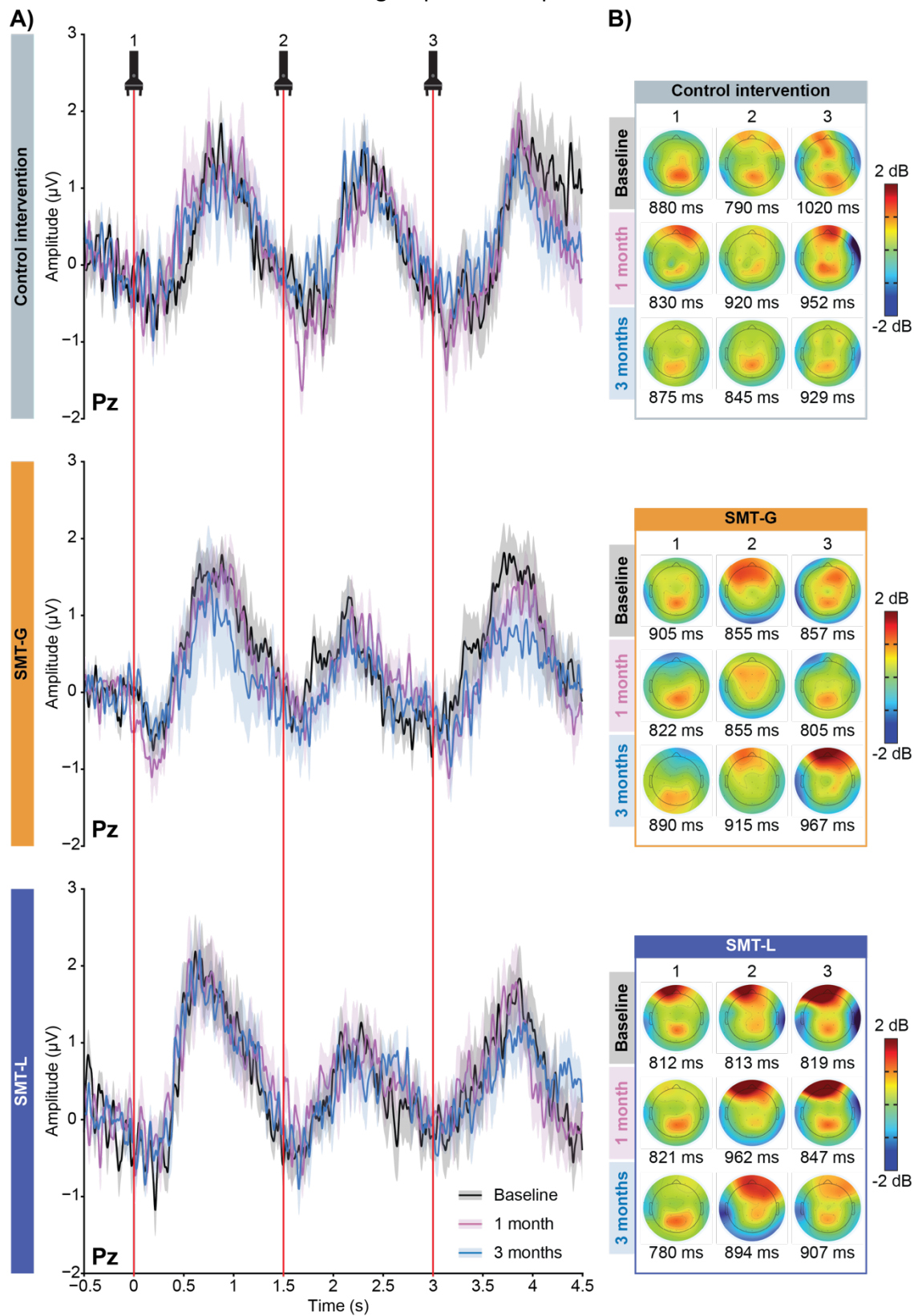
From baseline to the second primary endpoint, the mean change in temporal summation of the ERSP power within ROI2 (7-15 Hz $\times$ 1000-1500 ms) was -0.1 dB, 95% CI [-0.7, 0.5], in the SMT-G group, 0.3 dB, 95% CI [-0.4, 1.0], in the SMT-L group, and 0.1 dB, 95% CI [-0.4, 0.6], in the control intervention group. The efficacy of SMT in modulating ERSP power in ROI2 was assessed using a mixed ANOVA comparing the temporal summation of the ERSP power between groups over time (**Figure 5.11C**). ERSP power was not significantly different between groups (main effect: $F_{2,40} = 0.69$, $p = .51$, $\eta^2_p = .03$, 95% CI [0, 1]), over time (main effect: $F_{1.9,75.6} = 0.59$, $p = .55$, $\eta^2_p = .01$, 95% CI [0, 1]), or between groups over time (interaction: $F_{3.8,75.6} = 0.72$, $p = .57$, $\eta^2_p = .04$, 95%

CI [0, 1]), suggesting that temporal summation of the ERSP power within ROI2 remained stable across groups throughout the study period.

Because co-interventions may have confounded between-group differences, changes in C-fiber-related brain responses at 1 and 3 months were compared between groups using ANCOVAs, with the number of sessions during which co-interventions were reported entered as a covariate. At 1 month, after controlling for co-interventions, groups did not differ significantly in temporal summation of C-P2 peak amplitude ($F_{2, 39} = 0.62$, $p = .54$, $\eta^2_p = .03$, 95% CI [0, 1]), ERSP power within ROI1 ($F_{2, 39} = 3.04$, $p = .06$, $\eta^2_p = .13$, 95% CI [0, 1]), or ERSP power within ROI2 ($F_{2, 39} = 0.68$, $p = .51$, $\eta^2_p = .03$, 95% CI [0, 1]).

Similarly, at 3 months, after controlling for co-interventions, no significant between-group differences were observed for temporal summation of C-P2 peak amplitude ($F_{2, 39} = 0.29$, $p = .75$, $\eta^2_p = .01$, 95% CI [0, 1]) or ERSP power within ROI2 ($F_{2, 39} = 0.75$, $p = .48$, $\eta^2_p = .04$, 95% CI [0, 1]). In contrast, a significant between-group difference was found for temporal summation of ERSP power within ROI1 ($F_{2, 39} = 6.10$, $p = .005$, $\eta^2_p = .24$, 95% CI [0, 1]). Orthogonal planned contrasts indicated that the reduction in temporal summation of ERSP power within ROI1 was significantly greater in the two SMT groups compared with the control intervention group ($p = .001$), whereas no significant difference was observed between SMT-G and SMT-L ($p = .83$). These results indicate that the reduction in temporal summation of ERSP power within ROI1 observed between 1 and 3 months was not attributable to the use of co-interventions.

Figure 5.9 – Average LEP waveforms and topographic maps during pulse train laser stimuli for each group and time point



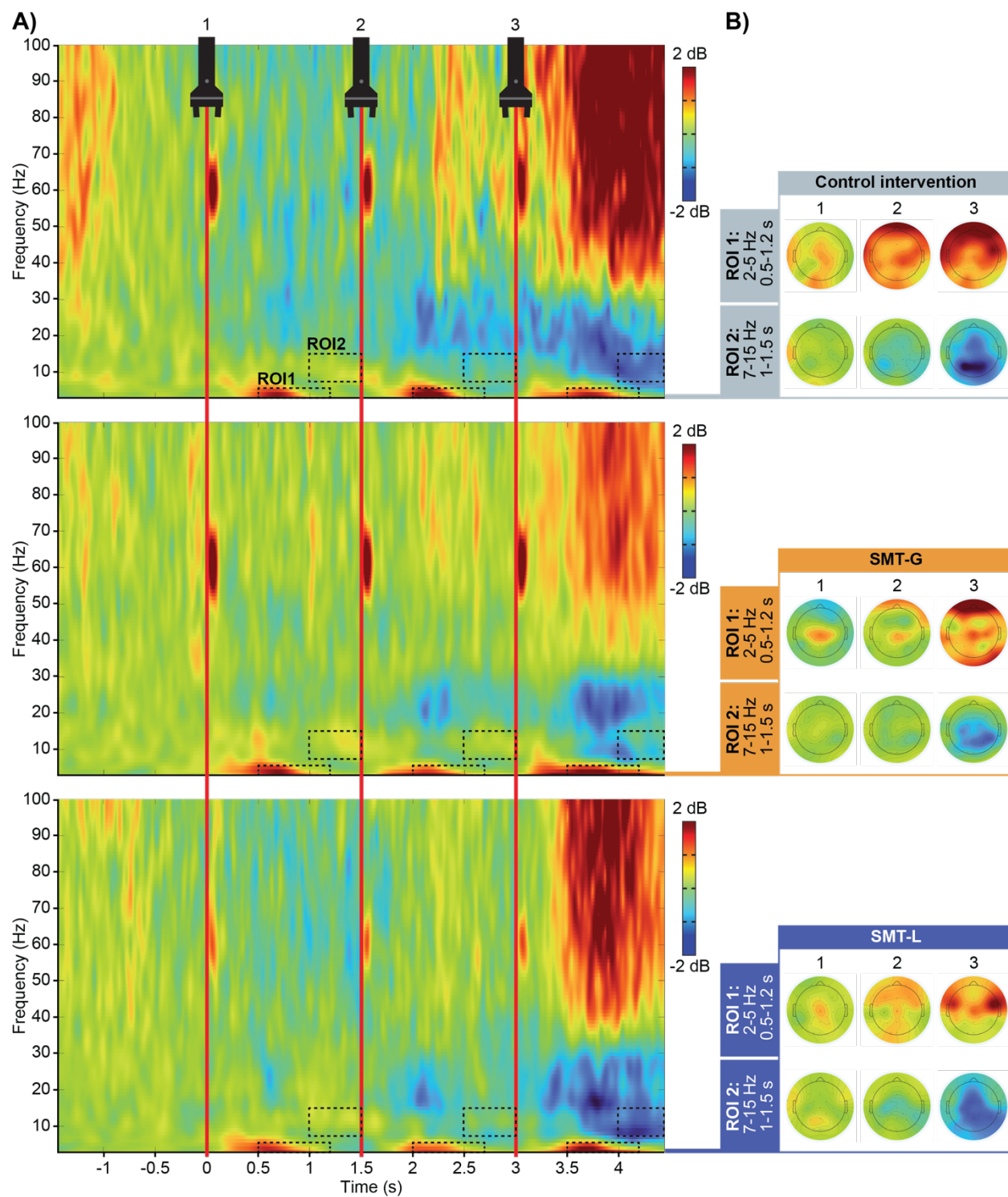
A) Average LEP waveforms at Pz for each group and time point. The lightly colored areas above and below the LEP waveforms represent the SEM. A slow wave was observed between 500 ms and 1500 ms in every group and time point, corresponding to the range of C-fiber conduction velocity.

B) Average topographic maps of the C-P2 components for each group, time point and each pulse of the pulse trains. Numbers 1, 2 and 3 represent the first, second and third pulse of the pulse trains.

Table 5.4 – C-LEPs peak amplitude (μV) and latency (ms) during pulse train stimuli (mean $\pm$ SD)

Time point	Pulse	Outcome	Control intervention	SMT-G	SMT-L
Baseline	1	C-P2 peak amplitude	2.8 $\pm$ 1.1	3.2 $\pm$ 1.3	3.4 $\pm$ 1.5
		C-P2 peak latency	880.6 $\pm$ 258.7	905.6 $\pm$ 254.1	812.5 $\pm$ 203.5
	2	C-P2 peak amplitude	2.7 $\pm$ 0.7	2.3 $\pm$ 1.4	2.6 $\pm$ 0.8
		C-P2 peak latency	790.5 $\pm$ 178.6	854.7 $\pm$ 277.1	811.7 $\pm$ 205.9
	3	C-P2 peak amplitude	3.3 $\pm$ 1.6	3.5 $\pm$ 1.2	3.4 $\pm$ 1.5
		C-P2 peak latency	1027.1 $\pm$ 303.9	857.3 $\pm$ 263	818.7 $\pm$ 255
1 month	1	C-P2 peak amplitude	3.1 $\pm$ 1.1	3.2 $\pm$ 1.3	3.4 $\pm$ 1.9
		C-P2 peak latency	829.8 $\pm$ 236.1	821.6 $\pm$ 227.5	820.8 $\pm$ 251.8
	2	C-P2 peak amplitude	2.8 $\pm$ 1.2	2.6 $\pm$ 1.5	2.8 $\pm$ 1.6
		C-P2 peak latency	920 $\pm$ 277.9	855.5 $\pm$ 180.1	961.6 $\pm$ 322.2
	3	C-P2 peak amplitude	2.5 $\pm$ 1.2	2.6 $\pm$ 1.8	3.1 $\pm$ 1.9
		C-P2 peak latency	952.9 $\pm$ 209.6	804.8 $\pm$ 264.2	846.7 $\pm$ 260.1
3 months	1	C-P2 peak amplitude	2.6 $\pm$ 1.5	2.4 $\pm$ 2.1	3.3 $\pm$ 1.3
		C-P2 peak latency	874.8 $\pm$ 290.1	889.9 $\pm$ 215.1	780 $\pm$ 217.1
	2	C-P2 peak amplitude	2.9 $\pm$ 1.0	2.7 $\pm$ 1.8	2.5 $\pm$ 1.2
		C-P2 peak latency	844.9 $\pm$ 248.8	914.9 $\pm$ 251.3	893.6 $\pm$ 241.7
	3	C-P2 peak amplitude	2.6 $\pm$ 1.2	2.7 $\pm$ 2.0	2.7 $\pm$ 1.0
		C-P2 peak latency	928.9 $\pm$ 264.4	967.2 $\pm$ 267.5	906.7 $\pm$ 296.7

Figure 5.10 – Average time-frequency and topographic maps during pulse train laser stimuli for each group at baseline



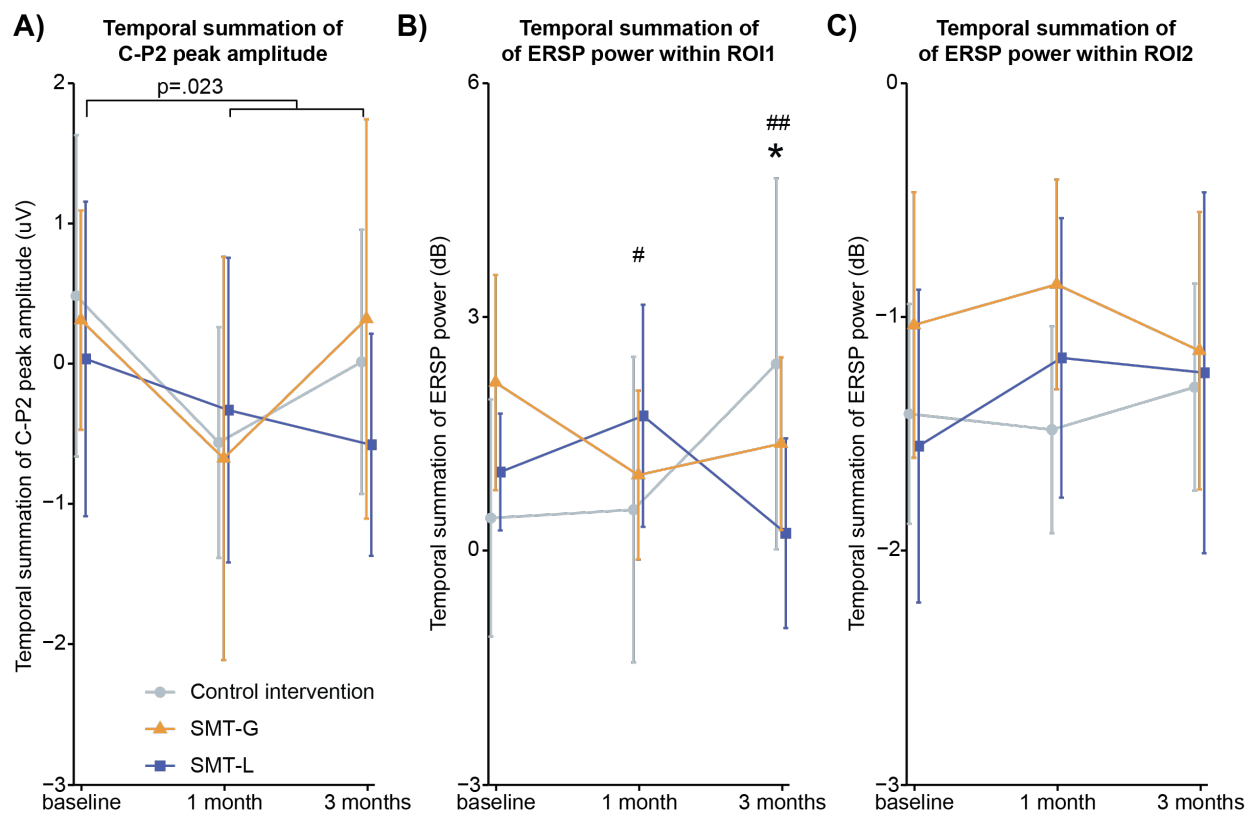
A) Average time-frequency maps at baseline for each group in each of the three regions of interest (ROI). **B)** Average topographic maps of the time-frequency activity in each ROI for each pulse of the pulse train stimuli. Numbers 1, 2 and 3 represent the first, second and third pulse of the pulse trains. ROIs are highlighted by the dashed-line rectangles and labeled 1 and 2. Note the synchronization between 2 Hz and 5 Hz and the desynchronization between 10 Hz and 30 Hz. See the main text and Figure 5.11 for detailed statistical comparisons. Note the stimulation artifact, visible as a power increase at 60 Hz immediately following stimulus onset. To avoid redundancy, only the average time-frequency and topographic maps at baseline are presented.

Table 5.5 – ERSP power (dB) in each region of interest during pulse train stimuli (mean $\pm$ SD)

Time point	Pulse	ROI	Control intervention	SMT-G	SMT-L
Baseline	1	1	2.2 $\pm$ 1.4	2.5 $\pm$ 2.0	2.0 $\pm$ 1.3
		2	-0.9 $\pm$ 0.8	-0.8 $\pm$ 0.4	-0.9 $\pm$ 1.0
	2	1	2.9 $\pm$ 2.5	2.7 $\pm$ 2.5	2.0 $\pm$ 1.5
		2	-1.5 $\pm$ 0.9	-0.9 $\pm$ 0.6	-1.3 $\pm$ 1.2
	3	1	2.6 $\pm$ 1.6	4.6 $\pm$ 3.7	3.0 $\pm$ 1.7
		2	-2.3 $\pm$ 1.0	-1.9 $\pm$ 1.1	-2.4 $\pm$ 1.1
1 month	1	1	2.2 $\pm$ 1.4	2.7 $\pm$ 1.4	2.4 $\pm$ 1.7
		2	-1.2 $\pm$ 0.6	-1.0 $\pm$ 0.4	-0.8 $\pm$ 0.8
	2	1	1.9 $\pm$ 1.1	2.5 $\pm$ 1.8	2.8 $\pm$ 2.4
		2	-1.5 $\pm$ 0.9	-1.1 $\pm$ 0.7	-1.2 $\pm$ 0.9
	3	1	2.7 $\pm$ 1.8	3.6 $\pm$ 2.8	4.1 $\pm$ 2.8
		2	-2.7 $\pm$ 1.0	-1.8 $\pm$ 1.3	-1.9 $\pm$ 1.0
3 months	1	1	1.9 $\pm$ 0.6	1.8 $\pm$ 1.1	2.4 $\pm$ 0.8
		2	-0.7 $\pm$ 0.6	-1.0 $\pm$ 0.7	-0.8 $\pm$ 0.4
	2	1	2.1 $\pm$ 0.9	1.9 $\pm$ 2.2	1.9 $\pm$ 1.2
		2	-1.2 $\pm$ 0.8	-1.2 $\pm$ 0.7	-1.0 $\pm$ 0.9
	3	1	4.3 $\pm$ 2.9	3.2 $\pm$ 3.1	2.6 $\pm$ 1.4
		2	-2.0 $\pm$ 1.3	-2.2 $\pm$ 1.2	-2.0 $\pm$ 1.3

ROI: region of interest

Figure 5.11 – Changes in temporal summation of the C-fibers related brain responses between groups over time



A) Average temporal summation of the peak amplitudes of the C-P2 component. C-P2 peak amplitude was not significantly different between groups ($p = .74$) but decreased significantly over time ($p = .03$), yet this effect was not significantly different between groups ($p = .47$). **B)** Average temporal summation in ERSP power within the first ROI (2-5 Hz $\times$ 500-1200 ms). ERSP power was not significantly different between groups ($p = .71$), or over time ($p = .79$). However, it was significantly different between groups over time ($p = .003$). Orthogonal planned contrasts revealed that the decrease in temporal summation of ERSP power from baseline to the two primary endpoints was significantly greater for the two SMT groups compared with the control intervention group (#: $p = .04$), but this effect was not significantly different between the SMT-G and SMT-L groups during the same time period ($p = .24$). Moreover, from 1 month to 3 months, the decrease in temporal summation of ERSP power was significantly greater for the two SMT groups compared with the control intervention group (##: $p = .005$). In addition, this effect was

significantly greater in the SMT-L group compared with the SMT-G group during the same time period (*: $p = .04$). **C)** Average temporal summation in ERSP power within the second region of interest (7-15 Hz $\times$ 1000-1500 ms). ERSP power was not significantly different between groups ($p = .51$), over time ($p = .55$), or between groups over time ($p = .57$). Values represent average delta scores (pulse 3 minus pulse 1) for each group and time point, and error bars indicate corrected SD. ROI: region of interest.

Assessment of potential confounding influences on low back pain intensity and C-fiber related brain responses

ANCOVAs were conducted to control for the potential influence of expectations of pain relief, therapeutic alliance, pain catastrophizing, kinesiophobia, depressive symptoms, and self-compassion on changes in LBP intensity. Unlike the other questionnaires, expectations and therapeutic alliance were assessed only at baseline and 1 month, and at 1 and 3 months, respectively (see the Experimental procedures section). Therefore, expectations at baseline and at 1 month, patient-provider connection scores at 1 and 3 months, and Δ scores (1 month minus baseline; 3 months minus baseline) for the PCS, TSK, BDI, and SCS were entered separately as covariates in individual models.

For changes in LBP intensity at 1 month, groups differed significantly after controlling for expectations at baseline ($F_{2, 39} = 5.33$, $p = .009$, $\eta^2_p = .21$, 95% CI [.04, 1]). Orthogonal planned contrasts revealed that pain relief in the two SMT groups was significantly greater compared with the control intervention group ($p = .03$), and that SMT-G produced greater effects compared with SMT-L ($p = .02$). At 3 months, groups also differed significantly after controlling for expectations at 1 month ($F_{2, 39} = 4.40$, $p = .02$, $\eta^2_p = .18$, 95% CI [.02, 1]). Orthogonal planned contrasts revealed that pain relief in the two SMT groups was not significantly greater compared with the control intervention group ($p = .09$), but SMT-G produced greater effects compared with SMT-L ($p = .02$).

For changes in LBP intensity at 1 month, groups were significantly different after controlling for therapeutic alliance at 1 month ($F_{2, 39} = 4.0$, $p = .03$, $\eta^2_p = .17$, 95% CI [.01, 1]). Orthogonal planned contrasts revealed that pain relief in the two SMT groups was not

significantly greater compared with the control intervention group ($p = .07$), but SMT-G produced greater effects compared with SMT-L ($p = .03$). At 3 months, groups were significantly different after controlling for therapeutic alliance at 3 months ($F_{2, 39} = 4.86$, $p = .01$, $\eta^2_p = .20$, 95% CI [.03, 1]). Orthogonal planned contrasts revealed that pain relief in the two SMT groups was not significantly greater compared with the control intervention group ($p = .07$), but SMT-G produced greater effects compared with SMT-L ($p = .02$).

Controlling for changes in pain catastrophizing, kinesiophobia, depressive symptoms, and self-compassion yielded a consistent pattern. At both 1 and 3 months, groups differed significantly after adjustment for changes in pain catastrophizing (1 month: ($F_{2, 39} = 5.42$, $p = .008$, $\eta^2_p = .22$, 95% CI [.04, 1]; 3 months: $F_{2, 39} = 5.72$, $p = .007$, $\eta^2_p = .23$, 95% CI [.05, 1]), kinesiophobia (1 month: $F_{2, 39} = 5.42$, $p = .008$, $\eta^2_p = .22$, 95% CI [.04, 1]; 3 months: $F_{2, 39} = 5.10$, $p = .01$, $\eta^2_p = .21$, 95% CI [.03, 1]), depressive symptoms (1 month: $F_{2, 39} = 5.27$, $p = .009$, $\eta^2_p = .21$, 95% CI [.04, 1]; 3 months: $F_{2, 39} = 4.65$, $p = .02$, $\eta^2_p = .19$, 95% CI [.02, 1]), and self-compassion (1 month: $F_{2, 39} = 5.42$, $p = .008$, $\eta^2_p = .22$, 95% CI [.04, 1]; 3 months: $F_{2, 39} = 5.20$, $p = .01$, $\eta^2_p = .21$, 95% CI [.03, 1]). Across these models, orthogonal planned contrasts showed that pain relief in the two SMT groups was significantly greater than in the control intervention group (all $p \leq .04$), and that SMT-G produced greater effects than SMT-L (all $p \leq .04$).

Overall, these results indicate that the greater reductions in LBP intensity observed with SMT, particularly SMT-G, persisted after controlling for expectations, therapeutic alliance, and changes in pain catastrophizing, kinesiophobia, depressive symptoms, and self-compassion. Although adjusting for expectations and therapeutic alliance attenuated differences between SMT and the control intervention at 3 months, SMT-G consistently produced greater pain relief than SMT-L across models.

Similarly, ANCOVAs were conducted to control for the potential influence of laser stimulation intensity on changes in C-fiber–related brain responses. Therefore, differences in laser stimulation intensity (1 month minus baseline; 3 months minus baseline) were entered separately as covariates in individual models. At 1 month, after controlling for changes in laser stimulation intensity, groups did not differ significantly in temporal summation of C-P2 peak

amplitude ($F_{2, 39} = 0.56$, $p = .57$, $\eta^2_p = .03$, 95% CI [0, 1]), ERSP power within ROI1 ($F_{2, 39} = 2.62$, $p = .08$, $\eta^2_p = .12$, 95% CI [0, 1]), or ERSP power within ROI2 ($F_{2, 39} = 0.87$, $p = .43$, $\eta^2_p = .04$, 95% CI [0, 1]). At 3 months, after controlling for changes in laser stimulation intensity, no significant between-group differences were observed for temporal summation of C-P2 peak amplitude ($F_{2, 39} = 0.45$, $p = .64$, $\eta^2_p = .02$, 95% CI [0, 1]) or ERSP power within ROI2 ($F_{2, 39} = 0.55$, $p = .58$, $\eta^2_p = .03$, 95% CI [0, 1]). However, groups differed significantly in temporal summation of ERSP power within ROI1 ($F_{2, 39} = 5.69$, $p = .007$, $\eta^2_p = .23$, 95% CI [.04, 1]). Orthogonal planned contrasts showed that the reduction of temporal summation of ERSP power within ROI1 was significantly greater in the two SMT groups than in the control intervention group ($p = .002$), with no significant difference between SMT-G and SMT-L ($p = .96$). These results indicate that the reduction in temporal summation of ERSP power within ROI1 was not attributable to individual differences in stimulation intensity.

Follow-up

Results from the secondary analysis are presented in Figure 5.12. Fifteen months post-randomization, the mean change in LBP intensity was -2.1, 95% confidence interval (CI) [-4.1, -0.1] for the SMT-G group, -2.4, 95% CI [-3.5, -1.2] for the SMT-L group, and -1.5 95% CI [-4.1, 1.0] for the control intervention group. The efficacy of SMT was first evaluated using a mixed ANOVA to compare LBP intensity between groups over time (Figure 5.12A). LBP intensity was not significantly different between groups (main effect: $F_{2, 38} = 0.53$, $p = .59$, $\eta^2_p = .03$, 95% CI [0, 1]) but it decreased over time (main effect: $F_{3.7, 140.7} = 11.65$, $p < .001$, $\eta^2_p = .24$, 95% CI: [.14, 1]). However, this effect was not significantly different between groups (interaction: $F_{7.4, 140.7} = 1.18$, $p = .32$, $\eta^2_p = .06$, 95% CI: [0, 1]). For the main effect of time, Bonferroni-corrected planned contrasts revealed that, compared to baseline, LBP intensity remained significantly lower at 6-, 9-, 12- and 15-months post-randomization (all $p \leq .01$), regardless of the intervention group.

The MCID was also calculated for each secondary endpoint using the same methods as in the primary analysis. Threshold values and corresponding proportions of participants meeting these criteria are reported in Table 5.6. The SMT-G group generally showed a higher proportion

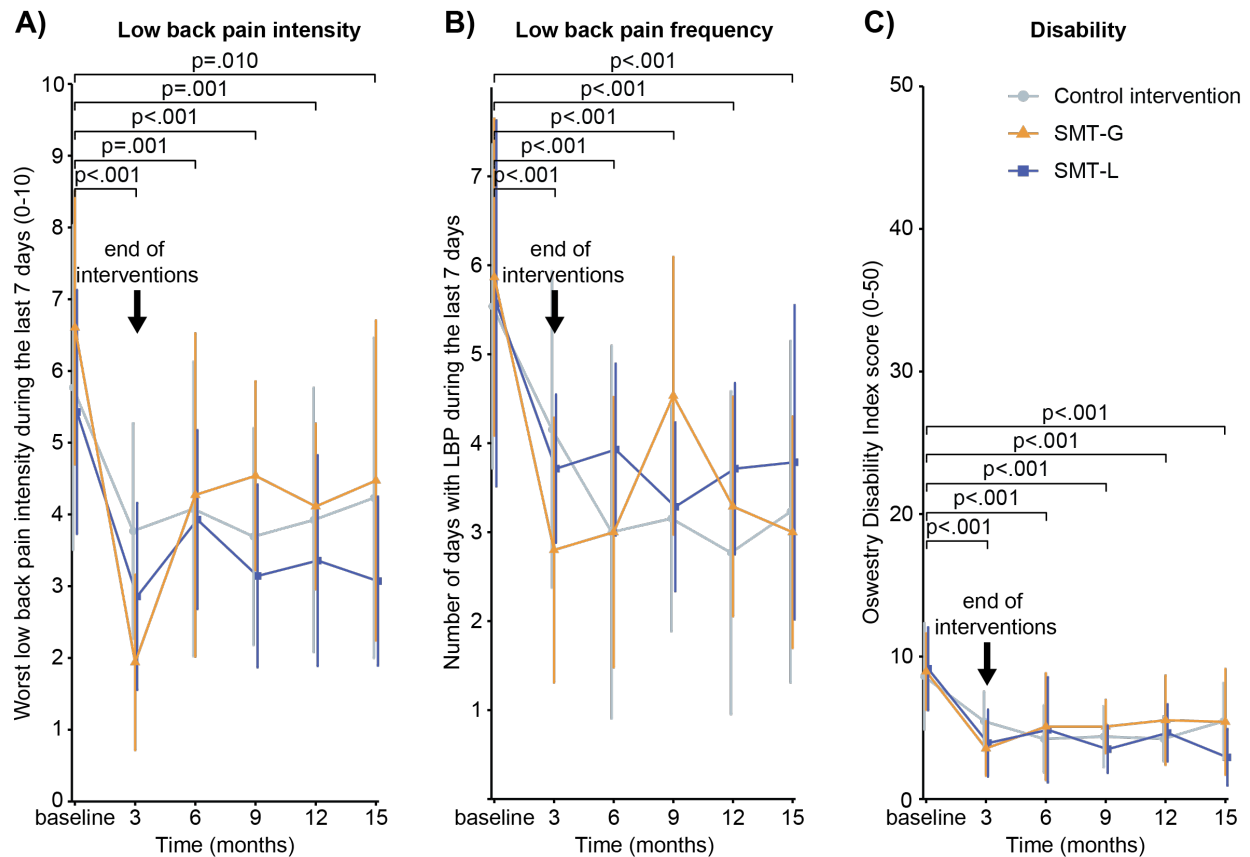
of participants reaching the MCID thresholds (20–85.7% across methods) at 6-, 9-, 12-, and 15-months post-randomization.

Fifteen months post-randomization, the mean change in LBP frequency (days per week) was -2.9, 95% confidence interval (CI) [-4.3, -1.4] for the SMT-G group, -1.8, 95% CI [-3.7, 0.1] for the SMT-L group, and -2.3 95% CI [-4.4, -0.2] for the control intervention group. Changes in LBP frequency were compared between groups over time using a mixed ANOVA (**Figure 5.12B**). LBP frequency was not significantly different between groups (main effect: $F_{2, 38} = 0.12$, $p = .89$, $\eta^2_p = .006$, 95% CI [0, 1]), but decreased over time (main effect: $F_{3.8, 143.3} = 11.9$, $p < .001$, $\eta^2_p = .24$, 95% CI [.14, 1]). However, this effect was not significantly different between groups (interaction: $F_{7.5, 143.4} = 1.3$, $p = .23$, $\eta^2_p = .07$, 95% CI [0, 1]). For the main effect of time, Bonferroni-corrected planned contrasts revealed that, compared with baseline, the number of days with LBP per week remained significantly lower at 6-, 9-, 12- and 15-months post-randomization (all $p < .001$), regardless of the intervention group.

Finally, 15 months post-randomization, the mean change in ODI scores was -3.5, 95% confidence interval (CI) [-6.7, -0.4] for the SMT-G group, -6.2, 95% CI [-8.5, -3.9] for the SMT-L group, and -3.2 95% CI [-6.7, 0.4] for the control intervention group. ODI scores were compared between groups over time (**Figure 5.12C**). Disability was not significantly different between groups (main effect: $F_{2, 38} = 0.31$, $p = .73$, $\eta^2_p = .02$, 95% CI [0, 1]) but decreased significantly over time (main effect: $F_{3.8, 144.6} = 14.8$, $p < .001$, $\eta^2_p = .28$, 95% CI [.18, 1]). However, this effect was not significantly different between groups (interaction: $F_{7.6, 144.6} = 1.10$, $p = .37$, $\eta^2_p = .05$, 95% CI [0, 1]). For the main effect of time, Bonferroni-corrected planned contrasts revealed that, compared with baseline, ODI scores remained significantly lower 6-, 9-, 12- and 15-months post-randomization (all $p < .001$), regardless of the intervention group.

Overall, these findings indicate that participants experienced sustained reductions in LBP intensity and frequency, as well as improved function, up to twelve months after the end of the intervention, regardless of the intervention group.

Figure 5.12 – Maintenance of clinical benefits over time



A) Average LBP intensity. B) Average LBP frequency. C) Average Oswestry Disability Index scores. LBP intensity, frequency and disability were not significantly different between groups (all $p > .69$) but remained significantly lower over time (all $p < .001$). However, this effect was not significantly different between groups (all $p = .13$). Bonferroni-corrected planned contrasts decomposing the main effect of time indicated that, compared to baseline levels, LBP intensity, frequency and disability remained significantly lower at 6-, 9-, 12- and 15-months post-randomization (all $p \leq .01$), regardless of the intervention group. Values represent average scores for each group and time point and error bars represent the corrected SD.

Table 5.6 – Participants maintaining the minimal clinically important difference (MCID) in low back pain intensity during follow-up, n (%)

6 months				
Methods	MCID	Control intervention (n =13)	SMT-G (n = 15)	SMT-L (n = 14)
Distribution-Based Methods				
MCID = 0.5 x SD of the Δ scores	1.3	7 (53.8)	10 (66.7)	7 (50.0)
MCID based on the medium effect size	0.3	9 (69.2)	12 (80.0)	13 (92.9)
Anchor-Based Methods				
95% limits of lower agreement	6.0	1 (7.7)	3 (20.0)	1 (7.1)
Within-patients score change	2.1	5 (38.5)	7 (46.7)	3 (21.4)
9 months				
Methods	MCID	Control intervention (n =13)	SMT-G (n = 15)	SMT-L (n = 14)
Distribution-Based Methods				
MCID = 0.5 x SD of the Δ scores	1.3	8 (61.5)	10 (66.7)	9 (64.3)
MCID based on the medium effect size	0.4	10 (76.9)	12 (80.0)	12 (85.7)
Anchor-Based Methods				
95% limits of lower agreement	3.3	5 (38.4)	3 (20.0)	4 (28.6)
Within-patients score change	2.5	5 (38.4)	7 (46.7)	6 (42.9)
12 months				
Methods	MCID	Control intervention (n =13)	SMT-G (n = 14)	SMT-L (n = 14)
Distribution-Based Methods				
MCID = 0.5 x SD of the Δ scores	1.5	5 (38.5)	8 (57.1)	7 (50.0)
MCID based on the medium effect size	0.4	10 (76.9)	12 (85.7)	11 (78.6)
Anchor-Based Methods				
95% limits of lower agreement	3.4	4 (30.8)	5 (35.7)	4 (28.6)
Within-patients score change	2.4	5 (38.4)	7 (50.0)	6 (42.9)
15 months				
Methods	MCID	Control intervention (n =13)	SMT-G (n = 15)	SMT-L (n = 14)
Distribution-Based Methods				
MCID = 0.5 x SD of the Δ scores	1.7	7 (53.8)	8 (53.3)	10 (71.4)
MCID based on the medium effect size	0.3	9 (69.2)	11 (73.3)	13 (92.9)
Anchor-Based Methods				
95% limits of lower agreement	1.4	7 (53.8)	8 (53.3)	10 (71.4)
Within-patients score change	2.4	6 (46.2)	7 (46.7)	6 (42.9)

Discussion

SMT-G was more effective than SMT-L in reducing LBP intensity, particularly at one month. This suggests that SMT-G relieves CPLBP partly through non-segmental mechanisms. These findings are consistent with a meta-analysis showing that the pain-relieving effects of SMT do not depend on the spinal region to which is applied (Nim, Downie, et al., 2021). In the present study, the effects of SMT were compared between manipulations in the lumbar region and manipulations to all spinal regions. Thus, pain relief observed in the SMT-G group could depend on additive effects produced by segmental (spinal) and non-segmental (propriospinal or supraspinal) mechanisms. This interpretation is consistent with greater pain relief by whole-spine or non-specific SMT compared with region-specific SMT (Nim et al., 2025). These effects may be explained by several mechanisms.

Mechanisms

Segmental mechanisms

In the present study, SMT was applied to the most painful vertebral segment in the lumbar area. Laser stimuli were delivered to the same vertebral segment to assess TSSP segmentally. TSSP is considered to reflect spinal facilitation of nociceptive transmission through wind-up, a physiological process that occurs in the dorsal horn of the spinal cord (R. L. Bosma et al., 2015; Herrero et al., 2000). Thus, a reduction in TSSP by SMT would reflect an attenuation of these segmental processes. Accordingly, the results revealed a significant long-term reduction in the temporal summation of low-frequency (2–5 Hz) brain oscillations by SMT (G and L) compared with the control intervention. These oscillations fall within the delta–theta range, and event-related synchronization in this frequency band has been shown to reflect the activity of nociceptive C-fibers (Jankovski et al., 2013; Mouraux et al., 2003; Ploner et al., 2017). The present results extend those of previous behavioral studies (Bialosky et al., 2009; Bialosky et al., 2014; Bishop et al., 2011; Randoll et al., 2017) and suggest that SMT may modulate C-fibers related nociceptive processing in the spinal cord. However, supraspinal processes cannot be excluded since they can

modulate TSSP (R. L. Bosma et al., 2015; Herrero et al., 2000). Also, this effect was mostly observed between one and three months, during which all interventions relieved pain. Thus, although the reduction in temporal summation of low-frequency (2–5 Hz) brain oscillations was independent of measured confounding factors, it is not clear if this mechanism is specific to SMT, and which proportion of pain relief by SMT can be attributed to this mechanism. One potential confound is the use of co-interventions, which was greater in the control intervention group. The apparent similarity in the pain-relieving effects between groups may thus be due to the effects of co-interventions, which may have compensated for the weaker pain relief produced by the control intervention. This finding is clinically relevant because the amount of co-intervention use provides a valuable indicator of intervention efficacy (Dworkin et al., 2005). Thus, the greater reduction of LBP intensity by SMT-G (specific effect) may extend beyond the first month of the intervention period.

The reduction in the temporal summation C-fibers related brain oscillations needs to be interpreted with caution, since no change in TSSP was observed. This result contrasts with several experimental and clinical studies that reported a reduction of TSSP by spinal manipulation (Bialosky et al., 2009; Bialosky et al., 2014; Bishop et al., 2011; Penza et al., 2017; Randoll et al., 2017). In these studies, the authors examined the immediate effects of spinal manipulation on TSSP. In the present study, the immediate effects were not examined. Instead, the long-term changes in TSSP were examined after 12 and 36 sessions of SMT. This suggests that the immediate effects of SMT on TSSP do not necessarily translate into long-lasting or cumulative changes over time. This highlights the importance of mechanistic RCTs, in which the clinical relevance of biomarkers identified in experimental studies can be assessed.

Propriospinal mechanisms

The inhibition of nociceptive processes mediated by propriospinal mechanisms may have contributed to the greater pain reduction observed in the SMT-G group. The cell bodies of propriospinal neurons are located in the spinal gray matter and their axons send ascending, descending, or contralateral projections that may synapse in an extended area of the spinal cord,

sometimes over five segments (Burton & Loewy, 1976; Gutierrez-Mecinas et al., 2018; Petkó & Antal, 2000; Skinner et al., 1980). Remote hypoalgesic effects reported after SMT have been suggested to rely on the activation of these propriospinal pathways (Bishop et al., 2011). Although direct evidence in humans remains limited, animal studies have shown that propriospinal pathways are activated by joint movements and pressure applied to deep tissues (Skinner et al., 1980), and that their activation can inhibit dorsal horn neurons' activity (Lindblom et al., 1977).

Cerebrospinal, supraspinal, and systemic mechanisms

Cerebrospinal and supraspinal, and systemic mechanisms may have contributed to the reduction in LBP intensity observed in the present study, including changes in endogenous inhibitory mechanisms, changes in psychological factors, placebo effects, and anti-inflammatory effects.

It has been proposed that SMT may activate descending inhibitory pathways (Gyer et al., 2019). To examine this possibility, a measure of spinal nociceptive activity that is sensitive to descending regulation is required. To our knowledge, no study on SMT has tested this mechanism directly. Descending inhibitory controls are commonly attributed to the effects of conditioned pain modulation (CPM), but several mechanisms may be activated during CPM protocols (Nahman-Averbuch et al., 2024; Piché, 2023). Therefore, although a CPM protocol may be a useful tool to examine changes in endogenous inhibitory mechanisms induced by SMT (Nim, Weber, et al., 2021), the involvement of descending inhibitory pathways remains to be confirmed. An indirect indication that endogenous inhibitory mechanisms may improve is an improvement of widespread hyperalgesia (Gyer et al., 2019; Millan et al., 2012). In the present study, no change in mechanical pain sensitivity in the upper limb (remote from the lumbar area) was observed, which argues against the involvement of endogenous inhibitory mechanisms in the pain-relieving effect of SMT. This finding is consistent with the results of a recent RCT on CPLBP, in which no change in remote mechanical sensitivity was observed following 12 SMT sessions (Gevers-Montoro et al., 2024). Generally, the lack of SMT-related effects on remote PPTs aligns with findings from a meta-analysis that showed no immediate change in either local or remote PPTs

after SMT compared with a sham treatment or inactive controls (Jung et al., 2023). Collectively, these findings suggest that the endogenous inhibitory mechanisms don't contribute to pain relief induced by SMT. Alternatively, mechanical sensitivity in remote body areas may not be sufficiently sensitive to capture SMT-related changes in endogenous inhibitory mechanisms.

Another effect of SMT that may mediate pain relief through endogenous inhibitory mechanisms is a change in pain-related factors, consistent with the biopsychosocial model of pain (Nicholas, 2022). The present results show that improvements in pain catastrophizing, kinesiophobia, depressive symptoms, and self-compassion did not contribute to pain relief by SMT-G compared with the two other groups at one and three months. This indicates that a reduction of psychological symptoms likely contributed to the reduction in LBP intensity observed in the control intervention group. This may be through improved inhibitory mechanisms or reduced facilitatory mechanisms. This interpretation is consistent with the results of previous RCTs in which reductions in pain catastrophizing and kinesiophobia contributed to the beneficial effects of various interventions for chronic LBP (Ryum & Stiles, 2023; Wood et al., 2023).

Regarding placebo effects, they likely contributed to pain relief by SMT in the present study. The clinical improvements observed in the control intervention group are consistent with this possibility and with a recent meta-analysis on sham manual therapy in individuals with back pain (Lavazza et al., 2021). This study revealed no significant difference between active and sham interventions. However, the studies included in the analysis were generally of low methodological quality and involved heterogeneous interventions, which limits the strength of the conclusions (Lavazza et al., 2021). One issue emphasized by the authors and reiterated in more recent methodological recommendations is the importance of ensuring effective participant blinding in manual therapy trials (Hohenschurz-Schmidt et al., 2023; Lavazza et al., 2021). In the present study, 73.3% of participants in the control group believed with high certainty (8/10) that they had received a real chiropractic intervention. This success rate is comparable to that reported in previous SMT trials (Chaibi et al., 2017; Chaibi et al., 2015; Gevers-Montoro et al., 2024) and

confirms that the blinding procedure is effective. In the present study, this is particularly true considering that SMT comprised 36 sessions over three months and that 80% of participants were not naïve to chiropractic interventions.

With respect to systemic anti-inflammatory effects, it was reported that spinal manipulation is more effective than control interventions in modulating inflammatory markers such as interleukins (Kovanur Sampath et al., 2024). In addition, systemic levels of interleukin-6, a pro-inflammatory cytokine, were elevated in individuals with CPLBP compared with asymptomatic controls, and these levels were significantly reduced following six SMT sessions delivered over a two-week period (Teodorczyk-Injeyan et al., 2021). Although inflammatory mediators were not assessed in the present study, the contribution of anti-inflammatory mechanisms cannot be excluded, particularly in light of the greater pain reduction observed in the SMT-G group. However, it is important to note that a general trend toward reductions in several pro-inflammatory cytokines has also been reported following a range of non-pharmacological interventions for chronic LBP (Puerto Valencia et al., 2024), suggesting that such effects may not be specific to SMT.

Cumulative pain relief over 3 months

The present findings indicate that most outcomes improved with a greater number of sessions. However, with the exception of the reduction in LBP intensity—which was significantly greater following SMT-G—these improvements occurred regardless of group allocation, suggesting that the mechanisms underlying these cumulative effects are not specific to SMT. Nonetheless, these findings are consistent with those of a randomized clinical trial on chronic LBP (Haas et al., 2014) and chronic cervicogenic headache (Haas et al., 2018). In the study on chronic LBP, 18 SMT sessions were superior to 6 and 12 SMT sessions in reducing LBP intensity compared with a control intervention, but only at long-term follow-up (52 weeks). In the present study, even with 36 sessions over three months, no plateau effect was observed. This suggests that even longer interventions may produce greater pain relief, particularly after SMT-G. One plausible explanation for the generalized improvement across groups is that contextual factors such as

therapeutic alliance contributed to pain relief. In support of this interpretation, patient–provider connection scores (Section 1 of the HEAL questionnaire) were generally high at the end of the intervention period (mean $\pm$ SD: 26.8 ± 2.3 , on a maximum of 28). Moreover, in a previous study on SMT and exercise for chronic LBP, higher therapeutic alliance was associated with greater improvements in pain intensity, disability, function, and global impression of change, regardless of the intervention (Ferreira et al., 2013). Also, in a large prospective cohort study, stronger therapeutic alliance predicted lower LBP-related disability (Bishop et al., 2021).

Importantly, although contextual factors likely contributed to cumulative pain relief, covariate-adjusted analyses in the present study indicated that the greater reductions in LBP intensity observed with SMT-G were not fully explained by expectations or therapeutic alliance. Thus, while non-specific factors may account for a substantial portion of the shared improvement across groups, the superior effect observed with SMT-G appears to reflect an additional, potentially specific intervention component.

Study limitations and future directions

The first limitation of this study is the reduced sample size due to limited resources. However, the observed effect sizes were substantially larger than those used in the original power calculation, and the sensitivity analysis confirmed that the reduced sample size remained adequate to test the study hypotheses.

Allowing co-interventions during the trial complicates the interpretation of between-group differences. However, given the three-month intervention period, this approach was necessary to ensure appropriate pain management when required. Importantly, co-intervention use was systematically recorded and statistically controlled for during analyses. Moreover, the extent of co-intervention use itself represents a meaningful indicator of intervention efficacy (Dworkin et al., 2005).

Another limitation inherent to all clinical trials involving SMT, is the impossibility of double-blinding. Indeed, the experimenter that delivers the interventions cannot be blind to

group allocation. Nonetheless, the success of the randomization and of the blinding procedures, the comparable patient–provider scores between groups, and the significant pain relief in all groups after three months suggest that the interventions were delivered with the same clinical commitment.

Conclusion

The present findings in individuals with CPLBP indicate that 12 sessions of whole-spine SMT over one month is more effective in reducing LBP intensity compared with lumbar SMT and a control intervention. Moreover, SMT reduced the temporal summation of C-fibers related brain oscillations, which may contribute to the long-term reduction of CPLBP. Non-specific effects, which may be attributable to contextual and psychological factors, also contributed to the observed improvements in clinical outcomes, particularly between 12 and 36 sessions. Altogether, these results suggest that although SMT may relieve pain through specific mechanisms, psychological and contextual factors should be considered in clinical practice to enhance the therapeutic effects of SMT and possibly, similar interventions for CPLBP and other musculoskeletal conditions.

Acknowledgments

This work was supported by a grant from the Canadian Chiropractic Research Foundation, the Natural Science and Engineering Research Council of Canada (grant number: 06559) and the Canadian Foundation for Innovation (grant number: 33731). The contribution of Benjamin Provencher was supported by the FRQS (<https://doi.org/10.69777/313919>), the Fondation Chiropratique du Québec and the Réseau de Bio-Imagerie du Québec.

Conflicts of interest

The authors declare no competing interests and no relationship that may lead to any conflict of interest.

References

- Alev, L., Fujikoshi, S., Yoshikawa, A., Enomoto, H., Ishida, M., Tsuji, T., Ogawa, K., & Konno, S. (2017). Duloxetine 60 mg for chronic low back pain: post hoc responder analysis of double-blind, placebo-controlled trials. *J Pain Res*, 10, 1723–1731. <https://doi.org/10.2147/jpr.S138297>
- Ben-Shachar, M., Lüdtke, D., & Makowski, D. (2020). effectsize: Estimation of Effect Size Indices and Standardized Parameters. *Journal of Open Source Software*, 5(56), 2815. <https://doi.org/10.21105/joss.02815>
- Bergmann, T. F., & Peterson, D. H. (2011). *Chiropractic Technique Principles and Procedures* (Third ed.). Elsevier Mosby.
- Bialosky, J. E., Bishop, M. D., Robinson, M. E., Zeppieri, G., Jr., & George, S. Z. (2009). Spinal manipulative therapy has an immediate effect on thermal pain sensitivity in people with low back pain: a randomized controlled trial. *Phys Ther*, 89(12), 1292–1303. <https://doi.org/10.2522/ptj.20090058>
- Bialosky, J. E., George, S. Z., Horn, M. E., Price, D. D., Staud, R., & Robinson, M. E. (2014). Spinal manipulative therapy-specific changes in pain sensitivity in individuals with low back pain (NCT01168999). *The Journal of Pain*, 15(2), 136–148. <https://doi.org/10.1016/j.jpain.2013.10.005>
- Bishop, F., Al-Abbadey, M., Roberts, L., MacPherson, H., Stuart, B., Carnes, D., Fawkes, C., Yardley, L., & Bradbury, K. (2021). Direct and mediated effects of treatment context on low back pain outcome: a prospective cohort study. *BMJ Open*, 11(5), e044831. <https://doi.org/10.1136/bmjopen-2020-044831>
- Bishop, M. D., Beneciuk, J. M., & George, S. Z. (2011). Immediate reduction in temporal sensory summation after thoracic spinal manipulation. *Spine J*, 11(5), 440–446. <https://doi.org/10.1016/j.spinee.2011.03.001>
- Bosma, R. L., Ameli Mojarad, E., Leung, L., Pukall, C., Staud, R., & Stroman, P. W. (2015). Neural correlates of temporal summation of second pain in the human brainstem and spinal cord. *Hum Brain Mapp*, 36(12), 5038–5050. <https://doi.org/10.1002/hbm.22993>
- Bourque, P., & Beaudette, D. (1982). Étude psychométrique du questionnaire de dépression de Beck auprès d'un échantillon d'étudiants universitaires francophones. [Psychometric study of the Beck Depression Inventory on a sample of French-speaking university students.]. *Canadian Journal of Behavioural Science / Revue canadienne des sciences du comportement*, 14, 211–218. <https://doi.org/10.1037/h0081254>

- Burton, H., & Loewy, A. D. (1976). Descending projections from the marginal cell layer and other regions of the monkey spinal cord. *Brain Res*, 116(3), 485–491. [https://doi.org/10.1016/0006-8993\(76\)90495-9](https://doi.org/10.1016/0006-8993(76)90495-9)
- Chaibi, A., Benth, J., Tuchin, P. J., & Russell, M. B. (2017). Chiropractic spinal manipulative therapy for migraine: a three-armed, single-blinded, placebo, randomized controlled trial. *Eur J Neurol*, 24(1), 143–153. <https://doi.org/10.1111/ene.13166>
- Chaibi, A., Šaltytė Benth, J., & Bjørn Russell, M. (2015). Validation of Placebo in a Manual Therapy Randomized Controlled Trial. *Sci Rep*, 5(1), 11774. <https://doi.org/10.1038/srep11774>
- Cohen, M. X. (2014). *Analyzing Neural Time Series Data: Theory and Practice*. The MIT Press.
- Cormier, S., Lavigne, G. L., Choinière, M., & Rainville, P. (2016). Expectations predict chronic pain treatment outcomes. *Pain*, 157(2), 329–338. <https://doi.org/10.1097/j.pain.0000000000000379>
- Corp, N., Mansell, G., Stynes, S., Wynne-Jones, G., Morsø, L., Hill, J. C., & van der Windt, D. A. (2021). Evidence-based treatment recommendations for neck and low back pain across Europe: A systematic review of guidelines. *Eur J Pain*, 25(2), 275–295. <https://doi.org/10.1002/ejp.1679>
- Daut, R. L., Cleeland, C. S., & Flanery, R. C. (1983). Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. *Pain*, 17(2), 197–210. [https://doi.org/10.1016/0304-3959\(83\)90143-4](https://doi.org/10.1016/0304-3959(83)90143-4)
- Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods*, 134, 9–21. <https://doi.org/10.1016/j.jneumeth.2003.10.009>
- Denis, I., & Fortin, L. (2012). Development of a French-Canadian version of the Oswestry Disability Index: cross-cultural adaptation and validation. *Spine (Phila Pa 1976)*, 37(7), E439–444. <https://doi.org/10.1097/BRS.0b013e318233eaf9>
- Desrochers, G., Bergeron, S., Khalifé, S., Dupuis, M. J., & Jodoin, M. (2009). Fear avoidance and self-efficacy in relation to pain and sexual impairment in women with provoked vestibulodynia. *Clin J Pain*, 25(6), 520–527. <https://doi.org/10.1097/AJP.0b013e31819976e3>
- Dworkin, R. H., Turk, D. C., Farrar, J. T., Haythornthwaite, J. A., Jensen, M. P., Katz, N. P., Kerns, R. D., Stucki, G., Allen, R. R., Bellamy, N., Carr, D. B., Chandler, J., Cowan, P., Dionne, R., Galer, B. S., Hertz, S., Jadad, A. R., Kramer, L. D., Manning, D. C.,...Witter, J. (2005). Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*, 113(1-2), 9–19. <https://doi.org/10.1016/j.pain.2004.09.012>

- Emmerich, A. C., Friehs, T., Crombez, G., & Glombiewski, J. A. (2020). Self-compassion predicting pain, depression and anger in people suffering from chronic pain: A prospective study. *Eur J Pain*, 24(10), 1902–1914. <https://doi.org/10.1002/ejp.1638>
- Ferreira, P. H., Ferreira, M. L., Maher, C. G., Refshauge, K. M., Latimer, J., & Adams, R. D. (2013). The therapeutic alliance between clinicians and patients predicts outcome in chronic low back pain. *Phys Ther*, 93(4), 470–478. <https://doi.org/10.2522/ptj.20120137>
- Franceschini, M., Boffa, A., Pignotti, E., Andriolo, L., Zaffagnini, S., & Filardo, G. (2023). The Minimal Clinically Important Difference Changes Greatly Based on the Different Calculation Methods. *Am J Sports Med*, 51(4), 1067–1073. <https://doi.org/10.1177/03635465231152484>
- French, D. J., Noël, M., Vigneau, F., French, J. A., Cyr, C. P., & Evans, R. T. (2005). L'Échelle de dramatisation face à la douleur PCS-CF: Adaptation canadienne en langue française de l'échelle «Pain Catastrophizing Scale». [PCS-CF: A French-language, French-Canadian adaptation of the Pain Catastrophizing Scale.]. *Canadian Journal of Behavioural Science / Revue canadienne des sciences du comportement*, 37, 181–192. <https://doi.org/10.1037/h0087255>
- Funabashi, M., Gorrell, L. M., Pohlman, K. A., Bergna, A., & Heneghan, N. R. (2022). Definition and classification for adverse events following spinal and peripheral joint manipulation and mobilization: A scoping review. *PLOS ONE*, 17(7), e0270671. <https://doi.org/10.1371/journal.pone.0270671>
- Gauthier, J., & Bouchard, S. (1993). Adaptation canadienne-française de la forme révisée du State-Trait Anxiety Inventory de Spielberger. [A French-Canadian adaptation of the revised version of Spielberger's State-Trait Anxiety Inventory.]. *Canadian Journal of Behavioural Science / Revue canadienne des sciences du comportement*, 25, 559–578. <https://doi.org/10.1037/h0078881>
- GBD 2021 Diseases and Injuries Collaborators. (2024). Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet*, 403(10440), 2133–2161. [https://doi.org/10.1016/s0140-6736\(24\)00757-8](https://doi.org/10.1016/s0140-6736(24)00757-8)
- George, S. Z., Bishop, M. D., Bialosky, J. E., Zeppieri, G., Jr., & Robinson, M. E. (2006). Immediate effects of spinal manipulation on thermal pain sensitivity: an experimental study. *BMC Musculoskeletal Disorders*, 7, 68–78. <https://doi.org/10.1186/1471-2474-7-68>
- Gerger, H., Buergler, S., Sezer, D., Grethler, M., Gaab, J., & Locher, C. (2019). The Healing Encounters and Attitudes Lists (HEAL): Psychometric Properties of a German Version

- (HEAL-D) in Comparison With the Original HEAL. *Front Psychiatry*, 10, 897. <https://doi.org/10.3389/fpsyt.2019.00897>
- Gevers-Montoro, C., Provencher, B., Descarreaux, M., Ortega de Mues, A., & Piché, M. (2021). Neurophysiological mechanisms of chiropractic spinal manipulation for spine pain. *European Journal of Pain*, 25(7), 1429–1448. <https://doi.org/10.1002/ejp.1773>
- Gevers-Montoro, C., Provencher, B., Northon, S., Stedile-Lovatel, J. P., Ortega de Mues, A., & Piché, M. (2021). Chiropractic Spinal Manipulation Prevents Secondary Hyperalgesia Induced by Topical Capsaicin in Healthy Individuals. *Frontiers in Pain Research*, 2(33), 702429. <https://doi.org/10.3389/fpain.2021.702429>
- Gevers-Montoro, C., Romero-Santiago, B., Medina-García, I., Larranaga-Arzamendi, B., Álvarez-Gálovich, L., Ortega-De Mues, A., & Piché, M. (2024). Reduction of Chronic Primary Low Back Pain by Spinal Manipulative Therapy is Accompanied by Decreases in Segmental Mechanical Hyperalgesia and Pain Catastrophizing: A Randomized Placebo-controlled Dual-blind Mixed Experimental Trial. *J Pain*, 25(8), 104500. <https://doi.org/10.1016/j.jpain.2024.02.014>
- Giovanazzi, A., Jones, K., Carr, R. M., Fairhurst, C. M., Backhouse, M. R., & Adamson, J. A. (2022). Current practice in the measurement and interpretation of intervention adherence in randomised controlled trials: A systematic review. *Contemp Clin Trials*, 118, 106788. <https://doi.org/10.1016/j.cct.2022.106788>
- Greco, C. M., Yu, L., Johnston, K. L., Dodds, N. E., Morone, N. E., Glick, R. M., Schneider, M. J., Klem, M. L., McFarland, C. E., Lawrence, S., Colditz, J., Maihoefer, C. C., Jonas, W. B., Ryan, N. D., & Pilkonis, P. A. (2016). Measuring nonspecific factors in treatment: item banks that assess the healthcare experience and attitudes from the patient's perspective. *Quality of Life Research*, 25(7), 1625–1634. <https://doi.org/10.1007/s11136-015-1178-1>
- Gupta, V., & Sharma, V. K. (2019). Skin typing: Fitzpatrick grading and others. *Clinics in Dermatology*, 37(5), 430–436. <https://doi.org/10.1016/j.clindermatol.2019.07.010>
- Gutierrez-Mecinas, M., Polgár, E., Bell, A. M., Herau, M., & Todd, A. J. (2018). Substance P-expressing excitatory interneurons in the mouse superficial dorsal horn provide a propriospinal input to the lateral spinal nucleus. *Brain Struct Funct*, 223(5), 2377–2392. <https://doi.org/10.1007/s00429-018-1629-x>
- Gyer, G., Michael, J., Inklebarger, J., & Tedla, J. S. (2019). Spinal manipulation therapy: Is it all about the brain? A current review of the neurophysiological effects of manipulation. *J Integr Med*, 17(5), 328–337. <https://doi.org/10.1016/j.joim.2019.05.004>
- Haas, M., Bronfort, G., Evans, R., Schulz, C., Vavrek, D., Takaki, L., Hanson, L., Leininger, B., & Neadilek, M. B. (2018). Dose-response and efficacy of spinal manipulation for care of

- cervicogenic headache: a dual-center randomized controlled trial. *Spine J*, 18(10), 1741–1754. <https://doi.org/10.1016/j.spinee.2018.02.019>
- Haas, M., Group, E., & Kraemer, D. F. (2004). Dose-response for chiropractic care of chronic low back pain. *The Spine Journal*, 4(5), 574–583. <https://doi.org/10.1016/j.spinee.2004.02.008>
- Haas, M., Vavrek, D., Peterson, D., Polissar, N., & Neradilek, M. B. (2014). Dose-response and efficacy of spinal manipulation for care of chronic low back pain: a randomized controlled trial. *Spine J*, 14(7), 1106–1116. <https://doi.org/10.1016/j.spinee.2013.07.468>
- Herrero, J. F., Laird, J. M., & Lopez-Garcia, J. A. (2000). Wind-up of spinal cord neurones and pain sensation: much ado about something? *Prog Neurobiol*, 61(2), 169–203. [https://doi.org/10.1016/s0301-0082\(99\)00051-9](https://doi.org/10.1016/s0301-0082(99)00051-9)
- Hohenschurz-Schmidt, D., Vase, L., Scott, W., Annoni, M., Ajayi, O. K., Barth, J., Bennell, K., Berna, C., Bialosky, J., Braithwaite, F., Finnerup, N. B., Williams, A. C. d. C., Carlino, E., Cerritelli, F., Chaibi, A., Cherkin, D., Colloca, L., Côté, P., Darnall, B. D.,...Draper-Rodi, J. (2023). Recommendations for the development, implementation, and reporting of control interventions in efficacy and mechanistic trials of physical, psychological, and self-management therapies: the CoPPS Statement. *BMJ*, 381, e072108. <https://doi.org/10.1136/bmj-2022-072108>
- Hüllemann, P., Shao, Y. Q., Manthey, G., Binder, A., & Baron, R. (2016). Central habituation and distraction alter C-fibre-mediated laser-evoked potential amplitudes. *European Journal of Pain*, 20(3), 377–385. <https://doi.org/10.1002/ejp.735>
- Jakobsen, J. C., Gluud, C., Wetterslev, J., & Winkel, P. (2017). When and how should multiple imputation be used for handling missing data in randomised clinical trials – a practical guide with flowcharts. *BMC Medical Research Methodology*, 17(1), 162. <https://doi.org/10.1186/s12874-017-0442-1>
- Jankovski, A., Plaghki, L., & Mouraux, A. (2013). Reliable EEG responses to the selective activation of C-fibre afferents using a temperature-controlled infrared laser stimulator in conjunction with an adaptive staircase algorithm. *Pain*, 154(9), 1578–1587. <https://doi.org/10.1016/j.pain.2013.04.032>
- Jung, A., Adamczyk, W. M., Ahmed, A., van der Schalk, L., Poesl, M., Luedtke, K., & Szikszay, T. M. (2023). No Sufficient Evidence for an Immediate Hypoalgesic Effect of Spinal Manual Therapy on Pressure Pain Thresholds in Asymptomatic and Chronic Pain Populations: A Systematic Review and Meta-Analysis. *Physical Therapy*, 103(3), 1–9. <https://doi.org/10.1093/ptj/pzad003>

- K'Delant, P., & Gana, K. (2009). Analyse multitraits–multiméthodes des scores au Questionnaire d'attributs personnels (Personal attributes questionnaire [PAQ]) auprès d'un échantillon féminin. [A multitrait-multimethod analysis of scores on a French version of the Personal Attributes questionnaire (PAQ) among a female sample.]. *Psychologie Française*, 54(4), 323–336. <https://doi.org/10.1016/j.psfr.2009.06.002>
- Kirkwood, J., Allan, G. M., Korownyk, C. S., McCormack, J., Garrison, S., Thomas, B., Ton, J., Perry, D., Kolber, M. R., Dugré, N., Moe, S., & Lindblad, A. J. (2021). PEER simplified decision aid: chronic back pain treatment options in primary care. *Canadian Family Physician*, 67(1), 31. <https://doi.org/10.46747/cfp.670131>
- Knezevic, N. N., Candido, K. D., Vlaeyen, J. W. S., Van Zundert, J., & Cohen, S. P. (2021). Low back pain. *Lancet*, 398(10294), 78–92. [https://doi.org/10.1016/s0140-6736\(21\)00733-9](https://doi.org/10.1016/s0140-6736(21)00733-9)
- Kolber, M. R., Ton, J., Thomas, B., Kirkwood, J., Moe, S., Dugré, N., Chan, K., Lindblad, A. J., McCormack, J., Garrison, S., Allan, G. M., Korownyk, C. S., Craig, R., Sept, L., Rouble, A. N., & Perry, D. (2021). PEER systematic review of randomized controlled trials: Management of chronic low back pain in primary care. *Canadian Family Physician*, 67(1), e20–e30. <https://doi.org/10.46747/cfp.6701e20>
- Korownyk, C. S., Montgomery, L., Young, J., Moore, S., Singer, A. G., MacDougall, P., Darling, S., Ellis, K., Myers, J., Rochford, C., Taillefer, M. C., Allan, G. M., Perry, D., Moe, S. S., Ton, J., Kolber, M. R., Kirkwood, J., Thomas, B., Garrison, S.,...Lindblad, A. J. (2022). PEER simplified chronic pain guideline: Management of chronic low back, osteoarthritic, and neuropathic pain in primary care. *Canadian family physician Medecin de famille canadien*, 68(3), 179–190. <https://doi.org/10.46747/cfp.6803179>
- Kosek, E., Clauw, D., Nijs, J., Baron, R., Gilron, I., Harris, R. E., Mico, J.-A., Rice, A. S. C., & Sterling, M. (2021). Chronic nociplastic pain affecting the musculoskeletal system: clinical criteria and grading system. *Pain*, 162(11), 2629–2634. <https://doi.org/10.1097/j.pain.0000000000002324>
- Kotsou, I., & Leys, C. (2016). Self-Compassion Scale (SCS): Psychometric Properties of The French Translation and Its Relations with Psychological Well-Being, Affect and Depression. *PLOS ONE*, 11(4), e0152880. <https://doi.org/10.1371/journal.pone.0152880>
- Kovanur Sampath, K., Treffel, L., O, P. T., Rodi, J. D., Fleischmann, M., & Tumilty, S. (2024). Changes in biochemical markers following a spinal manipulation - a systematic review update. *J Man Manip Ther*, 32(1), 28–50. <https://doi.org/10.1080/10669817.2023.2252187>
- Lavazza, C., Galli, M., Abenavoli, A., & Maggiani, A. (2021). Sham treatment effects in manual therapy trials on back pain patients: a systematic review and pairwise meta-analysis. *BMJ Open*, 11(5), e045106. <https://doi.org/10.1136/bmjopen-2020-045106>

- Lee, M. W., McPhee, R. W., & Stringer, M. D. (2008). An evidence-based approach to human dermatomes. *Clin Anat*, 21(5), 363–373. <https://doi.org/10.1002/ca.20636>
- Lenoir, C., Plaghki, L., Mouraux, A., & van den Broeke, E. N. (2018). Quickly responding C-fibre nociceptors contribute to heat hypersensitivity in the area of secondary hyperalgesia. *J Physiol*, 596(18), 4443–4455. <https://doi.org/10.1113/jp275977>
- Lindblom, U., Tapper, D. N., & Wiesenfeld, Z. (1977). The effect of dorsal column stimulation on the nociceptive response of dorsal horn cells and its relevance for pain suppression. *Pain*, 4(2), 133–144. [https://doi.org/10.1016/0304-3959\(77\)90127-0](https://doi.org/10.1016/0304-3959(77)90127-0)
- Liu, H., Huang, L., Yang, Z., Li, H., Wang, Z., & Peng, L. (2021). Fear of Movement/(Re)Injury: An Update to Descriptive Review of the Related Measures. *Front Psychol*, 12, 696762. <https://doi.org/10.3389/fpsyg.2021.696762>
- Loftus, G. R., & Masson, M. E. J. (1994). Using confidence intervals in within-subject designs. *Psychonomic Bulletin & Review*, 1(4), 476–490. <https://doi.org/10.3758/BF03210951>
- Machado, L. A., Kamper, S. J., Herbert, R. D., Maher, C. G., & McAuley, J. H. (2008). Imperfect placebos are common in low back pain trials: a systematic review of the literature. *Eur Spine J*, 17(7), 889–904. <https://doi.org/10.1007/s00586-008-0664-3>
- McCracken, L. M. (1997). “Attention” to pain in persons with chronic pain: A behavioral approach. *Behavior Therapy*, 28(2), 271–284. [https://doi.org/10.1016/S0005-7894\(97\)80047-0](https://doi.org/10.1016/S0005-7894(97)80047-0)
- Medcalf, E., Turner, R. M., Espinoza, D., He, V., & Bell, K. J. L. (2024). Addressing missing outcome data in randomised controlled trials: A methodological scoping review. *Contemp Clin Trials*, 143, 107602. <https://doi.org/10.1016/j.cct.2024.107602>
- Millan, M., Leboeuf-Yde, C., Budgell, B., & Amorim, M. A. (2012). The effect of spinal manipulative therapy on experimentally induced pain: a systematic literature review. *Chiropr Man Therap*, 20(1), 26. <https://doi.org/10.1186/2045-709X-20-26>
- Mohammadian, P., Gonsalves, A., Tsai, C., Hummel, T., & Carpenter, T. (2004). Areas of capsaicin-induced secondary hyperalgesia and allodynia are reduced by a single chiropractic adjustment: a preliminary study. *J Manipulative Physiol Ther*, 27(6), 381–387. <https://doi.org/10.1016/j.jmpt.2004.05.002>
- Mouraux, A., Guérit, J. M., & Plaghki, L. (2003). Non-phase locked electroencephalogram (EEG) responses to CO₂ laser skin stimulations may reflect central interactions between Aδ- and C-fibre afferent volleys. *Clinical Neurophysiology*, 114(4), 710–722. [https://doi.org/10.1016/S1388-2457\(03\)00027-0](https://doi.org/10.1016/S1388-2457(03)00027-0)

- Mouraux, A., & Iannetti, G. D. (2008). Across-trial averaging of event-related EEG responses and beyond. *Magn Reson Imaging*, 26(7), 1041–1054. <https://doi.org/10.1016/j.mri.2008.01.011>
- Mücke, M., Cuhls, H., Radbruch, L., Baron, R., Maier, C., Tölle, T., Treede, R. D., & Rolke, R. (2021). Quantitative sensory testing (QST). English version. *Schmerz*, 35(Suppl 3), 153–160. <https://doi.org/10.1007/s00482-015-0093-2> (Original work published Quantitative sensorische Testung (QST).)
- Nahman-Averbuch, H., Piché, M., Bannister, K., & Coghill, R. C. (2024). Involvement of propriospinal processes in conditioned pain modulation. *Pain*, 165(9), 1907–1913. <https://doi.org/10.1097/j.pain.0000000000003217>
- Nicholas, M. K. (2022). The biopsychosocial model of pain 40 years on: time for a reappraisal? *Pain*, 163(Suppl 1), S3–S14. <https://doi.org/10.1097/j.pain.0000000000002654>
- Nijs, J., Kosek, E., Chiarotto, A., Cook, C., Danneels, L. A., Fernández-de-las-Peñas, C., Hodges, P. W., Koes, B., Louw, A., Ostelo, R., Scholten-Peeters, G. G. M., Sterling, M., Alkassabi, O., Alsobayel, H., Beales, D., Bilika, P., Clark, J. R., De Baets, L., Demoulin, C.,...George, S. Z. (2024). Nociceptive, neuropathic, or nociplastic low back pain? The low back pain phenotyping (BACPAP) consortium's international and multidisciplinary consensus recommendations. *The Lancet Rheumatology*, 6(3), e178–e188. [https://doi.org/10.1016/S2665-9913\(23\)00324-7](https://doi.org/10.1016/S2665-9913(23)00324-7)
- Nim, C., Aspinall, S. L., Cook, C. E., Corrêa, L. A., Donaldson, M., Downie, A. S., Harsted, S., Hansen, S., Jenkins, H. J., McNaughton, D., Nyirö, L., Perle, S. M., Roseen, E. J., Young, J. J., Young, A., Zhao, G.-H., Hartvigsen, J., & Juhl, C. B. (2025). The Effectiveness of Spinal Manipulative Therapy in Treating Spinal Pain Does Not Depend on the Application Procedures: A Systematic Review and Network Meta-analysis. *Journal of orthopaedic & sports physical therapy*, 55(2), 109–122. <https://doi.org/10.2519/jospt.2025.12707>
- Nim, C. G., Downie, A., O'Neill, S., Kawchuk, G. N., Perle, S. M., & Leboeuf-Yde, C. (2021). The importance of selecting the correct site to apply spinal manipulation when treating spinal pain: Myth or reality? A systematic review. *Sci Rep*, 11(1), 23415. <https://doi.org/10.1038/s41598-021-02882-z>
- Nim, C. G., Weber, K. A., Kawchuk, G. N., & O'Neill, S. (2021). Spinal manipulation and modulation of pain sensitivity in persistent low back pain: a secondary cluster analysis of a randomized trial. *Chiropr Man Therap*, 29(1), 10. <https://doi.org/10.1186/s12998-021-00367-4>
- Osborne, N. R., & Davis, K. D. (2022). Sex and gender differences in pain. *Int Rev Neurobiol*, 164, 277–307. <https://doi.org/10.1016/bs.irn.2022.06.013>

- Özüdoğru, A., Canlı, M., Ceylan, İ., Kuzu, Ş., Alkan, H., & Karaçay, B. (2022). Five Times Sit-to-Stand Test in people with non-specific chronic low back pain-a cross-sectional test-retest reliability study. *Ir J Med Sci.* <https://doi.org/10.1007/s11845-022-03223-3>
- Pasquier, M., Daneau, C., Marchand, A. A., Lardon, A., & Descarreaux, M. (2019). Spinal manipulation frequency and dosage effects on clinical and physiological outcomes: a scoping review. *Chiropr Man Therap*, 27, 23. <https://doi.org/10.1186/s12998-019-0244-0>
- Patel, K. V., Amtmann, D., Jensen, M. P., Smith, S. M., Veasley, C., & Turk, D. C. (2021). Clinical outcome assessment in clinical trials of chronic pain treatments. *Pain reports*, 6(1), e784. <https://doi.org/10.1097/pr9.0000000000000784>
- Paungmali, A., Silitertpisan, P., Taneyhill, K., Pirunsan, U., & Uthaikhup, S. (2012). Intrarater reliability of pain intensity, tissue blood flow, thermal pain threshold, pressure pain threshold and lumbo-pelvic stability tests in subjects with low back pain. *Asian J Sports Med*, 3(1), 8–14. <https://doi.org/10.5812/asjism.34718>
- Penza, C. W., Horn, M. E., George, S. Z., & Bishop, M. D. (2017). Comparison of 2 Lumbar Manual Therapies on Temporal Summation of Pain in Healthy Volunteers. *J Pain*, 18(11), 1397–1408. <https://doi.org/10.1016/j.jpain.2017.07.007>
- Petkó, M., & Antal, M. (2000). Propriospinal afferent and efferent connections of the lateral and medial areas of the dorsal horn (laminae I-IV) in the rat lumbar spinal cord. *J Comp Neurol*, 422(2), 312–325. [https://doi.org/10.1002/\(sici\)1096-9861\(20000626\)422:2<312::aid-cne11>3.0.co;2-a](https://doi.org/10.1002/(sici)1096-9861(20000626)422:2<312::aid-cne11>3.0.co;2-a)
- Piché, M. (2023). Mechanistic perspective on conditioned pain modulation. *Pain*, 164(1), e1–e2. <https://doi.org/10.1097/j.pain.0000000000002717>
- Pinheiro, J., Bates, D., DebRoy, S., Sarkar, D., & R Core Team. (2025). nlme: Linear and Nonlinear Mixed Effects Models.
- Pion-Tonachini, L., Kreutz-Delgado, K., & Makeig, S. (2019). ICLabel: An automated electroencephalographic independent component classifier, dataset, and website. *Neuroimage*, 198, 181–197. <https://doi.org/10.1016/j.neuroimage.2019.05.026>
- Ploner, M., Sorg, C., & Gross, J. (2017). Brain Rhythms of Pain. *Trends Cogn Sci*, 21(2), 100–110. <https://doi.org/10.1016/j.tics.2016.12.001>
- Poquet, N., & Lin, C. (2016). The Brief Pain Inventory (BPI). *Journal of Physiotherapy*, 62(1), 52. <https://doi.org/10.1016/j.jphys.2015.07.001>
- Provencher, B., Northon, S., Gevers Montoro, C., O'Shaughnessy, J., & Piché, M. (2021). Effects of chiropractic spinal manipulation on laser-evoked pain and brain activity. *The Journal of Physiological Sciences*, 71(1), 20–33. <https://doi.org/10.1186/s12576-021-00804-2>

- Provencher, B., Northon, S., & Piché, M. (2021). Segmental Chiropractic Spinal Manipulation Does not Reduce Pain Amplification and the Associated Pain-Related Brain Activity in a Capsaicin-Heat Pain Model. *Frontiers in Pain Research*, 2(86), 733727. <https://doi.org/10.3389/fpain.2021.733727>
- Provencher, B., & Piché, M. (2025). C-fiber-related brain responses evoked by laser heat pulses applied to the back. *The Journal of Physiological Sciences*, 75(2), 100018. <https://doi.org/10.1016/j.jphyss.2025.100018>
- Puerto Valencia, L. M., He, Y., & Wippert, P. M. (2024). The changes of blood-based inflammatory biomarkers after non-pharmacologic interventions for chronic low back pain: a systematic review. *BMC Musculoskelet Disord*, 25(1), 209. <https://doi.org/10.1186/s12891-024-07289-1>
- Puhl, A. A., Reinhart, C. J., Doan, J. B., & Vernon, H. (2017). The quality of placebos used in randomized, controlled trials of lumbar and pelvic joint thrust manipulation-a systematic review. *Spine J*, 17(3), 445–456. <https://doi.org/10.1016/j.spinee.2016.11.003>
- R Core Team. (2025). R: A Language and Environment for Statistical Computing. In R Foundation for Statistical Computing. <https://www.R-project.org/>
- Randoll, C., Gagnon-Normandin, V., Tessier, J., Bois, S., Rustamov, N., O'Shaughnessy, J., Descarreaux, M., & Piche, M. (2017). The mechanism of back pain relief by spinal manipulation relies on decreased temporal summation of pain. *Neuroscience*, 349, 220–228. <https://doi.org/10.1016/j.neuroscience.2017.03.006>
- Reed, W. R., Lima, C. R., Liebschner, M. A. K., Hurt, C. P., Li, P., & Gudavalli, M. R. (2023). Measurement of Force and Intramuscular Pressure Changes Related to Thrust Spinal Manipulation in an In Vivo Animal Model. *Biology*, 12, 62. <https://doi.org/10.3390/biology12010062>
- Rodrigues, J., Weiß, M., Hewig, J., & Allen, J. J. B. (2021). EPOS: EEG Processing Open-Source Scripts. *Frontiers in Neuroscience*, 15, 660449. <https://doi.org/10.3389/fnins.2021.660449>
- Roelofs, J., Sluiter, J. K., Frings-Dresen, M. H., Goossens, M., Thibault, P., Boersma, K., & Vlaeyen, J. W. (2007). Fear of movement and (re)injury in chronic musculoskeletal pain: Evidence for an invariant two-factor model of the Tampa Scale for Kinesiophobia across pain diagnoses and Dutch, Swedish, and Canadian samples. *Pain*, 131(1-2), 181–190. <https://doi.org/10.1016/j.pain.2007.01.008>
- Rogers, A. H., & Farris, S. G. (2022). A meta-analysis of the associations of elements of the fear-avoidance model of chronic pain with negative affect, depression, anxiety, pain-related

disability and pain intensity. *Eur J Pain*, 26(8), 1611–1635.
<https://doi.org/10.1002/ejp.1994>

- Rossettini, G., Carlino, E., & Testa, M. (2018). Clinical relevance of contextual factors as triggers of placebo and nocebo effects in musculoskeletal pain. *BMC Musculoskelet Disord*, 19(1), 27. <https://doi.org/10.1186/s12891-018-1943-8>
- Rustamov, N., Northon, S., Tessier, J., Leblond, H., & Piché, M. (2019). Integration of bilateral nociceptive inputs tunes spinal and cerebral responses. *Sci Rep*, 9(1), 7143. <https://doi.org/10.1038/s41598-019-43567-y>
- Ryum, T., & Stiles, T. C. (2023). Changes in pain catastrophizing, fear-avoidance beliefs, and pain self-efficacy mediate changes in pain intensity on disability in the treatment of chronic low back pain. *Pain reports*, 8(5), e1092. <https://doi.org/10.1097/pr9.0000000000001092>
- Salamon, K. S., Davies, W. H., Fuentes, M. R., Weisman, S. J., & Hainsworth, K. R. (2014). The pain frequency-severity-duration scale as a measure of pain: preliminary validation in a pediatric chronic pain sample. *Pain Res Treat*, 2014, 653592. <https://doi.org/10.1155/2014/653592>
- Salas-González, J., Heredia-Rizo, A. M., Fricke-Comellas, H., Chimenti, R. L., & Casuso-Holgado, M. J. (2025). Patterns of pain perception in individuals with anxiety or depressive disorders: A systematic review and meta-analysis of experimental pain research. *J Pain*, 35, 105530. <https://doi.org/10.1016/j.jpain.2025.105530>
- Schliessbach, J., Siegenthaler, A., Bütikofer, L., Limacher, A., Juni, P., Vuilleumier, P. H., Stamer, U., Arendt-Nielsen, L., & Curatolo, M. (2018). Effect of single-dose imipramine on chronic low-back and experimental pain. A randomized controlled trial. *PLOS ONE*, 13(5), e0195776. <https://doi.org/10.1371/journal.pone.0195776>
- Sean, M., Coulombe-Lévêque, A., Nadeau, W., Charest, A. C., Martel, M., Léonard, G., & Tétreault, P. (2024). Counting your chickens before they hatch: improvements in an untreated chronic pain population, beyond regression to the mean and the placebo effect. *Pain reports*, 9(3), e1157. <https://doi.org/10.1097/pr9.0000000000001157>
- Sedaghat, A. R. (2019). Understanding the Minimal Clinically Important Difference (MCID) of Patient-Reported Outcome Measures. *Otolaryngol Head Neck Surg*, 161(4), 551–560. <https://doi.org/10.1177/0194599819852604>
- Sherriff, B., Clark, C., Killingback, C., & Newell, D. (2022). Impact of contextual factors on patient outcomes following conservative low back pain treatment: systematic review. *Chiropr Man Therap*, 30(1), 20. <https://doi.org/10.1186/s12998-022-00430-8>

- Singmann, H., Bolker, B., Westfall, J., Aust, F., & Ben-Shachar, M. S. (2025). afex: Analysis of Factorial Experiments.
- Skinner, R. D., Adams, R. J., & Rempel, R. S. (1980). Responses of long descending propriospinal neurons to natural and electrical types of stimuli in cat. *Brain Res*, 196(2), 387–403. [https://doi.org/10.1016/0006-8993\(80\)90403-5](https://doi.org/10.1016/0006-8993(80)90403-5)
- Starkweather, A. R., Heineman, A., Storey, S., Rubia, G., Lyon, D. E., Greenspan, J., & Dorsey, S. G. (2016). Methods to measure peripheral and central sensitization using quantitative sensory testing: A focus on individuals with low back pain. *Appl Nurs Res*, 29, 237–241. <https://doi.org/10.1016/j.apnr.2015.03.013>
- Stone, A. A., Broderick, J. E., Goldman, R. E., Junghaenel, D. U., Bolton, A., May, M., & Schneider, S. (2021). I. Indices of Pain Intensity Derived From Ecological Momentary Assessments: Rationale and Stakeholder Preferences. *J Pain*, 22(4), 359–370. <https://doi.org/10.1016/j.jpain.2020.08.003>
- Strand, L. I., Moe-Nilssen, R., & Ljunggren, A. E. (2002). Back Performance Scale for the assessment of mobility-related activities in people with back pain. *Phys Ther*, 82(12), 1213–1223.
- Tabachnick, B. G., & Fidell, L. S. (2013). Using multivariate statistics (6th ed ed.). Pearson Education.
- Teodorczyk-Injeyan, J. A., Triano, J. J., Gringmuth, R., DeGraauw, C., Chow, A., & Injeyan, H. S. (2021). Effects of spinal manipulative therapy on inflammatory mediators in patients with non-specific low back pain: a non-randomized controlled clinical trial. *Chiropr Man Therap*, 29(1), 3. <https://doi.org/10.1186/s12998-020-00357-y>
- Triano, J. J., Budgell, B., Bagnulo, A., Roffey, B., Bergmann, T., Cooperstein, R., Gleberzon, B., Good, C., Perron, J., & Tepe, R. (2013). Review of methods used by chiropractors to determine the site for applying manipulation. *Chiropr Man Therap*, 21(1), 36. <https://doi.org/10.1186/2045-709x-21-36>
- Vlaeyen, J. W. S., & Linton, S. J. (2000). Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. *Pain*, 85(3), 317–332. [https://doi.org/10.1016/S0304-3959\(99\)00242-0](https://doi.org/10.1016/S0304-3959(99)00242-0)
- Wang, Y. P., & Gorenstein, C. (2013). Psychometric properties of the Beck Depression Inventory-II: a comprehensive review. *Braz J Psychiatry*, 35(4), 416–431. <https://doi.org/10.1590/1516-4446-2012-1048>
- Wheeler, C. H. B., Williams, A. C. C., & Morley, S. J. (2019). Meta-analysis of the psychometric properties of the Pain Catastrophizing Scale and associations with participant

characteristics. Pain, 160(9), 1946–1953.
<https://doi.org/10.1097/j.pain.0000000000001494>

Wickham, H., Averick, M., Bryan, J., Chang, W., D'Agostino McGowan, L., François, R., Golemund, G., Hayes, A., Henry, L., Hester, J., Kuhn, M., Lin Pedersen, T., Miller, E., Milton Bache, S., Müller, K., Ooms, J., Robinson, D., Seidel, D., Spinu, V.,...Yutani, H. (2019). Welcome to the Tidyverse. Journal of Open Source Software, 4(43), 1686.
<https://doi.org/10.21105/joss.01686>

Wood, L., Bejarano, G., Csiernik, B., Miyamoto, G. C., Mansell, G., Hayden, J. A., Lewis, M., & Cashin, A. G. (2023). Pain catastrophising and kinesiophobia mediate pain and physical function improvements with Pilates exercise in chronic low back pain: a mediation analysis of a randomised controlled trial. J Physiother, 69(3), 168–174.
<https://doi.org/10.1016/j.jphys.2023.05.008>

World Health Organisation (WHO). (2019). International Classification of Diseases, Eleventh Revision (ICD-11). <https://icd.who.int/browse/2025-01/mms/en>

World Health Organization. (2023). WHO guideline for non-surgical management of chronic primary low back pain in adults in primary and community care settings. World Health Organization.

Zaina, F., Côté, P., Cancelliere, C., Di Felice, F., Donzelli, S., Rauch, A., Verville, L., Negrini, S., & Nordin, M. (2023). A Systematic Review of Clinical Practice Guidelines for Persons With Non-specific Low Back Pain With and Without Radiculopathy: Identification of Best Evidence for Rehabilitation to Develop the WHO's Package of Interventions for Rehabilitation. Arch Phys Med Rehabil, 104(11), 1913–1927.
<https://doi.org/10.1016/j.apmr.2023.02.022>

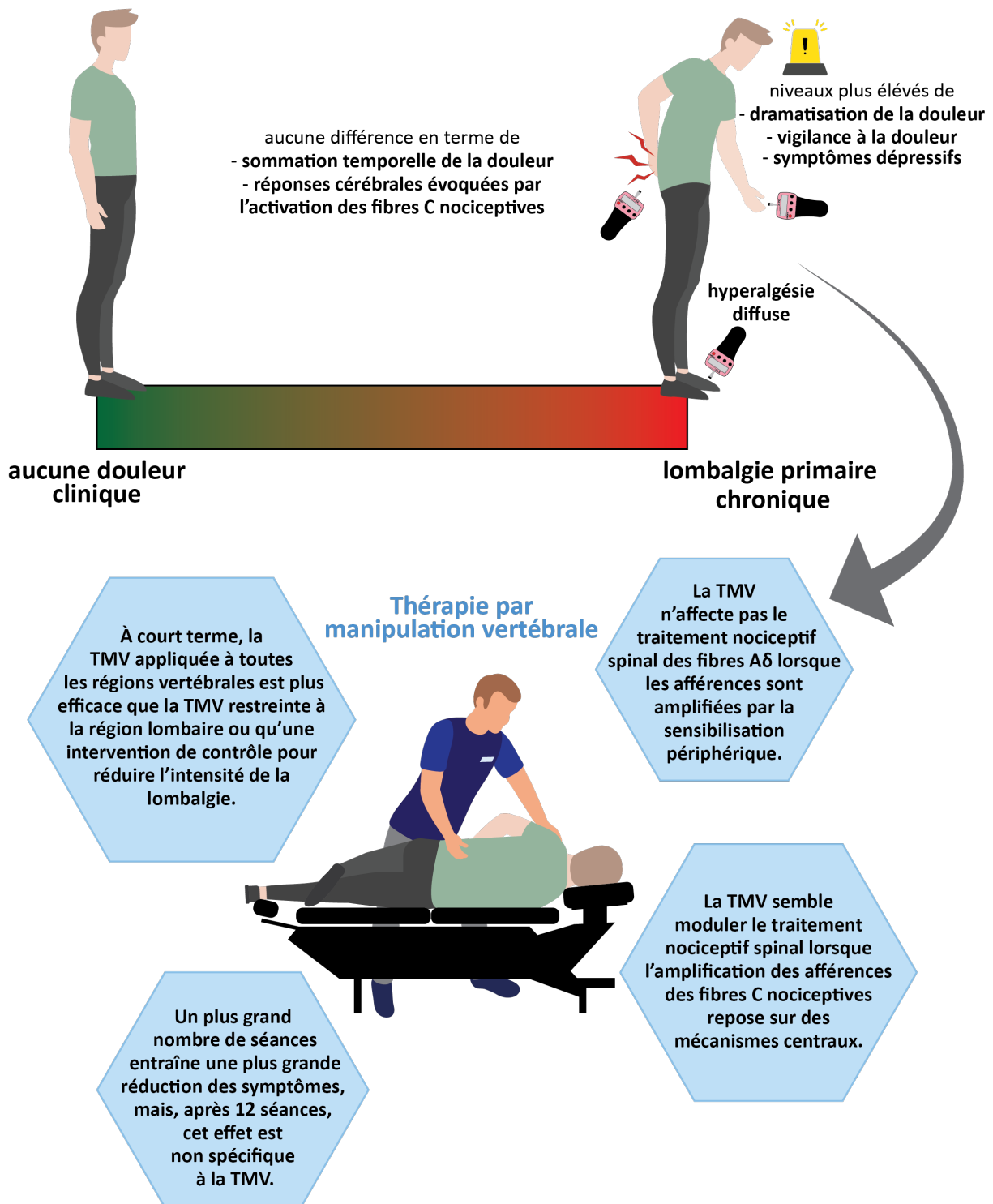
Zhang, Y. K., Wang, J. X., Ge, Y. Z., Wang, Z. B., & Chang, F. (2025). Low back pain among the working-age population: from the global burden of disease study 2021. BMC Musculoskelet Disord, 26(1), 441. <https://doi.org/10.1186/s12891-025-08704-x>

Chapitre 6 – Discussion générale et conclusion

6.1 Contribution des résultats au domaine de recherche

Cette thèse contribue à l'avancement des connaissances de plusieurs façons. D'abord, sur le plan méthodologique, elle propose un protocole de stimulation simple (trois impulsions laser de 7 ms chacune délivrées à une fréquence de 0,67 Hz) et reproductible. Ce protocole, éprouvé auprès de trois échantillons distincts et à trois temps de mesure chez l'un d'entre eux, permet de mesurer les réponses cérébrales évoquées par la stimulation des fibres C nociceptives au niveau du dos, ainsi que l'activité électroencéphalographique associée à la sommation temporelle de la douleur. À notre connaissance, les études présentées dans cette thèse sont les premières à quantifier l'activité électroencéphalographique évoquée par la stimulation des fibres C nociceptives en lien avec la sommation temporelle de la douleur. Par ailleurs, cette thèse propose une intervention de contrôle pertinente pour de futurs essais cliniques portant sur la TMV. En effet, cette intervention comprenant des manœuvres de contrôle pour chaque position utilisée lors de la TMV a eu un impact comparable à cette dernière sur l'ensemble des facteurs contextuels mesurés (attentes, alliance thérapeutique, environnement de soins), a généré des événements indésirables et a permis d'assurer l'insu de la majorité des participants quant à leur groupe expérimental. Ce résultat est d'autant plus notable que l'essai contrôlé randomisé réalisé dans le cadre de cette thèse est possiblement celui comportant le plus grand nombre de séances de TMV à ce jour, et que la majorité des participants n'étaient pas naïfs aux soins chiropratiques. Ensuite, en plus de sa contribution à la caractérisation des signes associés à la lombalgie primaire chronique, cette thèse répond à son objectif principal en apportant une meilleure compréhension des mécanismes neurophysiologiques sous-jacents aux effets hypoalgésiques de la TMV, ainsi que de plusieurs facteurs susceptibles d'influencer ces effets. Les contributions de la thèse à cet égard sont synthétisées à la **Figure 6.1**. La signification et la portée de ces résultats sont discutées dans les sections suivantes, en veillant à limiter les redondances avec les discussions présentées dans les articles, tout en approfondissant certains aspects lorsque cela s'avère pertinent.

Figure 6.1 – Synthèse des principales contributions de la thèse



TMV : thérapie par manipulation vertébrale. Cette figure a été créée à l'aide d'images provenant d'Adobe Stock (stock.adobe.com), utilisées conformément aux conditions de la licence.

6.2 Les mécanismes neurophysiologiques sous-jacents aux effets hypoalgésiques de la thérapie par manipulation vertébrale

6.2.1 Les mécanismes spécifiques

Dans cette thèse, les études 1 et 4 ont examiné si la manipulation vertébrale segmentaire, c'est-à-dire appliquée au même niveau vertébral que la douleur expérimentale, module la douleur ainsi que l'activité cérébrale évoquée par la stimulation sélective des fibres nociceptives. Comme mentionné au chapitre 2, l'absence d'effet observée dans l'étude 1 pourrait s'expliquer par plusieurs facteurs, notamment le modèle expérimental de douleur au dos utilisé, l'application de la manipulation sur une région déjà sensibilisée, ou encore une dose d'intervention insuffisante pour induire un effet mesurable. Néanmoins, une étude antérieure a montré qu'une manipulation vertébrale segmentaire réduit significativement la douleur expérimentale induite par des stimuli laser identiques à ceux utilisés dans l'étude 1, lorsque ces stimuli sont appliqués sur une région non sensibilisée (Provencher et al., 2021). De plus, une autre étude a rapporté qu'une manipulation vertébrale segmentaire prévient l'hyperalgésie secondaire induite par l'application topique de capsaïcine (Gevers-Montoro et al., 2021b). Pris ensemble, ces résultats, combinés à ceux de l'étude 1, suggèrent que les mécanismes neurophysiologiques sous-jacents aux effets hypoalgésiques de la TMV sont indépendants d'une modulation de l'hyperalgésie primaire.

Par ailleurs, la modulation de la sommation temporelle d'une des mesures de l'activité cérébrale évoquée par la stimulation des fibres C nociceptives observée lors de l'essai contrôlé randomisé suggère que la TMV pourrait réduire l'intensité de la lombalgie à long terme — et non uniquement dans les minutes suivant l'intervention — en modulant des mécanismes centraux d'amplification des afférences nociceptives. Toutefois, ces résultats doivent être interprétés à la lumière de plusieurs éléments.

Tout d'abord, la réduction de la sommation temporelle de l'activité EEG doit être mise en relation avec l'absence de changement au niveau de la sommation temporelle de la douleur et plusieurs facteurs doivent être considérés. Premièrement, cette dernière a diminué de manière

significative dans tous les groupes durant le premier mois d'intervention, et ce, malgré une augmentation significative de l'intensité des stimuli au cours de la même période. Ces observations sont probablement attribuables à un phénomène d'habituation des participants aux procédures expérimentales. À cet égard, une étude antérieure menée chez des individus sans douleur a également rapporté une diminution de la perception douloureuse entre deux séances expérimentales, malgré une augmentation de l'intensité des stimuli laser (Bi et al., 2021). Deuxièmement, la divergence entre les résultats perceptuels et neurophysiologiques pourrait, en théorie, s'expliquer par une fluctuation temporelle des variables mesurées. À cet égard, une méta-analyse récente portant sur la fiabilité des mesures de sommation temporelle de la douleur a mis en évidence une fiabilité interséance modérée lorsque cette mesure est réalisée auprès de populations cliniques (Chen et al., 2025). Plus précisément, lorsque les changements absolus sont utilisés — c'est-à-dire la différence entre l'évaluation de la douleur associée au dernier stimulus répété et celle du premier, comme dans les études de cette thèse — un coefficient de corrélation intraclasse de 0,71 a été rapporté (Chen et al., 2025). En revanche, aucune donnée n'est actuellement disponible concernant la fiabilité interséance des mesures électroencéphalographiques employées. Afin d'établir de telles valeurs normatives, l'approche optimale aurait consisté à comparer la variabilité des réponses dans le temps au sein d'un groupe ne recevant aucune intervention, ou chez les participants témoins de l'étude 3. Cette option n'a toutefois pas pu être retenue dans le cadre de cette thèse en raison de l'insuffisance des ressources nécessaires à sa mise en œuvre. Malgré cela, les résultats d'une étude récente indiquent que l'amplitude des potentiels évoqués par des stimuli laser répétés demeure stable lorsqu'elle est remesurée à une à deux semaines d'intervalle (Wang et al., 2026). De plus, il est peu probable que la réduction de la sommation temporelle de l'activité EEG observée dans l'étude 4 soit attribuable à la variabilité de cette mesure répétée, puisque cet effet a été observé exclusivement dans les deux groupes ayant reçu la TMV.

Une explication plus probable de la dissociation observée entre la sommation temporelle de l'activité EEG et celle de la douleur est que ces deux variables reflètent des processus distincts, soit le traitement nociceptif — un processus inconscient et objectif — et l'expérience subjective et consciente de la douleur, respectivement (Garcia-Larrea & Bastuji, 2018). En effet, il a été

démontré expérimentalement qu'en modifiant les paramètres de stimulation, il est possible de réduire l'amplitude des potentiels évoqués laser sans modifier l'intensité de la douleur perçue (Iannetti et al., 2008). À ce propos, une revue de la littérature a émis une mise en garde quant à l'utilisation des mesures d'activité cérébrale comme biomarqueurs « objectifs » de l'intensité de la douleur, puisque l'activité mesurée est souvent non spécifique à la douleur et peut également être observée pour d'autres modalités sensorielles (Mouraux & Iannetti, 2018). Les auteurs encouragent néanmoins l'utilisation de ces biomarqueurs pour classer les individus selon les mécanismes physiopathologiques sous-jacents ou pour quantifier la réponse aux interventions (Mouraux & Iannetti, 2018), raisons pour lesquelles l'électroencéphalographie a été utilisée dans cette thèse. Toutefois, il importe de souligner qu'une seule des mesures de l'activité cérébrale évoquée par la stimulation des fibres C nociceptives a été modulée par la TMV. Des études supplémentaires seront donc nécessaires afin de valider ce résultat.

Un autre élément important à considérer dans l'interprétation de la réduction de la sommation temporelle de l'activité EEG rapportée dans l'étude 4 est la similitude des réponses cérébrales observées, dans l'étude 3, entre les participants atteints de lombalgie primaire chronique et les participants témoins. Autrement dit, comment une réduction de la sommation temporelle de l'activité EEG peut-elle contribuer à expliquer une diminution de la douleur clinique si cette sommation temporelle ne différait pas initialement de celle observée chez des individus sans douleur? Bien que complexe, cette question met en évidence la valeur méthodologique des travaux réalisés dans le cadre de cette thèse. En effet, c'est une force de la thèse d'avoir examiné les marqueurs potentiellement associés à une pathologie en comparant des individus symptomatiques et asymptomatiques, puis d'avoir investigué l'évolution de ces marqueurs à la suite d'une intervention. Ainsi, en l'absence de l'étude 3, l'interprétation des résultats de l'étude 4 aurait été plus simple, mais également moins rigoureuse. À cet égard, des études antérieures ont également rapporté une absence de différence dans l'activité cérébrale évoquée par des stimuli laser entre des témoins sans douleur et des individus atteints de douleur chronique au membre supérieur (Asci et al., 2023) ou au cou (Goudman et al., 2020). De plus, une revue systématique incluant des études comparant l'activité cérébrale évoquée par des stimuli

nociceptifs entre diverses conditions de douleur chronique et des témoins sans douleur rapporte que des différences significatives ne sont observées que lorsque la douleur chronique est d'origine neuropathique (Lenoir et al., 2020). En effet, une lésion neuronale compromettant l'intégrité des voies nociceptives entraîne généralement une réduction de l'amplitude et une augmentation de la latence des potentiels évoqués, tandis qu'aucune modification systématique n'est observée lorsque la douleur est de nature nociceptive ou nociplastique (Lenoir et al., 2020). L'absence de différence rapportée dans l'étude 3 de cette thèse est donc conforme à l'état actuel des connaissances.

En ce qui concerne la réduction de la sommation temporelle d'une des mesures de l'activité cérébrale observée spécifiquement dans les groupes ayant reçu la TMV, il est possible que les nombreuses afférences provenant des mécanorécepteurs à seuil élevé aient induit des changements dans la connectivité fonctionnelle de structures impliquées dans le traitement nociceptif. En effet, plusieurs études récentes ont rapporté des altérations de la connectivité fonctionnelle de différents réseaux neuronaux après la TMV (Haavik et al., 2024; Isenburg et al., 2021; Zhou et al., 2023; Zhou et al., 2024). L'une de ces études a également mis en évidence des corrélations significatives entre les changements de connectivité observés après 14 séances d'intervention et la réduction de l'intensité de la lombalgie ($r = .71$), ainsi que de l'incapacité fonctionnelle ($r = .57$) (Zhou et al., 2024). Ainsi, l'effet observé pourrait refléter un état compensatoire dans lequel le traitement nociceptif lié aux fibres C nociceptives est davantage régulé en raison de ces changements neuroplastiques. Des études longitudinales supplémentaires, intégrant à la fois des mesures de connectivité fonctionnelle et des réponses cérébrales évoquées par la stimulation des fibres C nociceptives, seront toutefois nécessaires afin de confirmer cette hypothèse.

En somme, les résultats de cette thèse indiquent qu'une modulation de l'amplification centrale des afférences provenant des fibres C nociceptives constitue, à l'heure actuelle, un des mécanismes neurophysiologiques spécifiques les plus plausibles pour expliquer l'effet hypoalgésique à long terme de la TMV.

6.2.2 Les mécanismes non spécifiques : l'influence des facteurs contextuels

Dans cette thèse, les deux études ayant évalué les effets de la manipulation vertébrale incluaient une intervention de contrôle, ce qui est essentiel pour estimer l'impact des facteurs contextuels et distinguer les effets spécifiques de l'intervention des effets non spécifiques (Hohenschurz-Schmidt et al., 2023). Dans l'étude 1, aucune des interventions n'a modulé la douleur induite par le modèle expérimental utilisé. En revanche, dans l'étude 4, les effets spécifiques de la TMV ont principalement été observés au cours des douze premières séances. Au-delà de ce seuil, l'amélioration significative de l'ensemble des variables cliniques, indépendamment de l'intervention reçue, suggère une influence importante des facteurs contextuels dans la réponse au traitement. Ces résultats sont cohérents avec l'état actuel des connaissances concernant cette modalité thérapeutique.

En effet, la TMV est recommandée dans la prise en charge de la lombalgie chronique par la majorité des guides de pratique clinique (Oliveira et al., 2018; Zaina et al., 2023), ce qui indique un effet supérieur à la réponse placebo sur la réduction de la douleur. Ces recommandations reposent sur des données issues d'essais contrôlés randomisés, lesquels utilisent généralement entre trois et dix-huit séances d'intervention (Castro-Sánchez et al., 2016; Didehdar et al., 2020; Eklund et al., 2018; Fisher et al., 2020; Fritz et al., 2021; Ghasabmahaleh et al., 2021; Thomas et al., 2020), une dose de dix à douze séances étant fréquemment rapportée (de Oliveira et al., 2020; Haas et al., 2014; Maiers et al., 2019; Nambi et al., 2018; Senna & Machaly, 2011; Xia et al., 2017). Par ailleurs, les facteurs contextuels ou la réponse placebo (voir la **Figure 1.4**), contribuent à l'évolution de l'ensemble des conditions de santé, qu'elles soient prises en charge par des interventions pharmacologiques, psychologiques ou physiques (Krogsbøll et al., 2009). À cet égard, une méta-analyse concernant l'efficacité des chirurgies et autres interventions invasives rapporte que les facteurs contextuels expliquent 65% des effets thérapeutiques observés (toutes interventions invasives et conditions confondues) et que, pour les conditions douloureuses chroniques, cette proportion s'élève à 78% (Jonas et al., 2015).

Puisque les facteurs contextuels sont inhérents à toute intervention, il apparaît pertinent de les considérer en pratique clinique. Maximiser l'efficacité d'une intervention, en exploitant des mécanismes spécifiques ou non spécifiques, permet ultimement d'optimiser les bénéfices pour

les personnes traitées. En ce sens, une revue de la littérature a recensé une trentaine de procédures contribuant à la réponse placebo observée lors d'études expérimentales et cliniques sur la douleur qui pourraient être utilisées en clinique (Bishop et al., 2017). De plus, des recommandations ont été formulées par un groupe d'experts de la « Society for Interdisciplinary Placebo Studies » afin d'aider les cliniciens à utiliser éthiquement les facteurs contextuels pour maximiser l'efficacité des interventions effectuées (Evers et al., 2018). Ces recommandations incluent, entre autres, l'établissement d'une relation patient-clinicien chaleureuse, basée sur la confiance et l'empathie ainsi que d'informer les gens des risques et effets secondaires des interventions de manière à minimiser l'effet nocébo (Evers et al., 2018). Cette seconde recommandation est particulièrement pertinente dans le domaine des thérapies manuelles, où le contexte thérapeutique joue un rôle central et où plusieurs sources potentielles d'effet nocébo ont été identifiées en lien avec la chiropratique, l'ostéopathie et la physiothérapie (Hohenschurz-Schmidt et al., 2022).

Les résultats de l'étude 4 concernant les événements indésirables suggèrent d'ailleurs une possible influence de l'effet nocébo. Aucun événement indésirable grave n'est survenu au cours de cette étude, ce qui concorde avec la très faible incidence d'événements indésirables graves associés à la TMV, estimée à 0,21 pour 100 000 séances dans une vaste analyse rétrospective portant sur 960 140 séances de TMV (Chu et al., 2023). Toutefois, des événements indésirables légers à modérés — principalement des courbatures musculaires transitoires ou une exacerbation temporaire de la lombalgie — ont été rapportés dans tous les groupes, mais plus fréquemment dans le groupe recevant l'intervention contrôle. Ce résultat est quelque peu inattendu, compte tenu du caractère non invasif de l'intervention contrôle, qui comprenait uniquement des touchers légers et de brefs changements de la position du tronc et des membres inférieurs dans une amplitude de mouvement non douloureuse. Une explication plausible réside dans la contribution d'un effet nocebo. En effet, les questions répétées et systématiques concernant les événements indésirables ont possiblement accru l'attention des participants aux sensations corporelles habituelles, lesquelles ont possiblement été interprétées comme des événements indésirables dans le contexte de l'étude (Hohenschurz-Schmidt et al., 2022). La proportion élevée (87,8%) de participants ayant rapporté au moins un événement indésirable léger durant l'étude 4 —

comparativement aux 55% rapportés dans un sondage auprès de patients fréquentant des cliniques universitaires de chiropratique (Funabashi et al., 2020) — appuie cette hypothèse. Néanmoins, puisque les procédures d'évaluation des événements indésirables étaient identiques dans tous les groupes, les raisons expliquant la fréquence plus élevée observée dans le groupe ayant reçu l'intervention contrôle demeurent incertaines.

Dans un autre ordre d'idée, le taux d'adhérence de 90,6% observé dans l'étude 4 se compare favorablement au taux d'adhérence moyen de 80,8% rapporté dans une revue systématique incluant 76 essais contrôlés randomisés non pharmacologiques (Giovanazzi et al., 2022). De plus, l'ensemble des participants ont assisté aux séances d'intervention en respectant la fréquence prescrite de trois séances par semaine. Pris ensemble, ces résultats témoignent de l'efficacité des stratégies mises en place pour favoriser l'adhérence, notamment la flexibilité des horaires, l'envoi fréquent de rappels de rendez-vous et la possibilité de suspendre temporairement la participation pendant deux semaines après la 12^e séance. Par ailleurs, bien que les scores observés pour la dimension « Connexion patient – prestataire de soins » du questionnaire HEAL (*Healing Encounters and Attitudes Lists*) n'étaient pas significativement entre les groupes, ils étaient généralement élevés à la fin de la période d'intervention (moyenne $\pm$ écart-type : $26,8 \pm 2,3$, pour un maximum de 28). Ces résultats suggèrent que l'alliance thérapeutique a probablement contribué de manière importante aux effets non spécifiques observés, et ce, malgré l'absence de procédures explicitement conçues pour renforcer cette relation. Cette interprétation est appuyée par des données montrant que l'alliance thérapeutique prédit l'évolution de la douleur, de l'incapacité et de l'impression globale de changement chez des personnes atteintes de lombalgie chronique traitées par des exercices ou par TMV (Ferreira et al., 2013). Le fort taux de réponse aux questionnaires de suivi (96,9%) témoigne aussi possiblement de la solidité de cette alliance, d'autant plus que les questionnaires de suivi étaient transmis par le clinicien ayant réalisé les interventions. Enfin, le contexte inhérent à la participation à une étude universitaire de cette ampleur — incluant la fréquence des rendez-vous, les interactions avec l'équipe de recherche et les évaluations en laboratoire — a vraisemblablement contribué aux effets non spécifiques observés. Il importe toutefois de souligner que les facteurs contextuels

évalués ne différaient pas significativement entre les groupes et que l'effet de la TMV, particulièrement à 1 mois, est demeuré significatif après ajustement statistique pour ces variables. Ces éléments suggèrent que, au-delà des facteurs contextuels, des mécanismes spécifiques à l'intervention étaient également impliqués.

6.2.3 Mécanismes chez les participants symptomatiques et asymptomatiques

Dans le cadre de cette thèse, des données ont été recueillies auprès de personnes sans douleur ainsi que chez des individus atteints de lombalgie primaire chronique. Il est donc pertinent de se demander si les mécanismes hypoalgésiques associés à la manipulation vertébrale diffèrent entre ces deux populations. À cet égard, une revue systématique portant sur les effets de la manipulation vertébrale sur le système nerveux autonome rapporte que la direction des changements observés — principalement en ce qui concerne la variabilité de la fréquence cardiaque et la réponse galvanique de la peau — est parfois inconstante entre les individus symptomatiques et asymptomatiques (Wirth et al., 2019). Cette variabilité pourrait notamment s'expliquer par des différences dans les niveaux de base des marqueurs autonomiques mesurés entre les groupes (Wirth et al., 2019).

Dans le contexte de l'étude des mécanismes de la douleur, cette problématique peut toutefois être atténuée par l'utilisation de stimuli expérimentaux contrôlés. En effet, l'intensité du stimulus peut être ajustée de manière à induire une douleur expérimentale similaire entre les groupes. Plusieurs études ayant examiné les effets hypoalgésiques de la manipulation vertébrale ont rapporté une réduction de la sommation temporelle de la douleur tant chez des individus sans douleur (Bialosky et al., 2008; Bishop et al., 2011; George et al., 2006; Penza et al., 2017; Randoll et al., 2017) que chez des personnes atteintes de lombalgie chronique (Bialosky et al., 2009; Bialosky et al., 2014). À l'inverse, une étude n'a observé aucune modification de cette variable dans la population clinique (Aspinall et al., 2019a), indépendamment du succès de la première séance à réduire l'intensité de la douleur lombaire (Aspinall et al., 2020). De manière concordante, aucun changement de la sommation temporelle de la douleur entre les groupes n'a été observé au fil du temps dans l'essai clinique réalisé dans cette thèse. Ainsi, à la lumière des

données actuelles, il demeure difficile d'affirmer ou d'infirmer que la manipulation vertébrale agit différemment chez les individus symptomatiques et asymptomatiques. Toutefois, plusieurs considérations méthodologiques permettent de nuancer les disparités rapportées.

Premièrement, une revue narrative incluant 406 études réalisées chez des participants sains et des individus atteints de douleur musculosquelettique rapporte que les méthodes utilisées pour induire la sommation temporelle de la douleur varient considérablement entre les études, ce qui complique la comparaison des résultats (Kielstra et al., 2024). Dans le contexte de la TMV, les travaux ayant rapporté un effet de la manipulation vertébrale utilisaient des stimuli thermiques (Bialosky et al., 2008; Bialosky et al., 2014; Bishop et al., 2011; George et al., 2006; Penza et al., 2017) ou électriques (Randoll et al., 2017), tandis que l'étude n'ayant observé aucun changement recourait à des stimuli mécaniques piquants (Aspinall et al., 2019a). Bien que l'essai clinique réalisé dans cette thèse ait également utilisé des stimuli thermiques, aucun effet n'a été observé sur la sommation temporelle de la douleur. Cette divergence pourrait toutefois s'expliquer par le moment choisi pour effectuer les mesures. En effet, toutes les études ayant rapporté un effet ont évalué les changements à très court terme, soit dans les minutes suivant l'intervention, alors que la présente thèse s'est intéressée aux effets à plus long terme, en comparant les mesures avant et après une série prolongée de séances s'échelonnant sur plusieurs mois. La question de la durée des effets sera d'ailleurs approfondie dans la section suivante.

Au-delà des méthodes expérimentales, l'hétérogénéité des phénotypes de lombalgie inclus dans les essais cliniques mentionnés pourrait également contribuer à expliquer les résultats divergents (Aspinall et al., 2019a; Bialosky et al., 2009; Bialosky et al., 2014). Les études précédentes incluaient des participants présentant divers types de lombalgie, sans exclusion fondée sur l'étiologie, hormis la présence de pathologies graves ou de contre-indications à la manipulation. De plus, bien que majoritairement composées d'individus atteints de lombalgie chronique, ces études incluaient également des participants atteints de lombalgie aiguë. L'une d'elles a aussi inclus des participants avec une lombalgie récurrente qui pouvaient être asymptomatiques depuis plusieurs mois (Aspinall et al., 2019a). À l'inverse, l'étude présentée dans cette thèse portait exclusivement sur des individus symptomatiques atteints de lombalgie primaire chronique. Il est plausible que l'hétérogénéité des résultats retrouvés dans la littérature

s'explique par le fait que les effets de la TMV puissent varier selon les mécanismes physiopathologiques impliqués dans la condition douloureuse. Des travaux additionnels seront toutefois requis pour valider cette interprétation.

6.2.4 La durée des effets

La connaissance de la durée des effets est essentielle pour évaluer la pertinence clinique des résultats issus d'études expérimentales. De nombreuses recherches ont rapporté des effets possiblement associés aux mécanismes neurophysiologiques sous-jacents aux effets hypoalgésiques de la manipulation vertébrale, notamment une réduction de l'hyperalgésie secondaire (Gevers-Montoro et al., 2021b; Mohammadian et al., 2004), de l'allodynie mécanique (Mohammadian et al., 2004), de la sommation temporelle de la douleur (Bialosky et al., 2008; Bialosky et al., 2009; Bialosky et al., 2014; Bishop et al., 2011; George et al., 2006; Penza et al., 2017; Randoll et al., 2017), une augmentation des seuils de douleur à la pression (de Camargo et al., 2011; Dorrón et al., 2016; Fernandez-de-las-Penas et al., 2007; Honore et al., 2018), ainsi que des changements dans l'activité cérébrale (Ellingsen et al., 2018; Gay et al., 2014; Sparks et al., 2013; Sparks et al., 2017; Tan et al., 2020; Weber et al., 2019). Toutefois, l'ensemble de ces effets a été observé dans les minutes suivant l'intervention, et leur influence sur la symptomatologie des participants demeure incertaine.

À ce sujet, une analyse secondaire des données issues d'une revue systématique indique que, chez des individus asymptomatiques, l'effet de la manipulation vertébrale sur les seuils de douleur à la pression est maximal dans les cinq minutes suivant l'intervention et que la taille de l'effet diminue progressivement à partir de dix minutes post-intervention (Honore et al., 2019). Par ailleurs, quelques études ont mesuré une amélioration significative de l'intensité de la douleur ou de l'incapacité associée à la lombalgie chronique après des séances de TMV, avec des effets observés jusqu'à 52 semaines après la randomisation (Haas et al., 2014; Maiers et al., 2019; Nambi et al., 2018). Toutefois, à notre connaissance, l'essai contrôlé randomisé réalisé dans le cadre de cette thèse est le premier à quantifier la modulation à long terme — soit après trois mois — d'une mesure indirecte du traitement nociceptif, à savoir la sommation temporelle de l'activité

cérébrale évoquée par la stimulation des fibres C nociceptives. Cela contribue de manière originale à la compréhension des mécanismes sous-jacents, bien que des travaux supplémentaires soient nécessaires afin de mieux caractériser la persistance temporelle de cet effet de la TMV.

6.4 Retombées et directions futures

Cette thèse est susceptible d’avoir des retombées tant sur le plan de la recherche que sur celui de la pratique clinique. En recherche, les méthodes développées et rapportées pourraient être reprises et adaptées dans de futures études. Plus précisément, le protocole de stimulation laser permettant de mesurer les réponses cérébrales évoquées par la stimulation des fibres C nociceptives ouvre la voie à plusieurs projets de recherche. Comme ce protocole a été développé pour la stimulation du dos, il serait pertinent d’évaluer si des réponses similaires peuvent être observées lors de la stimulation d’autres régions corporelles, telles que le pied ou la main, qui sont plus fréquemment utilisées en recherche expérimentale (Hu et al., 2014; Jankovski et al., 2013; Moayedi et al., 2016; Obi et al., 2007). À cet égard, les résultats d’études récentes utilisant un protocole comparable — soit un train de trois impulsions laser, avec la distinction importante que celles-ci sont appliquées dans un même dermatome, mais en déplaçant le faisceau laser entre les impulsions — suggèrent qu’il est probable que des réponses analogues puissent être obtenues (Wang et al., 2023; Wang et al., 2025). Cela permettrait d’employer le protocole développé dans cette thèse afin d’investiguer les altérations du traitement nociceptif associées à d’autres conditions cliniques ou encore pour quantifier les effets d’interventions thérapeutiques variées.

Par ailleurs, le protocole de stimulation pourrait être optimisé afin de mieux capter les réponses cérébrales associées à la sommation temporelle de la douleur. En effet, un patron similaire a été observé dans les études 2, 3 et 4 concernant les potentiels évoqués laser mesurés à la suite de stimuli répétés, soit une diminution de l’amplitude de la composante P2 associée à la stimulation des fibres C nociceptives entre la première et la deuxième impulsion, suivie d’une augmentation entre la deuxième et la troisième (voir les **Figures 3.5C, 4.4C et 5.9A**). Comme discuté dans l’étude 2, ce patron pourrait refléter une interaction entre la sommation temporelle

et l'habituation, attribuable à l'intervalle interstimulus constant. À ce propos, plusieurs études ont rapporté une réduction de l'amplitude des potentiels évoqués lorsque la prévisibilité temporelle des stimuli est élevée (Iannetti et al., 2008; Ronga et al., 2013; Wang et al., 2010). Ainsi, une modification du protocole de stimulation intégrant une durée aléatoire entre les impulsions pourrait favoriser la détection d'une sommation temporelle des potentiels évoqués laser. L'intervalle entre les impulsions d'un même train devrait idéalement varier entre 1 et 3 s (0,33 à 1 Hz) afin d'induire une sommation temporelle de la douleur tout en permettant la mesure des réponses associées aux fibres C nociceptives. En appui à cette proposition, une étude antérieure a démontré que des intervalles interstimulus variant entre 0,25 et 2 s permettent d'annuler l'effet d'habituation observé avec un intervalle constant (Wang et al., 2010).

De plus, les résultats de l'étude 2 indiquent qu'un nombre croissant de fibres A δ nociceptives est recruté avec la répétition des stimuli (voir les LEP à Cz à **Figure 3.5A**), ce qui est probablement attribuable à une augmentation progressive de la température cutanée qui va jusqu'à atteindre le seuil d'activation thermique de ces fibres. En effet, il a été démontré que la température de la peau retourne beaucoup plus lentement à son niveau initial après une impulsion d'un laser Nd:YAP — tel que celui utilisé dans cette thèse — comparativement à un laser CO₂ (Leandri et al., 2006). L'utilisation d'un laser dont la puissance serait ajustée en fonction d'une mesure continue de la température cutanée au site de stimulation permettrait de limiter ce phénomène et de cibler plus spécifiquement les fibres C nociceptives. Ce type de laser a déjà été utilisé dans des études antérieures pour mesurer les réponses cérébrales évoquées par la stimulation des fibres C nociceptives (Churyukanov et al., 2012; Jankovski et al., 2013), bien qu'il n'ait pas encore été employé dans le cadre de protocoles comprenant des trains de stimulation.

Une autre avenue de recherche prometteuse consisterait à comparer la sommation temporelle de la douleur induite par le protocole de stimulation laser utilisé dans cette thèse à celle induite par une stimulation mécanique répétée de tissus profonds, tels que les muscles. En effet, les résultats d'une étude menée chez des adultes sans douleur indiquent que la sommation temporelle de la douleur est plus marquée lorsque la pression est appliquée sur des tissus profonds que lorsque des stimuli thermiques sont appliqués à la surface de la peau (Lautenbacher et al., 2005). À cet égard, un outil simple et abordable permettant de provoquer une sommation

temporelle de la douleur par la répétition de stimuli mécaniques comparables à ceux produits par un algomètre a récemment été validé expérimentalement (O'Neill et al., 2024). Dans la continuité logique des travaux réalisés dans cette thèse, il serait donc pertinent d'utiliser cet outil afin de comparer la sommation temporelle de la douleur induite par différentes modalités sensibles chez des individus sans douleur et chez des personnes atteintes de lombalgie primaire chronique. Selon les résultats obtenus, cet outil pourrait éventuellement être utilisé plus largement pour quantifier l'impact d'interventions tant en laboratoire qu'en clinique, compte tenu de sa simplicité d'utilisation et de son coût moindre comparativement aux dispositifs de stimulation thermique.

Dans un autre ordre d'idées, cette thèse pourrait également influencer les pratiques des professionnels de la santé ayant recours à la TMV. D'une part, les connaissances générées appuient les lignes directrices actuelles quant à l'utilisation de cette intervention. D'autre part, elles fournissent certaines indications fondées sur les données probantes concernant les paramètres d'application de l'intervention, notamment la région manipulée et le nombre de séances. Afin d'affiner ces connaissances, il serait pertinent d'évaluer l'impact de ces paramètres dans d'autres populations cliniques pour lesquelles la TMV est indiquée (Côté et al., 2019; Lim et al., 2025). Il pourrait également être instructif de tenter de reproduire les résultats cliniques observés dans un contexte plus écologique, où la TMV serait intégrée à une approche multimodale incluant d'autres interventions reconnues comme efficaces, telles que l'éducation, les exercices thérapeutiques et les anti-inflammatoires non stéroïdiens. Toutefois, une telle étude nécessiterait un échantillon plus important afin d'atteindre une puissance statistique suffisante pour distinguer l'effet spécifique de la région manipulée de l'effet thérapeutique global.

Dans cette même perspective, l'influence du nombre de séances sur les symptômes et la fonction apparaît essentielle à examiner dans un contexte de soins multimodaux. Il est en effet plausible qu'une approche combinant plusieurs interventions permette de réduire le nombre de séances nécessaires pour obtenir un soulagement comparable à celui observé avec une approche unimodale. À ce propos, plusieurs essais contrôlés randomisés ont rapporté des améliorations

plus importantes de l'intensité de la douleur lombaire et de la fonction lorsque la TMV est combinée à d'autres interventions (Fritz et al., 2021; Ghasabmahaleh et al., 2021; Nambi et al., 2018; Vining et al., 2020). Il est également possible qu'un plus grand nombre de séances utilisant une approche multimodale (incluant la TMV) entraîne des bénéfices cliniques supplémentaires, comme cela a été observé dans cette thèse et dans des études antérieures portant sur cette approche unimodale (Haas et al., 2018; Haas et al., 2014).

En lien avec ces considérations, il serait pertinent d'examiner l'impact des soins de maintien sur la pérennité des améliorations cliniques observées. Les résultats de l'étude 4 montrent que, chez la majorité des participants, l'intensité et la fréquence de la douleur ainsi que l'incapacité associée à la lombalgie sont demeurées significativement inférieures aux valeurs initiales jusqu'à neuf mois après la fin des interventions. Toutefois, bien que ces paramètres soient restés inférieurs au niveau initial, une certaine recrudescence des symptômes a été observée dans les mois suivant l'arrêt des soins. Il serait donc intéressant de déterminer si la poursuite des interventions à une fréquence réduite permettrait de mieux préserver les bénéfices acquis. À cet égard, deux essais contrôlés randomisés ayant évalué l'effet de séances supplémentaires de TMV après une phase intensive de soins suggèrent un avantage en termes de maintien des améliorations chez des individus atteints de lombalgie chronique (Eklund et al., 2018; Senna & Machaly, 2011). La fréquence des soins de maintien dans ces études variait entre deux visites par mois (Senna & Machaly, 2011) et quatre à douze visites par an (Eklund et al., 2018). En revanche, un autre essai clinique portant sur des individus atteints de cervicalgie chronique, randomisés en trois groupes de soins de maintien — TMV seule, TMV combinée à des exercices à domicile, ou suivi périodique sans intervention — n'a rapporté aucune différence significative entre les groupes (Martel et al., 2011). Ces résultats suggèrent que les bénéfices associés aux soins de maintien pourraient être largement attribuables aux facteurs contextuels, ce qui est cohérent avec les observations de l'étude 4, où les améliorations se sont maintenues dans l'ensemble des groupes après la fin des interventions. Des études supplémentaires intégrant des groupes contrôles appropriés seront donc nécessaires afin de confirmer l'efficacité de la TMV en prévention tertiaire de la lombalgie primaire chronique.

D'autre part, une meilleure compréhension des mécanismes neurophysiologiques sous-jacents aux effets hypoalgésiques de la TMV soulève inévitablement de nouvelles questions de recherche. Si la modulation de l'amplification centrale des afférences provenant des fibres C nociceptives est reproduite par des travaux futurs, une piste de recherche consisterait à évaluer l'efficacité de la TMV en prévention secondaire, c'est-à-dire lorsqu'elle est appliquée rapidement après l'apparition des premiers symptômes afin de prévenir la chronicisation de la lombalgie. En appui à cette hypothèse, une étude récente menée aux États-Unis et portant sur 29 806 cas de lombalgie aiguë a montré que, sur une période de 12 mois, le coût total des soins associés à l'épisode douloureux était significativement plus faible chez les personnes consultant initialement en chiropratique ou en physiothérapie comparativement à celles consultant d'abord en médecine (Bise et al., 2023), suggérant que la lombalgie était de plus courte durée ou moins inconfortable. Une première consultation en chiropratique ou en physiothérapie était également associée à une moindre utilisation d'opioïdes, d'imagerie diagnostique, d'injections, de références vers des médecins spécialistes et de chirurgies (Bise et al., 2023). Par ailleurs, un essai contrôlé randomisé de grande envergure, visant à recruter 1000 participants et conçu pour évaluer l'efficacité de huit semaines de TMV — seule ou combinée à des stratégies d'autogestion de la douleur — comparativement aux soins médicaux usuels en prévention secondaire de la lombalgie chronique, est actuellement en phase de recrutement (Bronfort et al., 2023). Les résultats de cette étude, s'ils sont concluants, pourraient contribuer de manière significative à la réduction du fardeau associé à la lombalgie.

Enfin, à la lumière des mécanismes neurophysiologiques mis en évidence dans cette thèse, il serait également intéressant d'examiner le potentiel de la TMV à soulager d'autres douleurs chroniques de type nociplastique, telles que la fibromyalgie. Toutefois, une revue narrative récente n'a recensé que cinq essais cliniques où la TMV était utilisée pour cette condition, avec une qualité méthodologique et des résultats variables (Roecker & Hewawasam, 2025). Des essais contrôlés randomisés rigoureux seront donc nécessaires afin d'évaluer adéquatement l'efficacité de la TMV dans le soulagement d'autres douleurs chroniques nociplastiques.

6.5 Conclusion

L'objectif général de cette thèse était de mieux caractériser les mécanismes neurophysiologiques sous-jacents aux effets hypoalgésiques de la TMV dans le soulagement de la douleur au dos, en mettant un accent particulier sur son influence sur les processus neuronaux d'amplification de la douleur liés à l'activation des fibres C nociceptives. Une étape nécessaire à l'atteinte de cet objectif consistait à développer une méthode permettant de mesurer les réponses cérébrales évoquées par la stimulation des fibres C nociceptives. Cette méthode a été établie et sa reproductibilité a été démontrée à plusieurs reprises au cours de cette thèse.

Les résultats obtenus indiquent que la TMV n'affecte pas le traitement nociceptif spinal lorsque les afférences sont amplifiées par la sensibilisation périphérique, mais qu'elle semble moduler ce traitement lorsque l'amplification des afférences des fibres C nociceptives repose sur des mécanismes centraux. Ce mécanisme neurophysiologique contribuerait à la réduction à long terme de l'intensité de la lombalgie primaire chronique observée après l'intervention. Des effets non spécifiques, possiblement attribuables aux facteurs contextuels, participent également aux effets hypoalgésiques observés, particulièrement après 12 séances d'intervention. De plus, la TMV appliquée à l'ensemble du rachis est plus efficace que la TMV limitée à la région lombaire ou qu'une intervention contrôle pour réduire l'intensité de la lombalgie durant le premier mois d'intervention, et possiblement au-delà de cette période.

Enfin, bien que ces résultats apportent des éléments nouveaux à la compréhension des effets de la TMV, des études supplémentaires demeurent nécessaires afin de les valider sur des échantillons de plus grande taille et d'étendre ces connaissances à d'autres conditions douloureuses.

Bibliographie

- Ailliet, L., Rubinstein, S. M., Hoekstra, T., van Tulder, M. W., & de Vet, H. C. W. (2018). Long-term trajectories of patients with neck pain and low back pain presenting to chiropractic care: A latent class growth analysis. *Eur J Pain*, 22(1), 103–113. <https://doi.org/10.1002/ejp.1094>
- Alanazi, M. S., Degenhardt, B., Kelley-Franklin, G., Cox, J. M., Lipke, L., & Reed, W. R. (2025). Neuromuscular Response to High-Velocity, Low-Amplitude Spinal Manipulation-An Overview. *Medicina*, 61(2). <https://doi.org/10.3390/medicina61020187>
- Alonso-Perez, J. L., Lopez-Lopez, A., La Touche, R., Lerma-Lara, S., Suarez, E., Rojas, J., Bishop, M. D., Villafane, J. H., & Fernandez-Carnero, J. (2017). Hypoalgesic effects of three different manual therapy techniques on cervical spine and psychological interaction: A randomized clinical trial. *J Bodyw Mov Ther*, 21(4), 798–803. <https://doi.org/10.1016/j.jbmt.2016.12.005>
- Anderson, R. J., Craggs, J. G., Bialosky, J. E., Bishop, M. D., George, S. Z., Staud, R., & Robinson, M. E. (2013). Temporal summation of second pain: variability in responses to a fixed protocol. *European Journal of Pain*, 17(1), 67–74. <https://doi.org/10.1002/j.1532-2149.2012.00190.x>
- Arendt-Nielsen, L. (2015). Central sensitization in humans: assessment and pharmacology. *Handb Exp Pharmacol*, 227, 79–102. https://doi.org/10.1007/978-3-662-46450-2_5
- Arribas-Romano, A., Fernández-Carnero, J., Molina-Rueda, F., Angulo-Díaz-Parreño, S., & Navarro-Santana, M. J. (2020). Efficacy of Physical Therapy on Nociceptive Pain Processing Alterations in Patients with Chronic Musculoskeletal Pain: A Systematic Review and Meta-analysis. *Pain Med*, 21(10), 2502–2517. <https://doi.org/10.1093/pm/pnz366>
- Asci, F., Di Stefano, G., Di Santo, A., Bianchini, E., Leone, C., La Cesa, S., Zampogna, A., Cruccu, G., & Suppa, A. (2023). Pain-motor integration in chronic pain: A neurophysiological study. *Clin Neurophysiol*, 154, 107–115. <https://doi.org/10.1016/j.clinph.2023.07.010>
- Aspinall, S. L., Jacques, A., Leboeuf-Yde, C., Etherington, S. J., & Walker, B. F. (2019a). No difference in pressure pain threshold and temporal summation after lumbar spinal manipulation compared to sham: A randomised controlled trial in adults with low back pain. *Musculoskelet Sci Pract*, 43, 18–25. <https://doi.org/10.1016/j.msksp.2019.05.011>
- Aspinall, S. L., Leboeuf-Yde, C., Etherington, S. J., & Walker, B. F. (2019b). Manipulation-induced hypoalgesia in musculoskeletal pain populations: a systematic critical review and meta-analysis. *Chiropractic & Manual Therapies*, 27(1), 7. <https://doi.org/10.1186/s12998-018-0226-7>

- Aspinall, S. L., Leboeuf-Yde, C., Etherington, S. J., & Walker, B. F. (2020). Changes in pressure pain threshold and temporal summation in rapid responders and non-rapid responders after lumbar spinal manipulation and sham: A secondary analysis in adults with low back pain. *Musculoskelet Sci Pract*, 47, 102137. <https://doi.org/10.1016/j.msksp.2020.102137>
- Baron, R., Hans, G., & Dickenson, A. H. (2013). Peripheral input and its importance for central sensitization. *Ann Neurol*, 74(5), 630–636. <https://doi.org/10.1002/ana.24017>
- Battaglia, A. A. (2016). *An Introduction to Pain and its relation to Nervous System Disorders* (A. A. Battaglia, Ed. John Wiley & Sons, Ltd ed.). Wiley Blackwell. <https://doi.org/10.1002/9781118455968.index>
- Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Arch Gen Psychiatry*, 4, 561–571. <https://doi.org/10.1001/archpsyc.1961.01710120031004>
- Beliveau, P. J. H., Wong, J. J., Sutton, D. A., Simon, N. B., Bussieres, A. E., Mior, S. A., & French, S. D. (2017). The chiropractic profession: a scoping review of utilization rates, reasons for seeking care, patient profiles, and care provided. *Chiropr Man Therap*, 25, 35–52. <https://doi.org/10.1186/s12998-017-0165-8>
- Bi, Y., Hou, X., Zhong, J., & Hu, L. (2021). Test–retest reliability of laser evoked pain perception and fMRI BOLD responses. *Sci Rep*, 11(1), 1322. <https://doi.org/10.1038/s41598-020-79196-z>
- Bialosky, J. E., Beneciuk, J. M., Bishop, M. D., Coronado, R. A., Penza, C. W., Simon, C. B., & George, S. Z. (2018). Unraveling the Mechanisms of Manual Therapy: Modeling an Approach. *J Orthop Sports Phys Ther*, 48(1), 8–18. <https://doi.org/10.2519/jospt.2018.7476>
- Bialosky, J. E., Bishop, M. D., Robinson, M. E., Barabas, J. A., & George, S. Z. (2008). The influence of expectation on spinal manipulation induced hypoalgesia: an experimental study in normal subjects. *BMC Musculoskelet Disord*, 9, 19. <https://doi.org/10.1186/1471-2474-9-19>
- Bialosky, J. E., Bishop, M. D., Robinson, M. E., Zeppieri, G., Jr., & George, S. Z. (2009). Spinal manipulative therapy has an immediate effect on thermal pain sensitivity in people with low back pain: a randomized controlled trial. *Phys Ther*, 89(12), 1292–1303. <https://doi.org/10.2522/ptj.20090058>
- Bialosky, J. E., George, S. Z., Horn, M. E., Price, D. D., Staud, R., & Robinson, M. E. (2014). Spinal manipulative therapy-specific changes in pain sensitivity in individuals with low back pain (NCT01168999). *The Journal of Pain*, 15(2), 136–148. <https://doi.org/10.1016/j.jpain.2013.10.005>
- Bise, C. G., Schneider, M., Freburger, J., Fitzgerald, G. K., Switzer, G., Smyda, G., Peele, P., & Delitto, A. (2023). First Provider Seen for an Acute Episode of Low Back Pain Influences

- Subsequent Health Care Utilization. *Phys Ther*, 103(9), 1–9. <https://doi.org/10.1093/ptj/pzad067>
- Bishop, F. L., Coghlan, B., Geraghty, A. W., Everitt, H., Little, P., Holmes, M. M., Seretis, D., & Lewith, G. (2017). What techniques might be used to harness placebo effects in non-malignant pain? A literature review and survey to develop a taxonomy. *BMJ Open*, 7(6), e015516. <https://doi.org/10.1136/bmjopen-2016-015516>
- Bishop, M. D., Beneciuk, J. M., & George, S. Z. (2011). Immediate reduction in temporal sensory summation after thoracic spinal manipulation. *Spine J*, 11(5), 440–446. <https://doi.org/10.1016/j.spinee.2011.03.001>
- Blumenfeld, H. (2011). *Neuroanatomy through clinical cases* (second edition ed.). Sinauer Associates, Inc.
- Bosma, R. L., Ameli Mojarad, E., Leung, L., Pukall, C., Staud, R., & Stroman, P. W. (2015). Neural correlates of temporal summation of second pain in the human brainstem and spinal cord. *Hum Brain Mapp*, 36(12), 5038–5050. <https://doi.org/10.1002/hbm.22993>
- Bouhassira, D. (2019). Neuropathic pain: Definition, assessment and epidemiology. *Rev Neurol (Paris)*, 175(1-2), 16–25. <https://doi.org/10.1016/j.neurol.2018.09.016>
- Bourque, P., & Beaudette, D. (1982). Étude psychométrique du questionnaire de dépression de Beck auprès d'un échantillon d'étudiants universitaires francophones. [Psychometric study of the Beck Depression Inventory on a sample of French-speaking university students.]. *Canadian Journal of Behavioural Science / Revue canadienne des sciences du comportement*, 14, 211–218. <https://doi.org/10.1037/h0081254>
- Bragard, D., Chen, A. C., & Plaghki, L. (1996). Direct isolation of ultra-late (C-fibre) evoked brain potentials by CO2 laser stimulation of tiny cutaneous surface areas in man. *Neurosci Lett*, 209(2), 81–84. [https://doi.org/10.1016/0304-3940\(96\)12604-5](https://doi.org/10.1016/0304-3940(96)12604-5)
- Bromm, B., Jahnke, M. T., & Treede, R. D. (1984). Responses of human cutaneous afferents to CO2 laser stimuli causing pain. *Exp Brain Res*, 55(1), 158–166. <https://doi.org/10.1007/BF00240510>
- Bromm, B., & Treede, R. D. (1987). Human cerebral potentials evoked by CO2 laser stimuli causing pain. *Exp Brain Res*, 67(1), 153–162. <https://doi.org/10.1007/BF00269463>
- Bronfort, G., Delitto, A., Schneider, M., Heagerty, P. J., Chou, R., Connett, J., Evans, R., George, S., Glick, R. M., Greco, C., Hanson, L., Keefe, F., Leininger, B., Licciardone, J., McFarland, C., Meier, E., Schulz, C., & Turk, D. (2023). Effectiveness of spinal manipulation and biopsychosocial self-management compared to medical care for low back pain: a randomized trial study protocol. *BMC Musculoskelet Disord*, 24(1), 415. <https://doi.org/10.1186/s12891-023-06549-w>

- Bronfort, G., Maiers, M., Schulz, C., Leininger, B., Westrom, K., Angstman, G., & Evans, R. (2022). Multidisciplinary integrative care versus chiropractic care for low back pain: a randomized clinical trial. *Chiropr Man Therap*, 30(1), 10. <https://doi.org/10.1186/s12998-022-00419-3>
- Bruyère, O., Demoulin, M., Beaudart, C., Hill, J. C., Maquet, D., Genevay, S., Mahieu, G., Reginster, J. Y., Crielaard, J. M., & Demoulin, C. (2014). Validity and reliability of the french version of the start back screening tool for patients with low back pain. *Spine*, 39(2), E123–E128. <https://doi.org/10.1097/BRS.0000000000000062>
- Buzsáki, G. (2006). *Rhythms of The Brain*. Oxford University Press. <https://doi.org/10.1093/acprof:oso/9780195301069.001.0001>
- Buzsáki, G., Anastassiou, C. A., & Koch, C. (2012). The origin of extracellular fields and currents-- EEG, ECoG, LFP and spikes. *Nat Rev Neurosci*, 13(6), 407–420. <https://doi.org/10.1038/nrn3241>
- Camirand, H., & collaborateurs. (2023). *Enquête québécoise sur la santé de la population 2020-2021*. Québec, Institut de la statistique du Québec, Retrieved from <https://statistique.quebec.ca/fr/fichier/enquete-quebecoise-sante-population-2020-2021.pdf>
- Campbell, F., Hudspith, M., Choinière, M., El-Gabalawy, H., Laliberté, J., Sangster, M., Swidrovich, J., & Wilhelm, L. (2021). *Un plan d'action pour la douleur au Canada*. Santé Canada
- Cashin, A. G., Furlong, B. M., Kamper, S. J., De Carvalho, D., Machado, L. A., Davidson, S. R., Bursey, K. K., Abdel Shaheed, C., & Hall, A. M. (2025). Analgesic effects of non-surgical and non-interventional treatments for low back pain: a systematic review and meta-analysis of placebo-controlled randomised trials. *BMJ Evid Based Med*, 30(4), 222–232. <https://doi.org/10.1136/bmjebm-2024-112974>
- Cashin, A. G., Wand, B. M., O'Connell, N. E., Lee, H., Rizzo, R. R., Bagg, M. K., O'Hagan, E., Maher, C. G., Furlan, A. D., van Tulder, M. W., & McAuley, J. H. (2023). Pharmacological treatments for low back pain in adults: an overview of Cochrane Reviews. *Cochrane Database Syst Rev*, 4(4), Cd013815. <https://doi.org/10.1002/14651858.CD013815.pub2>
- Castro-Sánchez, A. M., Lara-Palomo, I. C., Matarán-Peñarrocha, G. A., Fernández-de-Las-Peñas, C., Saavedra-Hernández, M., Cleland, J., & Aguilar-Ferrándiz, M. E. (2016). Short-term effectiveness of spinal manipulative therapy versus functional technique in patients with chronic nonspecific low back pain: a pragmatic randomized controlled trial. *Spine J*, 16(3), 302–312. <https://doi.org/10.1016/j.spinee.2015.08.057>
- Cayrol, T., Draper-Rodi, J., Fabre, L., Pitance, L., & van den Broeke, E. N. (2021). Stuck in the Middle With You: Why a Broad-Brush Approach to Defining Central Sensitization Does Not Help Clinicians and Patients. *J Orthop Sports Phys Ther*, 51(5), 204–206. <https://doi.org/10.2519/jospt.2021.10340>

- Chang, A. Y., Cowling, K., Micah, A. E., Chapin, A., Chen, C. S., Ikilezi, G., Sadat, N., Tsakalos, G., Wu, J., Younker, T., Zhao, Y., Zlavog, B. S., Abbafati, C., Ahmed, A. E., Alam, K., Alipour, V., Aljunid, S. M., Almalki, M. J., Alvis-Guzman, N.,...Dieleman, J. L. (2019). Past, present, and future of global health financing: a review of development assistance, government, out-of-pocket, and other private spending on health for 195 countries, 1995-2050. *The Lancet*, 393(10187), 2233–2260. [https://doi.org/10.1016/S0140-6736\(19\)30841-4](https://doi.org/10.1016/S0140-6736(19)30841-4)
- Chen, K. K., Rolan, P., Hutchinson, M. R., & de Zoete, R. M. J. (2025). Reliability of Temporal Summation of Pain in Healthy and Clinical Populations: A Systematic Review and Meta-Analysis. *Eur J Pain*, 29(8), e70097. <https://doi.org/10.1002/ejp.70097>
- Chiarotto, A., & Koes, B. W. (2022). Nonspecific Low Back Pain. *N Engl J Med*, 386(18), 1732–1740. <https://doi.org/10.1056/NEJMcp2032396>
- Chu, E. C. P., Trager, R. J., Lee, L. Y. K., & Niazi, I. K. (2023). A retrospective analysis of the incidence of severe adverse events among recipients of chiropractic spinal manipulative therapy. *Sci Rep*, 13(1), 1254. <https://doi.org/10.1038/s41598-023-28520-4>
- Churyukanov, M., Plaghki, L., Legrain, V., & Mouraux, A. (2012). Thermal detection thresholds of Aδ- and C-fibre afferents activated by brief CO2 laser pulses applied onto the human hairy skin. *PLOS ONE*, 7(4), e35817. <https://doi.org/10.1371/journal.pone.0035817>
- Clijsters, M., Fronzoni, F., & Jenkins, H. (2014). Chiropractic treatment approaches for spinal musculoskeletal conditions: a cross-sectional survey. *Chiropr Man Therap*, 22(1), 33. <https://doi.org/10.1186/s12998-014-0033-8>
- Cohen, M., Quintner, J., & van Rysewyk, S. (2018). Reconsidering the International Association for the Study of Pain definition of pain. *Pain reports*, 3(2), e634–e634. <https://doi.org/10.1097/PR9.0000000000000634>
- Cohen, M. X. (2014). *Analyzing Neural Time Series Data: Theory and Practice*. The MIT Press.
- Conde-Vázquez, O., García-Cancela, J., Navarro-Ledesma, S., & Pruimboom, L. (2026). The effectiveness of manual therapy in people with chronic non-specific low back pain: an umbrella review with meta-analysis. *Ann Phys Rehabil Med*, 69(2), 102049. <https://doi.org/10.1016/j.rehab.2025.102049>
- Cormier, S., Lavigne, G. L., Choinière, M., & Rainville, P. (2016). Expectations predict chronic pain treatment outcomes. *Pain*, 157(2), 329–338. <https://doi.org/10.1097/j.pain.0000000000000379>
- Coronado, R. A., Gay, C. W., Bialosky, J. E., Carnaby, G. D., Bishop, M. D., & George, S. Z. (2012). Changes in pain sensitivity following spinal manipulation: a systematic review and meta-analysis. *J Electromyogr Kinesiol*, 22(5), 752–767. <https://doi.org/10.1016/j.jelekin.2011.12.013>

- Côté, P., Yu, H., Shearer, H. M., Randhawa, K., Wong, J. J., Mior, S., Ameis, A., Carroll, L. J., Nordin, M., Varatharajan, S., Sutton, D., Southerst, D., Jacobs, C., Stupar, M., Taylor-Vaisey, A., Gross, D. P., Brison, R. J., Paulden, M., Ammendolia, C.,...Lacerte, M. (2019). Non-pharmacological management of persistent headaches associated with neck pain: A clinical practice guideline from the Ontario protocol for traffic injury management (OPTIMa) collaboration. *Eur J Pain*, 23(6), 1051–1070. <https://doi.org/10.1002/ejp.1374>
- Cramer, G. D., Ross, K., Raju, P. K., Cambron, J., Cantu, J. A., Bora, P., Dexheimer, J. M., McKinnis, R., Habeck, A. R., Selby, S., Pocius, J. D., & Gregerson, D. (2012). Quantification of cavitation and gapping of lumbar zygapophyseal joints during spinal manipulative therapy. *J Manipulative Physiol Ther*, 35(8), 614–621. <https://doi.org/10.1016/j.jmpt.2012.06.007>
- Crombez, G., Eccleston, C., Van Damme, S., Vlaeyen, J. W., & Karoly, P. (2012). Fear-avoidance model of chronic pain: the next generation. *Clin J Pain*, 28(6), 475–483. <https://doi.org/10.1097/AJP.0b013e3182385392>
- Cruccu, G., & García-Larrea, L. (2004). Clinical utility of pain--laser evoked potentials. *Suppl Clin Neurophysiol*, 57, 101–110. [https://doi.org/10.1016/s1567-424x\(09\)70348-4](https://doi.org/10.1016/s1567-424x(09)70348-4)
- Cruccu, G., Pennisi, E., Truini, A., Iannetti, G. D., Romaniello, A., Le Pera, D., De Armas, L., Leandri, M., Manfredi, M., & Valeriani, M. (2003). Unmyelinated trigeminal pathways as assessed by laser stimuli in humans. *Brain*, 126(10), 2246–2256. <https://doi.org/10.1093/brain/awg227>
- Cruccu, G., Sommer, C., Anand, P., Attal, N., Baron, R., Garcia-Larrea, L., Haanpaa, M., Jensen, T. S., Serra, J., & Treede, R. D. (2010). EFNS guidelines on neuropathic pain assessment: revised 2009. *Eur J Neurol*, 17(8), 1010–1018. <https://doi.org/10.1111/j.1468-1331.2010.02969.x>
- de Camargo, V. M., Alburquerque-Sendin, F., Berzin, F., Stefanelli, V. C., de Souza, D. P., & Fernandez-de-las-Penas, C. (2011). Immediate effects on electromyographic activity and pressure pain thresholds after a cervical manipulation in mechanical neck pain: a randomized controlled trial [Randomized Controlled Trial]. *J Manipulative Physiol Ther*, 34(4), 211–220. <https://doi.org/10.1016/j.jmpt.2011.02.002>
- de Oliveira, R. F., Costa, L. O. P., Nascimento, L. P., & Rissato, L. L. (2020). Directed vertebral manipulation is not better than generic vertebral manipulation in patients with chronic low back pain: a randomised trial. *J Physiother*, 66(3), 174–179. <https://doi.org/10.1016/j.jphys.2020.06.007>
- de Tommaso, M., Betti, V., Bocci, T., Bolognini, N., Di Russo, F., Fattapposta, F., Ferri, R., Invitto, S., Koch, G., Miniussi, C., Piccione, F., Ragazzoni, A., Sartucci, F., Rossi, S., Arcara, G., Berchicci, M., Bianco, V., Delussi, M., Gentile, E.,...Valeriani, M. (2020). Pearls and pitfalls in brain functional analysis by event-related potentials: a narrative review by the Italian Psychophysiology and Cognitive Neuroscience Society on methodological limits and

- clinical reliability-part I. *Neurol Sci*, 41(10), 2711–2735. <https://doi.org/10.1007/s10072-020-04420-7>
- Didehdar, D., Kamali, F., Yoosefinejad, A. K., & Lotfi, M. (2020). The effect of spinal manipulation on brain neurometabolites in chronic nonspecific low back pain patients: a randomized clinical trial. *Ir J Med Sci*, 189(2), 543–550. <https://doi.org/10.1007/s11845-019-02140-2>
- Dieleman, J. L., Cao, J., Chapin, A., Chen, C., Li, Z., Liu, A., Horst, C., Kaldjian, A., Matyas, T., Scott, K. W., Bui, A. L., Campbell, M., Duber, H. C., Dunn, A. C., Flaxman, A. D., Fitzmaurice, C., Naghavi, M., Sadat, N., Shieh, P.,...Murray, C. J. L. (2020). US Health Care Spending by Payer and Health Condition, 1996–2016. *JAMA*, 323(9), 863–884. <https://doi.org/10.1001/jama.2020.0734>
- do Carmo Silva Parreira, P., Maher, C. G., Latimer, J., Steffens, D., Blyth, F., Li, Q., & Ferreira, M. L. (2015). Can patients identify what triggers their back pain? Secondary analysis of a case-crossover study. *Pain*, 156(10), 1913–1919. <https://doi.org/10.1097/j.pain.0000000000000252>
- Domnick, C., Hauck, M., Casey, K. L., Engel, A. K., & Lorenz, J. (2009). C-fiber-related EEG-oscillations induced by laser radiant heat stimulation of capsaicin-treated skin. *J Pain Res*, 2, 49–56. <https://doi.org/10.2147/jpr.s4860>
- Dorron, S. L., Losco, B. E., Drummond, P. D., & Walker, B. F. (2016). Effect of lumbar spinal manipulation on local and remote pressure pain threshold and pinprick sensitivity in asymptomatic individuals: a randomised trial. *Chiropr Man Therap*, 24, 47. <https://doi.org/10.1186/s12998-016-0128-5>
- Downie, A. S., Hancock, M. J., Rzewuska, M., Williams, C. M., Lin, C. C., & Maher, C. G. (2016). Trajectories of acute low back pain: a latent class growth analysis. *Pain*, 157(1), 225–234. <https://doi.org/10.1097/j.pain.0000000000000351>
- Dunning, J., Mourad, F., Zingoni, A., Iorio, R., Perreault, T., Zacharko, N., de Las Peñas, C. F., Butts, R., & Cleland, J. A. (2017). Cavitation sounds during cervicothoracic spinal manipulation. *International journal of sports physical therapy*, 12(4), 642–654.
- Dworkin, R. H., Turk, D. C., Farrar, J. T., Haythornthwaite, J. A., Jensen, M. P., Katz, N. P., Kerns, R. D., Stucki, G., Allen, R. R., Bellamy, N., Carr, D. B., Chandler, J., Cowan, P., Dionne, R., Galer, B. S., Hertz, S., Jadad, A. R., Kramer, L. D., Manning, D. C.,...Witter, J. (2005). Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*, 113(1-2), 9–19. <https://doi.org/10.1016/j.pain.2004.09.012>
- Edwards, R. R., Dworkin, R. H., Sullivan, M. D., Turk, D. C., & Wasan, A. D. (2016). The Role of Psychosocial Processes in the Development and Maintenance of Chronic Pain. *J Pain*, 17(9 Suppl), T70–92. <https://doi.org/10.1016/j.jpain.2016.01.001>

- Eklund, A., Jensen, I., Lohela-Karlsson, M., Hagberg, J., Leboeuf-Yde, C., Kongsted, A., Bodin, L., & Axén, I. (2018). The Nordic Maintenance Care program: Effectiveness of chiropractic maintenance care versus symptom-guided treatment for recurrent and persistent low back pain-A pragmatic randomized controlled trial. *PLOS ONE*, 13(9), e0203029. <https://doi.org/10.1371/journal.pone.0203029>
- Ellingsen, D. M., Napadow, V., Protsenko, E., Mawla, I., Kowalski, M. H., Swensen, D., O'Dwyer-Swensen, D., Edwards, R. R., Kettner, N., & Loggia, M. L. (2018). Brain Mechanisms of Anticipated Painful Movements and Their Modulation by Manual Therapy in Chronic Low Back Pain. *J Pain*, 19(11), 1352–1365. <https://doi.org/10.1016/j.jpain.2018.05.012>
- Evans, D. W. (2002). Mechanisms and effects of spinal high-velocity, low-amplitude thrust manipulation: Previous theories. *Journal of Manipulative and Physiological Therapeutics*, 25(4), 251–262. <https://doi.org/10.1067/mmt.2002.123166>
- Evans, D. W. (2010). Why do spinal manipulation techniques take the form they do? Towards a general model of spinal manipulation. *Man Ther*, 15(3), 212–219. <https://doi.org/10.1016/j.math.2009.03.006>
- Evans, D. W. (2022). Why is the prevailing model of joint manipulation (still) incorrect? *Chiropr Man Therap*, 30(1), 51. <https://doi.org/10.1186/s12998-022-00460-2>
- Evans, D. W., & Breen, A. C. (2006). A Biomechanical Model for Mechanically Efficient Cavitation Production During Spinal Manipulation: Prethrust Position and the Neutral Zone. *Journal of Manipulative and Physiological Therapeutics*, 29(1), 72–82. <https://doi.org/10.1016/j.jmpt.2005.11.011>
- Evers, A. W. M., Colloca, L., Blease, C., Annoni, M., Atlas, L. Y., Benedetti, F., Bingel, U., Büchel, C., Carvalho, C., Colagiuri, B., Crum, A. J., Enck, P., Gaab, J., Geers, A. L., Howick, J., Jensen, K. B., Kirsch, I., Meissner, K., Napadow, V.,...Kelley, J. M. (2018). Implications of Placebo and Nocebo Effects for Clinical Practice: Expert Consensus. *Psychother Psychosom*, 87(4), 204–210. <https://doi.org/10.1159/000490354>
- Fenton, B. W., Shih, E., & Zolton, J. (2015). The neurobiology of pain perception in normal and persistent pain. *Pain Manag*, 5(4), 297–317. <https://doi.org/10.2217/pmt.15.27>
- Fernandez-de-las-Penas, C., Perez-de-Heredia, M., Brea-Rivero, M., & Miangolarra-Page, J. C. (2007). Immediate effects on pressure pain threshold following a single cervical spine manipulation in healthy subjects. *J Orthop Sports Phys Ther*, 37(6), 325–329. <https://doi.org/10.2519/jospt.2007.2542>
- Ferreira, P. H., Ferreira, M. L., Maher, C. G., Refshauge, K. M., Latimer, J., & Adams, R. D. (2013). The therapeutic alliance between clinicians and patients predicts outcome in chronic low back pain. *Phys Ther*, 93(4), 470–478. <https://doi.org/10.2522/ptj.20120137>

- Finley, C. R., Chan, D. S., Garrison, S., Korownyk, C., Kolber, M. R., Campbell, S., Eurich, D. T., Lindblad, A. J., Vandermeer, B., & Allan, G. M. (2018). What are the most common conditions in primary care? Systematic review. *Canadian family physician Medecin de famille canadien*, 64(11), 832–840.
- Fisher, L. R., Alvar, B. A., Maher, S. F., & Cleland, J. A. (2020). Short-term Effects of Thoracic Spine Thrust Manipulation, Exercise, and Education in Individuals With Low Back Pain: A Randomized Controlled Trial. *J Orthop Sports Phys Ther*, 50(1), 24–32. <https://doi.org/10.2519/jospt.2020.8928>
- Fritz, J. M., Sharpe, J., Greene, T., Lane, E., Hadizadeh, M., McFadden, M., Santillo, D., Farley, J., Magel, J., Thackeray, A., & Kawchuk, G. (2021). Optimization of Spinal Manipulative Therapy Protocols: A Factorial Randomized Trial Within a Multiphase Optimization Framework. *J Pain*, 22(6), 655–668. <https://doi.org/10.1016/j.jpain.2020.11.008>
- Funabashi, M., Pohlman, K. A., Goldsworthy, R., Lee, A., Tibbles, A., Mior, S., & Kawchuk, G. (2020). Beliefs, perceptions and practices of chiropractors and patients about mitigation strategies for benign adverse events after spinal manipulation therapy. *Chiropr Man Therap*, 28(1), 46–54. <https://doi.org/10.1186/s12998-020-00336-3>
- Gandløse, J. S., Sørensen, C. W. M., Hemmingsen, C. T., Larsen, K. W., & Palsson, T. S. (2025). Mapping Comorbidities in Patients With Low Back Pain-A Systematic Review. *Physiother Res Int*, 30(4), e70109. <https://doi.org/10.1002/pri.70109>
- Garcia-Larrea, L., & André-Obadia, N. (2025). Electroencephalography, magnetoencephalography and pain: where do we stand, and where are we going. *Pain*, 166(11S), S65–S70. <https://doi.org/10.1097/j.pain.0000000000003689>
- Garcia-Larrea, L., & Bastuji, H. (2018). Pain and consciousness. *Prog Neuropsychopharmacol Biol Psychiatry*, 87(Pt B), 193–199. <https://doi.org/10.1016/j.pnpbp.2017.10.007>
- Gay, C. W., Robinson, M. E., George, S. Z., Perlstein, W. M., & Bishop, M. D. (2014). Immediate changes after manual therapy in resting-state functional connectivity as measured by functional magnetic resonance imaging in participants with induced low back pain. *Journal of Manipulative and Physiological Therapeutics*, 37(9), 614–627. <https://doi.org/10.1016/j.jmpt.2014.09.001>
- GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*, 392(10159), 1789–1858. [https://doi.org/10.1016/S0140-6736\(18\)32279-7](https://doi.org/10.1016/S0140-6736(18)32279-7)
- GBD 2021 Diseases and Injuries Collaborators. (2024). Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational

- locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet*, 403(10440), 2133–2161. [https://doi.org/10.1016/s0140-6736\(24\)00757-8](https://doi.org/10.1016/s0140-6736(24)00757-8)
- GBD 2021 Forecasting Collaborators. (2024). Burden of disease scenarios for 204 countries and territories, 2022-2050: a forecasting analysis for the Global Burden of Disease Study 2021. *Lancet*, 403(10440), 2204–2256. [https://doi.org/10.1016/s0140-6736\(24\)00685-8](https://doi.org/10.1016/s0140-6736(24)00685-8)
- George, S. Z., Bishop, M. D., Bialosky, J. E., Zeppieri, G., Jr., & Robinson, M. E. (2006). Immediate effects of spinal manipulation on thermal pain sensitivity: an experimental study. *BMC Musculoskeletal Disorders*, 7, 68–78. <https://doi.org/10.1186/1471-2474-7-68>
- Gevers-Montoro, C., Provencher, B., Descarreaux, M., Ortega de Mues, A., & Piché, M. (2021a). Neurophysiological mechanisms of chiropractic spinal manipulation for spine pain. *European Journal of Pain*, 25(7), 1429–1448. <https://doi.org/10.1002/ejp.1773>
- Gevers-Montoro, C., Provencher, B., Northon, S., Stedile-Lovatel, J. P., Ortega de Mues, A., & Piché, M. (2021b). Chiropractic Spinal Manipulation Prevents Secondary Hyperalgesia Induced by Topical Capsaicin in Healthy Individuals. *Frontiers in Pain Research*, 2(33), 702429. <https://doi.org/10.3389/fpain.2021.702429>
- Gevers-Montoro, C., Romero-Santiago, B., Medina-García, I., Larranaga-Arzamendi, B., Álvarez-Gálovich, L., Ortega-De Mues, A., & Piché, M. (2024). Reduction of Chronic Primary Low Back Pain by Spinal Manipulative Therapy is Accompanied by Decreases in Segmental Mechanical Hyperalgesia and Pain Catastrophizing: A Randomized Placebo-controlled Dual-blind Mixed Experimental Trial. *J Pain*, 25(8), 104500. <https://doi.org/10.1016/j.jpain.2024.02.014>
- Gewandter, J. S., Eisenach, J. C., Gross, R. A., Jensen, M. P., Keefe, F. J., Lee, D. A., & Turk, D. C. (2019). Checklist for the preparation and review of pain clinical trial publications: a pain-specific supplement to CONSORT. *Pain reports*, 4(3), e621. <https://doi.org/10.1097/pr9.0000000000000621>
- Ghasabmahaleh, S. H., Rezasoltani, Z., Dadarkhah, A., Hamidipanah, S., Mofrad, R. K., & Najafi, S. (2021). Spinal Manipulation for Subacute and Chronic Lumbar Radiculopathy: A Randomized Controlled Trial. *Am J Med*, 134(1), 135–141. <https://doi.org/10.1016/j.amjmed.2020.08.005>
- Giovanazzi, A., Jones, K., Carr, R. M., Fairhurst, C. M., Backhouse, M. R., & Adamson, J. A. (2022). Current practice in the measurement and interpretation of intervention adherence in randomised controlled trials: A systematic review. *Contemp Clin Trials*, 118, 106788. <https://doi.org/10.1016/j.cct.2022.106788>
- Goudman, L., Daenen, L., Mouraux, A., Nijs, J., Cras, P., Roussel, N., Moens, M., Coppieters, I., Huysmans, E., & De Kooning, M. (2020). Processing of Laser-Evoked Potentials in Patients with Chronic Whiplash-Associated Disorders, Chronic Fatigue Syndrome, and Healthy

- Controls: A Case-Control Study. *Pain Med*, 21(10), 2553–2563. <https://doi.org/10.1093/pm/pnaa068>
- Green, B. N., Johnson, C. D., Haldeman, S., Griffith, E., Clay, M. B., Kane, E. J., Castellote, J. M., Rajasekaran, S., Smuck, M., Hurwitz, E. L., Randhawa, K., Yu, H., & Nordin, M. (2018). A scoping review of biopsychosocial risk factors and co-morbidities for common spinal disorders. *PLOS ONE*, 13(6), e0197987. <https://doi.org/10.1371/journal.pone.0197987>
- Greffrath, W., Nemenov, M. I., Schwarz, S., Baumgärtner, U., Vogel, H., Arendt-Nielsen, L., & Treede, R.-D. (2002). Inward currents in primary nociceptive neurons of the rat and pain sensations in humans elicited by infrared diode laser pulses. *Pain*, 99(1), 145–155. [https://doi.org/https://doi.org/10.1016/S0304-3959\(02\)00071-4](https://doi.org/https://doi.org/10.1016/S0304-3959(02)00071-4)
- Gyer, G., Michael, J., Inklebarger, J., & Tedla, J. S. (2019). Spinal manipulation therapy: Is it all about the brain? A current review of the neurophysiological effects of manipulation. *J Integr Med*, 17(5), 328–337. <https://doi.org/10.1016/j.joim.2019.05.004>
- Haas, M., Bronfort, G., Evans, R., Schulz, C., Vavrek, D., Takaki, L., Hanson, L., Leininger, B., & Neradilek, M. B. (2018). Dose-response and efficacy of spinal manipulation for care of cervicogenic headache: a dual-center randomized controlled trial. *Spine J*, 18(10), 1741–1754. <https://doi.org/10.1016/j.spinee.2018.02.019>
- Haas, M., Vavrek, D., Peterson, D., Polissar, N., & Neradilek, M. B. (2014). Dose-response and efficacy of spinal manipulation for care of chronic low back pain: a randomized controlled trial. *Spine J*, 14(7), 1106–1116. <https://doi.org/10.1016/j.spinee.2013.07.468>
- Haavik, H., Niazi, I. K., Amjad, I., Kumari, N., Ghani, U., Ashfaq, M., Rashid, U., Navid, M. S., Kamavuako, E. N., Pujari, A. N., & Holt, K. (2024). Neuroplastic Responses to Chiropractic Care: Broad Impacts on Pain, Mood, Sleep, and Quality of Life. *Brain Sci*, 14(11). <https://doi.org/10.3390/brainsci14111124>
- Haflíðadóttir, S. H., Juhl, C. B., Nielsen, S. M., Henriksen, M., Harris, I. A., Bliddal, H., & Christensen, R. (2021). Placebo response and effect in randomized clinical trials: meta-research with focus on contextual effects. *Trials*, 22(1), 493. <https://doi.org/10.1186/s13063-021-05454-8>
- Harte, S. E., Harris, R. E., & Clauw, D. J. (2018). The neurobiology of central sensitization. *Journal of Applied Biobehavioral Research*, 23(2), e12137. <https://doi.org/10.1111/jabr.12137>
- Hartvigsen, J., Hancock, M. J., Kongsted, A., Louw, Q., Ferreira, M. L., Genevay, S., Hoy, D., Karppinen, J., Pransky, G., Sieper, J., Smeets, R. J., & Underwood, M. (2018). What low back pain is and why we need to pay attention. *Lancet*, 391(10137), 2356–2367. [https://doi.org/10.1016/S0140-6736\(18\)30480-X](https://doi.org/10.1016/S0140-6736(18)30480-X)
- Henschke, N., Maher, C. G., Refshauge, K. M., Herbert, R. D., Cumming, R. G., Bleasel, J., York, J., Das, A., & McAuley, J. H. (2009). Prevalence of and screening for serious spinal pathology

- in patients presenting to primary care settings with acute low back pain. *Arthritis Rheum*, 60(10), 3072–3080. <https://doi.org/10.1002/art.24853>
- Herrero, J. F., Laird, J. M., & Lopez-Garcia, J. A. (2000). Wind-up of spinal cord neurones and pain sensation: much ado about something? *Prog Neurobiol*, 61(2), 169–203. [https://doi.org/10.1016/s0301-0082\(99\)00051-9](https://doi.org/10.1016/s0301-0082(99)00051-9)
- Herzog, W. (2010). The biomechanics of spinal manipulation. *J Bodyw Mov Ther*, 14(3), 280–286. <https://doi.org/10.1016/j.jbmt.2010.03.004>
- Hohenschurz-Schmidt, D., Lene, V., & and Draper-Rodi, J. (2025). From placebos and shams to high-quality control interventions in manual therapy trials to study efficacy and mechanisms. *Journal of Manual & Manipulative Therapy*, 1–2. <https://doi.org/10.1080/10669817.2025.2471477>
- Hohenschurz-Schmidt, D., Thomson, O. P., Rossettini, G., Miciak, M., Newell, D., Roberts, L., Vase, L., & Draper-Rodi, J. (2022). Avoiding nocebo and other undesirable effects in chiropractic, osteopathy and physiotherapy: An invitation to reflect. *Musculoskelet Sci Pract*, 62, 102677. <https://doi.org/10.1016/j.msksp.2022.102677>
- Hohenschurz-Schmidt, D., Vase, L., Scott, W., Annoni, M., Ajayi, O. K., Barth, J., Bennell, K., Berna, C., Bialosky, J., Braithwaite, F., Finnerup, N. B., Williams, A. C. d. C., Carlino, E., Cerritelli, F., Chaibi, A., Cherkin, D., Colloca, L., Côté, P., Darnall, B. D.,...Draper-Rodi, J. (2023). Recommendations for the development, implementation, and reporting of control interventions in efficacy and mechanistic trials of physical, psychological, and self-management therapies: the CoPPS Statement. *BMJ*, 381, e072108. <https://doi.org/10.1136/bmj-2022-072108>
- Honore, M., Leboeuf-Yde, C., & Gagey, O. (2018). The regional effect of spinal manipulation on the pressure pain threshold in asymptomatic subjects: a systematic literature review. *Chiropr Man Therap*, 26, 11. <https://doi.org/10.1186/s12998-018-0181-3>
- Honore, M., Leboeuf-Yde, C., Gagey, O., & Wedderkopp, N. (2019). How big is the effect of spinal manipulation on the pressure pain threshold and for how long does it last? - secondary analysis of data from a systematic review. *Chiropr Man Therap*, 27, 22. <https://doi.org/10.1186/s12998-019-0240-4>
- Hopewell, S., Chan, A.-W., Collins, G. S., Hróbjartsson, A., Moher, D., Schulz, K. F., Tunn, R., Aggarwal, R., Berkwits, M., Berlin, J. A., Bhandari, N., Butcher, N. J., Campbell, M. K., Chidebe, R. C. W., Elbourne, D., Farmer, A., Fergusson, D. A., Golub, R. M., Goodman, S. N.,...Boutron, I. (2025). CONSORT 2025 statement: updated guideline for reporting randomised trials. *The Lancet*, 405(10489), 1633–1640. [https://doi.org/10.1016/S0140-6736\(25\)00672-5](https://doi.org/10.1016/S0140-6736(25)00672-5)

- Hu, L., Cai, M. M., Xiao, P., Luo, F., & Iannetti, G. D. (2014). Human brain responses to concomitant stimulation of Adelta and C nociceptors. *J Neurosci*, 34(34), 11439–11451. <https://doi.org/10.1523/JNEUROSCI.1355-14.2014>
- Iannetti, G. D., Hughes, N. P., Lee, M. C., & Mouraux, A. (2008). Determinants of laser-evoked EEG responses: pain perception or stimulus saliency? *J Neurophysiol*, 100(2), 815–828. <https://doi.org/10.1152/jn.00097.2008>
- Iannetti, G. D., Leandri, M., Truini, A., Zambreanu, L., Cruccu, G., & Tracey, I. (2004). Adelta nociceptor response to laser stimuli: selective effect of stimulus duration on skin temperature, brain potentials and pain perception. *Clinical Neurophysiology*, 115(11), 2629–2637. <https://doi.org/10.1016/j.clinph.2004.05.023>
- Ilie, M. A., Caruntu, C., Tampa, M., Georgescu, S. R., Matei, C., Negrei, C., Ion, R. M., Constantin, C., Neagu, M., & Boda, D. (2019). Capsaicin: Physicochemical properties, cutaneous reactions and potential applications in painful and inflammatory conditions. *Exp Ther Med*, 18(2), 916–925. <https://doi.org/10.3892/etm.2019.7513>
- International Association for the Study of Pain. (1979). Pain terms: a list with definitions and notes on usage. Recommended by the IASP Subcommittee on Taxonomy. *Pain*, 6(3), 249.
- Ioannidis, J. P., Evans, S. J., Gøtzsche, P. C., O'Neill, R. T., Altman, D. G., Schulz, K., & Moher, D. (2004). Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med*, 141(10), 781–788. <https://doi.org/10.7326/0003-4819-141-10-200411160-00009>
- Isenburg, K., Mawla, I., Loggia, M. L., Ellingsen, D. M., Protsenko, E., Kowalski, M. H., Swensen, D., O'Dwyer-Swensen, D., Edwards, R. R., Napadow, V., & Kettner, N. (2021). Increased Salience Network Connectivity Following Manual Therapy is Associated with Reduced Pain in Chronic Low Back Pain Patients. *J Pain*, 22(5), 545–555. <https://doi.org/10.1016/j.jpain.2020.11.007>
- Jankovski, A., Plaghki, L., & Mouraux, A. (2013). Reliable EEG responses to the selective activation of C-fibre afferents using a temperature-controlled infrared laser stimulator in conjunction with an adaptive staircase algorithm. *Pain*, 154(9), 1578–1587. <https://doi.org/10.1016/j.pain.2013.04.032>
- Jensen, T. S., Baron, R., Haanpää, M., Kalso, E., Loeser, J. D., Rice, A. S. C., & Treede, R. D. (2011). A new definition of neuropathic pain. *Pain*, 152(10), 2204–2205. <https://doi.org/10.1016/j.pain.2011.06.017>
- Jonas, W. B., Crawford, C., Colloca, L., Kaptchuk, T. J., Moseley, B., Miller, F. G., Kriston, L., Linde, K., & Meissner, K. (2015). To what extent are surgery and invasive procedures effective beyond a placebo response? A systematic review with meta-analysis of randomised, sham controlled trials. *BMJ Open*, 5(12), e009655. <https://doi.org/10.1136/bmjopen-2015-009655>

- Julius, D., & Basbaum, A. I. (2001). Molecular mechanisms of nociception. *Nature*, 413(6852), 203–210. <https://doi.org/10.1038/35093019>
- Jumbo, S. U., MacDermid, J. C., Kalu, M. E., Packham, T. L., Athwal, G. S., & Faber, K. J. (2021). Measurement Properties of the Brief Pain Inventory-Short Form (BPI-SF) and Revised Short McGill Pain Questionnaire Version-2 (SF-MPQ-2) in Pain-related Musculoskeletal Conditions: A Systematic Review. *Clin J Pain*, 37(6), 454–474. <https://doi.org/10.1097/ajp.0000000000000933>
- Jun, P., Pagé, I., Vette, A., & Kawchuk, G. (2020). Potential mechanisms for lumbar spinal stiffness change following spinal manipulative therapy: a scoping review. *Chiropr Man Therap*, 28(1), 15. <https://doi.org/10.1186/s12998-020-00304-x>
- Jung, A., Adamczyk, W. M., Ahmed, A., van der Schalk, L., Poesl, M., Luedtke, K., & Szikszay, T. M. (2023). No Sufficient Evidence for an Immediate Hypoalgesic Effect of Spinal Manual Therapy on Pressure Pain Thresholds in Asymptomatic and Chronic Pain Populations: A Systematic Review and Meta-Analysis. *Physical Therapy*, 103(3), 1–9. <https://doi.org/10.1093/ptj/pzad003>
- Kamper, S. J., Logan, G., Copsey, B., Thompson, J., Machado, G. C., Abdel-Shaheed, C., Williams, C. M., Maher, C. G., & Hall, A. M. (2020). What is usual care for low back pain? A systematic review of health care provided to patients with low back pain in family practice and emergency departments. *Pain*, 161(4), 694–702. <https://doi.org/10.1097/j.pain.0000000000001751>
- Kaplan, C. M., Kelleher, E., Irani, A., Schrepf, A., Clauw, D. J., & Harte, S. E. (2024). Deciphering nociplastic pain: clinical features, risk factors and potential mechanisms. *Nat Rev Neurol*, 20(6), 347–363. <https://doi.org/10.1038/s41582-024-00966-8>
- Kaptchuk, T. J., Hemond, C. C., & Miller, F. G. (2020). Placebos in chronic pain: evidence, theory, ethics, and use in clinical practice. *BMJ*, 370, m1668. <https://doi.org/10.1136/bmj.m1668>
- Karcz, M., Abd-Elseyed, A., Chakravarthy, K., Aman, M. M., Strand, N., Malinowski, M. N., Latif, U., Dickerson, D., Suvar, T., Lubenow, T., Peskin, E., D'Souza, R., Cornidez, E., Dudas, A., Lam, C., Farrell Ii, M., Sim, G. Y., Sebai, M., Garcia, R.,...Deer, T. (2024). Pathophysiology of Pain and Mechanisms of Neuromodulation: A Narrative Review (A Neuron Project). *J Pain Res*, 17, 3757–3790. <https://doi.org/10.2147/jpr.S475351>
- Keter, D. L., Bialosky, J. E., Brochetti, K., Courtney, C. A., Funabashi, M., Karas, S., Learman, K., & Cook, C. E. (2025). The mechanisms of manual therapy: A living review of systematic, narrative, and scoping reviews. *PLOS ONE*, 20(3), e0319586. <https://doi.org/10.1371/journal.pone.0319586>
- Kielstra, S. C., Reezigt, R. R., Coppieters, M. W., de Vries, R., Arendt-Nielsen, L., Petersen, K. K., Yarnitsky, D., & Scholten-Peeters, G. G. M. (2024). A myriad of methods to determine temporal summation of pain in people with musculoskeletal pain and healthy participants:

a scoping review. *Pain reports*, 9(5), e1176.
<https://doi.org/10.1097/pr9.0000000000001176>

Kirkwood, J., Allan, G. M., Korownyk, C. S., McCormack, J., Garrison, S., Thomas, B., Ton, J., Perry, D., Kolber, M. R., Dugré, N., Moe, S., & Lindblad, A. J. (2021). PEER simplified decision aid: chronic back pain treatment options in primary care. *Canadian Family Physician*, 67(1), 31.
<https://doi.org/10.46747/cfp.670131>

Knezevic, N. N., Candido, K. D., Vlaeyen, J. W. S., Van Zundert, J., & Cohen, S. P. (2021). Low back pain. *Lancet*, 398(10294), 78–92. [https://doi.org/10.1016/s0140-6736\(21\)00733-9](https://doi.org/10.1016/s0140-6736(21)00733-9)

Knutti, I. A., Suter, M. R., & Opsommer, E. (2014). Test-retest reliability of thermal quantitative sensory testing on two sites within the L5 dermatome of the lumbar spine and lower extremity. *Neurosci Lett*, 579, 157–162. <https://doi.org/10.1016/j.neulet.2014.07.023>

Kolber, M. R., Ton, J., Thomas, B., Kirkwood, J., Moe, S., Dugré, N., Chan, K., Lindblad, A. J., McCormack, J., Garrison, S., Allan, G. M., Korownyk, C. S., Craig, R., Sept, L., Rouble, A. N., & Perry, D. (2021). PEER systematic review of randomized controlled trials: Management of chronic low back pain in primary care. *Canadian Family Physician*, 67(1), e20–e30.
<https://doi.org/10.46747/cfp.6701e20>

Kongsted, A., Kent, P., Axen, I., Downie, A. S., & Dunn, K. M. (2016). What have we learned from ten years of trajectory research in low back pain? *BMC Musculoskelet Disord*, 17, 220.
<https://doi.org/10.1186/s12891-016-1071-2>

Kongsted, A., Kent, P., Hestbaek, L., & Vach, W. (2015). Patients with low back pain had distinct clinical course patterns that were typically neither complete recovery nor constant pain. A latent class analysis of longitudinal data. *Spine J*, 15(5), 885–894.
<https://doi.org/10.1016/j.spinee.2015.02.012>

Korownyk, C. S., Montgomery, L., Young, J., Moore, S., Singer, A. G., MacDougall, P., Darling, S., Ellis, K., Myers, J., Rochford, C., Taillefer, M. C., Allan, G. M., Perry, D., Moe, S. S., Ton, J., Kolber, M. R., Kirkwood, J., Thomas, B., Garrison, S.,...Lindblad, A. J. (2022). PEER simplified chronic pain guideline: Management of chronic low back, osteoarthritic, and neuropathic pain in primary care. *Canadian family physician Medecin de famille canadien*, 68(3), 179–190. <https://doi.org/10.46747/cfp.6803179>

Kosek, E. (2024). The concept of nociplastic pain-where to from here? *Pain*, 165(11s), S50–s57.
<https://doi.org/10.1097/j.pain.0000000000003305>

Kosek, E., Cohen, M., Baron, R., Gebhart, G. F., Mico, J. A., Rice, A. S. C., Rief, W., & Sluka, A. K. (2016). Do we need a third mechanistic descriptor for chronic pain states? *Pain*, 157(7), 1382–1386. <https://doi.org/10.1097/j.pain.0000000000000507>

- Kovanur Sampath, K., Treffel, L., O, P. T., Rodi, J. D., Fleischmann, M., & Tumilty, S. (2024). Changes in biochemical markers following a spinal manipulation - a systematic review update. *J Man Manip Ther*, 32(1), 28–50. <https://doi.org/10.1080/10669817.2023.2252187>
- Kovanur-Sampath, K., Mani, R., Cotter, J., Gisselman, A. S., & Tumilty, S. (2017). Changes in biochemical markers following spinal manipulation-a systematic review and meta-analysis. *Musculoskelet Sci Pract*, 29, 120–131. <https://doi.org/10.1016/j.msksp.2017.04.004>
- Krogsbøll, L. T., Hróbjartsson, A., & Gøtzsche, P. C. (2009). Spontaneous improvement in randomised clinical trials: meta-analysis of three-armed trials comparing no treatment, placebo and active intervention. *BMC Med Res Methodol*, 9, 1. <https://doi.org/10.1186/1471-2288-9-1>
- Laframboise, M. A., Vernon, H., & Srbely, J. (2016). Effect of two consecutive spinal manipulations in a single session on myofascial pain pressure sensitivity: a randomized controlled trial. *J Can Chiropr Assoc*, 60(2), 137–145.
- LaMotte, R. H., Lundberg, L. E., & Torebjork, H. E. (1992). Pain, hyperalgesia and activity in nociceptive C units in humans after intradermal injection of capsaicin. *J Physiol*, 448, 749–764. <https://doi.org/10.1113/jphysiol.1992.sp019068>
- Latremoliere, A., & Woolf, C. J. (2009). Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain*, 10(9), 895–926. <https://doi.org/10.1016/j.jpain.2009.06.012>
- Lautenbacher, S., Kunz, M., Strate, P., Nielsen, J., & Arendt-Nielsen, L. (2005). Age effects on pain thresholds, temporal summation and spatial summation of heat and pressure pain. *Pain*, 115(3), 410–418. <https://doi.org/10.1016/j.pain.2005.03.025>
- Leandri, M., Saturno, M., Spadavecchia, L., Iannetti, G. D., Cruccu, G., & Truini, A. (2006). Measurement of skin temperature after infrared laser stimulation. *Clinical Neurophysiology*, 36(4), 207–218. <https://doi.org/10.1016/j.neucli.2006.08.004>
- Lenoir, D., Willaert, W., Coppieters, I., Malfliet, A., Ickmans, K., Nijs, J., Vonck, K., Meeus, M., & Cagnie, B. (2020). Electroencephalography During Nociceptive Stimulation in Chronic Pain Patients: A Systematic Review. *Pain Med*, 21(12), 3413–3427. <https://doi.org/10.1093/pm/pnaa131>
- Li, J., Simone, D. A., & Larson, A. A. (1999). Windup leads to characteristics of central sensitization. *Pain*, 79(1), 75–82. [https://doi.org/10.1016/s0304-3959\(98\)00154-7](https://doi.org/10.1016/s0304-3959(98)00154-7)
- Li, Y., Zou, C., Guo, W., Han, F., Fan, T., Zang, L., & Huang, G. (2024). Global burden of low back pain and its attributable risk factors from 1990 to 2021: a comprehensive analysis from the global burden of disease study 2021. *Front Public Health*, 12, 1480779. <https://doi.org/10.3389/fpubh.2024.1480779>

- Lim, T. H., Mak, H. Y., Ngai, S. M. M., Man, Y. T., Tang, C. H., Wong, A. Y., Bussi res, A., & Al Zoubi, F. (2025). Non-Pharmacological Spine Pain Management in Clinical Practice Guidelines: A Systematic Review Using AGREE II and AGREE-REX Tools. *Journal of orthopaedic & sports physical therapy*, 55(1), 12–25. <https://doi.org/10.2519/jospt.2024.12729>
- Lin, X.-M., Guo, L.-F., Ni, B., Zhang, J.-Q., Zhang, X.-S., Zhang, L.-B., Wei, Z.-X., Duan, Y.-Y., Hu, L., Zhang, M., Zhang, J.-Y., Shao, M., Jiang, Z.-Y., Huang, Y.-J., Liu, J.-X., Cheng, L.-M., Brooks, J. C. W., Wager, T. D., Tracey, I.,...Kong, Y.-Z. (2025). A corticospinal signature for interindividual pain sensitivity. *Nat Commun*, 17(1), 445. <https://doi.org/10.1038/s41467-025-67132-6>
- Luck, S. J. (2014). *An introduction to the event-related potential technique* (2nd ed.). The MIT Press.
- MacMahon, S. B., Koltzenburg, M., Tracey, I., & Turk, D. C. (2013). *Wall and Melzack's textbook of pain* (6th ed.). Saunders.
- Madden, V. J., Catley, M. J., Grabherr, L., Mazzola, F., Shohag, M., & Moseley, G. L. (2016). The effect of repeated laser stimuli to ink-marked skin on skin temperature-recommendations for a safe experimental protocol in humans. *PeerJ*, 4, e1577. <https://doi.org/10.7717/peerj.1577>
- Magerl, W., Ali, Z., Ellrich, J., Meyer, R. A., & Treede, R. D. (1999). C- and A delta-fiber components of heat-evoked cerebral potentials in healthy human subjects. *Pain*, 82(2), 127–137. [https://doi.org/10.1016/s0304-3959\(99\)00061-5](https://doi.org/10.1016/s0304-3959(99)00061-5)
- Magerl, W., Fuchs, P. N., Meyer, R. A., & Treede, R.-D. (2001). Roles of capsaicin-insensitive nociceptors in cutaneous pain and secondary hyperalgesia. *Brain*, 124(9), 1754–1764. <https://doi.org/10.1093/brain/124.9.1754>
- Maher, C., Underwood, M., & Buchbinder, R. (2017). Non-specific low back pain. *Lancet*, 389(10070), 736–747. [https://doi.org/10.1016/S0140-6736\(16\)30970-9](https://doi.org/10.1016/S0140-6736(16)30970-9)
- Maiers, M., Hartvigsen, J., Evans, R., Westrom, K., Wang, Q., Schulz, C., Leininger, B., & Bronfort, G. (2019). Short- or Long-Term Treatment of Spinal Disability in Older Adults With Manipulation and Exercise. *Arthritis Care Res (Hoboken)*, 71(11), 1516–1524. <https://doi.org/10.1002/acr.23798>
- Marcuzzi, A., Wrigley, P. J., Dean, C. M., Adams, R., & Hush, J. M. (2017). The long-term reliability of static and dynamic quantitative sensory testing in healthy individuals. *Pain*, 158(7), 1217–1223. <https://doi.org/10.1097/j.pain.0000000000000901>
- Martel, J., Dugas, C., Dubois, J. D., & Descarreaux, M. (2011). A randomised controlled trial of preventive spinal manipulation with and without a home exercise program for patients with chronic neck pain. *BMC Musculoskelet Disord*, 12, 41. <https://doi.org/10.1186/1471-2474-12-41>

- Mathieu, J., Pasquier, M., Descarreaux, M., & Marchand, A. A. (2023). Diagnosis Value of Patient Evaluation Components Applicable in Primary Care Settings for the Diagnosis of Low Back Pain: A Scoping Review of Systematic Reviews. *J Clin Med*, 12(10), 3581. <https://doi.org/10.3390/jcm12103581>
- McKenzie, B. J., Haas, R., Ferreira, G. E., Gorelik, A., Cyril, S., Han, J. X., Gilbert, S., Grobler, L., Maher, C. G., & Buchbinder, R. (2025). Agreement between high-quality clinical practice guidelines in their treatment recommendations for low back pain: a systematic review. *Spine J*, 25(12), 2587–2604. <https://doi.org/10.1016/j.spinee.2025.07.015>
- Menke, J. M. (2014). Do manual therapies help low back pain? A comparative effectiveness meta-analysis. *Spine*, 39(7), E463–472. <https://doi.org/10.1097/brs.0000000000000230>
- Meucci, R. D., Fassa, A. G., & Faria, N. M. (2015). Prevalence of chronic low back pain: systematic review. *Rev Saude Publica*, 49, 73. <https://doi.org/10.1590/S0034-8910.2015049005874>
- Meyer, A.-L., Amorim, M.-A., Schubert, M., Schweinhardt, P., & Leboeuf-Yde, C. (2019). Unravelling functional neurology: does spinal manipulation have an effect on the brain? - a systematic literature review. *Chiropractic & Manual Therapies*, 27(1), 60. <https://doi.org/10.1186/s12998-019-0265-8>
- Minnucci, S., Innocenti, T., Salvioli, S., Giagio, S., Yousif, M. S., Riganelli, F., Carletti, C., Feller, D., Brindisino, F., Faletra, A., Chiarotto, A., & Mourad, F. (2023). Benefits and Harms of Spinal Manipulative Therapy for Treating Recent and Persistent Nonspecific Neck Pain: A Systematic Review With Meta-analysis. *J Orthop Sports Phys Ther*, 53(9), 510–528. <https://doi.org/10.2519/jospt.2023.11708>
- Moayedi, M., Stefano, G., Stubbs, M., Djeugam, B., Liang, M., & Iannetti, G. (2016). Nociceptive-Evoked Potentials Are Sensitive to Behaviorally Relevant Stimulus Displacements in Egocentric Coordinates. *eNeuro*, 3(3), e0151–e0163. <https://doi.org/10.1523/ENEURO.0151-15.2016>
- Mohammadian, P., Gonsalves, A., Tsai, C., Hummel, T., & Carpenter, T. (2004). Areas of capsaicin-induced secondary hyperalgesia and allodynia are reduced by a single chiropractic adjustment: a preliminary study. *J Manipulative Physiol Ther*, 27(6), 381–387. <https://doi.org/10.1016/j.jmpt.2004.05.002>
- Moore, R. A., Straube, S., & Aldington, D. (2013). Pain measures and cut-offs - 'no worse than mild pain' as a simple, universal outcome. *Anaesthesia*, 68(4), 400–412. <https://doi.org/10.1111/anae.12148>
- Moorman, A. C., & Newell, D. (2022). Impact of audible pops associated with spinal manipulation on perceived pain: a systematic review. *Chiropr Man Therap*, 30(1), 42. <https://doi.org/10.1186/s12998-022-00454-0>

- Morales, S., & Bowers, M. E. (2022). Time-frequency analysis methods and their application in developmental EEG data. *Developmental Cognitive Neuroscience*, 54, 101067. <https://doi.org/10.1016/j.dcn.2022.101067>
- Morillon, G. F., Benkhalti, M., Dagenais, P., & Poder, T. G. (2023). Preferences of patients with chronic low back pain about nonsurgical treatments: Results of a discrete choice experiment. *Health Expectations*, 26(1), 510–530. <https://doi.org/10.1111/hex.13685>
- Mouraux, A., Guérit, J. M., & Plaghki, L. (2003). Non-phase locked electroencephalogram (EEG) responses to CO2 laser skin stimulations may reflect central interactions between Aδ- and C-fibre afferent volleys. *Clinical Neurophysiology*, 114(4), 710–722. [https://doi.org/10.1016/S1388-2457\(03\)00027-0](https://doi.org/10.1016/S1388-2457(03)00027-0)
- Mouraux, A., & Iannetti, G. D. (2018). The search for pain biomarkers in the human brain. *Brain*, 141(12), 3290–3307. <https://doi.org/10.1093/brain/awy281>
- Mouraux, A., & Plaghki, L. (2007a). Are laser-evoked brain potentials modulated by attending to first or second pain? *Pain*, 129(3), 321–331. <https://doi.org/10.1016/j.pain.2006.10.018>
- Mouraux, A., & Plaghki, L. (2007b). Cortical interactions and integration of nociceptive and non-nociceptive somatosensory inputs in humans. *Neuroscience*, 150(1), 72–81. <https://doi.org/10.1016/j.neuroscience.2007.08.035>
- Mücke, M., Cuhls, H., Radbruch, L., Baron, R., Maier, C., Tölle, T., Treede, R. D., & Rolke, R. (2021). Quantitative sensory testing (QST). English version. *Schmerz*, 35(Suppl 3), 153–160. <https://doi.org/10.1007/s00482-015-0093-2>
- Nambi, G., Kamal, W., Es, S., Joshi, S., & Trivedi, P. (2018). Spinal manipulation plus laser therapy versus laser therapy alone in the treatment of chronic non-specific low back pain: a randomized controlled study. *Eur J Phys Rehabil Med*, 54(6), 880–889. <https://doi.org/10.23736/s1973-9087.18.05005-0>
- Neuper, C., & Pfurtscheller, G. (2001). Event-related dynamics of cortical rhythms: frequency-specific features and functional correlates. *Int J Psychophysiol*, 43(1), 41–58. [https://doi.org/10.1016/s0167-8760\(01\)00178-7](https://doi.org/10.1016/s0167-8760(01)00178-7)
- Nguena Nguefack, H. L., Pagé, M. G., Katz, J., Choinière, M., Vanasse, A., Dorais, M., Samb, O. M., & Lacasse, A. (2020). Trajectory Modelling Techniques Useful to Epidemiological Research: A Comparative Narrative Review of Approaches. *Clin Epidemiol*, 12, 1205–1222. <https://doi.org/10.2147/clep.S265287>
- Nicholas, M., Vlaeyen, J. W. S., Rief, W., Barke, A., Aziz, Q., Benoliel, R., Cohen, M., Evers, S., Giamberardino, M. A., Goebel, A., Korwisi, B., Perrot, S., Svensson, P., Wang, S. J., & Treede, R. D. (2019). The IASP classification of chronic pain for ICD-11: chronic primary pain. *Pain*, 160(1), 28–37. <https://doi.org/10.1097/j.pain.0000000000001390>

- Nicholas, M. K. (2022). The biopsychosocial model of pain 40 years on: time for a reappraisal? *Pain*, 163(Suppl 1), S3–S14. <https://doi.org/10.1097/j.pain.0000000000002654>
- Nijs, J., George, S. Z., Clauw, D. J., Fernández-de-las-Peñas, C., Kosek, E., Ickmans, K., Fernández-Carnero, J., Polli, A., Kapreli, E., Huysmans, E., Cuesta-Vargas, A. I., Mani, R., Lundberg, M., Laysen, L., Rice, D., Sterling, M., & Curatolo, M. (2021). Central sensitisation in chronic pain conditions: latest discoveries and their potential for precision medicine. *The Lancet Rheumatology*, 3(5), e383–e392. [https://doi.org/10.1016/S2665-9913\(21\)00032-1](https://doi.org/10.1016/S2665-9913(21)00032-1)
- Nijs, J., Kosek, E., Chiarotto, A., Cook, C., Danneels, L. A., Fernández-de-las-Peñas, C., Hodges, P. W., Koes, B., Louw, A., Ostelo, R., Scholten-Peeters, G. G. M., Sterling, M., Alkassabi, O., Alsobayel, H., Beales, D., Bilika, P., Clark, J. R., De Baets, L., Demoulin, C.,...George, S. Z. (2024). Nociceptive, neuropathic, or nociplastic low back pain? The low back pain phenotyping (BACPAP) consortium's international and multidisciplinary consensus recommendations. *The Lancet Rheumatology*, 6(3), e178–e188. [https://doi.org/10.1016/S2665-9913\(23\)00324-7](https://doi.org/10.1016/S2665-9913(23)00324-7)
- Nijs, J., Malfliet, A., & Nishigami, T. (2023). Nociplastic pain and central sensitization in patients with chronic pain conditions: a terminology update for clinicians. *Brazilian Journal of Physical Therapy*, 27, 100518. <https://doi.org/10.1016/j.bjpt.2023.100518>
- Nim, C., Aspinall, S. L., Cook, C. E., Corrêa, L. A., Donaldson, M., Downie, A. S., Harsted, S., Hansen, S., Jenkins, H. J., McNaughton, D., Nyirö, L., Perle, S. M., Roseen, E. J., Young, J. J., Young, A., Zhao, G.-H., Hartvigsen, J., & Juhl, C. B. (2025). The Effectiveness of Spinal Manipulative Therapy in Treating Spinal Pain Does Not Depend on the Application Procedures: A Systematic Review and Network Meta-analysis. *Journal of orthopaedic & sports physical therapy*, 55(2), 109–122. <https://doi.org/10.2519/jospt.2025.12707>
- Nim, C. G., Aspinall, S. L., Weibel, R., Steenfelt, M. G., & O'Neill, S. (2022). Pressure pain thresholds in a real-world chiropractic setting: topography, changes after treatment, and clinical relevance? *Chiropractic and Manual Therapies*, 30(1), Article 25. <https://doi.org/10.1186/s12998-022-00436-2>
- Nim, C. G., Downie, A., O'Neill, S., Kawchuk, G. N., Perle, S. M., & Leboeuf-Yde, C. (2021). The importance of selecting the correct site to apply spinal manipulation when treating spinal pain: Myth or reality? A systematic review. *Sci Rep*, 11(1), 23415. <https://doi.org/10.1038/s41598-021-02882-z>
- Nothnagel, H., Puta, C., Lehmann, T., Baumbach, P., Menard, M. B., Gabriel, B., Gabriel, H. H. W., Weiss, T., & Musial, F. (2017). How stable are quantitative sensory testing measurements over time? Report on 10-week reliability and agreement of results in healthy volunteers. *J Pain Res*, 10, 2067–2078. <https://doi.org/10.2147/jpr.S137391>

- Nuwer, M. R. (1998). Fundamentals of evoked potentials and common clinical applications today. *Electroencephalogr Clin Neurophysiol*, 106(2), 142–148. [https://doi.org/10.1016/s0013-4694\(97\)00117-x](https://doi.org/10.1016/s0013-4694(97)00117-x)
- O'Neill, S., Nim, C. G., & Chang, N. H. S. (2024). Validation of a spring loaded probe for single and repeat pressure pain testing, including public domain specifications for design and manufacture. *PLOS ONE*, 19(1), e0292809. <https://doi.org/10.1371/journal.pone.0292809>
- Obi, T., Takatsu, M., Yamazaki, K., Kuroda, R., Terada, T., & Mizoguchi, K. (2007). Conduction velocities of Adelta-fibers and C-fibers in human peripheral nerves and spinal cord after CO2 laser stimulation. *Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society*, 24(3), 294–297. <https://doi.org/10.1097/WNP.0b013e318038f45f>
- Oliveira, C. B., Maher, C. G., Pinto, R. Z., Traeger, A. C., Lin, C. C., Chenot, J. F., van Tulder, M., & Koes, B. W. (2018). Clinical practice guidelines for the management of non-specific low back pain in primary care: an updated overview. *Eur Spine J*, 27, 2791–2803. <https://doi.org/10.1007/s00586-018-5673-2>
- Opsommer, E., Korogod, N., Stockinger, L., & Landmann, G. (2021). Multimodal sensory evaluation of neuropathic spinal cord injury pain: an experimental study. *Spinal Cord*, 59(8), 842–854. <https://doi.org/10.1038/s41393-020-00607-z>
- Owens, M. A., Thomas, P. A., Crowe, C., Goodin, B. R., & Overstreet, D. S. (2025). Quantitative sensory testing for pain: What exactly are we measuring? *Curr Opin Psychol*, 62, 101988. <https://doi.org/10.1016/j.copsyc.2025.101988>
- Pak, D. J., Yong, R. J., Kaye, A. D., & Urman, R. D. (2018). Chronification of Pain: Mechanisms, Current Understanding, and Clinical Implications. *Curr Pain Headache Rep*, 22(2), 9. <https://doi.org/10.1007/s11916-018-0666-8>
- Paungmali, A., Silitertpisan, P., Taneyhill, K., Pirunsan, U., & Uthaikhup, S. (2012). Intrarater reliability of pain intensity, tissue blood flow, thermal pain threshold, pressure pain threshold and lumbo-pelvic stability tests in subjects with low back pain. *Asian J Sports Med*, 3(1), 8–14. <https://doi.org/10.5812/asjasm.34718>
- Peng, W., & Tang, D. (2016). Pain Related Cortical Oscillations: Methodological Advances and Potential Applications. *Front Comput Neurosci*, 10, 9. <https://doi.org/10.3389/fncom.2016.00009>
- Penza, C. W., Horn, M. E., George, S. Z., & Bishop, M. D. (2017). Comparison of 2 Lumbar Manual Therapies on Temporal Summation of Pain in Healthy Volunteers. *J Pain*, 18(11), 1397–1408. <https://doi.org/10.1016/j.jpain.2017.07.007>

- Perchet, C., Godinho, F., Mazza, S., Frot, M., Legrain, V., Magnin, M., & Garcia-Larrea, L. (2008). Evoked potentials to nociceptive stimuli delivered by CO₂ or Nd:YAP lasers. *Clinical Neurophysiology*, 119(11), 2615–2622. <https://doi.org/10.1016/j.clinph.2008.06.021>
- Perrot, S., Cohen, M., Barke, A., Korwisi, B., Rief, W., & Treede, R. D. (2019). The IASP classification of chronic pain for ICD-11: chronic secondary musculoskeletal pain. *Pain*, 160(1), 77–82. <https://doi.org/10.1097/j.pain.0000000000001389>
- Pfurtscheller, G., & Lopes da Silva, F. H. (1999). Event-related EEG/MEG synchronization and desynchronization: basic principles. *Clin Neurophysiol*, 110(11), 1842–1857. [https://doi.org/10.1016/s1388-2457\(99\)00141-8](https://doi.org/10.1016/s1388-2457(99)00141-8)
- Pickar, J. G. (2002). Neurophysiological effects of spinal manipulation. *Spine J*, 2(5), 357–371. [https://doi.org/10.1016/s1529-9430\(02\)00400-x](https://doi.org/10.1016/s1529-9430(02)00400-x)
- Pickar, J. G., & Bolton, P. S. (2012). Spinal manipulative therapy and somatosensory activation. *Journal of Electromyography and Kinesiology*, 22(5), 785–794. <https://doi.org/10.1016/j.jelekin.2012.01.015>
- Plaghki, L., & Mouraux, A. (2003). How do we selectively activate skin nociceptors with a high power infrared laser? Physiology and biophysics of laser stimulation. *Clinical Neurophysiology*, 33(6), 269–277. <https://doi.org/10.1016/j.neucli.2003.10.003>
- Plaghki, L., & Mouraux, A. (2005). EEG and laser stimulation as tools for pain research. *Current Opinion in Investigational Drugs*, 6(1), 58–64.
- Ploner, M., Gross, J., Timmermann, L., & Schnitzler, A. (2002). Cortical representation of first and second pain sensation in humans. *Proceedings of the National Academy of Sciences*, 99(19), 12444. <https://doi.org/10.1073/pnas.182272899>
- Ploner, M., Sorg, C., & Gross, J. (2017). Brain Rhythms of Pain. *Trends Cogn Sci*, 21(2), 100–110. <https://doi.org/10.1016/j.tics.2016.12.001>
- Provencher, B., Northon, S., Gevers Montoro, C., O'Shaughnessy, J., & Piché, M. (2021). Effects of chiropractic spinal manipulation on laser-evoked pain and brain activity. *The Journal of Physiological Sciences*, 71(1), 20–33. <https://doi.org/10.1186/s12576-021-00804-2>
- Quesada, C., Kostenko, A., Ho, I., Leone, C., Nochi, Z., Stouffs, A., Wittayer, M., Caspani, O., Finnerup, N. B., Mouraux, A., Pickering, G., Tracey, I., Truini, A., Treede, R. D., & Garcia-Larrea, L. (2021). Human surrogate models of central sensitization: a critical review and practical guide. *Eur J Pain*, 25, 1389–1428. <https://doi.org/10.1002/ejp.1768>
- Raja, S. N., Carr, D. B., Cohen, M., Finnerup, N. B., Flor, H., Gibson, S., Keefe, F. J., Mogil, J. S., Ringkamp, M., Sluka, K. A., Song, X.-J., Stevens, B., Sullivan, M. D., Tutelman, P. R., Ushida, T., & Vader, K. (2020). The revised International Association for the Study of Pain definition

- of pain: concepts, challenges, and compromises. *Pain*, 161(9), 1976–1982.
<https://doi.org/10.1097/j.pain.0000000000001939>
- Randoll, C., Gagnon-Normandin, V., Tessier, J., Bois, S., Rustamov, N., O'Shaughnessy, J., Descarreaux, M., & Piche, M. (2017). The mechanism of back pain relief by spinal manipulation relies on decreased temporal summation of pain. *Neuroscience*, 349, 220–228. <https://doi.org/10.1016/j.neuroscience.2017.03.006>
- Rizzo, R. R., Cashin, A. G., Wand, B. M., Ferraro, M. C., Sharma, S., Lee, H., O'Hagan, E., Maher, C. G., Furlan, A. D., van Tulder, M. W., & McAuley, J. H. (2025). Non-pharmacological and non-surgical treatments for low back pain in adults: an overview of Cochrane reviews. *Cochrane Database Syst Rev*, 3(3), Cd014691. <https://doi.org/10.1002/14651858.CD014691.pub2>
- Roecker, C. B., & Hewawasam, S. R. (2025). Spinal manipulation for fibromyalgia: a narrative review. *J Can Chiropr Assoc*, 69(1), 33–48.
- Rogers, A. H., & Farris, S. G. (2022). A meta-analysis of the associations of elements of the fear-avoidance model of chronic pain with negative affect, depression, anxiety, pain-related disability and pain intensity. *Eur J Pain*, 26(8), 1611–1635. <https://doi.org/10.1002/ejp.1994>
- Ronga, I., Valentini, E., Mouraux, A., & Iannetti, G. D. (2013). Novelty is not enough: laser-evoked potentials are determined by stimulus saliency, not absolute novelty. *J Neurophysiol*, 109(3), 692–701. <https://doi.org/10.1152/jn.00464.2012>
- Salamon, K. S., Davies, W. H., Fuentes, M. R., Weisman, S. J., & Hainsworth, K. R. (2014). The pain frequency-severity-duration scale as a measure of pain: preliminary validation in a pediatric chronic pain sample. *Pain Res Treat*, 2014, 653592. <https://doi.org/10.1155/2014/653592>
- Sandkühler, J. (2009). Models and mechanisms of hyperalgesia and allodynia. *Physiol Rev*, 89(2), 707–758. <https://doi.org/10.1152/physrev.00025.2008>
- Schepers, R. J., & Ringkamp, M. (2010). Thermoreceptors and thermosensitive afferents. *Neuroscience and Biobehavioral Reviews*, 34(2), 177–184. <https://doi.org/10.1016/j.neubiorev.2009.10.003>
- Scholz, J., Finnerup, N. B., Attal, N., Aziz, Q., Baron, R., Bennett, M. I., Benoliel, R., Cohen, M., Cruccu, G., Davis, K. D., Evers, S., First, M., Giamberardino, M. A., Hansson, P., Kaasa, S., Korwisi, B., Kosek, E., Lavand'homme, P., Nicholas, M.,...Classification Committee of the Neuropathic Pain Special Interest, G. (2019). The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. *Pain*, 160(1), 53–59. <https://doi.org/10.1097/j.pain.0000000000001365>

- Schomer, D. L. (2018). *Niedermeyer's electroencephalography : basic principles, clinical applications, and related fields* (7th ed.). Oxford University Press.
- Schulz, K. F., Altman, D. G., & Moher, D. (2010). CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ*, 340, c332. <https://doi.org/10.1136/bmj.c332>
- Senna, M. K., & Machaly, S. A. (2011). Does maintained spinal manipulation therapy for chronic nonspecific low back pain result in better long-term outcome? *Spine (Phila Pa 1976)*, 36(18), 1427–1437. <https://doi.org/10.1097/BRS.0b013e3181f5dfe0>
- Sherriff, B., Clark, C., Killingback, C., & Newell, D. (2022). Impact of contextual factors on patient outcomes following conservative low back pain treatment: systematic review. *Chiropr Man Therap*, 30(1), 20. <https://doi.org/10.1186/s12998-022-00430-8>
- Sneddon, L. U. (2018). Comparative Physiology of Nociception and Pain. *Physiology*, 33(1), 63–73. <https://doi.org/10.1152/physiol.00022.2017>
- Sonjon, Y., Gonthier, A., Léplinge, C., Van der Henst, J. B., Reilly, K. T., & Chabanat, E. (2025). Social factors contributing to the development of chronic low back pain: a scoping review. *BMC Musculoskelet Disord*, 26(1), 999. <https://doi.org/10.1186/s12891-025-09216-4>
- Sørensen, P. W., Nim, C. G., Poulsen, E., & Juhl, C. B. (2023). Spinal Manipulative Therapy for Nonspecific Low Back Pain: Does Targeting a Specific Vertebral Level Make a Difference?: A Systematic Review With Meta-analysis. *J Orthop Sports Phys Ther*, 53(9), 529–539. <https://doi.org/10.2519/jospt.2023.11962>
- Sparks, C., Cleland, J. A., Elliott, J. M., Zagardo, M., & Liu, W. C. (2013). Using functional magnetic resonance imaging to determine if cerebral hemodynamic responses to pain change following thoracic spine thrust manipulation in healthy individuals. *J Orthop Sports Phys Ther*, 43(5), 340–348. <https://doi.org/10.2519/jospt.2013.4631>
- Sparks, C. L., Liu, W. C., Cleland, J. A., Kelly, J. P., Dyer, S. J., Szetela, K. M., & Elliott, J. M. (2017). Functional Magnetic Resonance Imaging of Cerebral Hemodynamic Responses to Pain Following Thoracic Thrust Manipulation in Individuals With Neck Pain: A Randomized Trial. *J Manipulative Physiol Ther*, 40(9), 625–634. <https://doi.org/10.1016/j.jmpt.2017.07.010>
- Starkweather, A. R., Heineman, A., Storey, S., Rubia, G., Lyon, D. E., Greenspan, J., & Dorsey, S. G. (2016). Methods to measure peripheral and central sensitization using quantitative sensory testing: A focus on individuals with low back pain. *Appl Nurs Res*, 29, 237–241. <https://doi.org/10.1016/j.apnr.2015.03.013>
- Staud, R., Robinson, M. E., & Price, D. D. (2007). Temporal summation of second pain and its maintenance are useful for characterizing widespread central sensitization of fibromyalgia patients. *J Pain*, 8(11), 893–901. <https://doi.org/10.1016/j.jpain.2007.06.006>

- Steffens, D., Ferreira, M. L., Latimer, J., Ferreira, P. H., Koes, B. W., Blyth, F., Li, Q., & Maher, C. G. (2015). What triggers an episode of acute low back pain? A case-crossover study. *Arthritis Care Res*, 67(3), 403–410. <https://doi.org/10.1002/acr.22533>
- Tagliaferri, S. D., Mitchell, U. H., Saueressig, T., Owen, P. J., Miller, C. T., & Belavy, D. L. (2022). Classification Approaches for Treating Low Back Pain Have Small Effects That Are Not Clinically Meaningful: A Systematic Review With Meta-analysis. *J Orthop Sports Phys Ther*, 52(2), 67–84. <https://doi.org/10.2519/jospt.2022.10761>
- Tan, W., Wang, W., Yang, Y., Chen, Y., Kang, Y., Huang, Y., Gong, Z., Zhan, S., Ke, Z., Wang, J., Yuan, W., Huang, W., Zee, C., Chen, Z., & Chen, B. T. (2020). Spinal Manipulative Therapy Alters Brain Activity in Patients With Chronic Low Back Pain: A Longitudinal Brain fMRI Study. *Frontiers in integrative neuroscience*, 14, 534595. <https://doi.org/10.3389/fnint.2020.534595>
- Taylor, A. M., Phillips, K., Patel, K. V., Turk, D. C., Dworkin, R. H., Beaton, D., Clauw, D. J., Gignac, M. A. M., Markman, J. D., Williams, D. A., Bujanover, S., Burke, L. B., Carr, D. B., Choy, E. H., Conaghan, P. G., Cowan, P., Farrar, J. T., Freeman, R., Gewandter, J.,...Witter, J. (2016). Assessment of physical function and participation in chronic pain clinical trials: IMMPACT/OMERACT recommendations. *Pain*, 157(9), 1836–1850. <https://doi.org/10.1097/j.pain.0000000000000577>
- Thomas, J. S., Clark, B. C., Russ, D. W., France, C. R., Ploutz-Snyder, R., & Corcos, D. M. (2020). Effect of Spinal Manipulative and Mobilization Therapies in Young Adults With Mild to Moderate Chronic Low Back Pain: A Randomized Clinical Trial. *JAMA Netw Open*, 3(8), e2012589. <https://doi.org/10.1001/jamanetworkopen.2020.12589>
- Trager, R. J., Bejarano, G., Perfecto, R. T., Blackwood, E. R., & Goertz, C. M. (2024). Chiropractic and Spinal Manipulation: A Review of Research Trends, Evidence Gaps, and Guideline Recommendations. *J Clin Med*, 13(19). <https://doi.org/10.3390/jcm13195668>
- Treede, R.-D. (2018). The International Association for the Study of Pain definition of pain: as valid in 2018 as in 1979, but in need of regularly updated footnotes. *Pain reports*, 3(2), e643–e643. <https://doi.org/10.1097/PR9.0000000000000643>
- Treede, R. D., Lorenz, J., & Baumgärtner, U. (2003). Clinical usefulness of laser-evoked potentials. *Clinical Neurophysiology*, 33(6), 303–314. <https://doi.org/10.1016/j.neucli.2003.10.009>
- Treede, R. D., Meyer, R. A., Raja, S. N., & Campbell, J. N. (1992). Peripheral and central mechanisms of cutaneous hyperalgesia. *Prog Neurobiol*, 38(4), 397–421. [https://doi.org/10.1016/0301-0082\(92\)90027-c](https://doi.org/10.1016/0301-0082(92)90027-c)
- Treede, R. D., Rief, W., Barke, A., Aziz, Q., Bennett, M. I., Benoliel, R., Cohen, M., Evers, S., Finnerup, N. B., First, M. B., Giamberardino, M. A., Kaasa, S., Korwisi, B., Kosek, E., Lavand'homme, P., Nicholas, M., Perrot, S., Scholz, J., Schug, S.,...Wang, S. J. (2019). Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the

- International Classification of Diseases (ICD-11). *Pain*, 160(1), 19–27. <https://doi.org/10.1097/j.pain.0000000000001384>
- Truini, A., Galeotti, F., Cruccu, G., & Garcia-Larrea, L. (2007). Inhibition of cortical responses to Adelta inputs by a preceding C-related response: testing the "first come, first served" hypothesis of cortical laser evoked potentials. *Pain*, 131(3), 341–347. <https://doi.org/10.1016/j.pain.2007.06.023>
- Turk, D. C., Dworkin, R. H., Allen, R. R., Bellamy, N., Brandenburg, N., Carr, D. B., Cleeland, C., Dionne, R., Farrar, J. T., Galer, B. S., Hewitt, D. J., Jadad, A. R., Katz, N. P., Kramer, L. D., Manning, D. C., McCormick, C. G., McDermott, M. P., McGrath, P., Quessy, S.,...Witter, J. (2003). Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain*, 106(3), 337–345. <https://doi.org/10.1016/j.pain.2003.08.001>
- van Driel, M. E. C., Huygen, F., & Rijdsdijk, M. (2024). Quantitative sensory testing: a practical guide and clinical applications. *BJA Educ*, 24(9), 326–334. <https://doi.org/10.1016/j.bjae.2024.05.004>
- van Strien, W. W. J., & Hollmann, M. W. (2025). Pain Perception and Modulation: Fundamental Neurobiology and Recent Advances. *Eur J Neurosci*, 62(8), e70275. <https://doi.org/10.1111/ejn.70275>
- Varga, I., & Mravec, B. (2015). Chapter 8 - Nerve Fiber Types. In R. S. Tubbs, E. Rizk, M. M. Shoja, M. Loukas, N. Barbaro, & R. J. Spinner (Eds.), *Nerves and Nerve Injuries* (pp. 107–113). Academic Press. <https://doi.org/10.1016/B978-0-12-410390-0.00008-1>
- Verdugo, R. J., Matamala, J. M., Inui, K., Kakigi, R., Valls-Solé, J., Hansson, P., Nilsen, K. B., Lombardi, R., Lauria, G., Petropoulos, I. N., Malik, R. A., Treede, R. D., Baumgärtner, U., Jara, P. A., & Campero, M. (2022). Review of techniques useful for the assessment of sensory small fiber neuropathies: Report from an IFCN expert group. *Clinical Neurophysiology*, 136, 13–38. <https://doi.org/10.1016/j.clinph.2022.01.002>
- Vining, R., Long, C. R., Minkalis, A., Gudavalli, M. R., Xia, T., Walter, J., Coulter, I., & Goertz, C. M. (2020). Effects of Chiropractic Care on Strength, Balance, and Endurance in Active-Duty U.S. Military Personnel with Low Back Pain: A Randomized Controlled Trial. *J Altern Complement Med*, 26(7), 592–601. <https://doi.org/10.1089/acm.2020.0107>
- Vlaeyen, J. W., & Crombez, G. (2009). La psychologie de la peur et de la douleur. *Revue du Rhumatisme*, 76(6), 511–516. <https://doi.org/10.1016/j.rhum.2009.03.004>
- Vlaeyen, J. W. S., Crombez, G., & Linton, S. J. (2016). The fear-avoidance model of pain. *Pain*, 157(8), 1588–1589. <https://doi.org/10.1097/j.pain.0000000000000574>
- Vlaeyen, J. W. S., & Linton, S. J. (2000). Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. *Pain*, 85(3), 317–332. [https://doi.org/10.1016/S0304-3959\(99\)00242-0](https://doi.org/10.1016/S0304-3959(99)00242-0)

- Vlaeyen, J. W. S., Maher, C. G., Wiech, K., Van Zundert, J., Meloto, C. B., Diatchenko, L., Battie, M. C., Goossens, M., Koes, B., & Linton, S. J. (2018). Low back pain. *Nat Rev Dis Primers*, 4(1), 52–70. <https://doi.org/10.1038/s41572-018-0052-1>
- Wager, T. D., & Atlas, L. Y. (2015). The neuroscience of placebo effects: connecting context, learning and health. *Nat Rev Neurosci*, 16(7), 403–418. <https://doi.org/10.1038/nrn3976>
- Wakui, E., Fidanza, F., & Martini, M. (2025). Neural response associated with the modulation of temporal summation of second pain by affective touch. *J Pain*, 29, 105349. <https://doi.org/10.1016/j.jpain.2025.105349>
- Wang, A. L., Mouraux, A., Liang, M., & Iannetti, G. D. (2010). Stimulus novelty, and not neural refractoriness, explains the repetition suppression of laser-evoked potentials. *J Neurophysiol*, 104(4), 2116–2124. <https://doi.org/10.1152/jn.01088.2009>
- Wang, D., Moosa, S., Ishaque, M., Finan, P., Quigg, M., Jeffrey Elias, W., & Liu, C. C. (2023). Painful Cutaneous Laser Stimulation for Temporal Summation of Pain Assessment. *J Pain*, 24(12), 2283–2293. <https://doi.org/10.1016/j.jpain.2023.07.012>
- Wang, D., Ye, S., Zhang, X., Carter, W., Finan, P., Quigg, M., Moosa, S., Elias, W. J., & Liu, C. C. (2025). Temporal summation of pain varies across body regions: A cutaneous laser stimulation study in healthy controls. *J Pain*, 34, 105453. <https://doi.org/10.1016/j.jpain.2025.105453>
- Wang, D., Zhang, X., Ye, S., Carter, W., Finan, P., Quigg, M., Moosa, S., Elias, W. J., & Liu, C. C. (2026). Reliable Biomarkers of Descending Pain Inhibition: A Laser-Evoked Potential and Behavioural Study. *Eur J Pain*, 30(1), e70181. <https://doi.org/10.1002/ejp.70181>
- Weber Li, K. A., Wager, T. D., Mackey, S., Elliott, J. M., Liu, W.-C., & Sparks, C. L. (2019). Evidence for decreased Neurologic Pain Signature activation following thoracic spinal manipulation in healthy volunteers and participants with neck pain. *NeuroImage: Clinical*, 24, 102042. <https://doi.org/10.1016/j.nicl.2019.102042>
- Weiss, T., Straube, T., Boettcher, J., Hecht, H., Spohn, D., & Miltner, W. H. (2008). Brain activation upon selective stimulation of cutaneous C- and Delta-fibers. *Neuroimage*, 41(4), 1372–1381. <https://doi.org/10.1016/j.neuroimage.2008.03.047>
- Wen, Y., Chen, X. M., Jin, X., Ling, D. Y., Chen, S., Huang, Q., Kong, N., Chai, J. E., Wang, Q., Xu, M. S., & Du, H. G. (2022). A spinal manipulative therapy altered brain activity in patients with lumbar disc herniation: A resting-state functional magnetic resonance imaging study. *Front Neurosci*, 16, 974792. <https://doi.org/10.3389/fnins.2022.974792>
- Whalen, W. M., Hawk, C., Farabaugh, R. J., Daniels, C. J., Taylor, D. N., Anderson, K. R., Crivelli, L. S., Anderson, D. R., Thomson, L. M., & Sarnat, R. L. (2022). Best Practices for Chiropractic Management of Adult Patients With Mechanical Low Back Pain: A Clinical Practice

- Guideline for Chiropractors in the United States. *J Manipulative Physiol Ther*, 45(8), 551–565. <https://doi.org/10.1016/j.jmpt.2023.04.010>
- Wirth, B., Gassner, A., de Bruin, E. D., Axen, I., Swanenburg, J., Humphreys, B. K., & Schweinhardt, P. (2019). Neurophysiological Effects of High Velocity and Low Amplitude Spinal Manipulation in Symptomatic and Asymptomatic Humans: A Systematic Literature Review. *Spine (Phila Pa 1976)*, 44(15), E914–E926. <https://doi.org/10.1097/BRS.0000000000003013>
- Wirth, B., & Schweinhardt, P. (2024). Personalized assessment and management of non-specific low back pain. *Eur J Pain*, 28(2), 181–198. <https://doi.org/10.1002/ejp.2190>
- Woolf, C. J. (2011). Central sensitization: implications for the diagnosis and treatment of pain. *Pain*, 152(3 Suppl), S2–15. <https://doi.org/10.1016/j.pain.2010.09.030>
- World Health Organisation (WHO). (2019). *International Classification of Diseases, Eleventh Revision (ICD-11)*. <https://icd.who.int/browse/2025-01/mms/en>
- World Health Organization. (2023). *WHO guideline for non-surgical management of chronic primary low back pain in adults in primary and community care settings*. World Health Organization.
- Xia, T., Long, C. R., Vining, R. D., Gudavalli, M. R., DeVocht, J. W., Kawchuk, G. N., Wilder, D. G., & Goertz, C. M. (2017). Association of lumbar spine stiffness and flexion-relaxation phenomenon with patient-reported outcomes in adults with chronic low back pain - a single-arm clinical trial investigating the effects of thrust spinal manipulation. *BMC Complement Altern Med*, 17(1), 303. <https://doi.org/10.1186/s12906-017-1821-1>
- Yang, Y. C., Zeng, K., Wang, W., Gong, Z. G., Chen, Y. L., Cheng, J. M., Zhang, M., Huang, Y. W., Men, X. B., Wang, J. W., Zhan, S., & Tan, W. L. (2022). The Changes of Brain Function After Spinal Manipulation Therapy in Patients with Chronic Low Back Pain: A Rest BOLD fMRI Study. *Neuropsychiatr Dis Treat*, 18, 187–199. <https://doi.org/10.2147/ndt.S339762>
- Yarnitsky, D. (2010). Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states. *Current Opinion in Anesthesiology*, 23(5), 611–615. <https://doi.org/10.1097/ACO.0b013e32833c348b>
- Young, K. J., Leboeuf-Yde, C., Gorrell, L., Bergström, C., Evans, D. W., Axén, I., Chance-Larsen, K., Gagey, O., Georgopoulos, V., Goncalves, G., Harris, C., Harsted, S., Kerry, R., Lee, E., McCarthy, C., Nim, C., Nyirö, L., Schweinhardt, P., & Vogel, S. (2024). Mechanisms of manipulation: a systematic review of the literature on immediate anatomical structural or positional changes in response to manually delivered high-velocity, low-amplitude spinal manipulation. *Chiropr Man Therap*, 32(1), 28. <https://doi.org/10.1186/s12998-024-00549-w>

- Zaina, F., Côté, P., Cancelliere, C., Di Felice, F., Donzelli, S., Rauch, A., Verville, L., Negrini, S., & Nordin, M. (2023). A Systematic Review of Clinical Practice Guidelines for Persons With Non-specific Low Back Pain With and Without Radiculopathy: Identification of Best Evidence for Rehabilitation to Develop the WHO's Package of Interventions for Rehabilitation. *Arch Phys Med Rehabil*, 104(11), 1913–1927. <https://doi.org/10.1016/j.apmr.2023.02.022>
- Zhang, Y. K., Wang, J. X., Ge, Y. Z., Wang, Z. B., & Chang, F. (2025). Low back pain among the working-age population: from the global burden of disease study 2021. *BMC Musculoskelet Disord*, 26(1), 441. <https://doi.org/10.1186/s12891-025-08704-x>
- Zhou, X. C., Huang, Y. B., Wu, S., Hong, S. W., Tian, Y., Hu, H. J., Lv, L. J., & Lv, Z. Z. (2023). Lever positioning manipulation alters real-time brain activity in patients with lumbar disc herniation: An amplitude of low-frequency fluctuation and regional homogeneity study. *Psychiatry Res Neuroimaging*, 334, 111674. <https://doi.org/10.1016/j.psychresns.2023.111674>
- Zhou, X. C., Wu, S., Wang, K. Z., Chen, L. H., Hong, S. W., Tian, Y., Hu, H. J., Lin, J., Wei, Z. C., Xie, Y. X., Yin, Z. H., Lv, Z. Z., & Lv, L. J. (2024). Default mode network and dorsal attentional network connectivity changes as neural markers of spinal manipulative therapy in lumbar disc herniation. *Sci Rep*, 14(1), 29541. <https://doi.org/10.1038/s41598-024-81126-2>
- Zhou, X. C., Wu, S., Wang, K. Z., Chen, L. H., Wei, Z. C., Li, T., Hua, Z. H., Xia, Q., Lyu, Z. Z., & Lyu, L. J. (2025). Impact of Spinal Manipulative Therapy on Brain Function and Pain Alleviation in Lumbar Disc Herniation: A Resting-State fMRI Study. *Chin J Integr Med*, 31(2), 108–117. <https://doi.org/10.1007/s11655-024-4205-7>

Annexes

Matériel supplémentaire de l'article 2 (table S1)

Table S1. Stimulation parameters used to record C-LEP in previous human studies

Study	Sample size (n)	Type of laser	Beam diameter (mm)	Maximal fluence (mJ/mm ²)	Pulse duration (ms)	ISI (s)	Number of stimuli	Area stimulated	Additional parameters
De Stefano 2022	65 patients	Nd:YAP	10	44.6	10	10-15	1 x 10 to 15	perioral or supraorbital region	
Hülleman 2016	10	Nd:YAP	10	38	10	8.4-15.6	3x25	perioral region	
Truini 2015	20 patients + 15 healthy controls	Nd:YAP	10	44.6	20	not specified	1x15	perioral region	
Naro 2015	38 patients + 15 healthy controls	Nd:YAP	≈0.4 (after spatial filter)	80	10	7.5-12.5	2x30	right maxillary region	An aluminum sheet drilled with tiny holes (0.15 mm ²) was placed between the laser and the skin (original laser beam diameter = 4 mm).
Hu 2014	Exp1: 34; Exp2: 96	Nd:YAP	7	≈117	4	10-15	Exp 1: 2x60 to 75; Exp2: 4x10	hand dorsum (left)	Advanced signal processing techniques were applied to minimize the between-subject latency variability of LEP waves.
Truini 2007	6	Nd:YAP	10	44.6	10	10-30	4x20	perioral region	
Crucchi 2003	5 patients + 16 healthy controls	Nd:YAP	15	37	10	10-30	2x20	perioral or supraorbital region	

Table 1. (continued)

Study	Sample size (n)	Type of laser	Beam diameter (mm)	Maximal fluence (mJ/mm ²)	Pulse duration (ms)	ISI (s)	Number of stimuli	Area stimulated	Additional parameters
Terhaar 2011	22 patients + 27 healthy controls	Tm:YAG	≈0.4 (after spatial filter)	≈21	1	not specified	1x100 to 130	hand dorsum (left)	An aluminum sheet drilled with tiny holes (0.15 mm ²) was placed between the laser and the skin (original laser beam diameter = 6 mm).
Domnick 2009	16	Tm:YAG	5	≈31	1	2-10	8x40	anterior arm and forearm (bilaterally)	Two 5x5 cm capsaicin patches (0.1%) were applied to one upper limb for 30 min.
Forss 2005 (MEG)	10	Tm:YAG	≈0.6 (after spatial filter)	235	1	4.5-5.5	not specified	hand dorsum (left)	A plastic plate drilled with tiny holes (0.3 mm ²) was placed between the laser and the skin (original laser beam diameter ≈ 4 mm).
Ploner 2002 (MEG)	10	Tm:YAG	6	≈21	1	10-14	1x40	hand dorsum (right)	
Opsommer 2001	9	Tm:YAG	≈0.5 (after spatial filter)	12	1.4	20-30	2x60	hand dorsum (left)	An aluminum sheet drilled with tiny holes (0.23 mm ²) was placed between the laser and the skin (original laser beam diameter not specified).

Table 1. (continued)

Study	Sample size (n)	Type of laser	Beam diameter (mm)	Maximal fluence (mJ/mm ²)	Pulse duration (ms)	ISI (s)	Number of stimuli	Area stimulated	Additional parameters
Azevedo 2016	20	Infrared diode	0.1 (after spatial filter)	not specified	50	5	1x100	hand dorsum (right)	An aluminum sheet drilled with tiny holes (0.1 mm) was placed between the laser and the skin (original laser beam diameter not specified).
Tzabazis 2011	10	Infrared diode	≈3.7	not specified	1500	30	20	hand dorsum	
Lenoir 2018	18	CO ₂	0.3 (after focusing lens)	≈13	10	7-10	2x30	anterior forearm (bilaterally)	A) A convex focusing lens was used to get the laser beam from 10 mm to 0.3 mm. B) A procedure based on reaction times was used to determine the intensity of laser stimuli for C-fibers stimulation. C) High-frequency electrical stimulation was applied on one forearm to induce secondary hyperalgesia.

Table S1. (continued)

Study	Sample size (n)	Type of laser	Beam diameter (mm)	Maximal fluence (mJ/mm ²)	Pulse duration (ms)	ISI (s)	Number of stimuli	Area stimulated	Additional specifications
Colon 2017	8	CO ₂	12	not specified	not specified	not specified	2x20	hand dorsum (bilaterally)	Laser stimulation consisted in sustained periodic heat stimulus (15 cycles of 5 s) during which the skin temperature oscillated between baseline skin temperature and 50°C.
Torta 2015	8	CO ₂	6	not specified	100	5-10	3x40	hand dorsum	A procedure based on reaction times was used to determine the intensity of laser stimuli for C-fibers stimulation.
van den Broeke 2014	15	CO ₂	6	not specified	100	3-5	≤ 50	anterior forearm (bilaterally)	A) A procedure based on reaction times was used to determine the intensity of laser stimuli for C-fibers stimulation. B) High-frequency electrical stimulation was applied on one forearm to induce secondary hyperalgesia.

Table S1. (continued)

Study	Sample size (n)	Type of laser	Beam diameter (mm)	Maximal fluence (mJ/mm ²)	Pulse duration (ms)	ISI (s)	Number of stimuli	Area stimulated	Additional specifications
Jankovski 2013	10	CO ₂	12	not specified	100	5-10	4x40	hand and foot dorsum (bilaterally)	A procedure based on reaction times was used to determine the intensity of laser stimuli for C-fibers stimulation.
Mouraux 2011	8	CO ₂	5	6	20	7-10 (between trains)	8x10 pulse trains (16 pulses delivered at 7 Hz)	hand and foot dorsum (bilaterally)	The laser beam was moved by $\approx$ 5 mm between each pulse of the trains.
Obi 2007	22	CO ₂	$\approx$ 0.4 (after spatial filter)	19.1	20	3	2x10	hand and foot dorsum (right), and the skin over C7 and T12	An aluminum sheet drilled with tiny holes (0.125 mm ²) was placed between the laser and the skin (original laser beam diameter = 2 mm).
Mouraux 2004	13	CO ₂	10	8.8	50	20-30	Session 1: 1x24; Session 2: 4x60	hand dorsum (right)	
Qiu 2003	5	CO ₂	$\approx$ 0.4 (after spatial filter)	not specified	20	20-40	not specified	foot dorsum	An aluminum sheet drilled with tiny holes (0.125 mm ²) was placed between the laser and the skin (original laser beam diameter = 2 mm).

Table S1. (continued)

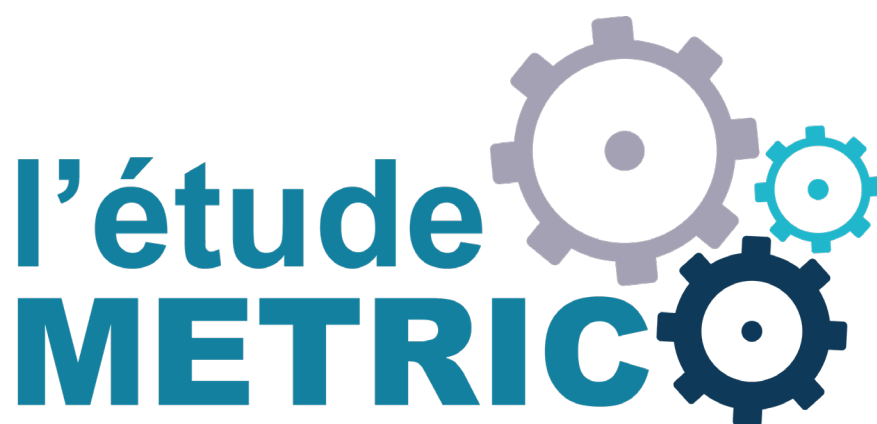
Study	Sample size (n)	Type of laser	Beam diameter (mm)	Maximal fluence (mJ/mm ²)	Pulse duration (ms)	ISI (s)	Number of stimuli	Area stimulated	Additional specifications
Opsommer 2003	8	CO ₂	≈0.6 (after focusing lens)	9.37	5	15-20	5x40	proximal phalanx of the left index or middle finger	A convex focusing lens was used reduce the laser beam to 0.25 mm ² .
Mouraux 2003	10	CO ₂	10	10.9	40	30-40	4x30	hand dorsum (left)	
Ianetti 2003	15	CO ₂	5	7.5	30-50	15-30	≥30	skin over C5 and T10	
Tran 2002	13	CO ₂	≈0.4 (after spatial filter)	not specified	20	4-20	3x40 (10 per location)	hand and foot dorsum, elbow and knee (left)	An aluminum sheet drilled with tiny holes (0.125 mm ²) was placed between the laser and the skin (original laser beam diameter = 2 mm).
Qiu 2001	11	CO ₂	≈0.4 (after spatial filter)	not specified	20	3-10	≥40	skin over C7, T4, T8, T12	An aluminum sheet drilled with tiny holes (0.125 mm ²) was placed between the laser and the skin (original laser beam diameter = 2 mm).

Table S1. (continued)

Study	Sample size (n)	Type of laser	Beam diameter (mm)	Maximal fluence (mJ/mm ²)	Pulse duration (ms)	ISI (s)	Number of stimuli	Area stimulated	Additional specifications
Opsommer 1999	10	CO ₂	≈0.6 (after spatial filter)	15	not specified	not specified	3x60 (60 per location)	foot dorsum, knee and upper thigh (right)	An aluminum sheet drilled with tiny holes (<0.25 mm ²) was placed between the laser and the skin (original laser beam diameter not specified).
Magerl 1999	12	CO ₂	11	not specified	500	not specified	4x25 (25 per location)	hand dorsum and upper arm (bilaterally)	The skin temperature was raised to 40°C and held there for 5 s. It was then raised to 48°C and held there for 500 ms.
Bragard 1996	9	CO ₂	≈0.4 (after spatial filter)	not specified	10	not specified	600 over several sessions (3 to 5x20 per session)	hand dorsum (left)	An aluminum sheet drilled with tiny holes (0.15 mm ²) was placed between the laser and the skin (original laser beam diameter = 20 mm).
Brom 1983	6	CO ₂	5	not specified	20	20-40	≥40	hand dorsum (left)	An ischemic compression block was used (it compressed the superficial branch of the radial nerve during more than 1 h).

Matériel supplémentaire de l'article 4 (educational booklet)

QUE FAIRE APRÈS LES 3 MOIS DE TRAITEMENTS?



D'abord

NOTRE ÉQUIPE DE
RECHERCHE TIENT À
VOUS REMERCIER D'AVOIR
ASSISTÉ AUX SÉANCES DE
PRISES DE MESURES ET DE
TRAITEMENTS!

Rappelez-vous que votre participation se poursuit.

En effet, 3, 6, 9 et 12 mois après la fin des traitements, nous vous enverrons un bref questionnaire par courriel afin de suivre l'état de votre dos. Vos réponses à ce questionnaire seront d'une aide précieuse pour faire avancer les connaissances concernant les maux de dos.



Ce document contient des recommandations pour prévenir ou soulager la douleur au bas du dos.

Essayez les recommandations qui vous intéressent en y allant à votre rythme. Soyez indulgent avec vous-même et donnez-vous le temps. Modifier nos habitudes de vie est un processus difficile et il est normal de retomber dans nos anciennes habitudes de temps à autre. L'important c'est de ne pas s'y arrêter et de continuer de progresser peu à peu.

Prévenir la douleur

les traitements chiropratiques

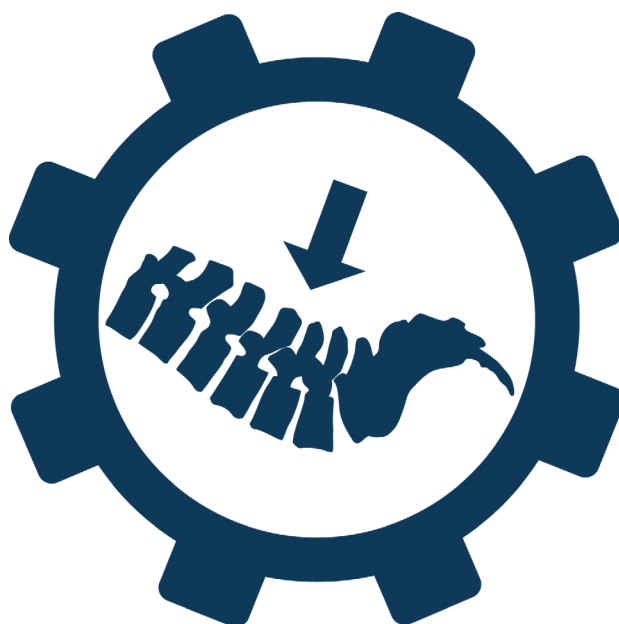
Serait-il bénéfique de continuer à recevoir des traitements chiropratiques après l'étude?

À ce jour, une seule étude a été faite sur le sujet (1). Celle-ci a démontré que les personnes qui reçoivent des traitements de maintien ont moins souvent mal au dos dans l'année que des gens qui consultent uniquement lorsque la douleur revient.

La fréquence des traitements de maintien utilisés dans l'étude variait d'**un traitement par mois (12 par année) à un traitement par 3 mois (4 par année)**, selon les besoins individuels des gens.

SI VOUS AVEZ SENTI UNE AMÉLIORATION AVEC LES TRAITEMENTS CHIROPRATIQUES LORS DE VOTRE PARTICIPATION À L'ÉTUDE METRIC, IL EST PROBABLE QUE DE RECEVOIR D'AUTRES TRAITEMENTS CHIROPRATIQUES SOIT BÉNÉFIQUE POUR VOUS.

DISCUTEZ-EN AVEC LE CHIROPRATIEN QUE VOUS CONSULTEREZ.



Prévenir la douleur



Le sommeil

LA PLUPART DES GENS ONT DÉJÀ VU LEUR SOMMEIL PERTURBÉ PAR UNE DOULEUR QUELCONQUE. CEPENDANT, CETTE RELATION FONCTIONNE DANS LES DEUX SENS ET LE SOMMEIL PEUT AUSSI INFLUENCER LA DOULEUR.

De nombreuses études ont démontré qu'un sommeil déficient, en qualité comme en quantité, augmente la sévérité de la douleur aiguë et chronique même en l'absence d'un diagnostic d'insomnie (2).

Une bonne gestion du sommeil peut aider à prévenir la douleur.

Comportements qui favorisent le sommeil

1

Se lever à la même heure chaque matin (fin de semaine et jour de congé inclus), et ce, peu importe la durée du sommeil de la nuit précédente. Ceci aidera à normaliser le cycle sommeil-éveil.

2

Éviter les siestes le jour. Si une sieste est nécessaire, celle-ci devrait être de moins d'une heure et avoir lieu avant 15h00.

3

Se coucher à la même heure chaque soir.

la suite...

4

Avant d'aller se coucher, favoriser une routine relaxante comme:

- pratiquer une ou des techniques de relaxation
- prendre une marche
- prendre un bain (pas trop chaud) plus d'une heure avant l'heure du coucher

5

Avant d'aller se coucher, éviter:

- de prendre un repas trop lourd
- de se coucher en ayant trop faim
- de pratiquer un exercice physique intense près de l'heure du coucher, ce qui pourrait avoir un effet stimulant.
- de pratiquer une activité intellectuelle intense et prolongée près de l'heure du coucher
- les stimulants (caféine, nicotine) au moins 4-6 h avant l'heure du coucher.
- l'alcool près de l'heure du coucher. S'il peut faciliter l'endormissement initial, il peut fragmenter le sommeil.
- l'exposition à la lumière bleue (téléviseur, ordinateur, téléphone, tablette, etc.), car elle supprime la sécrétion de mélatonine (hormone du sommeil).

6

Restreindre le temps passé au lit à ne pas dormir en évitant de faire ces activités au lit:

- lire / regarder la télévision
- écouter de la musique
- travailler ou jouer à l'ordinateur ou sur son téléphone

7

Créer des conditions favorables au sommeil, comme:

- une bonne circulation d'air
- la température de la chambre ni trop froide, ni trop chaude
- un lit confortable
- une chambre sombre et silencieuse
- éviter de trop réfléchir ou de ruminer au lit. Favoriser plutôt un environnement calme et serein, car tout ce qui diminue le stress et l'anxiété est favorable au sommeil.
- mettre le réveille-matin hors de la vue pour prévenir l'inquiétude reliée au calcul du temps jusqu'au réveil

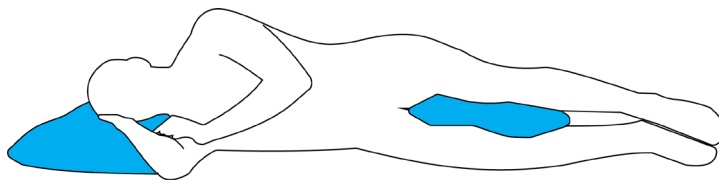
La position de sommeil

Si vous avez des douleurs au dos la nuit ou le matin en lever, il peut être judicieux de vérifier votre position de sommeil afin d'alléger la charge appliquée sur votre dos.

1

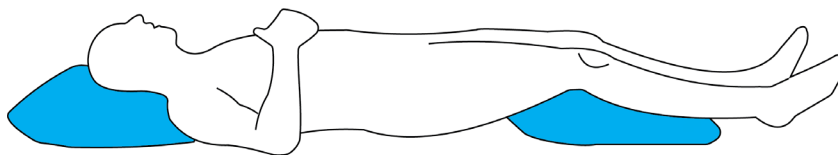
Sur le côté

Si vous dormez sur le côté, ramenez légèrement vos jambes vers votre poitrine et placez un oreiller entre vos jambes. Fléchir les genoux et avoir un oreiller entre les jambes peut aider à aligner la colonne vertébrale, le bassin et les hanches. Cette position soulage la colonne vertébrale. Utilisez un oreiller de corps (oreiller plus long) si vous préférez.

**2**

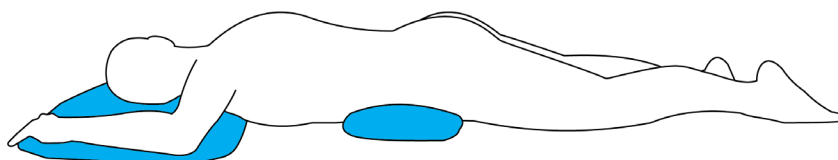
Sur le dos

Si vous dormez sur le dos, placez un oreiller sous vos genoux. Cela peut aider à détendre les muscles de votre dos et à maintenir la courbe du bas du dos. Si vous avez besoin d'un soutien supplémentaire, essayez une petite serviette roulée sous votre taille. Utilisez un oreiller qui supporte votre cou. Votre oreiller doit maintenir votre cou aligné avec votre poitrine et votre dos. Il ne doit pas être trop haut.

**3**

Sur le ventre

Dormir sur le ventre peut être dur pour le dos. **Essayez d'autres positions de sommeil si possible.** Si vous ne pouvez pas dormir autrement, réduisez la tension du dos en plaçant un oreiller sous vos hanches et sous votre ventre. Utilisez un oreiller sous votre tête si cela ne sollicite pas trop votre dos.



Prévenir la douleur



CHEZ LES GENS DE 50 ANS ET PLUS, LA PRATIQUE HEBDOMADAIRE D'ACTIVITÉ PHYSIQUE VIGOUREUSE DIMINUE LE RISQUE DE DÉVELOPPER DES DOULEURS CHRONIQUES (4).

La pratique d'activité physique permet une diminution de l'intensité de la douleur en plus d'améliorer (3) :

- la fonction physique (force, endurance, flexibilité, coordination, équilibre)
- la fonction psychologique (diminution du stress, amélioration de l'humeur, meilleure estime de soi)
- la qualité de vie (meilleur sommeil, maintien d'un poids santé, diminution de l'isolement social, aide à prévenir plusieurs maladies: diabète, hypertension, ostéoporose, etc.)

Comment débiter?

1

Utilisez la règle du 10% : Déterminez le niveau d'activité qui ne provoque pas d'augmentation de la douleur et augmentez l'intensité ou la durée de l'activité de 10% à la fois par semaine.

2

Respectez vos limites et vos capacités. Sur une échelle de 0 à 10, la douleur ne devrait pas augmenter de plus de 2 et elle devrait revenir à son niveau initial. Par exemple, si la douleur est à 3/10, elle peut augmenter à 5/10 pendant l'exercice, mais elle doit revenir à 3/10 après l'activité.

Il n'est jamais trop tard pour commencer

1

Bouger davantage ne veut pas dire faire du sport, s'inscrire dans un gym ou dans une équipe sportive. Cela signifie un mode de vie plus actif. Intégrez ceci dans votre quotidien :

- Prenez les escaliers plutôt que l'ascenseur.
- Pendant que vous regardez la télévision, faites des étirements ou quelques exercices de renforcement musculaire.
- Prenez de courtes marches plusieurs fois par jour.
- Utilisez un podomètre pour suivre votre évolution, vos pas, vos progrès (la plupart des téléphones intelligents ont une application intégrée pour cela).

2

Débutez avec des activités simples, qui vous plaisent et que vous pourrez partager avec des proches:

- marche / course à pied / vélo
- natation
- jardinage
- danse sociale
- musculation avec ou sans poids
- étirements / [yoga](#) / pilates / tai-chi
- autres

5

Au besoin, n'hésitez pas à parler à un professionnel de la santé pour vous guider dans le choix d'activités appropriées pour vous:

- chiropraticien
- médecin
- physiothérapeute
- kinésologue

Soyez patient et n'abandonnez pas.
Les bienfaits de l'activité physique ne se ressentent pas instantanément.

3

Allez-y selon vos capacités.

Commencez doucement puis en augmentez progressivement l'intensité et la fréquence de l'activité.

4

Variez les activités afin de réduire le risque de blessures dues à la répétition de certains gestes.

**L'objectif ultime est de bouger
3 à 5 fois par semaine,
à raison de 20 à 60 min par jour.**

Prévenir la douleur



Le soutien social

LE SOUTIEN SOCIAL EST UN FACTEUR PROTECTEUR CONTRE LA DOULEUR CHRONIQUE (5-9). AVOIR UN ENTOURAGE QUI VOUS SOUTIENT ADÉQUATEMENT (ASSEZ, MAIS PAS TROP) PEUT AIDER À RÉDUIRE L'INTENSITÉ ET LA DURÉE DE LA DOULEUR.

Les gens peuvent offrir de nombreux et différents types de soutien :

- **Le soutien émotionnel** : cela peut être une personne avec laquelle vous communiquez lorsque vous désirez seulement parler d'un problème et partager vos pensées et vos sentiments. Le soutien émotionnel ne consiste pas nécessairement à trouver des solutions. Il s'agit vraiment d'empathie.
- **Des conseils avisés** : Il s'agit d'une personne avec laquelle vous parlez lorsque vous avez besoin de plus amples renseignements sur un sujet particulier.
- **De nouvelles perspectives** : C'est pouvoir appeler une personne en particulier lorsque vous devez examiner un problème de différents points de vue. D'autres personnes peuvent offrir d'excellentes perspectives que vous pourriez ne pas avoir considérées.
- **De l'aide pratique** : C'est avoir dans son entourage une personne que vous pouvez appeler lorsque vous avez besoin d'un coup de main. Parfois, même de petites tâches peuvent sembler accablantes et une aide pratique peut alors faire une grosse différence.

Comment créer son réseau d'aide?

Le réseau d'aide évolue habituellement avec le temps. Les situations de la vie et les gens peuvent changer, et il arrive que des gens perdent une personne importante dans leur vie. Parfois, une personne a beaucoup de gens dans son réseau d'aide, mais ceux-ci ne peuvent offrir le soutien dont elle a le plus besoin. D'autres personnes peuvent trouver qu'elles ont simplement besoin de plus de soutien qu'elles n'en reçoivent actuellement. Peu importe la situation, vous pouvez agir pour vous créer un réseau d'aide plus efficace. Voici comment renforcer un réseau existant :

- Prenez contact avec les gens qui composent votre réseau et demandez de l'aide. N'oubliez pas que cela demande du courage!
- Entretenez les relations importantes que vous avez déjà. Vous devez contribuer également à ces relations; vous ne pouvez pas seulement demander de l'aide. Offrez également du soutien aux autres membres de votre réseau.
- Soyez clair par rapport au type d'aide dont vous avez besoin. Dites aux gens ce dont vous avez besoin; ils pourraient mieux vous aider s'ils savent ce que vous recherchez.
- Demandez un soutien spécialisé, comme du counseling, au besoin. Assurez-vous de demander de l'aide aux bons endroits.
- Si vous faites des efforts pour entretenir une relation mais ne voyez pas les améliorations dont vous avez besoin, il peut être temps de mettre fin à cette relation. Les gens et les situations changent. Parfois, il vaut mieux mettre votre énergie dans des relations plus saines.



Comment agrandir son réseau?

- Créez des occasions de rencontrer de nouvelles personnes. Participez à des activités sociales, suivez des cours, faites du bénévolat ou impliquez-vous auprès d'une organisation ou d'un groupe. Vous pouvez également demander à des amis de vous présenter d'autres personnes.
- Donnez du temps à vos relations. Établir des relations demande un peu de travail. Vous ne développerez pas une amitié avec toutes les personnes que vous rencontrerez, et lorsque vous vous faites un nouvel ami, il faut du temps pour renforcer votre relation.
- Interagissez en personne. Si vous avez un problème précis, comme une maladie, joignez-vous à un groupe de soutien ou essayez d'obtenir un soutien individuel auprès d'un pair aidant. Ceci peut être une excellente façon d'interagir avec d'autres personnes qui peuvent comprendre certaines de vos expériences et vous transmettre de l'espoir, de bons renseignements et des ressources.
- Cherchez en ligne. Si vous n'avez pas beaucoup d'occasions de trouver des gens en personne, envisagez de chercher en ligne une communauté à laquelle vous joindre. Il vous suffit de faire preuve de jugement pour choisir les options qui sont sécuritaires et utiles.



Source: Association canadienne pour la santé mentale. 2018. Le soutien social. <https://cmha.ca/fr/brochure/le-soutien-social/>

Soulager la douleur

Voici les dernières recommandations de l'Organisation mondiale de la santé pour traiter la douleur au bas du dos (10).



TRAITEMENTS À ÉVITER

Ces traitements sont généralement à éviter parce qu'ils ont été démontrés inefficaces pour soulager la douleur au dos ou qu'ils comportent plus de risques que de bénéfices potentiels.

- Les opioïdes (codéine, morphine, fentanyl, etc.)
- Les relaxants musculaires (Robaxacet, etc.)
- Les ceintures lombaires
- Les tractions (tables motorisées qui étirent la colonne vertébrale)
- Les ultrasons
- Le TENS (de l'anglais transcutaneous electrical nerve stimulation)
- Les injections/infiltrations d'anesthésiques locaux

TRAITEMENTS RECOMMANDÉS

- Les programmes d'**exercices** structurés
[exercices pour le dos](#)
- Les manipulations vertébrales (**traitements chiropratiques**)

Les participants qui aimeraient continuer à recevoir des traitements à l'UQTR peuvent aller à la clinique universitaire de chiropratique. Celle-ci offre des traitements par le biais d'internes en chiropratique supervisés par des chiropraticiens expérimentés.

[clinique universitaire](#)

Pour consulter à l'extérieur de l'UQTR:

[trouver un chiropraticien](#)

- Les **massages** [trouver un massothérapeute](#)
- L'**acupuncture** [trouver un acupuncteur](#)
- La **thérapie cognitivo-comportementale** [trouver un psychologue](#)
- Prendre des **anti-inflammatoires non stéroïdiens** (Advil, Aspirin, Motrin, Naprosyn, Voltaren, etc.). Respectez la posologie et suivez les recommandations de votre médecin ou de votre pharmacien.

Bien choisir ses professionnels de la santé

IL A ÉTÉ DÉMONTRÉ QU'UNE BONNE RELATION ENTRE UN PATIENT ET SON THÉRAPEUTE (L'ALLIANCE THÉRAPEUTIQUE) AMÉLIORE L'EFFET DE PLUSIEURS TRAITEMENTS POUR LES MAUX DE DOS (11). LORSQUE C'EST POSSIBLE, IL EST DONC IMPORTANT DE BIEN CHOISIR SES PROFESSIONNELS DE LA SANTÉ AFIN D'OBTENIR LES MEILLEURS RÉSULTATS.

Choisissez quelqu'un :

- que vous sentez compétent
- en qui vous avez confiance
- qui est à l'écoute de vos besoins
- avec qui vous êtes prêt à travailler pour atteindre vos objectifs



Outils supplémentaires

Le programme « Agir pour moi »

Développé par le Réseau Québécois de Recherche sur la Douleur, «Agir pour moi» est un programme d'autogestion de la douleur chronique conçu pour être suivi sans le soutien d'un professionnel de la santé. Réparties sur huit semaines, les leçons proposées portent sur différentes stratégies qui permettent de mieux gérer la douleur au quotidien. De plus, le programme **est gratuit pour tous**.

[en apprendre plus sur ce programme](#)

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Références

1. Eklund A, Jensen I, Lohela-Karlsson M, Hagberg J, Leboeuf-Yde C, Kongsted A, et al. The Nordic Maintenance Care program: Effectiveness of chiropractic maintenance care versus symptom-guided treatment for recurrent and persistent low back pain-A pragmatic randomized controlled trial. PLoS One. 2018;13(9):e0203029.
2. Haack M, Simpson N, Sethna N, Kaur S, Mullington J. Sleep deficiency and chronic pain: potential underlying mechanisms and clinical implications. Neuropsychopharmacology. 2020;45(1):205-16.
3. Geneen LJ, Moore RA, Clarke C, Martin D, Colvin LA, Smith BH. Physical activity and exercise for chronic pain in adults: an overview of Cochrane Reviews. The Cochrane database of systematic reviews. 2017;4(4):Cd011279.
4. Fancourt D, Steptoe A. Physical and Psychosocial Factors in the Prevention of Chronic Pain in Older Age. The journal of pain : official journal of the American Pain Society. 2018;19(12):1385-91.
5. Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. Lancet. 2021;397(10289):2082-97.
6. Edwards RR, Dworkin RH, Sullivan MD, Turk DC, Wasan AD. The Role of Psychosocial Processes in the Development and Maintenance of Chronic Pain. The journal of pain : official journal of the American Pain Society. 2016;17(9 Suppl):T70-92.
7. Goubert L, Trompetter H. Towards a science and practice of resilience in the face of pain. Eur J Pain. 2017;21(8):1301-15.
8. Meints SM, Edwards RR. Evaluating psychosocial contributions to chronic pain outcomes. Prog Neuropsychopharmacol Biol Psychiatry. 2018;87(Pt B):168-82.
9. Sturgeon JA, Zautra AJ. Psychological resilience, pain catastrophizing, and positive emotions: perspectives on comprehensive modeling of individual pain adaptation. Current pain and headache reports. 2013;17(3):317.
10. World Health Organization. WHO guideline for non-surgical management of chronic primary low back pain in adults in primary and community care settings. Geneva: World Health Organization; 2023.
11. Bishop F, Al-Abbadey M, Roberts L, MacPherson H, Stuart B, Carnes D, et al. Direct and mediated effects of treatment context on low back pain outcome: a prospective cohort study. BMJ open. 2021;11(5):e044831.