PhD Thesis

What determines a positive outcome of spinal manipulation for persistent low back pain: stiffness or pain sensitivity?

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We can always kind of be average and do what's normal I'm not in this to do what's normal

Kobe Bryant (1978-2020)

Preface

I completed this PhD from January 1st, 2018, to December 31st, 2020, where I was enrolled at the Department of Regional Health Research, University of Southern Denmark, and employed at the Spine Center of Southern Denmark. I collected the data supporting this thesis during my PhD enrollment at the Spine Center (Manuscripts I-IV). Having spent almost 500 hours in the laboratory makes you genuinely appreciate the aspect of experimental research. As part of my PhD, I spent ~ 4 weeks at the University of Alberta in Edmonton, Canada, at Professor Greg Kawchuk's laboratory (Manuscript VI). Finally, we executed a systematic review on the topic (Manuscript V). Another important aspect of this PhD has been teaching. I have co-supervised six masters theses and have supervised 90 young chiropractic students in approximately 700 clinical settings at the Spine Center.

I have had a keen interest in research since my days as an undergraduate student at the University. Initially, as any master student from SDU would do, I spoke to Jan Hartvigsen about the opportunities to obtain a PhD degree. While what Jan and I discussed was of interest, it was not long before Søren O'Neill approached me to discuss experimental research focusing on quantifying pain in a clinical setting. This opportunity was directly in line with my interest, and the rest is history. However, the journey to this point was not straight forward. While being a PhD student is challenging, becoming one, to begin with, is even more complicated. The mixture between working full time, writing a PhD protocol, applying for funding, and so on is exhausting. Yet, in the end, I would have done it over 100 out of 100 times.

Ever since I was an undergraduate student and trained in the "art" of spinal manipulation and how important it was to be specific by directing the treatment at spinal dysfunctions. I had difficulty understanding and locating these dysfunctions that the lecturers spoke of with such confidence. Thus, I learned what we students considered normal: "fake it till you make it." The only barrier to this approach was that I never "made it," not after graduation or after six months in clinical practice. By then, I decided to quit trying, as the patients improved

regardless. Still, I was determined to explore whether we could quantify vertebral function and whether it really mattered for patient improvement.

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Publications

The manuscripts are reprinted in Appendix B on page 133.

I Nim CG, Kawchuk GN, Schiøttz-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, 10:14615

II Nim CG, Kawchuk GN, Schiøttz-Christensen B & O'Neill S **Changes in Pain Sensitivity and Spinal Stiffness in Relation to Responder Status following Spinal Manipulative Therapy in Chronic Low Back Pain: A secondary explorative analysis of a randomized trial –** Accepted December 14, 2020 at BMC Musculoskeletal Disorders

III Nim CG, Weber 2nd KA, Kawchuk GN & O'Neill S **Spinal Manipulation and Modulation of Pain Sensitivity in Persistent Low Back Pain: A Secondary Analysis of a Randomized Trial** – Under review at BMC Chiropractic and Manual Therapies - submitted September 7, 2020

IV Nim CG, O'Neill S, Geltoft AG, Jensen LK, Schiøttz-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** – Under review at Journal of Manipulative and Physiological Therapeutics - submitted April 25, 2020

V Nim CG, Downie A, Kawchuk GN, Perle S, Leboeuf-Yde C & O'Neill S **Spinal manipulative therapy applied at a specific target versus spinal manipulative therapy applied at a comparator target in the treatment of spinal pain: A systematic review** – Manuscript in preparation

VI Nim CG, Jun P, Hadizadeh M, O'Neill S, Schiøttz-Christensen B & Kawchuk GN **Spatial Synchronization of Spine Stiffness Data** – Under review at Journal of Back and Musculoskeletal Rehabilitation - submitted August 31, 2020

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Summary in English

Low back pain (LBP) is the number one cause of years lived with disability, and it is the most common reason for primary care visits. However, we have limited knowledge regarding its mechanism, and we are currently limited to categorizing 90% of LBP patients as *non-specific*. A standard treatment of non-specific LBP is spinal manipulative therapy (SMT), which aims to normalize specific spinal dysfunction. However, there is currently no available method of quantifying these spinal dysfunctions. This leaves clinicians using manual palpation to locate them and aim SMT at that vertebral target. Research indicates that locating a stiff or tender vertebra is used to determine the target.

Hence, quantifying stiffness has gained much traction using different mechanical indentation devices, and the preliminary results have been of interest. It appears that SMT does change stiffness but only for those who respond. Recently, a novel device, the VerteTrack (VT), has been developed. Through continuous rolling mechanical indentation of the lumbar spine, the VT allows us to record stiffness values at multiple vertebrae, non-invasively and rapidly, in a fashion that simulates manual palpation. Thus, the VT provides a new approach to quantifying stiffness. Tenderness and pain sensitivity are different aspects and is commonly measured in human subjects using quantitative sensory pain testing (QST). Much research has focused on changes in QST following SMT with conflicting results. However, it appears that regional mechanical pain sensitivity is affected by SMT.

We have little knowledge of how SMT works and whether further mechanistic knowledge can optimize the treatment. Finally, we do not know how joint stiffness and pain sensitivity interact together. Therefore, the objectives of this thesis were i) to elucidate the vertebral target site's effect when applying SMT in persistent LBP patients. More specifically, we will examine if SMT targeting the stiffest or most pain-sensitive vertebra can differentiate the responses from patient-reported and experimental outcomes. We will also examine whether responding to the treatment impacts the experimental outcomes and whether a general hyperalgesic state predicts these changes. Finally, we will examine how vertebral stiffness and pain sensitivity are associated. ii) We will incorporate these results into a systematic

review with comparative literature to examine whether applying SMT at a specific target improves patient-reported outcomes compared to a comparator target.

To answer objective I, we conducted a clinical trial that randomized 132 participants with non-specific LBP to receive four standardized SMT sessions directed at either the stiffest or most pain-sensitive vertebra. We used the VT to quantify stiffness and included an extensive QST battery a total of three times: at baseline, following the fourth and final treatment, and again after two weeks. A total of 123 completed the trial. Due to differences in vertebral markings at the different time points, we had to omit approximately 12% of the vertebral data (VT, pressure pain threshold (PPT), and heat pain threshold). However, we developed a mathematical method to avoid this potential limitation in future research by spatially synchronizing the lumbar trajectories/markings.

We examined changes in patient-reported LBP intensity, disability, and the experimental measures obtained at each time point compared to baseline using linear mixed methods. Afterward, we dichotomized the participants into responders/non-responders. We used latent class analysis to cluster the cohort using the baseline QST data into two groups: a sensitized and a non-sensitized group. We also examined how the different vertebral measures correlated with each other and how they differed between the individual vertebrae. Furthermore, we conducted a systematic review that examined four databases to answer objective ii. The literature was extracted independently by two investigators and scored for quality using Cochrane's risk of bias tool. We provide a narrative report of the results.

We found that the participants improved regardless of the targeted vertebra or the different attempts to subgroup. While their improvement was statistically significant, we questioned whether this was of clinical relevance. The limited change was most likely due to the persistence of LBP in this sample. Nevertheless, the lack of an effect when targeting a specific vertebra is consistent with our systematic literature review, which included ten studies. In contrast to the preliminary results, we failed to find any changes in stiffness. However, we did find that PPT increased in three different settings:

I The group where treatment was targeted at the most pain-sensitive vertebra, independent of responder status.

II The responders, independent of the targeted vertebra.

III The sensitive group, independent of the targeted vertebra.

Thus, SMT appears to mediate changes in PPT as a neurophysiological reflex, both non-specific and specific, to the vertebra targeted, independent of clinical improvement, but also, due to overall clinical improvement. A caveat was that this was not a placebo-controlled trial. Hence, the causality of our findings is questionable. The remaining QSTs displayed limited modulations throughout, and none of them were of clinical relevance. Finally, we unexpectedly found that high degrees of stiffness correlate with high PPT scores (low pain sensitivity), thereby questioning if a stiff spine is an unfavorable attribute or if psychological factors impact this relationship.

To conclude, based on the current results and the existing literature, there is no data to support the clinical relevance of being specific when targeting SMT. Future research that examines PPT changes following SMT should try to account for the three instances reported. Finally, future studies utilizing the VT as a repeated measure should ensure spatial synchronization before continuing with the data analysis.

Summary in Danish

Lændesmerter (LS) er en af de primære årsager til funktionstab og er den hyppigste årsag til besøg i primærsektoren. På trods af den markante byrde LS er for samfundet har vi beskeden viden omkring mekanismen bag og i op mod 90% af tilfældende kan vi ikke stille en konkret diagnose og ofte bliver LS til en kronisk problematik.

Klinikere forsøger ofte at finde dysfunktioner i ryggens led, enten ved at lokalisere stivhed eller smerte. Herefter benyttes en vanlig behandling, spinal manipulation (SM), som har til formål at normalisere dysfunktionerne.

På baggrund heraf har der været stor interesse for at kvantificere lændestivhed og smerteføls omhed. Stivhed er nyligt blevet målt ved mekanisk indrykning over lænderyggen, således er det muligt at vurdere hvor meget ryggen flytter sig mod en ekstern modstand, og de indledende undersøgelser har vakt interesse. Det er vist at SM kunne ændre stivhed men kun for dem som oplevede bedring af behandling. Måden hvorpå man kvantificerer stivhed er løbende blevet udviklet og den nyeste model er VerteTrack (VT). Tidligere har man anvendt punkt-målinger, hvor VT nu kan måle kontinuerligt langs lænderyggen, hvilket giver et mål af hvor stiv ryggen er for hver enkelt hvirvel.

I modsætning til lændestivhed er målingerne af ømhed eller smerteføls omhed valideret ved brug af kvantitative sensoriske smerte tests (KST). Der er foretaget megen forskning af ændringer i smerteføls omhed efter SM og det tyder på at ens smertetærskel for en mekanisk påvirkning stiger efter SM. Den viden vi har om mekanismen bag SM er begrænset og det er ligeledes uvist om øget viden kan optimere behandlingen. Vi ved heller ikke hvordan stivhed og smerteføls omhed interagerer for det enkelte individ og om effekten af SM afhænger af disse faktorer når behandlingen påføres.

I denne afhandling vil vi forsøge at målrette behandlingen mod en lændehvirvel som fremstår mest stiv eller med størst smerteføls omhed, for at vurdere evt. forskel i effekten efter behandling. Vi vil ligeledes undersøge om en generel bedring efter behandling påvirker stivhed og smerteføls omhed, og hvordan et generaliseret smerteføls omt nervesystem har

indflydelse på disse ændringer. Vi vil også undersøge hvordan stivhed og smerteføl somhed er associeret. Slutteligt, vil vi lave en systematisk litteratur gennemgang for at sammenligne vores resulter med lignende studier. Gennemgangen vil undersøge om SM er mere effektivt hvis det målrettes specifikt.

Vi gennemførte et klinisk studie hvor vi tilfældigt fordelte 132 deltagere med kroniske ikke specifikke LS til at modtage fire gange SM målrettet enten den stiveste eller den mest smerteføl somme lændehvirvel. Vi brugte VT til at kvantificere stivhed og målte smerteføl somhed med et bredt QST "batteri" – Vi målte disse parametre før behandlingen, efter den fjerde behandling og to uger herefter.

I alt gennemførte 123 deltagere studiet. I forbindelse med de gentagne målinger var der enkelte tilfælde hvor vores markeringer af deltagernes lændehvirvler var forskudt, hvorfor vi måtte ekskludere ca. 12% af data omhandlende VT, tryksmertetærskel og varme smertetærskel. Vi præsenterer dog en matematisk model som man fremadrettet kan bruge for at undgå denne metodiske begrænsning.

Ved brug af lineære modeller udforskede vi ændringer i lændesmerter, funktionstab, lændestivhed og smerteføl somhed for hvert tidspunkt sammenholdt med før behandlingen. Efterfølgende kategoriserede vi deltagerne som værende respondenter eller non-respondenter. Vi udførte en latent klasse analyse for at undersøge latente mønstre som kunne dele gruppen i to, generaliseret smertesensitive eller ikke generaliseret smertesensitive.

Udover dette gennemførte vi en systematisk litteratur søgning i fire databaser. To forskere udvalgte relevante artikler og eksporterede relevant data uafhængigt af hinanden. Vi scorede kvaliteten af studierne ud fra Cochranes risiko for bias skema og udførte en narrativ gennemgang af resultaterne.

Vi fandt at deltagerne havde færre smerter og øget funktion uafhængigt af hvilket niveau SM var målrettet mod, uafhængigt af den statistiske metode. Selvom forbedringen var statisk signifikant var den ikke definitivt klinisk relevant, da ændringerne var små og muligvis påvirket af deltagernes kronicitet. Dette var tilsvarende de resultater vi fandt i vores systematiske litteratur gennemgang. I kontrast til den tidligere forskning så vi ingen

ændringer i stivhed efter behandlingen. Vi observerede dog at deltagernes mekaniske tryksmertetærskel steg i tre forskellige tilfælde.

1 Den gruppe der blev behandlet med SM på den smertefølsomme hvirvel uafhængigt af om de var respondenter eller ej
2 Respondenterne uafhængigt af hvilken hvirvel SM var målrettet mod.
3 Den gruppe med generaliseret smertefølsomhed uafhængigt af hvilken hvirvel SM var målrettet mod.

Det tyder derfor på at SM kan mediere stigninger i mekanisk tryksmertetærskel som en neurofysiologisk refleks, både specifik og non-specifik ift. hvirvlen, uafhængigt af klinisk bedring og separat grundet klinisk bedring. Det er dog vigtigt at huske på at dette ikke var et placebo-kontrolleret studie og vi kan derfor ikke, for størstedelen af disse ændringer, berette om hvorvidt de er kausale. De resterende KST ændrede sig meget begrænset og ingen af dem i et klinisk relevant omfang. Slutteligt fandt vi, noget overraskende, at meget stivhed var korreleret med høj tryksmertetærskel, derved udfordrer vi hvorvidt en stiv ryg er en uhensigtsmæssigt faktor eller om det primært er psykologiske faktorer der påvirker dette forhold.

For at konkludere på vores resultater, alene og sammen med den øvrige litteratur, fremstår det ikke som værende vigtigt hvorhenne man vælger at behandle med SM. Fremtidig forskning der undersøger ændringer i mekanisk tryksmertetærskel bør tage højde for de tre tilfælde med stigning i tryksmertetærskel som vi reporterer.

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I also want to acknowledge all the funders who made contributions to ensure the thesis's completion: The Danish Chiropractic Fund for Research and Post Graduate Research, Hospital Lillebaelt, The Danish Rheumatism Association, and The Spine Center of Southern Denmark. I also extend my appreciation to the Chiropractic Knowledge Hub, who decided to fund a small pilot study/PhD preparation.

I would also like to acknowledge all the "others" I have encountered during the last three years – especially Steen Harsted for providing a shoulder to lean on whenever R was being stubborn. I also have to acknowledge Professors Jan Hartvigsen, Greg Kawchuk, and Jon Adams for establishing the CARL fellowship and allowing me to be part of the second cohort. I would also like to extend my gratitude to Ken Weber, Aron Downie, and Luana Nyirö. Finally, I would like to acknowledge Thorvaldur Palsson and Henrik Vægter for helping with the QST methodology.

I was also fortunate that my PhD allowed me to stay for ~ 4 weeks in Canada. Here, I made some great new acquaintances and would like to acknowledge Peter Jun and Maliheh Hadizadeh for helping on Paper V. Additionally, an extra thanks to Peter for showing me Korean cuisine and joining me for an NHL game. Finally, this trip was not possible without

the help and open-mindedness of the *Kawchuks* (Greg, Janet, and their two boys). Thank you for inviting me, taking me sight-seeing, and showing me that vegetarian food can be okay at times. In addition, I want to acknowledge Janet Kawchuk for proofreading the thesis.

I am also extremely grateful for my supervisor team. Berit Schiøttz-Christensen provided significant assistance to get this project underway and always knew who to ask for guidance. I want to thank Greg Kawchuk, whom I have been so fortunate to have worked with during my PhD, and this collaboration has led to multiple other projects. I always set aside extra time when he visits Denmark - a brilliant mind that inspires me almost every time we talk. Finally, I want to acknowledge my principal supervisor Søren O'Neill. Our relationship has progressed from a "supervisor-student" to a friendship during the last couple of years. I could not imagine a more appropriate mentor.

However, in the end, none of this would have been possible without the loving support from my family. My son Oliver, who was born during the PhD preparation – you provided me with numerous joyful hours when I lacked clarity and needed to get my mind at ease. My parents and mother-in-law have been an enormous resource whenever I traveled or was stuck in meetings. Finally, all of this was not possible without the support of my loving wife, Nickie – who has provided more support than she realizes.

Thank you

List of abbreviations

L1 - L5 = Lumbar vertebra 1 - 5

LBP = Low back pain

QST = Quantitative sensory pain testing

SMT = Spinal manipulative therapy

VT = VerteTrack

NRS = Numerical pain rating score

ODI = Oswestry disability index

GS = Global stiffness

TeS = Terminal stiffness

PPT = Pressure pain threshold

HPT = Heat pain threshold

CccA = Computer-controlled cuff algometer

eVAS = Electronic visual analog scale

wPPT = Widespread pressure pain threshold

wPTT = Widespread pressure pain tolerance threshold

TS = Temporal summation

CPM = Conditioned pain modulation

FD = Force-displacement value

ρ = Pearson's product-moment correlation

R_s = Spearman's rank correlation

ANOVA = One-way analysis of variance

BIC = Bayesian Information Criterion

This thesis is dedicated to my son Oliver Glissmann Nim, who is determined never to leave any question unanswered. Without you, I would most likely have submitted six months earlier – still – totally worth it

THESIS

Introduction

Low back pain is the leading cause of reported disability. Yet, we know little about how pain originates and how we should treat it. A typical treatment is spinal manipulative therapy, which aims to normalize movement or decrease pain at a specific point in the lower back. This point is theorized as the source of the pain. By treating it, the disability associated with low back pain is reduced. Chiropractors often choose either the stiffest point or the most tender point to treat. We know that both stiffness and tenderness can decrease following spinal manipulative therapy. However, we do not know if we can optimize the treatment by targeting spinal manipulative therapy at a specific point using either stiffness or tenderness as a mechanistic indicator. Thus, this thesis will examine if such a specific target helps the patient improve. Afterward, we will explore and compare the results systematically with similar literature.

The lumbar spine: Anatomy, pain and clinical practice

The spine is an integral part of the human locomotor system and has three principal functions: i) to protect the sensitive nerve structures, ii) to provide stability and balance, and iii) to enable motion. The lumbar spine comprises five bony structures, labeled as vertebrae, ranging from the top/cranially as lumbar vertebra 1 (L1) to the bottom/caudally, L5. Mechanical movement between these vertebrae is primarily caused by the facet joints, which function as a bridge and ensure contact between the vertebra above and below (1). Thus, enabling us to perform motion in all planes and, importantly, ensure stability and limits to this motion. These functions can be mechanically affected by minor morphological changes such as facet tropism typically associated with osteoarthritis (2). When acknowledging the paradigm between movement and stability, it is not surprising that minor structural changes can cause limitations or modifications and thereby theorized to cause pain.

Even though low back pain (LBP) is often considered a benign symptom, it is a rising challenge globally and causes the most years of lived with disability (3). In Denmark, LBP is no different, as almost one million Danes are affected by it. Further, LBP is the most common cause of primary care visits. Thus, it is not surprising that LBP constitutes a significant proportion of sick leave (4). So, while it might be benign in nature, it has

significant malignant consequences for society. Traditionally, we thought LBP was an acute event that transpired and disappeared. We know now that LBP often persists in a chronic or recurrent pattern (5).

Despite the significant contribution persistent LBP has on public health, we have limited knowledge regarding its etiology, and research continuously comes up short (5). At best, we can currently triage LBP into three categories: i) specific spinal pathology; this includes the culprits, cancer, fractures, infections, etc. Luckily, this only pertains to less than one percent of all LBP cases, ii) radicular syndromes; pain radiating from the lumbar spine possibly due to disc herniation or narrowing of the nerve root canals (approximately 5-10%), and finally, iii) non-specific LBP; this category completely overshadows the remaining two, as 90 - 95% of all LBP is of non-specific origins. We assume that pain in these cases is of musculoskeletal origin or structural changes within the lumbar spine. However, no test or diagnostic tool can help us filter out the structural specificities (6). While morphological or degenerative changes observed in the lumbar spine using advanced imaging can be quantified, they, unfortunately, provide little hope. While there appears to be an association between the cumulative number of degenerative findings and LBP (7–9), each finding on its own has limited value (10).

Thus, with no diagnosis in sight, much effort has been devoted to describing persistent pain in a quantifiable fashion that explains pain development. We present two meaningful options:

I A biomechanical understanding of the human locomotor system, e.g., movement. However, this may only affect some patients with LBP.

II The pain itself; this is the constant across all patients with LBP, as all patients experience pain by default. However, the intensity and frequency differ.

Biomechanical cause of pain

Biomechanics covers various aspects, from the highly theoretical concerning forces, vectors, and the complex relationships between those, to more practical applicable kinematics - relating to movement, measurable at different joints for different conditions (11). Currently, research indicates that persistent LBP patients have aberrant and stiff movement patterns (12). However, most of this research is cross-sectional, suggesting that we do not know if

patients with faulty biomechanics develop LBP or if they differ from healthy subjects as a result of continuous LBP.

Notwithstanding, there are more challenges in filtering out whether biomechanics is an essential constituent in LBP. Aberrant movement patterns are typically linked with psychological changes also occurring with LBP, such as catastrophizing and kinesiophobia (13). A further challenge is whether an aberrant movement pattern is the cause of faulty biomechanics or merely the psyche projection.

Neurophysiological cause of pain

Pain is entirely a subjective perception for each patient; thus, profoundly affected by psychology. The complexity of persistent pain has been extensively researched in the last decades. A growing body of research now demonstrates an increase in neural excitability that transpires when suffering from persistent pain. The nociceptive receptors become hyper-excitable, leading to increased transmission of nociceptive sensory input, causing central hypersensitivity and possibly attenuating the pain-inhibiting mechanism. This results in enhanced regional pain response and sometimes widespread pain hypersensitivity (generalized hyperalgesia) (14).

Many years of methodical animal research has helped us understand this process (15). Consistently, this has been translated and adapted into human testing. Thus, we can now describe pain in a quantifiable fashion, using a psychophysiological measure: quantifiable sensory pain testing (QST) (16). When applying QST to different LBP populations, we can separate persistent LBP patients from acute LBP patients (17) and healthy subjects (18,19). We can also repeatedly map out the somatosensory nervous system and observe how acute LBP patients who do not improve gradually become more sensitized (20). However, despite a well-validated methodology that arguably could provide a mechanistic explanation for the persistence of pain, the clinical value of QST is still questionable, as it does not predict outcomes in acute LBP (21). Nor does low pain thresholds predispose the development of persistent pain (22). Finally, we have limited knowledge concerning QSTs predictive value in the treatment of LBP (23).

Authenticity of science and clinical practice

Both the biomechanical and the pain aspect are two valid and essential methods quantifiable in LBP patients. However, there appears to be an artificial segregation between them in research. Both are often studied independently, arguably, as the methods and theories are still so complex that researchers only specialize in one regard. This is not a reflection of clinical practice. Here, clinicians have to deal with the patient holistically and take all the facets into account. While challenging, studying these factions together could, arguably, optimize our understanding of LBP and the already well-established link between experimental and physiological measures, possibly, providing insight into persistent LBP.

Treatment of low back pain

This dissociation between practice and science may be one reason why these more theoretical advances have not let us come closer to subgroup patients. Therefore, LBP treatment is continuously not limited and ranges from a broad spectrum of repetitive manual mobilization to complete fixation by performing fusion surgery (24). While these treatments differ significantly, an overall tendency can be estimated when enrolling patients into LBP research trials. Generally, the participants experience a significant pain reduction within the first four to 12 weeks. Hereafter, the pain levels stagnate entirely (25). As LBP is ubiquitous, challenging to subgroup into structural causes, and the treatment effects are limited, clinicians are challenged daily when a patient comes in complaining about LBP. Thus, there has been much focus on synthesizing the available evidence into different treatment guidelines. However, as we currently cannot define a specific therapeutic target or a specific spinal structure to treat, the recommendations are vague and potentially include endless possibilities (26–28). Thus, clinicians arguably have difficulty in implementing them. Who should be treated, how often, and what should the treatment target? For manual therapy, which often is guideline-recommended (29), there is a clinical tendency to speculate that perturbations of a single vertebral level can cause LBP. Thus, treatment is often aimed at that clinically.

Spinal manipulative therapy

Manual therapy is an ancient skill or *art form* first described in 400 BC. Iin the latter 1900s, manual therapy was popularized by an emerging profession, chiropractic, due to allopathic medicine's shortcomings. Here, the term spinal manipulative therapy (SMT) was adopted (30). Spinal manipulative therapy specifically tries to normalize spinal limitations of biomechanical or neurophysiological origin to decrease pain and improve function. This is achieved by applying a high-velocity, low-amplitude thrust at a specific spinal vertebra (31). In the field of chiropractic, SMT has gone through numerous changes. Initially, the theory was that a vertebra was "out of place" or subluxated, leading to disturbances in the nervous system, thereby causing diseases. When targeting SMT specifically to the vertebra in question, it could relocate the bone and discard the subluxation (32). Obviously, this is anatomically implausible, yet some chiropractors still hold these theories dear to heart (33). Currently, we do believe that most clinicians apply a more evidence-informed practice that focuses solely on musculoskeletal disorders. However, targeting a specific vertebra still lingers, but it is now called spinal dysfunction (34).

Spinal dysfunctions

Spinal dysfunctions are no longer coined the cause of all diseases, they do provide the basis and indication for SMT for many chiropractors. The issue with spinal dysfunctions is that no one can say what they are precise. From a biomechanical and clinical perspective, the theory is that the vertebral joint is fixated and immobile, thereby leading to pain and distress. While this theory is apprehensive from a modern view, practitioners have been challenged repeatedly (35) as spinal dysfunction has yet to be captured in a quantifiable and reproducible fashion (36,37).

Furthermore, it does not help that the term's validity is, at best, questionable. The intra-rater reliability is acceptable, while the inter-rater reliability is poor (38). Thus, the same clinician can find spinal dysfunctions repeatedly, but another clinician cannot replicate this finding. This leads us to question what we are looking for. Hence, using palpation to locate spinal dysfunction can only be considered guesswork, at best. While we cannot quantify them in a clinical setting, spinal dysfunctions have surprisingly been included in a clinical prediction rule (39). Chiropractors state that they most often use two estimates to find the dysfunctions

indicating the vertebral level to target the SMT. Those are in line with the preceding, namely: i) a biomechanically affected and stiff joint or ii) a neurophysiologically affected and pain sensitive joint (40).

Biomechanical (stiffness) dysfunction

It is not surprising that we blame intervertebral motion for many aspects regarding LBP, as each facet joint must administer the equilibrium between motion and stability (2,41). Recording vertebral motion is a daunting task, making it difficult to determine if stiffness is affected by SMT. Complex animal models have been compiled and studied in vitro, in which the vertebra is given a direct thrust and afterward surgically removed for further examination (42,43). The same theory has been applied to humans undergoing spinal surgery using markers (44). However, these invasive techniques are still far from a clinical procedure, which is why non-invasive manual and automated processes have been developed (37). The automated mechanical indentation method at a specific point in the lumbar spine or detection of the current level of stiffness gained traction when a preliminary study found a decrease in stiffness following SMT (45). This hypothesis was supported by Wong and colleagues, who showed that stiffness did change following SMT, but only in those responding to the treatment (46). This was a novel finding, and it appeared to successfully illustrate a mechanistic explanation of why some patients improved following SMT while others did not.

Neurophysiological (pain) dysfunction

The neurophysiology aspects differ from the biomechanical. First of all, the QST procedure is highly validated and can function as a specific surrogate for functions within the somatosensory nervous system (14). We also know that these estimates are modifiable following treatment, both in an experimental (47) and a more clinical context (49). There are considerable amounts of research examining the changes in the somatosensory nervous system following SMT; this may be a relic from the past when SMT was associated with optimizing the nervous system to cure diseases (32). Nevertheless, despite four systematic reviews (50–53), there is still no clear consensus on SMT's effect on pain sensitivity. It does appear that SMT affects mechanical deep pain sensitivity in the region of application. However, there are still many unanswered questions. Most of the cohorts included in the

systematic reviews used: a limited sample, mostly healthy subjects, a minimal QST procedure, and only re-measured immediately following a single SMT session.

Rationale

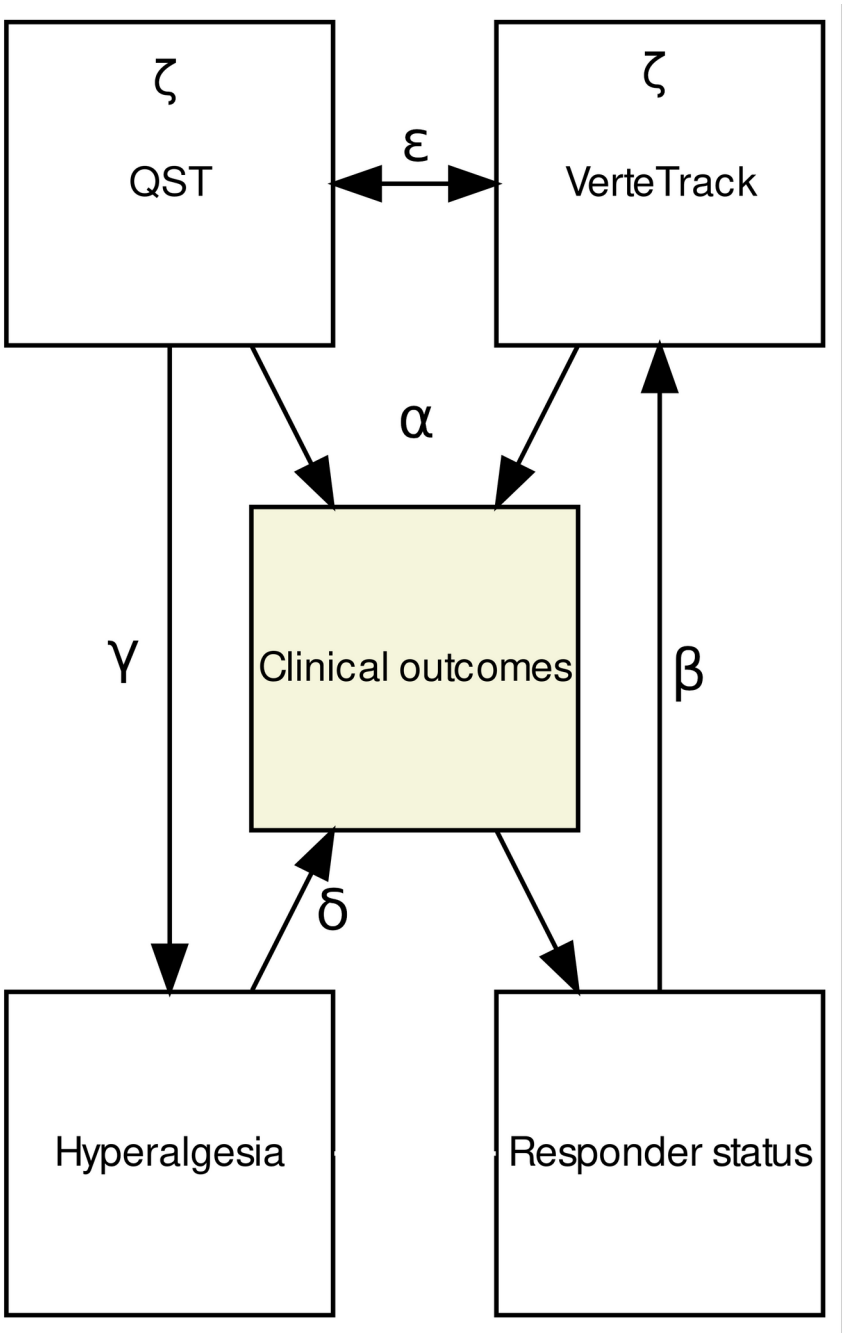
Spinal manipulative therapy appears to be as effective as other guideline-recommended treatments for persistent LBP (54). However, the mechanistic explanation of how and why it works is limited. Furthermore, clinicians put much effort into directing SMT at a specific vertebra due to a non-specific spinal dysfunction that we cannot record appropriately. Furthermore, we do not know if this specificity is of importance. It is unclear whether stiffness and pain sensitivity are inter-connected or increase following SMT, in a general fashion or specific to the vertebra targeted. Thus, we wanted to examine both biomechanics (vertebral stiffness) and neurophysiology (pain sensitivity) in unison. To mimic clinical practice, we applied SMT using these specific targets in the hope of increasing our mechanistic understanding and identify a specific subgroup of responders.

Objectives and hypothesis

The overall aim is to determine if SMT is more effective when applied at a specific target versus another comparator target. This will be answered using two different approaches.

Objective I We will aim to elucidate the vertebral target site's effect when applying SMT in persistent LBP patients. More specifically, we will examine whether SMT targeting the stiffest or most pain-sensitive vertebra can differentiate the responses from patient-reported and experimental outcomes. We will also examine whether being categorized as a responder impacts the experimental outcomes. We will cluster the cohort depending on their baseline QST scores and test whether being classified as having generalized hyperalgesia predicts changes in patient-reported outcomes and pain sensitivity. Finally, we will examine how vertebral stiffness and pain sensitivity are associated with one another. Six hypotheses are tested (Fig. 1).

Figure 1 Hypothesis for *objective 1*



An overview of hypothesis for *objective 1*
QST = Quantitative sensory pain testing

Hypothesis α: The target site at which SMT is applied affects patient-reported outcomes, but not experimental outcomes.

Hypothesis β: Stiffness and pain sensitivity change more specifically in a subgroup of patients who generally respond to the SMT.

Hypothesis γ: The cohort can be categorized into different levels of generalized hyperalgesia ranging from low sensitization (high pain thresholds) to high sensitization (low pain thresholds) depending on the QST score.

Hypothesis δ: Pain sensitivity changes more rapidly for the patient who had a lower threshold for the QST than the group who had a higher threshold.

Hypothesis ε: Higher degrees of stiffness are correlated with higher degrees of pain sensitivity (i.e., lower pain thresholds).

Hypothesis ζ: The regional experimental measures can distinguish the differences between the individual vertebrae.

Objective II We will compare our results (Hypothesis α) to similar literature examining whether SMT applied at a specific target is more effective than SMT applied at a comparator target. The specific target was defined as i) SMT based on clinical indication or ii) as pre-specified per-protocol. We defined *comparator target* as i) SMT not based on clinical indication or ii) as pre-specified per-protocol.

The hypothesis was that targeting SMT specifically outperformed a comparator target for any patient-reported outcome.

Method

Design

We conducted a randomized experimental trial examining an a-priori determined primary analysis and four secondary analyses to answer **objective I**.

Participants

We recruited patients with non-specific LBP from the Spine Center of Southern Denmark. We identified and invited participants using two methods, a broad and a specific.

Broad We included details of the project in the information material sent to patients before their first appointment. If the patients were interested, they could either call a research secretary concerning the inclusion or talk directly to the clinician in charge.

Specific Patients were informed verbally at the clinical consultation by the clinician in charge. The clinician diagnosed all potential participants with persistent LBP before the primary assessor (CGN) screened for enrollment.

Inclusion criteria

- Between the ages of 18 and 60.
- Body mass index under 35.
- Non-specific LBP for more than three months.
- No previous spine surgery and not currently a candidate for surgery.
- Must not have received SMT for LBP in the last month.
- Must not take other pain medication than paracetamol, non-steroid anti-inflammatory drugs, or opioids. However, opioids were limited to 40 mg of morphine or equivalent (oral intake).
- No competing diagnoses which could i) confound the diagnosis of non-specific LBP, e.g., osteoporosis or cancer, ii) interfere with the allocated treatment, or iii) interfere with the experimental testing.

Exclusion criteria

- Not completing the allocated intervention (minimum 75% of scheduled treatments).
- Receive other manual treatment to the lower back than that administered as part of the study.
- Deviate from the agreed-upon medication at baseline within the treatment period.

Study protocol

The study consisted of three visits to the Experimental Pain Laboratory at the Spine Center. We present an overview of the protocol below and further detail each point in the *data collection and variables of interest* section.

Baseline lab session This session consisted of the following: i) completion of the patient-reported outcomes, ii) marking of the spinal vertebrae, iii) experimental testing (VT and QST), and iv) vertebral randomization.

The initial SMT session The first treatment session followed immediately after the baseline lab session. Afterward, we repeated the VT procedure.

SMT sessions two to four Three additional SMT sessions were completed over the subsequent 14 days. The sessions were identical to the initial SMT session.

The post-SMT lab session Immediately following the fourth and final SMT session, the participants repeated the items performed in the baseline lab session i-iii.

The follow-up lab session The procedures i-iii were repeated 14 days after the post-SMT lab sessions.

Data collection and variables of interest

Marking of the spinal vertebrae

Using a permanent marker, we marked each vertebra by locating the spinous process from S1 to T12 using ultrasonography (Sonosite Titan Linear, L38 probe) (55). The participants were instructed not to wash off skin markings during the study period. If needed, we repeated the procedure at each lab session.

Patient-reported outcomes

Low back pain intensity

One measure was the intensity of the LBP. Here, we used the Low Back Pain Rating Scale. Three 11-point numerical rating scales (NRS) quantified the current, worst, and average LBP over the last 14 days, and these scores were combined into a single average score. This scale is often used in LBP research and is reliable for assessing LBP intensity (56).

Disability

We also measured the participants' daily functional limitation/disability using the Oswestry Disability Index (ODI) version 2.1 (57). The ODI is a10-item questionnaire with a five-point Likert rating scale, ranging from no disability to high disability. The items were combined and converted into percentages [0-100%]. This outcome measure has been translated into Danish and is responsive to clinical changes (58). One measure concerning sexual activity was elective, and if not answered, the score was simply calculated from the nine remaining items instead.

Responder status

We dichotomized the participants' overall responder status employing both patient-reported variables (NRS and ODI) at three different responder thresholds: i) a 50% improvement in order to better be able to compare with similar literature (45,46), ii) a 30% improvement as consensus recommended (59), and iii) a 0% improvement indicating the absolute dichotomization between deterioration and improvement. Each responder dichotomization was performed at follow-up.

We also obtained the following from the SpineData clinical registry (60): age, sex, LBP duration [months], and patient-reported leg pain intensity, similar to the NRS. We calculated the participant's psychological affection/profile using a brief screening questionnaire assessing anxiety, depression, social isolation, catastrophization, and kinesiophobia. This eight-item score was normalized and averaged as a single score. This averaged score ranged from 0 (low degree) to 8 (high degree). The concurrent validity for these brief screening questions is acceptable (61). We also examined the participants' expectations for pain relief,

as suggested in the literature (62), and the participants were potentially not naive to SMT. We used a Likert-scale scoring system anchored with 0 (strongly disagree to experience pain relief) to 5 (strongly agree to experience pain relief).

Experimental outcomes

We used a total of eight different tests (two biomechanical and six neurophysiological) to examine within-changes following SMT (Fig. 1). The biomechanical measures both focused on vertebral biomechanics using the VT. The neurophysiological tests all focused on pain hypersensitivity estimated by utilizing QST, covering multiple domains (regional, widespread, and centrally modulated) and by estimating both pain thresholds, tolerance, summation, and conditioned modulation. The total lab procedure took approximately 45 minutes to complete.

Table 1 An overview of the experimental measures

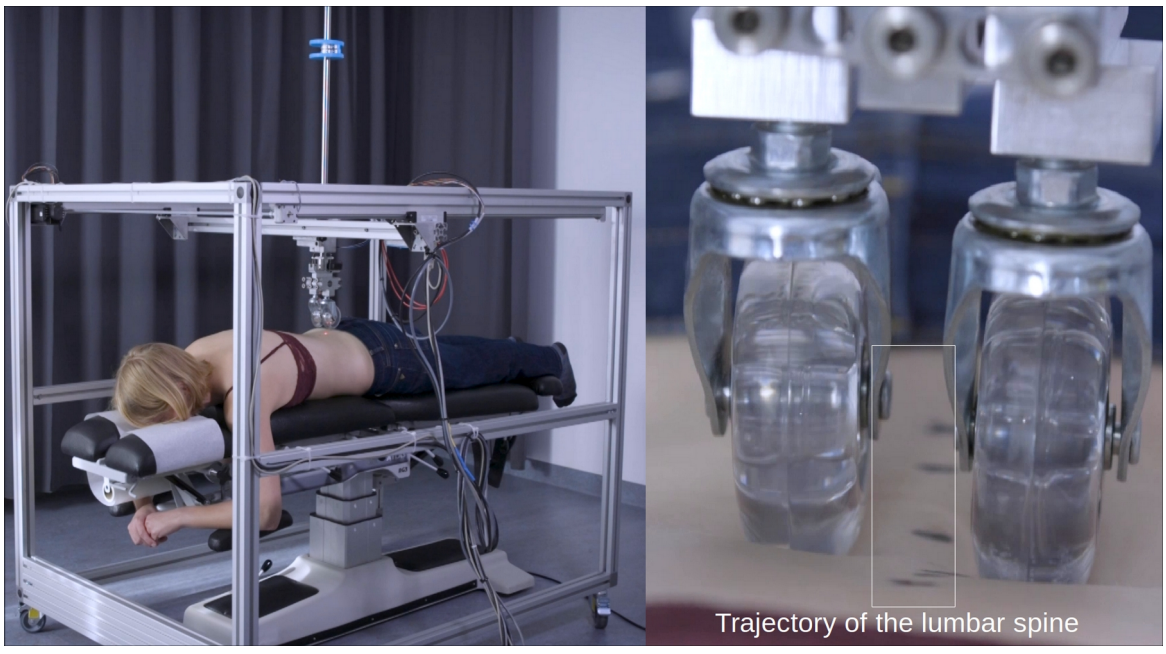
Parameter	Domain	Method	Outcome
Global stiffness	Regional	VerteTrack	Biomechanical
Terminal stiffness	Regional	VerteTrack	Biomechanical
Pressure pain detection threshold	Regional	Pressure algometer	Neurophysiological
Heat pain detection threshold	Regional	Thermode	Neurophysiological
Pressure pain detection threshold	Widespread	Cuff algometry	Neurophysiological
Pressure pain tolerance threshold	Widespread	Cuff algometry	Neurophysiological
Temporal summation	Centrally modulated	Cuff algometry	Neurophysiological
Conditioned pain modulation	Centrally modulated	Cuff algometry	Neurophysiological

A video illustrating some of the experimental measures can be found here: *http://smerteforskning.dk*

Vertebral biomechanics

We measured spinal vertebral stiffness as an indicator for the vertebral biomechanics using the VerteTrack (VT) (Fig. 2). The VT is an updated custom-made automated mechanical rolling indentation device. It functions by slowly rolling a weighted indenter on top of two wheels three cm apart along the lumbar spine at the paravertebral area, centered over the spinous process. The process began with 0N of added load and was repeated in discrete incremental increases of 10N up to 60N, resulting in repeated vertical spinal displacement trajectories for given loads. The vertebral markings defined the trajectory from S1 *landing spot* to T12 *lifting spot*. The displacement is measured continuously by a string potentiometer (TE Connectivity, USA). Thus, spinal tissues can be determined by the applied load over the total displacement (N/mm) along the lumbar spine's full length, indicating stiffness for each vertebra.

Figure 2 The VerteTrack and the trajectory of the lumbar spine



During VT testing, the participant remained in a prone position. Before indentation, we instructed the participant to inhale and exhale, then hold their breath around the residual air volume while completely relaxing the abdominal and back muscles until indentation was complete ~ 8 seconds. The procedure was repeated with added loads until pain or discomfort was perceived. If so, we repeated the load, and if pain or discomfort continued, we concluded the test. The analysis only included pain-free trials.

Afterward, we loaded each available trajectory (0-60N) into a custom-made LabView analysis program (version 15.0f3 for windows 10, National Instruments, USA). The data were graphically smoothed using a polynomial function and inspected subjectively for erroneous measures, e.g., muscle guarding, breathing, or other factors affecting the trial. See Appendix A1. Finally, data on each vertebra (L1 to L5) were extracted to a spreadsheet (LibreOffice, vers. 6.1 for Ubuntu 18.04). The *landing* and *lifting* spots were not included in the analysis.

While the VT has previously been examined as safe and reliable in healthy volunteers (63,64), no study has examined its validity in a persistent pain population. However, the data suggest that the device has similar measure capabilities as the previous single indentation device (65). Hence, suggesting that the VT can be used comfortably to evaluate the objective. This is further supported by a recent study examining the bench-top performance (66), which indicates that the VT is accurate in vivo both for rolling and single indentation.

Global stiffness (GS) was calculated as the force-displacement slope from the second load to the second-highest load (N/mm) for each vertebra (L1-L5), indicating a global stiffness score across multiple indentations while removing the terminal points, e.g., 0N and 60N. A higher score indicates higher vertebral stiffness.

Terminal stiffness (TeS) was calculated as the ratio between the highest load to maximum displacement (N/mm) for each vertebra (L1-L5), indicating a terminal stiffness score using the highest available load. A higher score indicates higher vertebral stiffness.

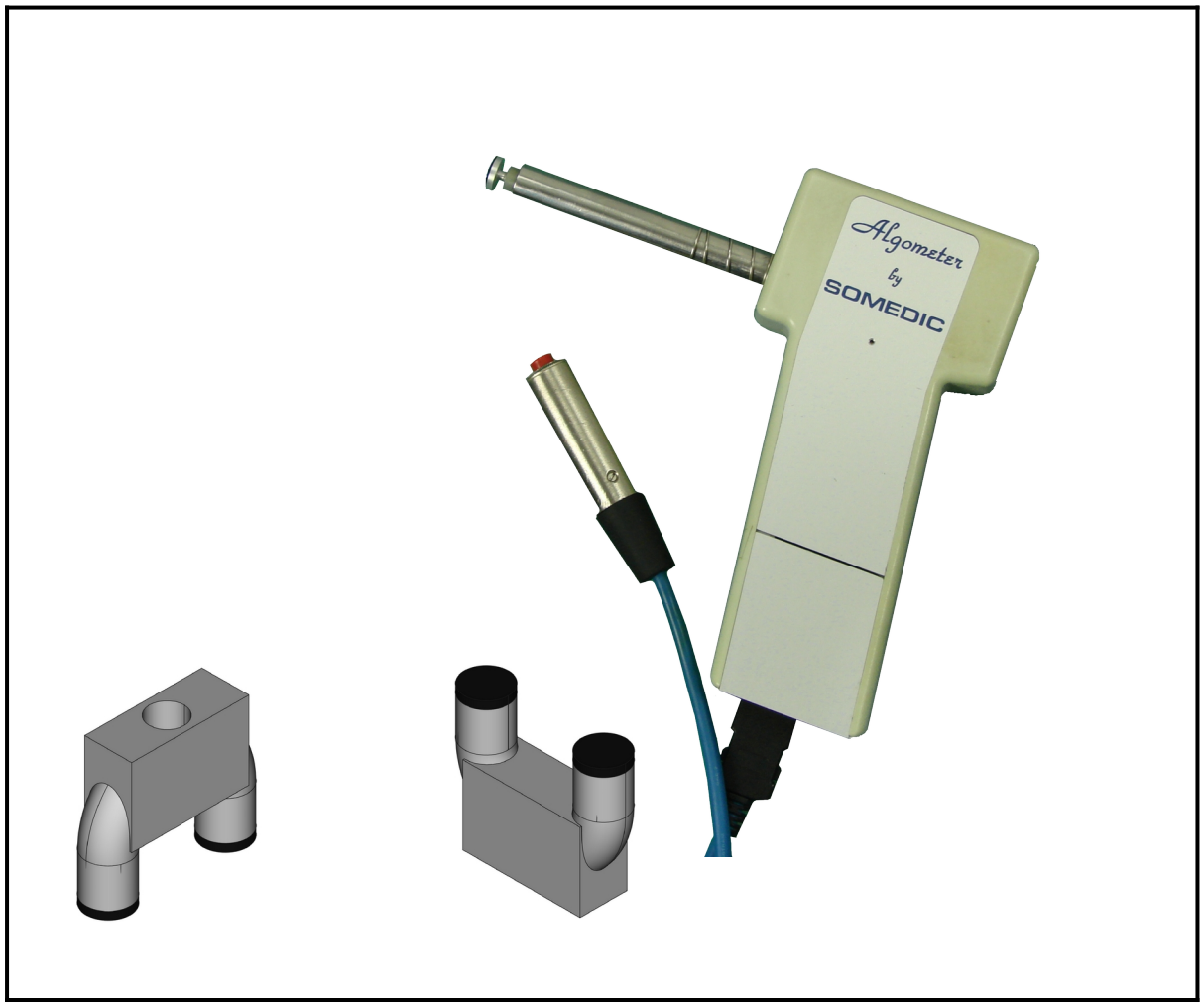
In some cases, both stiffness scores were applied per vertebra and, in other cases, summarized and averaged into a single score for each participant. In both instances, the data set was filtered to ensure Tidy format (67).

Quantitative sensory pain testing

Pressure algometry

We used pressure algometry (Model II, Somedic, Sweden) to assess deep mechanical pain sensitivity regionally at the lumbar spine (Fig. 3). Pressure algometry is a classic technique used in various research domains (68). Thus, the evidence when investigating deep muscle pain sensitivity in this field is strong (69–71). The pressure algometer is also a standard tool in SMT research to examine changes following treatment (50–53).

Figure 3 Pressure algometer and a sketch of the double-headed probe



For the procedure to i) mimic clinical practice, ii) be comparable to the VT findings, and iii) eliminate noxious attempts by stabilizing the head of the algometer on a spinous process, we attached a custom-made a 3D printed double-headed contact probe (2 × 1 cm², three cm

apart) to the algometer head, which allowed bilateral pressure into the paravertebral on each side of the spinous process. With the patient in a prone and relaxed position, the double-headed probe was manually applied perpendicular to the skin, and the pressure increased by an approximating nominal rate of 50 kPa/s.

Pressure pain threshold (PPT) was recorded as the point at which the pressure was perceived as painful, indicated by an indicator button. Each vertebra was measured three times in a predetermined randomized order with approximately 10 s rest intervals. If no pain was elicited by 1000 kPa, this was marked as the PPT. If the first two tests were 1000 kPa, a third would not be performed. Before initiating the trial, a test procedure of one to two PPTs was completed on the lower extremity and T12 to familiarize the patient with the upcoming procedure. A lower score indicates higher pain sensitivity or lower pain threshold.

For the analysis, the three trials were averaged as a mean score for each vertebra. For some analyses, each vertebral PPT was summarized and averaged into a single score for each participant.

Heat Thermode

We used a handheld thermode (TSA-II, Medoc, Israel) with a single 3 x 3 cm probe to assess superficial thermal pain sensitivity (Fig. 4).

Figure 4 An illustration of the Thermode

The probe was placed in the midline of the lumbar spine centered at the spinous process. During testing, the temperature increased from a pre-set fixed baseline temperature of 32 degrees Celsius (°C) to a maximum of 50 degrees °C, at an increase of 1 degree °C/s.

While not validated as rigorously as the pressure algometry, the thermode is still a standard procedure used to assess superficial pain sensitivity and could adequately be applied to this cohort (72,73).

Heat pain threshold (HPT) was recorded at the temperature perceived as painful, indicated by an indicator button. Each vertebra was measured three times in a predetermined randomized order with 10 s rest intervals. If no pain was elicited by 50 °C, this was marked as the HPT. If the first two tests were 50 °C, a third would not be performed. Before initiating the trial, a test procedure of one to two HPTs was completed on the lower extremity and T12 to familiarize the patient with the upcoming procedure. A lower score indicates higher pain sensitivity or lower pain threshold.

For the analysis, the three trials were averaged as a mean score for each vertebra. For some analyses, each vertebral HPT was summarized and averaged into a single score for each participant.

Computer-controlled cuff algometry

We used a computer-controlled cuff algometer (CccA) (CPAR, NociTech, Denmark) (Fig. 5) to assess widespread pain and centrally modulated pain. The CccA employed two 13-cm wide silicone tourniquet cuffs (VBM, Germany), each with an equal-sized proximal and distal chamber wrapped around both gastrocnemius muscles five cm inferior to the tibial tuberosity. This provided the possibility of assessing pain intensity by increasing the cuff's inflation as a stimulus-response curve. The dominant leg was predetermined as the experimental test site. The pressure within the cuffs could increase with 1 kPa/s in both chambers. The pressure limit was 100 kPa. Before initiating the test, we instructed the participants in using a controller with an incorporated computerized electronic visual analog scale (eVAS), which indicated "no pain" = 0 cm, and "worst pain imaginable" = 10 cm. The pressure stopped automatically when the CccA reached 100 kPa or if the participant pressed the indicator button, also located on the controller. Thus, the participant did not have to score

the pain as the “worst pain imaginable” for the pressure to cease. The CccA is also an innovative mechanism. However, a study has validated it to measure centrally modulated pain sensitivity and deemed it reliable to assess changes (74).

Figure 5 An illustration of the Computer-controlled cuff algometer

Widespread pressure pain threshold (wPPT) was noted at the pressure where the participant perceived it as painful, indicated by moving the eVAS beyond 0 (“no pain”).

Widespread pressure pain tolerance (wPTT) was noted at the pressure of termination, i.e., when the pressure could no longer be tolerated in the given moment. This was indicated by pressing the indicator button on the controller. If the cuff pressure was tolerated at the 100 kPa limit, this was recorded as the wPTT.

Both wPPT and WPTT were measured on the dominant and non-dominant leg.

Temporal summation (TS) was assessed by applying a series of 10 pulses of equal pressure corresponding to the individual’s wPTT at a rate of 1 Hz (i.e., 1 s of inflation to the target

pressure and 1 s of deflation). Temporal summation was calculated as the average pressure pain intensity (eVAS score) of the first three stimuli subtracted from the average of the last three stimuli. A higher score indicates higher pain sensitivity.

Conditioned pain modulation (CPM) was assessed as the final test. We repeated the dominant leg's wPPT procedure, with a continuous conditioning stimulus applied to the non-dominant leg, corresponding to 70% of the wPPT for the non-dominant leg. Conditioned pain modulation was recorded as the difference in wPPT before and during this continuous pressure stimulus applied to the non-dominant leg. A lower score indicates higher pain sensitivity.

Vertebral randomization procedure

To conduct the vertebral randomization, we used the i) VT's maximal force-displacement value (FD) at the maximally applied load as an indicator of vertebral stiffness, and ii) the mean value of the three PPT measurements as an indicator of vertebral pain sensitivity. We chose these two measures to mimic a clinical examination, i.e., what a therapist would palpate, as i) absolute joint stiffness in the posterior to anterior plane, and ii) pressure pain threshold as the reaction to a continuous tension.

We performed a pilot study on 20 participants with persistent non-specific LBP, and the value of these two parameters overlapped in 25% of the instances. Hence, identifying the *most stiff* and *most sensitive* vertebra was systematized using a ratio that enumerated all vertebrae between − 1 and + 1 (Eq. 1). Here, − 1 indicated the vertebra as characterized by the stiffest and the least pain sensitive. In contrast, + 1 indicated the vertebra as most pain sensitive and least stiff. We conducted this ratio using the following algorithm:

Equation 1

$$Vertebra_{\Delta normalized} = \frac{Vertebra_{FD} - Min_{FD}}{Max_{FD} - Min_{FD}} - \frac{Vertebra_{PPT} - Min_{PPT}}{Max_{PPT} - Min_{PPT}}$$

We assigned the absolute lowest (− 1) and highest (+ 1) ratio score to the stiffest and the most pain-sensitive vertebra, respectively. However, if the resulting vertebrae were adjacent, we scrutinized the remaining ratio scores to search for a ratio that differed by a score of less

than 0.1 compared to the original ratio of the absolute *most stiff* or *most sensitive* vertebra. If we found such a vertebra, that vertebra was used for the allocation instead.

Blinding

We constructed a computer-generated list that signed each ID with an "A" (indicating the stiff group) or "B" (indicating the pain group) in a 1:1 order. In this fashion, we provided each participant with an a-priori assignment of the group allocation. The assessor (CGN) identified two specific spinal vertebrae (L1-L5) after the baseline testing as "A" or "B". Thus, the assessor was aware of how vertebrae "A" and "B" were defined but simultaneously blinded to the randomization list. Conversely, the chiropractor was blinded to the "A"/"B" definition but used the randomization list to determine what spinal vertebra to treat. Finally, we assumed that the participants were blinded to both.

Spinal manipulative therapy

The SMT was delivered as a side-lying grade V mobilization using a high-velocity, low-amplitude thrust provided in a standardized manner (31). All thrusts targeted the randomized vertebra in a posterior to anterior direction using the spinous process as the contact point. We used prior evidence to optimize vertebral movement (43,75–78). Noticeably, all the available evidence was conducted on animals.

The method allowed up to 3 attempts for a successful SMT treatment. The chiropractor who performed the SMT determined if the treatment was successful subjectively and independent of the traditional joint cavitation sound typically accompanying SMT (79). The chiropractor also recorded adverse effects for each SMT session, and the assessor again recorded this at the final follow-up. Two chiropractors were responsible for the SMT, each with more than 12 years of clinical experience.

Statistical analysis

Data were examined and analyzed using R v. 4.0 with R-studio v. 1.3 for Linux (Ubuntu 20.04) (80). Data wrangling and visualization were completed using the Tidyverse package (81).

Sample size

We decided, a-priori, that patient-reported LBP intensity was our primary objective. As the two treatment arms entirely differed on the vertebra targeted, we expected a small between-group effect size (~10% difference in NRS [0 to 10]), with an alpha level set at 5% and a beta level at 80%. Sixty-two participants per treatment arm were needed.

Descriptive data

We reported descriptive data as means and standard deviations for normally distributed data, medians, interquartile ranges for non-normal distributed data, or count and frequency for categorical data. The cumulative proportion of responders is presented graphically for both NRS and ODI at 30% improvement. Normal distribution for each measure was visualized using density plots, QQ-plots, and was tested with the Shapiro-Wilks test when in doubt. Visual inspection for skewness and data shape was further conducted (82).

Shifted lumbar trajectories

Despite employing ultrasound to locate each vertebra (S1 to T12), we had to replicate this process at three different time points. Therefore, we performed a visual inspection of how well the trajectories at different time points overlapped with the baseline trajectory. For example, at baseline, we recorded the *landing site* as S1. However, at post-SMT, the *landing site* was shifted or moved cranially and was now recorded as L5, indicating that what we estimated to be L5 at post-SMT is actually S1 at baseline. We can translate these errors directly to the reproducibility of both PPT and HPT scores. If the visual inspection categorized the trajectories as incomparable to the baseline trajectory, we omitted the subsequent data points.

Baseline analysis

Correlation between the regional measures

We conducted a correlation analysis between the regional measures at baseline by utilizing Pearson's product-moment correlation (ρ) for normally distributed data and Spearman's rank correlation (R_s) for non-normally distributed data. If data points were not available for both the parameters in question, these were omitted. We evaluated the strength of the correlations

as poor (< 0.30), moderate (0.31 ≤ 0.50), good (0.51 ≤ 0.70) and strong (> 0.70) (83). This analysis was repeated for the summarized data and each vertebra. Correlations are presented as chi^2 scores and corresponding p-values.

Difference between vertebrae

Vertebral data are illustrated as means and 95% confidence intervals. We tested the vertebral association between the different measures using a one-way analysis of variance (ANOVA) with the vertebra as the independent variable. We tested the assumptions for i) normality by plotting the residuals versus the predicted values and ii) homogeneity of variances using Levene's test (84). The results are presented as F-scores, degrees of freedom residuals, and p-values. Further post-hoc testing was completed using Tukey multiple pairwise-comparisons (85) to investigate differences between vertebral levels.

Latent class analysis

We used a data-driven latent class analysis approach to cluster the participants with complete data sets into different pain hypersensitivity subgroups using QST variables (PPT, HPT, wPPT, wPTT, TS, and CPM). Sixty-four participants were needed for the analysis as 2^k participants had been suggested as sufficient; *k* denotes the number of variables included in the model, i.e., six in our setting (86). We calculated correlation coefficients to determine the independence of the QST variables. A-priori, we decided that if two variables were correlated with a coefficient >0.7, one of the variables would be omitted (87). The six variables were quantified using different continuous scales and limits. Hence, we Z-transformed (mean-centered and normalized to one standard deviation) each variable, and for ease, we reversed the TS score (opposite meaning than the remaining QST variables). We fitted the clustering models using the *Mclust* package for R (88). In addition to the number of component clusters, we also evaluated different covariance structures. This allowed us to make the model as parsimonious as possible. We investigated two to six component clusters corresponding to the number of variables. We scored the number of component clusters in the models using two approaches: i) the Bayesian Information Criterion (BIC) (89), and ii) a Bootstrap Likelihood Ratio Test comparing model fit between different numbers of component clusters (90). We presented the component clusters for the final fitted model as scaled means by QST variable for each participant.

After dividing the participants into different clusters depending on their pain sensitivity, we compared them, post-hoc, using non-parametric rank testing. These are presented as within-group means, standard deviations and whether the between-group means are statistically different, when scored by p-values (adjusted using the Benjamini-Hochberg method (91)). Finally, we wanted to describe the stability of the QST scores in groups at different time points. We applied the baseline fitted model cross-sectionally to post-SMT and the follow-up. The resulting stability is illustrated as a horizontal process flowchart.

Repeated outcome measures

We examined changes across the different time points using linear mixed models. In the different analyses, we considered the participant as the random intercept using an unstructured variance-covariance structure. Different aspects were handled as fixed effects and dependent variables (see below). Despite being a robust statistical approach, we tested model assumptions for normal distribution by plotting the residuals error in QQ-plots. The homogeneity of variance was tested by visually inspecting the residuals versus the predicted values. The different repeated outcomes are presented as within-group changes in mean values (visually) and between-group differences of mean values (tabulated), with 95% confidence intervals and p-values. We fitted the linear mixed models using the *lme4* package for R (92).

Target site The dependent variable differed across the different patient-reported and experimental outcomes. Target site and time were used as interacting fixed-effects.

Responder status Here, we applied a three-way mixed model. The dependent variable differed across all the different experimental outcomes. Target site, time, and responder status (0%, 30%, or 50%) were used as interacting fixed effects.

Pain hypersensitivity The dependent variable differed across the different patient-reported and experimental outcomes. The participants' hypersensitivity statuses were fitted using latent class analysis, and time was used as interacting fixed-effects in all instances. However, for the regional measures (GS, TeS, PPT, and HPT), a three-way approach was used (cluster:time:target site).

Target site by vertebra Finally, for the regional experimental measures (GS, TeS, PPT, and HPT), we characterized each participants vertebra as either i) the specific SMT targeted vertebra (e.g., L2), ii) the adjacent vertebra(e) (e.g., L1 and L3), and iii) remote vertebra(e) (e.g., L4 and L5). This vertebral categorization was added as an interaction term to the original two-way models for the experimental outcomes (time:target site).

Statistical significance was tested as differences of means, i.e., changes over time, e.g., baseline to post-SMT instead of between-group comparisons at a single time point, e.g., at post-SMT. Unless stated otherwise, we applied a p-value of < 0.05 as statistically significant. The p-values were obtained using the *multcomp* package and calculated using Wald statistics. We adjusted for multiple comparisons by the single-step method (93).

Systematic review

Design and setting

We performed a systematic review to answer **objective II**. Submitted and under review at *the international prospective register of systematic reviews* on November 16th, 2020 (94).

Inclusion criteria and study selection

We systematically searched four electronic databases (PubMed, Embase, Index to chiropractic literature, and CINAHL) from the point of origin to September 15th, 2020. See Appendix A2 for the search string. We searched for trials conducted on humans with spinal pain in any region. If the study compared targeted SMT to SMT applied at a comparator target using a randomized design, we included the study. We excluded studies that looked at mobilization (Maitland grade I - IV (95)) or studies providing additional treatment to a subset of the SMT groups. The SMT had to be provided in either a clinical or lab setting by a health practitioner. An assisted or automated procedure could also be used. The search was not restricted by language.

We used Covidence (96) for managing the review process. Two investigators (CGN and AD) independently reviewed the titles and abstracts, and agreed upon which to include. Afterward, we reviewed the full texts. If we could not reach an agreement on a study. A third investigator arbitrated the design (CLY). Data extraction was completed using a pre-set

template by two investigators (CGN and SON). Again, agreement had to be reached. We extracted between-group differences for any reported outcome at any time point. If the study only reported within-group changes, we would calculate a between-group effect size from the pooled standard deviations and means (97).

Risk of bias

Two investigators independently assessed for risks of bias using the *Cochrane Risk of Bias tool* (RoB) (98). This tool assesses the studies for *Selection bias* (Sequence generation, allocation concealment), *performance bias* (blinding of participants and personnel), *detection bias* (blinding of outcome assessors), *attrition bias* (incomplete outcome data), *reporting bias* (selective outcome reporting), and *other sources of bias*. However, we had to modify the last point to fit our objective. We extended this into i) an undefined risk of bias, ii) the participants' naivety to SMT, and iii) a thorough description of the SMT. If consensus could not be reached, a third investigator arbitrated the decision (SON). To assess the target site study conducted by most of the research group (Manuscript I), we had an external academic (DSZ) who assessed the study independently and compared the results with AD.

Data Synthesis

We could not pool the results to conduct a meta-analysis. Hence, the reporting follows the *Synthesis without meta-analysis in systematic reporting guideline* (SWiM) (99). The extracted between-group data were tabulated and reported in a narrative form. We subgrouped each study by targets: i) different targets within the same vertebra, ii) different targets within the same region, iii) specific versus generalized thrust, and iv) different regions. We summarized the data by counting reported statistically significant results and results favoring the intervention target.

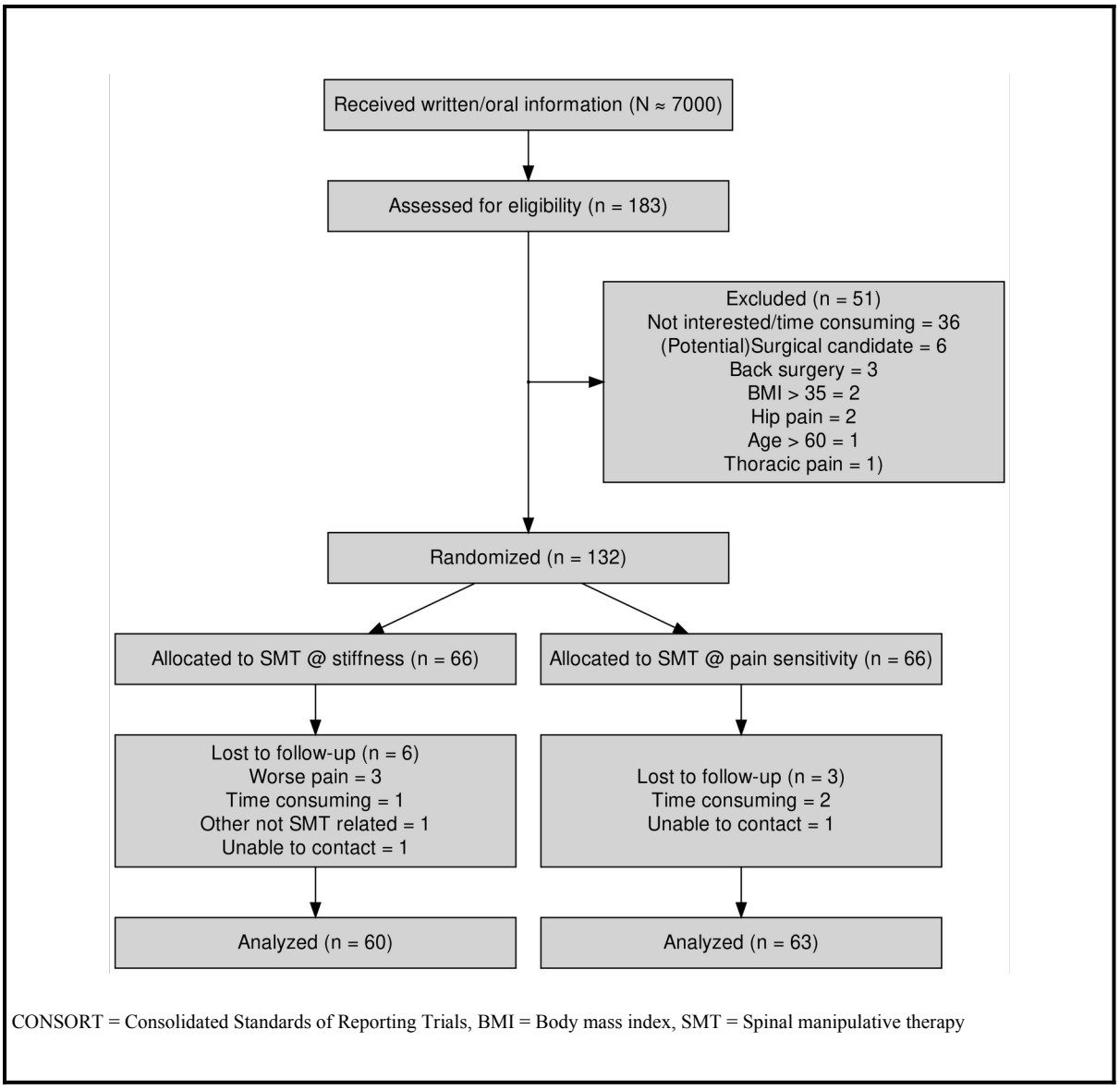
Results

Descriptive statistics

Participants

We recruited 132 participants; seven did not complete the SMT intervention, and two were unreachable for follow-up. We did not exclude any participants based on the exclusion criteria. Thus, the final sample consisted of 123 participants; see Figure 6 for a flowchart.

Figure 6 CONSORT Flowchart for the randomized trial



CONSORT = Consolidated Standards of Reporting Trials, BMI = Body mass index, SMT = Spinal manipulative therapy

One-hundred-and-nine participants were included directly from the clinic, and 23 called in themselves before their scheduled appointment. Descriptive statistics are presented in Table 2. The two groups, each with 66 participants, were equal across multiple patient-reported outcomes.

At baseline (n=132), there were some missing data for the experimental measures. One participant had faulty GS/TeS data, three had missing HPT data, and one had missing data for the CccA. However, all had complete PPT data; 127 participants remained with complete baseline experimental measures.

Table 2 Baseline Characteristics for participants included in the randomized trial

Parameter	Pain group n = 66	Stiff group n = 66
Patient-reported LBP intensity, mean(sd)	5.6(1.8)	5.6(1.9)
Disability, mean(sd)	27.4(11.5)	28.2(11.9)
Age, mean(sd)	46.7(8.7)	43.5(10.5)
Sex, Male(%)	40(61)	32(48)
LBP Duration [months], median(IQR)	14(67)	18(49)
Subjective leg pain, mean(sd)	4.3(2.7)	3.9(2.8)
Psychological profile, mean(sd)	3.9(1.9)	4.2(1.5)
Expectation for pain relief, Agree(%)	26(39)	32(48)

Patient-reported baseline characteristics for participants with persistent low back pain. Presented as arithmetic mean (standard deviation), median [interquartile range] or categorical

Spinal manipulative therapy

Of the 123 who completed the trial, 117 completed all four SMT sessions, while the remaining six completed three. The average duration from the baseline to post-SMT was 13 days (SD = 6), and follow-up occurred 14 days (SD = 6) post-SMT. The chiropractor reported joint cavitation in 89% of the sessions, yet 98% resulted in a successful treatment.

Mild side-effects were reported by the majority of the cohort across different time points (69%). The most common were local muscle pain (63%) and increased stiffness (33%). All events were momentary.

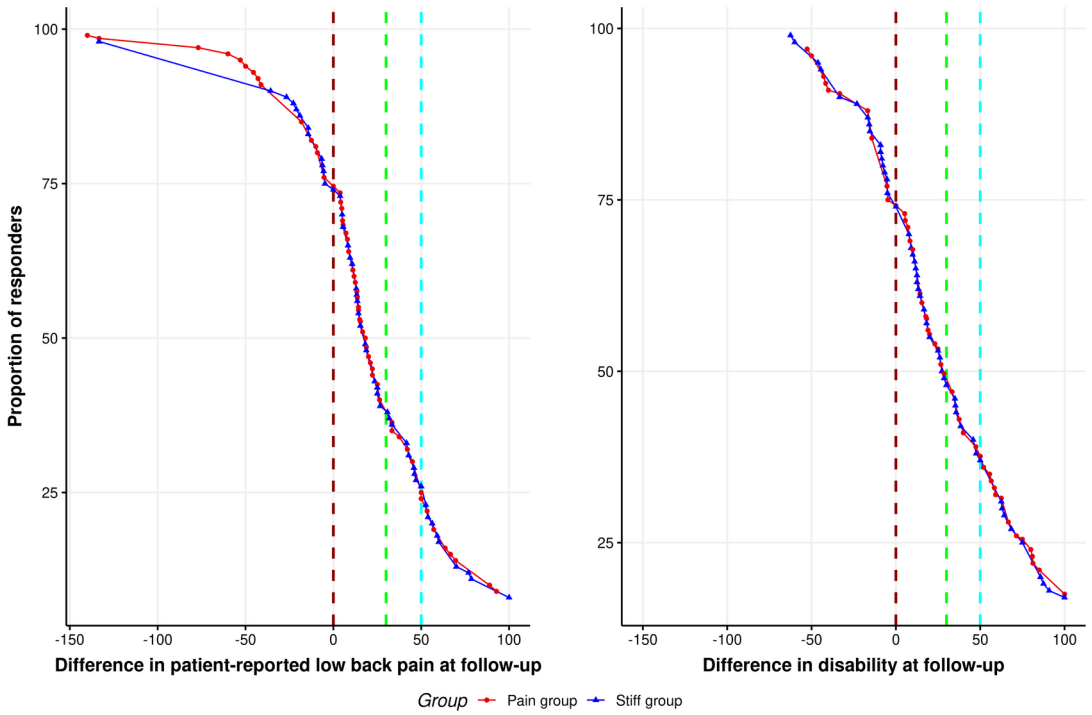
Responder status

Table 3 lists the distribution of responder status for the 123 participants. Figure 7 illustrates a cumulative proportion of responders graph for NRS and ODI responders at follow-up. The dashed vertical lines represent the investigated responder thresholds. It appears that the two groups respond similarly. Also, noticeably, 29 (24%) participants reported overall worsening in LBP pain intensity, and in accordance, 28 (23%) participants reported higher disability scores at follow-up.

Table 3 Proportion of responders/non-responders for patient-reported outcomes at all responder cut points

Parameter	Status	≥0% improvement n(%)	≥30% improvement n(%)	≥50% improvement n(%)
Patient-reported low back pain intensity	Non-Responder	29(24)	88(72)	104(85)
	Responder	94(76)	35(28)	19(15)
Disability	Non-Responder	28(23)	77(63)	94(76)
	Responder	95(77)	46(37)	29(24)

Figure 7 Cumulative proportion of responders



Responder status is measured at follow-up as a 30% improvement in patient-reported outcomes.

Non-overlapping vertebral analysis

Due to non-overlapping vertebrae, we had to exclude 11.9% of the vertebral data measured at different time points. Thus, for GS, TeS, PPT, and HPT, the total sample size (each participant measured three times) was reduced by 44 data points. We assumed that the immediate measures of GS and TeS following the first SMT session were approximating the same trajectory as the same markings were employed. We present a future solution to this problem when relying on locating vertebrae on multiple occasions. This new method and its potential impact are presented in a post-hoc section at the end of the results section.

Baseline analysis

Correlation between regional measures

The regional measures were normally distributed except for PPT. However, none were visually skewed and presented with consistent data shapes. For the correlation analysis, we only present results for GS, as GS and TeS are strongly correlated ($\rho = 0.79$ with a p-value < 0.001). Table 4 lists the correlations for the averaged vertebral data (first row) and each vertebra. The correlations were positive, and all, except the correlation between GS and HPT at L2, were statistically significant. We found a moderate correlation between GS and PPT for all vertebrae ($\rho = 0.38$). However, a poor correlation was found for GS and HPT ($R_s \geq 0.23$). In contrast, PPT and HPT had a good correlation ($\rho = 0.58$).

Table 4 Correlation between the experimental measures

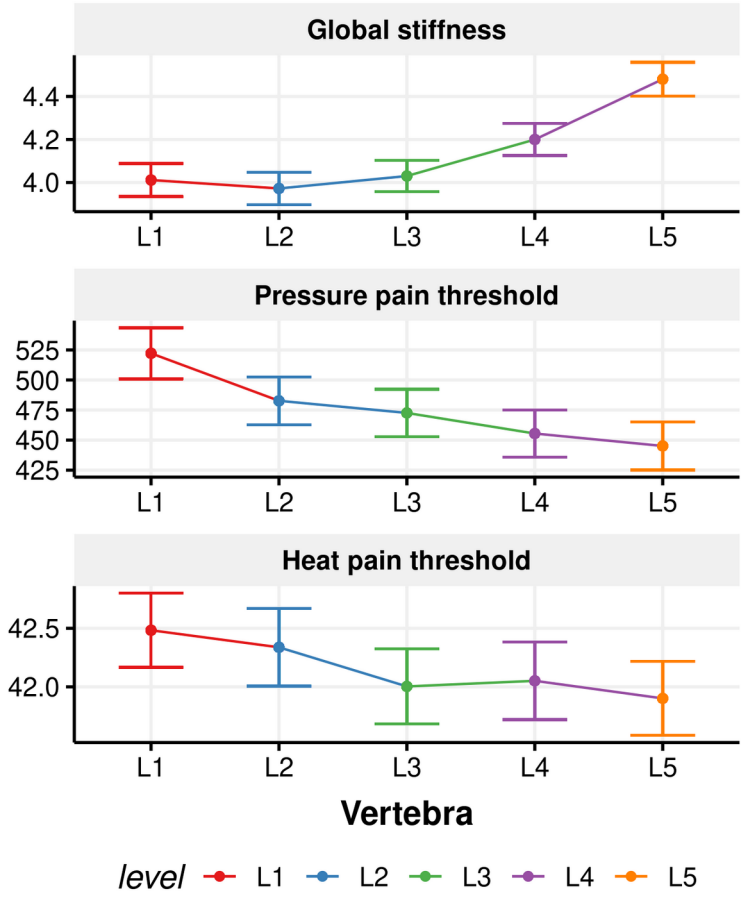
	Global stiffness vs Pressure pain threshold		**Pressure pain threshold vs Heat pain threshold**		**Global stiffness vs Heat pain threshold**	
Level	R_s	P-value	R_s	P-value	ρ	P-value
All	0.38	<0.01	0.58	<0.01	0.23	0.01
L1	0.36	<0.01	0.53	<0.01	0.19	0.03
L2	0.33	<0.01	0.55	<0.01	0.14	0.12
L3	0.34	<0.01	0.57	<0.01	0.21	0.02
L4	0.33	<0.01	0.56	<0.01	0.22	0.01
L5	0.38	<0.01	0.50	<0.01	0.28	<0.01

Correlation for each vertebra between global stiffness, pressure pain threshold, and heat pain threshold. Presented as chi² scores and p-values.
Rs = Spearman's rank correlation, ρ = Pearson's product-moment correlation

Difference between vertebrae

When examining Figure 8, a minor vertebral pattern appears, as the GS estimate increases caudally, while PPT and HPT decrease. The ANOVA's assumptions were upheld and revealed a statistically significant effect at the vertebral level for GS ($F_{4,650} = 7.7$, $p < 0.01$), whereas, we noticed no significant effect on PPT ($F_{4,655} = 2.2$, $p = 0.07$) or HPT ($F_{4,640} = 7.7$, $p = 0.68$). After post-hoc testing, GS indicated a statistically significant difference at L5 compared to L1, L2, and L3. However, PPT and HPT revealed no statistically significant vertebral pattern.

Figure 8 Vertebral distribution for the experimental measures



Arithmetic mean values for Global stiffness [N/mm], Pressure pain threshold [kPa], and Heat pain threshold [°C]. Error bars indicating 95% confidence intervals

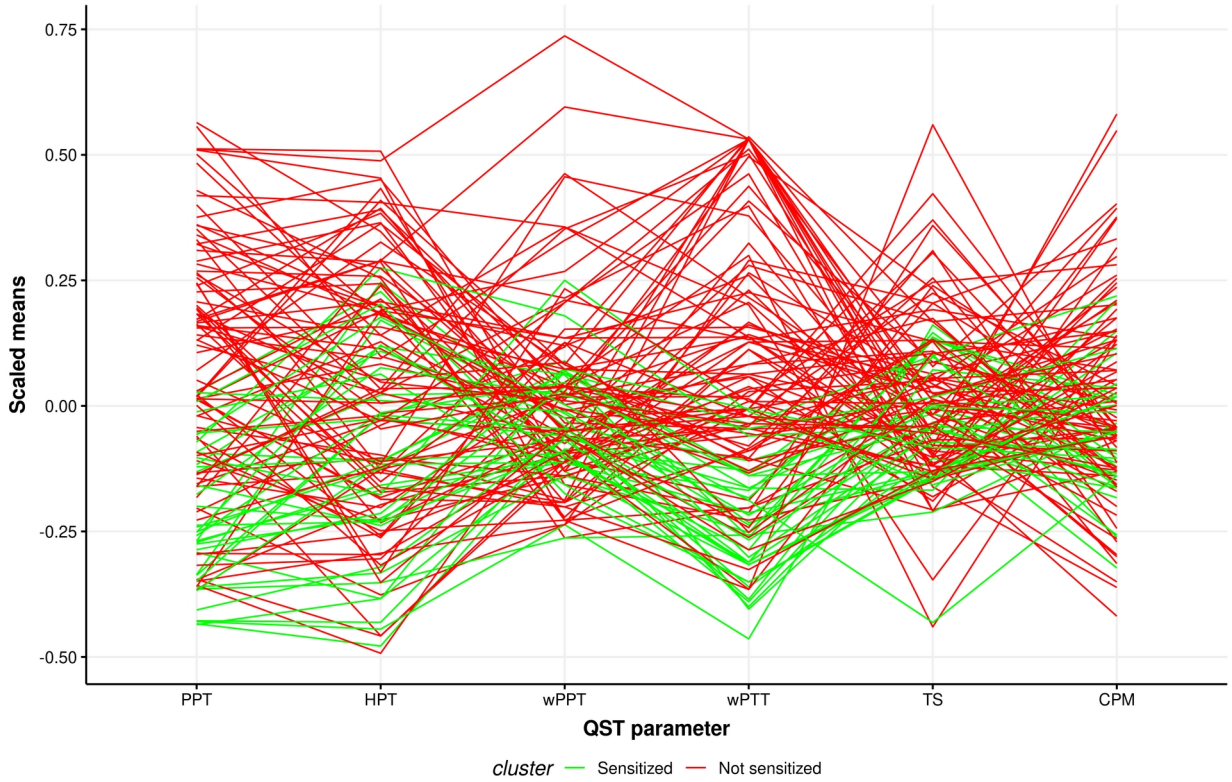
Latent class analysis

The a-priori correlation analysis did not find any strong correlation between the QST variables; see appendix A3. The final model consisted of two component clusters, with 38 and 89 participants assigned to each. See Figure 9 for an overview of the data distribution per QST variable per participant and Appendix A3 for model fitness. Based on the QST profile, we denoted each cluster as the *Sensitized* (showing a generalized hyperalgesic state) and *Not-sensitized* group, respectively.

Table 5 lists each QST parameter per group. The Sensitized group had statistically significantly lower PPT, HPT, wPTT, and CPM, indicating greater pain sensitivity than the Not-sensitized group. There was no between-group difference for TS and wPPT.

Figure 10 illustrates the baseline fitted latent class model's application to the other time points for the participants who had complete QST data at follow-up (n=105). A total of 73 were scored as Not-sensitized at baseline, and 32 were scored as Sensitized. At follow-up, the number of participants scored as Sensitized dropped to 19.

Figure 9 Scaled means for each quantitative sensory pain test by pain hypersensitivity group



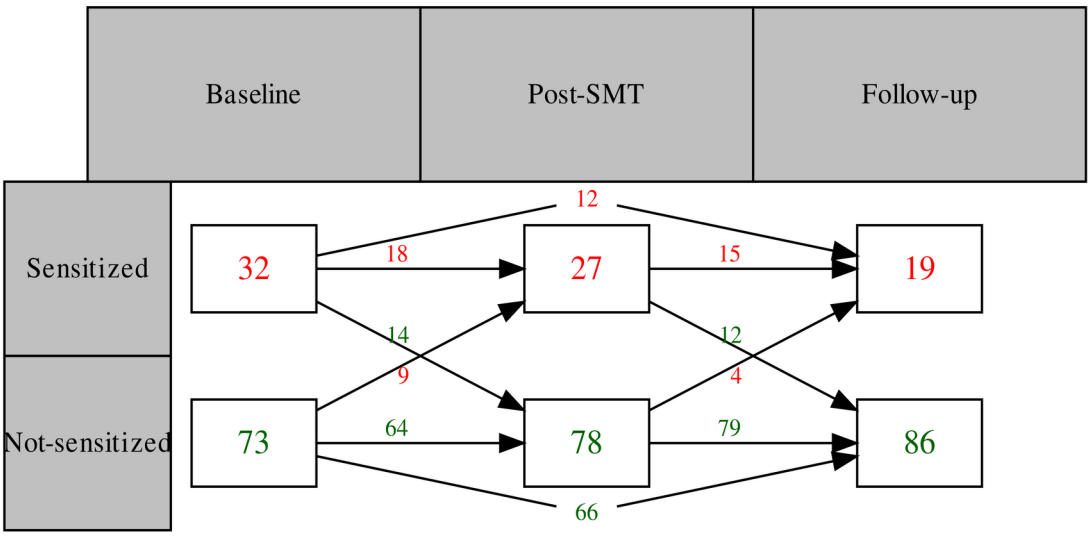
Z-scaled means [mean = 0, standard deviation = 1] , QST = Quantitative sensory pain test, PPT = Pressure pain threshold, HPT = Heat pain threshold, wPPT = Widespread pressure pain threshold, wPTT = Widespread pressure pain tolerance threshold, TS = Temporal summation, CPM = conditioned pain modulation

Table 5 Quantitative sensory test scores for the pain hypersensitive groups

Parameter	Sensitized	Not-sensitized	Adjusted P-value
Pressure pain threshold	289(116)	555(204)	<0.01
Heat pain threshold	40.8(3.0)	42.7(3.6)	<0.01
Widespread pressure pain threshold	13.4(4.7)	15.4(8.4)	0.42
Widespread pressure pain tolerance threshold	36.0(9.5)	62.5(19.5)	<0.01
Temporal summation	0.6(0.8)	1.0(1.0)	0.13
Conditioned pain modulation	2.6(5.4)	6.1(9.0)	<0.01

Arithmetic mean values and standard deviations. P-values are adjusted using the Benjamini-Hochberg method

Figure 10 Stability of the Latent class analysis



An overview of the stability pattern in the latent class analysis at the three time points following spinal manipulative therapy. The numbers above each arrow indicate the transition of participants over time. A red number indicates the transition to sensitized; a green number indicates transition to not-sensitized
SMT = Spinal manipulative therapy

Patient-reported outcomes

This section presents the results for the patient-reported outcomes (NRS and ODI) across different parameters. For each of the following models, the assumptions were upheld.

Target site

When examining changes in patient-reported LBP intensity dependent on the target site (stiffness or pain), there were statistically significant changes from baseline to post-SMT (Stiff = -0.6 [-1 to -0.2], Pain = -0.7 [-1.1 to -0.3]), and at follow-up (Stiff = -0.8 [-1.2 to -0.3], Pain = -0.7 [-1.1 to -0.2]). However, there were no statistically significant between-group differences at either time point. See Figure 11.

When examining changes in ODI, we again saw statistically significant changes from baseline to post-SMT (Stiff = -5 [-7.5 to -2.5], Pain = -5.4 [-7.8 to -2.9]), and at follow-up (Stiff = -5.2 [-7.6 to -2.7], Pain = -6.3 [-8.8 to -3.9]). Again, no statistically significant between-group differences were observed at either time point. See Figure 11.

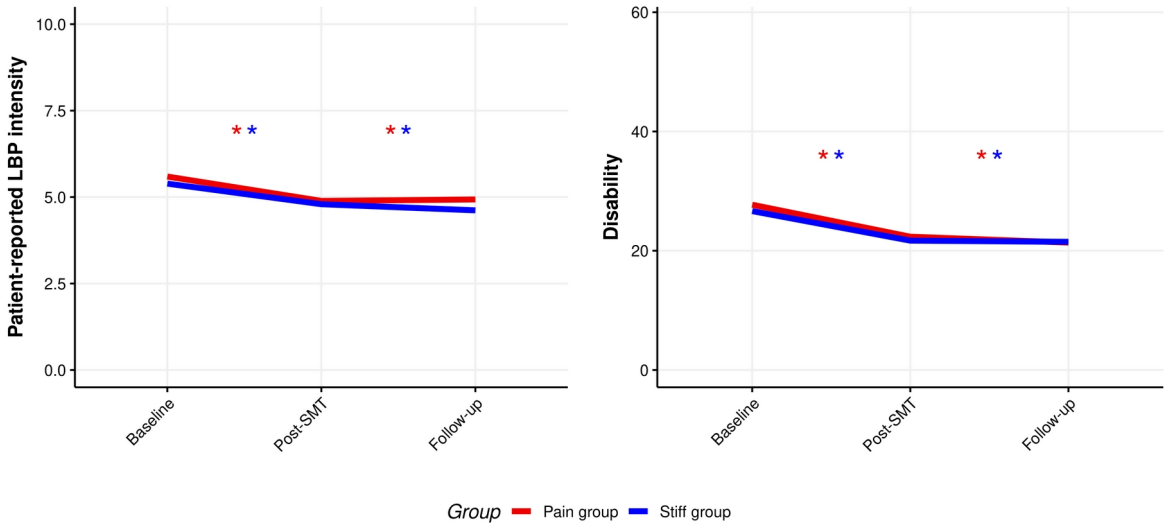
Post-hoc vertebra analysis

As the specific target site did not show any between-group differences, we examined post-hoc whether the vertebra to which SMT was applied was an inherent factor. We examined this by comparing the new models (presented below) with a simple model (one fixed effect (time)) using ANOVA. This process deduced whether adding an additional factor term was a better fit for the data.

Firstly, we examined whether the targeted vertebra was important, e.g., did participants treated at L5 improve at a higher rate than those treated at L1. However, this was not a significant term (NRS model - $Chi^2 = 8.2$, p-value = 0.8, ODI model - $Chi^2 = 16.5$, p-value = 0.2).

Secondly, we examined whether the distance between the absolute stiffest and the absolute most pain-sensitive vertebra was a significant factor, i.e., this parameter ranged from *0* if the vertebrae overlapped to *4* if the stiffest vertebra was L1 and most pain sensitive was L5. However, again, this was not statistically significant compared to the simple models (NRS model - $Chi^2 = 6.9$, p-value = 0.9, ODI model - $Chi^2 = 9.7$, p-value = 0.6).

Figure 11 Within-group changes and between-group differences in patient-reported outcomes (Target site)



Patient-reported LBP intensity		
Time point	**Mean difference (95 CI%)**	**P-value**
Baseline - Post-SMT	0.1(-0.5 to 0.7)	0.90
Baseline - Follow-up	-0.1(-0.7 to 0.5)	0.90
Disability		
Time point	**Mean difference (95 CI%)**	**P-value**
Baseline - Post-SMT	0.4(-3.1 to 3.9)	0.96
Baseline - Follow-up	1.2(-2.3 to 4.7)	0.69

Within-group changes (figure) and between-group differences (table) in patient-reported low back pain intensity and disability following four sessions of SMT at either the stiffest vertebra (stiff group) or the most pain-sensitive segment (pain group). Presented as arithmetic means, 95% confidence intervals and the corresponding p-value.
LBP = low back pain, SMT = Spinal manipulative therapy, * = p-value < 0.05

Finally, we conducted a subgroup analysis that only included the participants treated at the absolute stiffest or absolute most pain-sensitive vertebra. This procedure trimmed the sample down to 71 participants (204 data points). We compared this new subgrouped model to the original model using the coefficients from the interacting fixed effects, i.e., time:stiffgroup (pain group being the intercept).

For NRS, the original model presented the following between-group estimates (post-SMT: 0.11, p-value = 0.7. Follow-up: -0.11, p-value = 0.7) and the subgrouped model's coefficients were: (post-SMT: -0.20, p-value = 0.6. Follow-up: -0.22, p-value = 0.6).

For ODI, the original model presented the following between-group estimates (post-SMT: 0.40, p-value = 0.8. Follow-up: 1.19, p-value = 0.8) and the subgrouped model's between-group coefficients were: (post-SMT: 0.39, p-value = 0.9. Follow-up: -0.09, p-value ~ 1). Thus, the subgroup did not provide an important between-group difference for NRS or ODI compared to the original applied randomization.

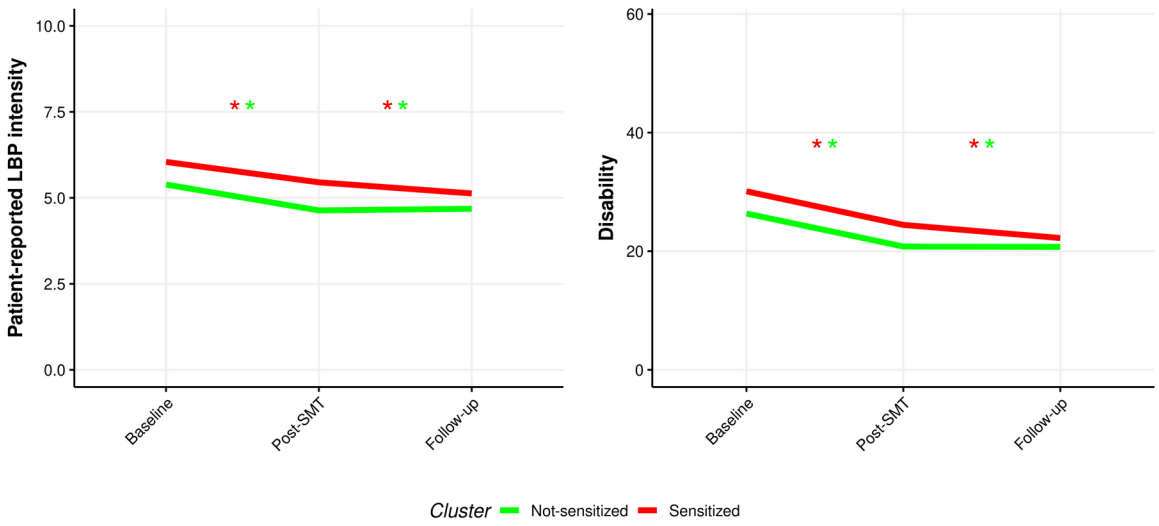
General hyperalgesia

As there were no statistically significant between-group differences for the target site, we omitted this fixed effect when examining whether applying our cluster-based solution to the data set provided additional insight.

For patient-reported LBP intensity, we again saw statistically significant within-group changes at both time points: at post-SMT, this was (Sensitized = -0.6 [-1.1 to -0.0], Not-sensitized = -0.8 [-1.1 to -0.4]), and at follow-up (Sensitized = -0.9 [-1.5 to -0.4], Not-sensitized = -0.7 [-1.1 to -0.3]).Also, at this parameter, the changes did not differ between groups. While the Sensitized group had a higher NRS score, at baseline, than the non-sensitized group, this was not statistically significant (-0.7 [-1.4 to 0.1], p-value = 0.01). See Figure 12.

The same findings emerged for disability at post-SMT corresponding to (Sensitized = -5.7 [-8.8 to -2.5], Not-sensitized = -5.6 [-7.6 to -3.5]), and at follow-up (Sensitized = -7.9 [-11 to -4.8], Not-sensitized = -5.6 [-7.7 to -3.5]). Also, at this parameter the changes did not differ between groups. As with NRS, the same findings emerged for the baseline differences (-3.7 [-8.3 to 0.8], p-value = 0.1). See Figure 12.

Figure 12 Within-group changes and between-group differences in patient-reported outcomes (Pain hypersensitivity)



Patient-reported LBP intensity		
Time point	**Mean difference (95 CI%)**	**P-value**
Baseline - Post-SMT	-0.2(-0.8 to 0.5)	0.84
Baseline - Follow-up	0.2(-0.4 to 0.9)	0.72
Disability		
Time point	**Mean difference (95 CI%)**	**P-value**
Baseline - Post-SMT	0.1(-3.7 to 3.9)	~1
Baseline - Follow-up	2.3(-1.5 to 6.0)	0.33

Within-group changes (figure) and between-group differences (table) for the not-sensitized group and sensitized group in patient-reported low back pain intensity and disability following four sessions of SMT. Presented as arithmetic means, 95% confidence intervals and the corresponding p-value.
SMT = Spinal manipulative therapy, * = p-value < 0.05

Spinal biomechanics

The next section will focus on changes for the two biomechanical measures of spinal stiffness.

Global stiffness

Target site

The change in GS was not statistically significant within-group from baseline to: i) immediately following the first SMT session (Stiff = -0.02 [-0.26 to 0.22], Pain = -0.08 [-0.31 to 0.15]), ii) post-SMT (Stiff = 0.01 [-0.22 to 0.24], Pain = 0.03 [-0.2 to 0.26]), or iii) at follow-up (Stiff = -0.13 [-0.36 to 0.1], Pain = 0.1 [-0.13 to 0.32]). There were also no statistically significant between-group differences at any time point when compared to baseline. This is illustrated in Appendix A4. The randomization process did not apply statistically significant between-group differences for GS at baseline (the stiff group had a score of -0.26 [-0.56 to 0.03] compared to the pain group with a p-value of 0.083).

Responder status

We also examined responder status. A total of 36 different between-group differences (NRS and ODI dichotomized at 0%, 30%, and 50% improvement faceted by the target site (stiff versus pain)) were available. When splitting the data in this fashion, none of the differences were statistically significant, indicating that both responders and non-responders to the treatment had similar minor changes in GS. Also, there were no baseline differences between any of the responder cut points. See Appendix A4.

Target site by vertebra

Global stiffness did not change significantly over time when comparing the target site to the adjacent or remote vertebral sites. There were no statistically significant within-group changes from baseline to any time point nor any between-group differences across the vertebral categorization, including baseline. Appendix A4 illustrates this.

Terminal stiffness

Target site

As with GS, we did not see any changes in TeS within-group from baseline to immediately following the first SMT session (Stiff = 0.15 [-0.27 to 0.58], Pain = -0.06 [-0.46 to 0.35]), at post-SMT (Stiff = 0.01 [-0.4 to 0.43], Pain = 0.03 [-0.38 to 0.44]), or at follow-up (Stiff = -0.01 [-0.43 to 0.4], Pain = 0.25 [-0.15 to 0.66]). Again, no statistically significant differences were found between groups at any time point. This is illustrated in Appendix A5. Also, for TeS, the randomization process did not show any significant between-group differences (the stiff group had a score of -0.35 [-0.78 to 0.09] compared to the pain group with a p-value of 0.1).

Responder status

Again, a total of 36 different between-group differences were available. However, none of them were statistically significant, indicating that both responders and non-responders had similar changes in TeS. The within-group changes were minor and not statistically significant. Finally, we did not observe any baseline differences for TeS between responder cut points. See Appendix A5.

Target site by vertebra

When comparing the vertebral categorization, there were no significant between-group differences for TeS between any time points. However, there was a minor statistically significant within-group change for the remote vertebrae (i.e., two vertebrae away from the target site) as TeS increased for the pain group from baseline to follow-up (0.4 [0 to 0.8], p-value = 0.05). The relation is illustrated in Appendix A5.

Quantitative sensory pain testing

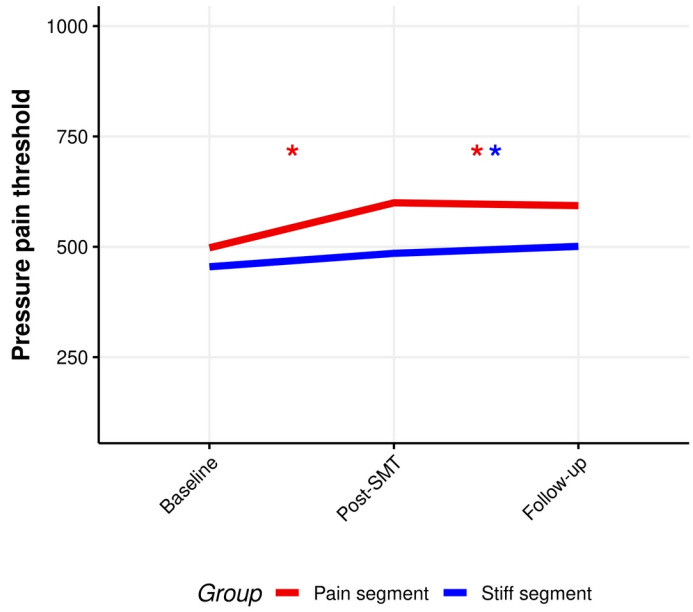
The next section will examine the different QST measures. We included the original omitted ~12% of data points for the following: *Pain hypersensitivity* analyses to ensure adequate power. This was possible as the between vertebra variations were trivial for PPT and HPT. See correlation analysis.

Pressure pain threshold

Target site

Pressure pain threshold showed statistically significant within-group changes from baseline to post-SMT for the pain group (Stiff = 30 [-14 to 75], Pain = 102 [59 to 145]) and for both groups at follow-up (Stiff = 46 [0 to 92], Pain = 96 [52 to 139]). This led to a statistically significant between-group difference from baseline to post-SMT. See Figure 13. Despite the randomization, no between-group difference was found at baseline, and the stiff group actually had lower PPT scores (-43 [-125 to 40]) compared to the pain group with a p-value of 0.3).

Figure 13 Within-group changes and between-group differences in pressure pain threshold (Target site)



Time point	Mean difference (95 CI%)	P-value
Baseline - Post-SMT	-72(-134 to -10)	0.02
Baseline - Follow-up	-49(-113 to 14)	0.16

Within-group changes (figure) and between-group differences (table) in pressure pain threshold [kPa] following four sessions of SMT at either the stiffest vertebra (stiff group) or the most pain-sensitive segment (pain group). Presented as arithmetic means, 95% confidence intervals and the corresponding p-value
SMT = Spinal manipulative therapy, * = p-value < 0.05

Responder status

We examined multiple within-group changes and between-group differences accounting for time, target site, and responder status for PPT. In short, we observed that PPT increased in two contexts: i) Within-group changes for the 24 *responder* subgroups (NRS and ODI dichotomized at 0%, 30%, and 50% improvement faceted by the target site (stiff versus pain) for each time point), PPT increased in all instances and was statistically significant in 16; for the 24 *non-responder* groups, the findings were more mixed. ii) for the 24 *pain* subgroups,

PPT increased in all instances and was statistically significant in 21. For the 24 *stiff* subgroups, the findings were again mixed. For all the responder cut points, we generally saw that the changes occurred from baseline to post-SMT, as the changes stagnate from post-SMT to follow-up. Besides, no statistically significant baseline difference was observed between responders subgrouped by the target site (stiff versus pain). Figure 14 illustrates the association between these three interacting factors, and the between-group differences are listed below.

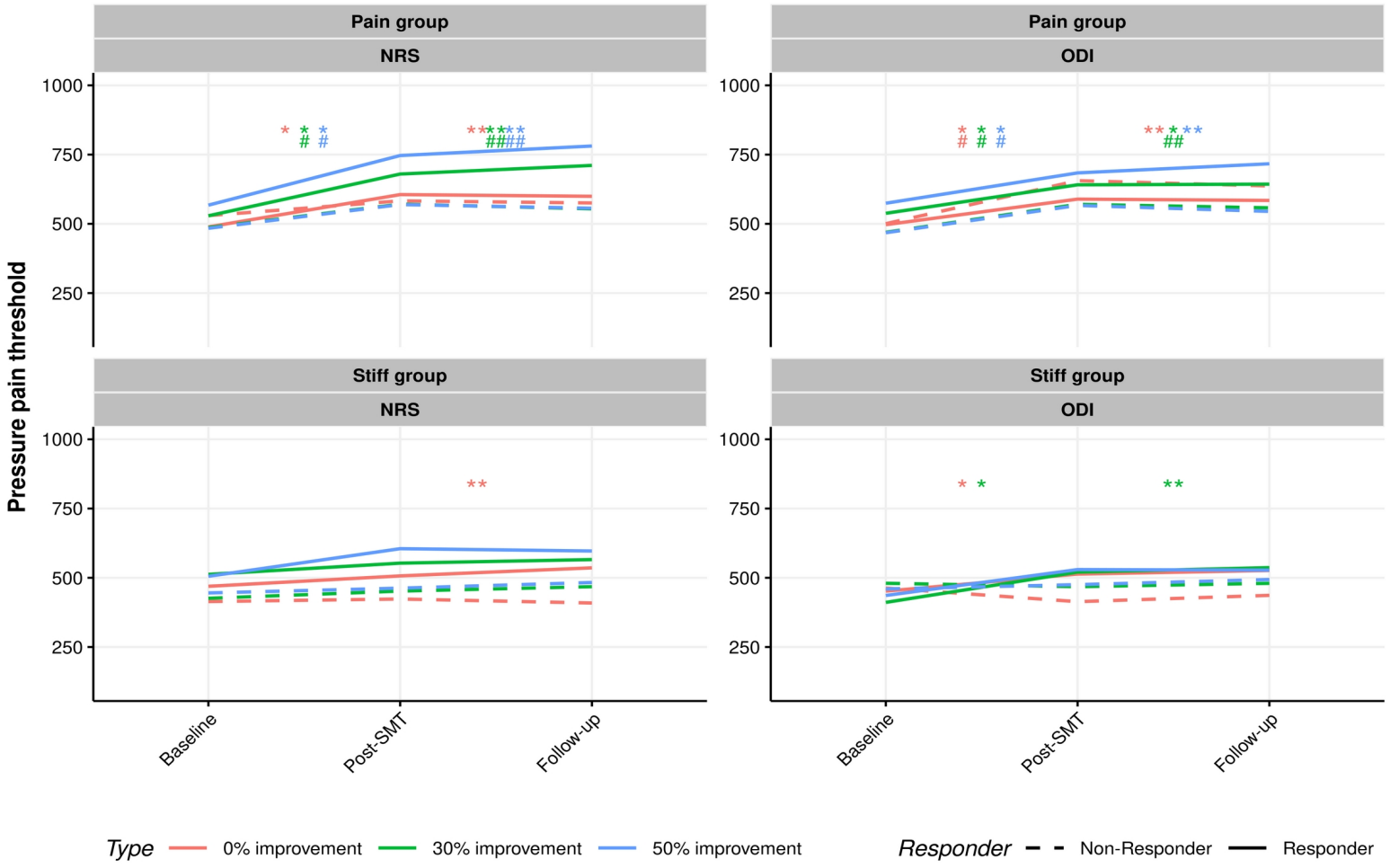
General hyperalgesia

When splitting the sample into sensitized or not-sensitized, we observed an increase of PPT in two distinct instances: i) The Sensitized group improved independently of the target site from baseline to post-SMT (Stiff = 93 [3 to 183], Pain = 146 [68 to 224]), and at follow-up (Stiff = 84 [-6 to 174] - p-value = 0.08, Pain = 118 [40 to 196]); ii) For the pain group, independent of general hyperalgesia, from baseline to post-SMT (Not-sensitized = 87 [31 to 143]), and at follow-up (Not-sensitized = 78 [22 to 135]). See Figure 15 for an overview.

Target site by vertebra

As with the biomechanical spinal measures, we did not observe any statistically significant between-group differences for PPT at any time point. Thus, the same within-group increases were observed dependent on the target site but independent of the specific vertebra targeted. The relation is illustrated in Appendix A6.

Figure 14 Within-group changes and between-group differences in pressure pain threshold (Target site and responder status)



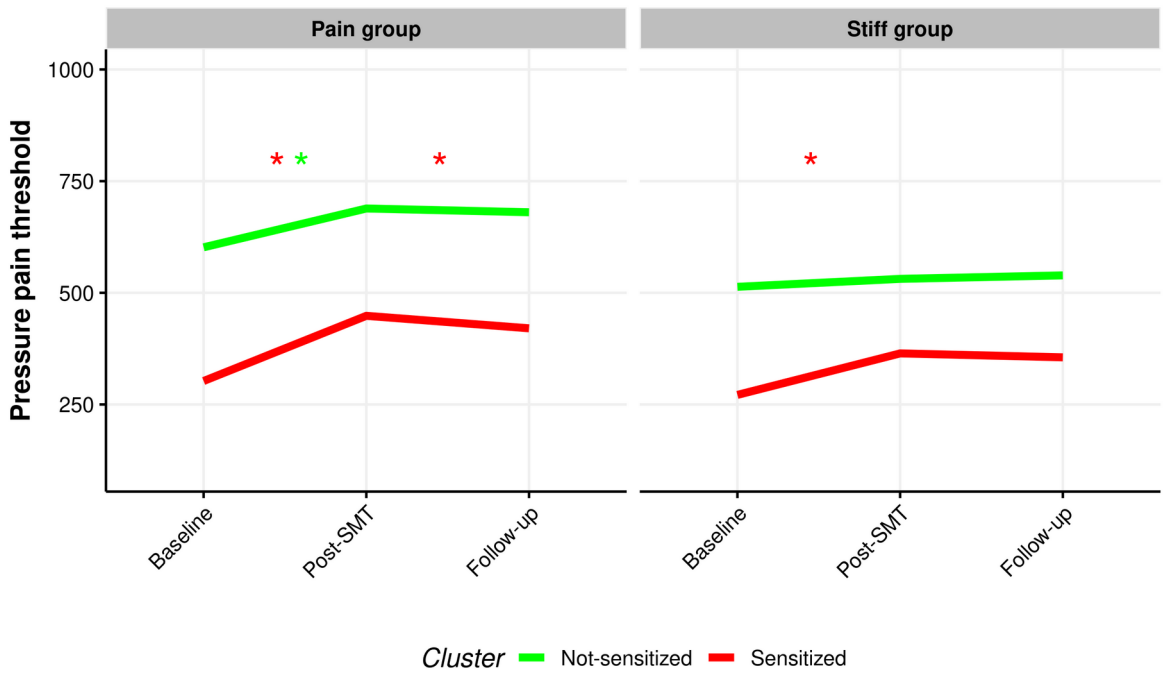
		Patient-reported LBP intensity		Disability	
		Pain group			
Time point	**Cut point**	**Mean difference (95 CI%)**	**P-value**	**Mean difference (95 CI%)**	**P-value**
Baseline - Post-SMT	0%	63(-53 to 179)	0.55	28(-90 to 147)	0.96
Baseline - Follow-up		65(-54 to 184)	0.56	72(-46 to 190)	0.44
Baseline - Post-SMT	30%	66(-45 to 178)	0.47	14(-96 to 125)	~1
Baseline - Follow-up		114(-3 to 231)	0.06	11(-99 to 122)	~1
Baseline - Post-SMT	50%	94(-35 to 222)	0.26	82(-55 to 219)	0.46
Baseline - Follow-up		141(7 to 275)	0.03	54(-84 to 191)	0.81
		Stiff group			
Baseline - Post-SMT	0%	-63(-199 to 73)	0.69	111(-2 to 223)	0.06
Baseline - Follow-up		-49(-180 to 83)	0.84	101(-15 to 217)	0.12
Baseline - Post-SMT	30%	2(-97 to 101)	~1	122(16 to 228)	0.02
Baseline - Follow-up		17(-84 to 118)	0.99	126(18 to 234)	0.01

Baseline - Post-SMT	50%	11(-97 to 119)	~1	78(-53 to 209)	0.46
Baseline - Follow-up		65(-47 to 178)	0.48	57(-71 to 186)	0.72

Within-group changes (figure) and between-group differences (table) in pressure pain threshold [kPa] for 50, 30 and 0% improvements in patient-reported low back pain intensity and disability following four sessions of SMT at either the stiffest vertebra (stiff group) or the most pain-sensitive segment (pain group). Presented as arithmetic means, 95% confidence intervals and the corresponding p-value.

NRS = Numerical rating scale, ODI = Oswestry disability index, SMT = Spinal manipulative therapy, * = Significant changes in responders from baseline to post-SMT. ** = Significant changes in responders from baseline to follow-up. # = Significant changes in non-responders from baseline to post-SMT. ## = Significant changes in non-responders from baseline to follow-up

Figure 15 Within-group changes and between-group differences in pressure pain threshold (Target site and pain hypersensitivity)



Time point	Target	Mean difference (95 CI%)	P-value
Baseline - Post-SMT	Pain group	-59(-155 to 37)	0.43
	Stiff group	-75(-180 to 30)	0.28
Baseline - Follow-up	Pain group	-39(-136 to 57)	0.78
	Stiff group	-58(-164 to 47)	0.54

Within-group changes (figure) and between-group differences (table) for the not-sensitized group and sensitized group in pressure pain threshold [kPa] following four sessions of SMT at either the stiffest vertebra (stiff group) or the most pain-sensitive segment (pain group). Presented as arithmetic means, 95% confidence intervals and the corresponding p-value.
SMT = Spinal manipulative therapy, * = p-value < 0.05

Heat pain threshold

Target site

For the target site, we observed minor increases of HPT at both time points. This increase reaches statistical significance from baseline to follow-up for the stiff group (0.8 [0 to 1.5]). However, there were no between-group differences nor baseline differences between the target sites. See Appendix A7.

Responder status

The responder analysis did not indicate a clear tendency in the data. There were no statistically significant findings for within-group changes nor between-group differences. The ODI analysis showed that the responders had a minor increase in HPT compared to the non-responders, whereas these were mixed for the NRS analysis. See Appendix A7.

General hyperalgesia

Overall, HPT increased for both the sensitized and Not-sensitized groups by both target sites at follow-up. However, the increase was not statistically significant. Consequently, there were no statistically significant between-group differences. See Appendix A7.

Target site by vertebra

As with the remaining analyses conducted at different vertebrae, this model also indicates that the vertebral change was consistent across treatment sites. However, both for the stiff and for the pain group, there were statistically significant but minor increases within-group at the remote vertebrae (stiff and pain) and the adjacent vertebrae (stiff) between baseline and follow-up. See Appendix A7.

Widespread pressure pain threshold

Target site

There were no statistically significant changes within-group, nor between-group differences for wPPT. Also, we did not find any baseline differences. See Appendix A8.

Responder status

There were no between-group differences for the dichotomized responder status. Furthermore, none of the responders/non-responders made statistically significant changes within-group. See Appendix A8.

General hyperalgesia

As with the other analyses, there were generally limited changes for wPPT. Hence, when applying the cluster results to the data set, no changes or differences emerged. See Appendix A8.

Widespread pressure pain tolerance

Target site

For wPTT, a trivial within-group change emerged for the pain group from baseline to follow-up (6 [2.5 to 9.5]). There were no between-group differences. See Appendix A9.

Responder status

There were no between-group differences for responders and non-responders. However, there were some within-group increases from baseline to follow-up for the responders. This was statistically significant in four out of six possibilities, whereas for the non-responders, the increase was statistically significant on all six occasions. See Appendix A9 for a visualization.

General hyperalgesia

We observed a statistically significant within-group change for the Sensitized group from baseline to follow-up (7.9 [3.3 to 12.5]). However, there were no between-group differences. See Appendix A9.

Temporal summation

Target site

Only minor changes transpired across time for the target sites, leading to no statistically significant within-group changes or between-group differences. See Appendix A10.

Responder status

Thus, due to the minimal changes observed, no meaningful within-group changes emerged when further dichotomizing into responders/non-responders. Only in the NRS model with the responder cut point set to 0% did we observe a minor, yet statistically significant, between-group difference. See Appendix A10.

General hyperalgesia

When splitting the cohort using our cluster-based approach, the Sensitized group had an increase (0.5 [0.1 to 1], p-value = 0.009), while the Not-sensitized group had a minor decrease. This leads to statistically significant between-group differences from baseline to post-SMT and follow-up. See Figure 16.

Conditioned pain modulation

Target site

As with TS, only minor changes were observed throughout the study period for CPM. None of them were statistically significant. See Appendix A11.

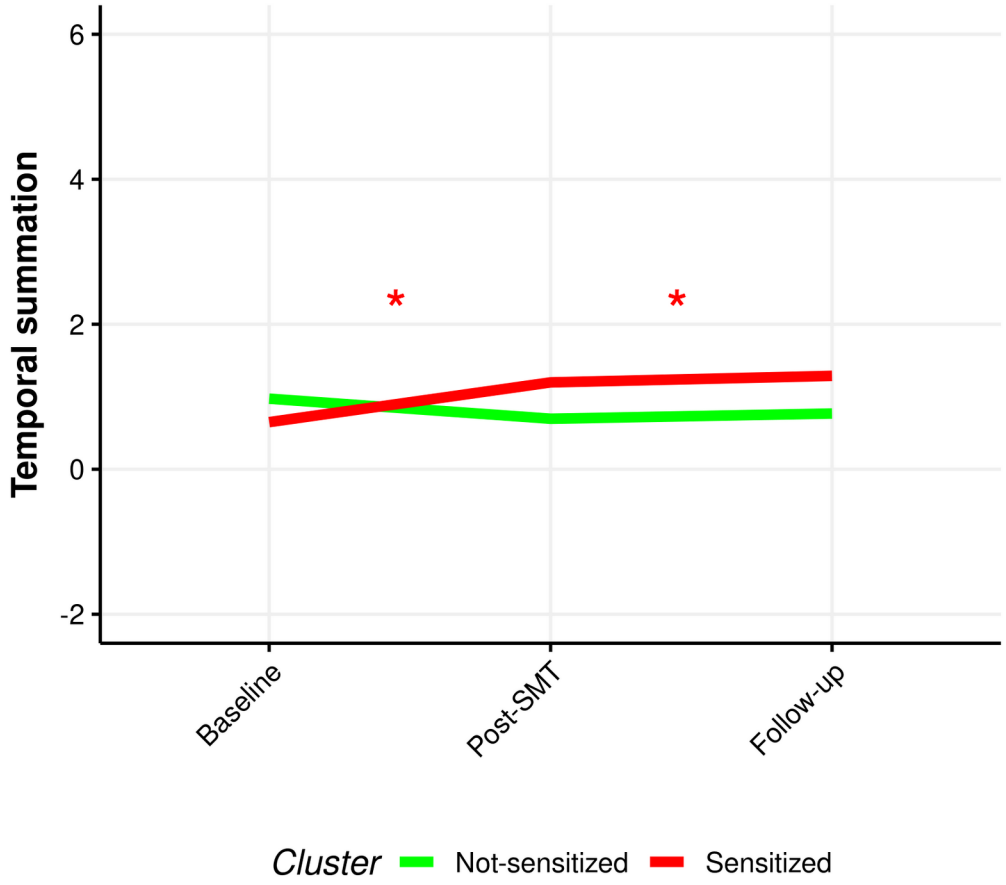
Responder status

Only non-systematic changes were observed in CPM between baseline and post-SMT, and follow-up; none were of significance. See Appendix A11.

General hyperalgesia

Lastly, even when splitting the sample into the sensitized and not-sensitized, despite substantial differences at baseline, it still did not yield any statistically significant changes across time. See Appendix A11.

Figure 16 Within-group changes and between-group differences in temporal summation (Pain sensitivity)



Time point	Mean difference (95 CI%)	P-value
Baseline - Post-SMT	-0.8(-1.3 to -0.3)	<0.01
Baseline - Follow-up	-0.8(-1.4 to -0.3)	<0.01

Within-group changes (figure) and between-group differences (table) for the not-sensitized group and sensitized group in temporal summation [kPa] following four sessions of SMT. Presented as arithmetic means, 95% confidence intervals and the corresponding p-value.

SMT = Spinal manipulative therapy, * = p-value < 0.05

Systematic review

SMT applied at a specific target versus a comparator target

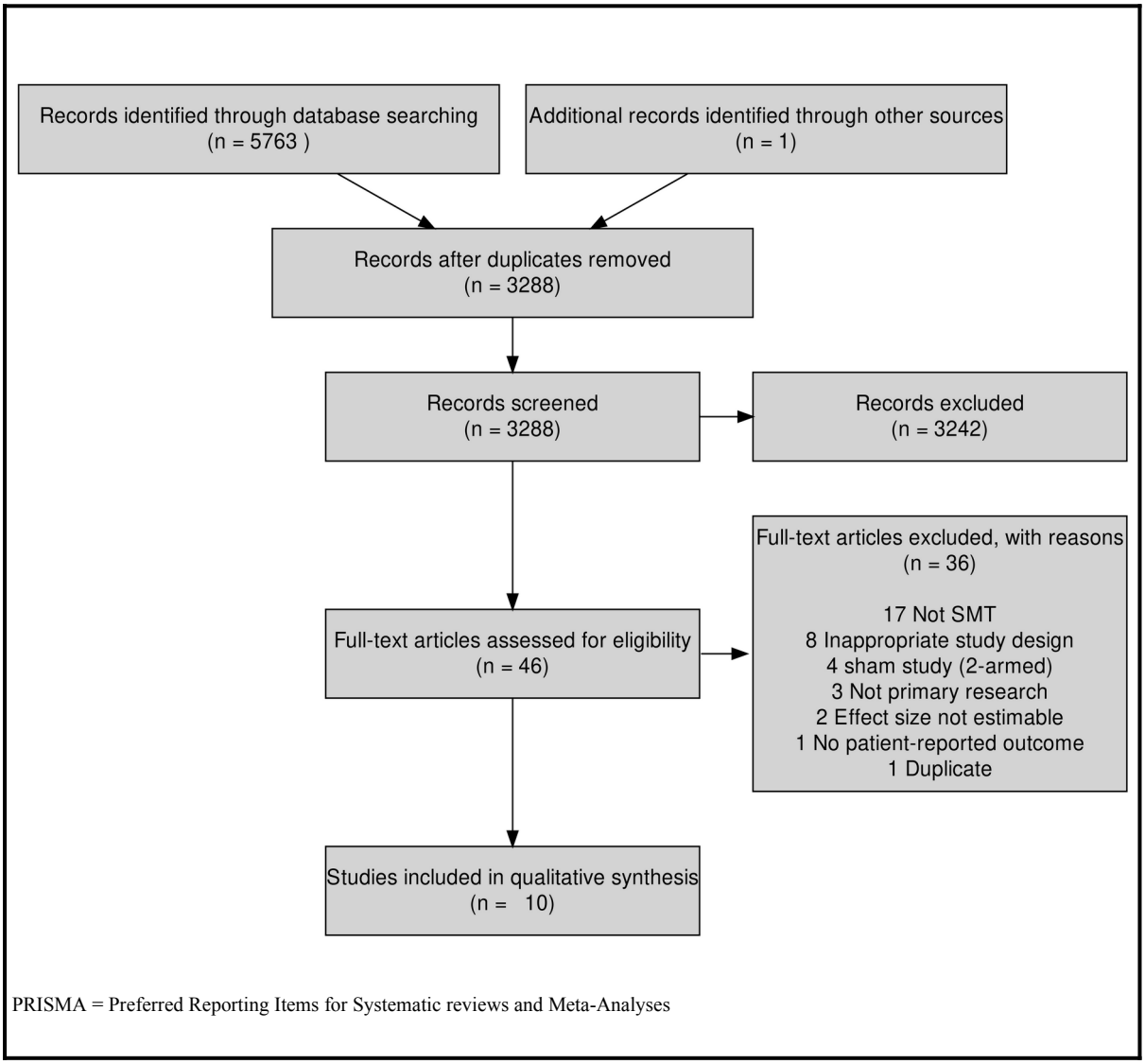
Figure 17 illustrates a *Preferred Reporting Items for Systematic reviews and Meta-Analyses* flowchart detailing the study inclusion. We included nine studies to compare with our results for *target site*. Thus, the review is based on ten studies (100–108). The studies were from 2003 to 2020. We did find another two studies but had to exclude them as we could not extract relevant data to determine a between-group effect (109,110).

Table 6 lists descriptive information for each study. The study samples ranged from 39 to 186. Five studies examined neck pain, and five studied LBP. The participants, who all were, at least, in part included in a clinical setting, received between one and 10 SMT sessions. We had to calculate effect sizes for six studies, which only reported within-group differences.

The quality assessment is presented in Figure 18. Generally, the studies were of low risks of bias concerning bias for selection, detection, and attrition, whereas intervention bias was mixed. However, the studies generally scored high risks for bias concerning performance bias, and none of the studies reported on participants' naivety and potentially introduces response bias.

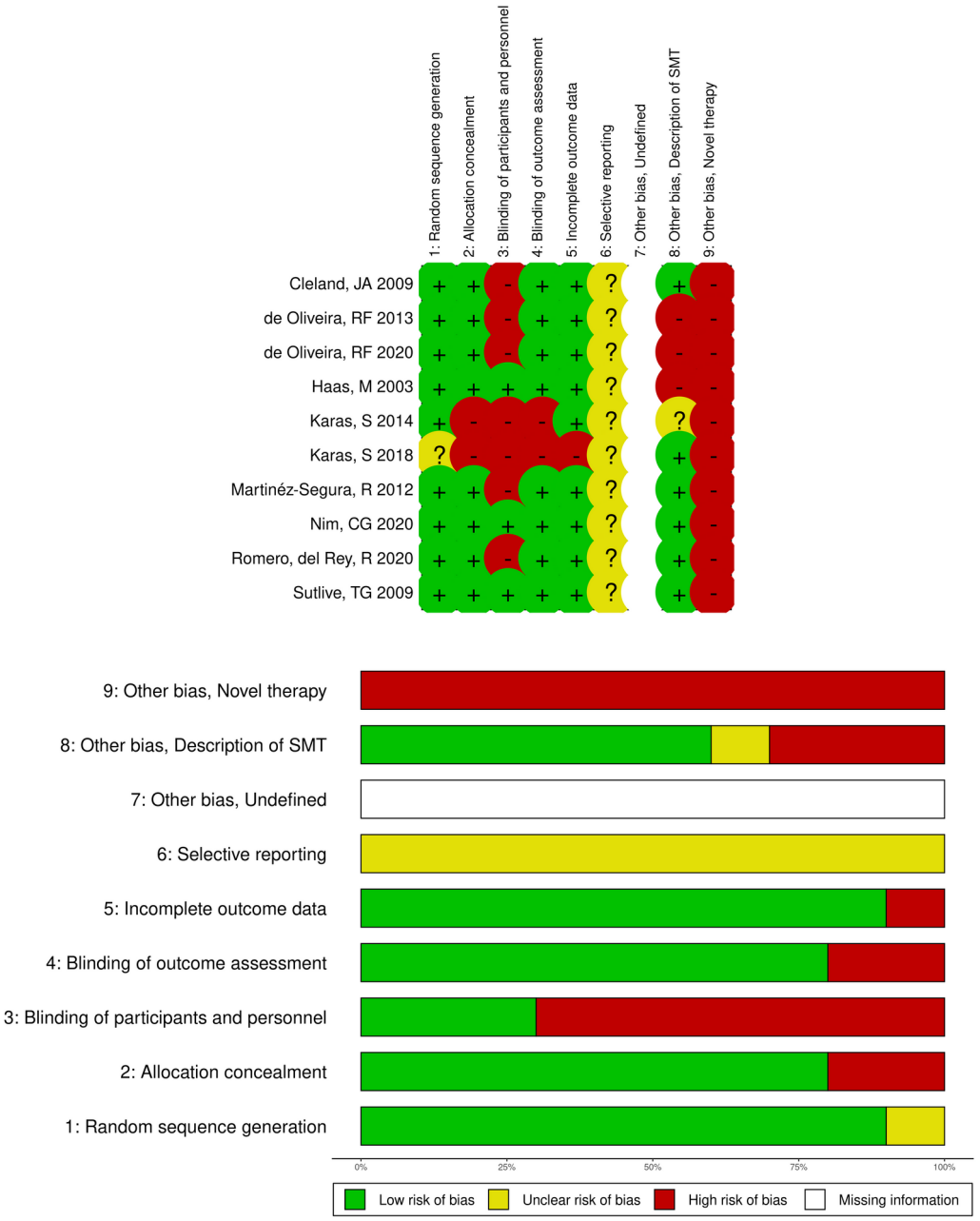
Table 7 highlights the extracted findings from different studies. The SMT intervention target was determined clinically in seven studies, two applied a per-protocol approach, and one mixed clinically with per-protocol. One comparator applied SMT at a non-clinical target, and the remaining were decided per-protocol.

Figure 17 PRISMA flowchart for the systematic review



PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses

Figure 18 Risk of bias for each study and across studies included in the systematic review



Risk of bias was assessed using the Cochrane Risk of Bias Tool for Randomized Controlled Trials. A green + indicates low risk of bias, a red - indicates high risk of bias, a yellow **?** indicates an unclear risk of bias, and a *white field* indicates missing information.

Table 6 Description of the 10 studies included in a systematic review

1st author, year	Study aim (IT vs CT)	Participants	Intervention target determined by	Comparator target determined by	SMT sessions
Haas M, 2003	To compare specific cervical SMT to a matched random target for pain intensity and subjective stiffness	Adult neck pain patients recruited from referral or advertisement	Clinically: SMT targeting a cervical vertebrae according to cervical endplay assessment	Study protocol: SMT targeting a random computer-generated matched target	1
Cleland JA, 2009	To compare SMT targeted a specific lumbar vertebra to a generalized thrust for pain intensity and disability	Adult low back pain patients who fit an SMT clinical prediction rule recruited from the military hospital	Clinically: SMT targeting a clinician selected lumbar vertebra	Study protocol: Generalized SMT targeting the lumbar spine	2
Sutlive TG, 2009	To compare SMT targeted a specific lumbar vertebra to a generalized thrust for pain intensity and disability	Adult low back pain patients who fit an SMT clinical prediction rule recruited from the military hospital	Clinically: SMT targeting a clinician selected lumbar vertebra	Study protocol: Generalized SMT targeting the lumbar spine	1
Martinéz-Segura R, 2012	To compare SMT targeting the right cervical spine to thoracic SMT for pain intensity	Adult bilateral chronic mechanical neck pain patients recruited from private practice.	Clinically, by study protocol: SMT targeting a clinician selected cervical vertebra on the right side	Study protocol: SMT targeting the midthoracic spine	1
de Oliveira RF, 2013	To compare SMT targeting a specific lumbar vertebra to thoracic SMT for pain intensity	Adult non-specific chronic low back pain patients recruited from private practice.	Clinically: SMT targeting a clinician selected lumbar vertebra (L2-L5)	Study protocol: SMT targeting the thoracic region (T1 and T5)	1

Karas S, 2014	To compare SMT targeting a specific thoracic vertebra to a generalized thrust for pain intensity	Adult with neck pain recruited from an out-patient hospital	Clinically: SMT targeting a clinician selected thoracic vertebra	Study protocol: Generalized SMT targeting the thoracic spine	1
Karas S, 2018	To compare SMT targeting a thoracic restriction to thoracic SMT targeting the counter restriction for pain intensity and disability	Adult mechanical neck pain patients recruited from out-patient practice	Clinically: SMT targeting a clinician selected thoracic vertebra in the opposite restriction vector as the intervention target	Not clinically: SMT targeting a clinician selected thoracic vertebra in the opposite restriction vector as the intervention target	2
Nim CG, 2020	*To compare SMT targeting lumbar stiffness to SMT targeting lumbar pain sensitivity for pain intensity*	*Adult non-specific chronic low back pain patients recruited from a hospital spine center*	*Study protocol: SMT targeting the stiffest lumbar vertebra measured using the VerteTrack*	*Study protocol: SMT targeting the most tender lumbar vertebra measured using a pressure algometer*	*4*
Romero Del Rey R, 2020	To compare upper cervical SMT to cervicothoracic SMT for pain intensity	Adult chronic mechanical neck pain patients recruited from private practice.	Study protocol: SMT targeting C1-C2	Study protocol: SMT targeting C3-C4, C7-T1, and T5-T6	1
de Oliveira RF, 2020	To compare SMT targeting a specific lumbar vertebra to thoracic SMT for pain intensity, disability, and global perceived change	Adult non-specific chronic low back pain patients recruited from private practice	Clinically: SMT targeting a clinician selected lumbar vertebra	Study protocol: SMT targeting T5/T6	10

The descriptive data has been modified to fit the systematic review.
SMT = Spinal manipulative therapy, IT = Intervention target, CT = Comparator target

Table 7 Results from the 10 studies included in a systematic review

1st author, year	N (Male/Female)	Side effects	Between group differences extracted/calculated	Summary of results
Haas M, 2003	Total = 99 IT = 47 (19/28) CT = 52 (17/35)	No between-group differences reported	Pain intensity[0 to 100] mean(SD): *Immediately = 0.9(3.5), Later same day = 2.2(3.5)* Subjective stiffness[0 to 100] mean (SD): *Immediately = 1.3(3.4), Later same day = 4(3.6)*	There were no between-group differences for the targets
Cleland JA, 2009	Total = 75 IT = 38 (17/21) CT = 37 (20/17)	IT = 9 CT = 9	Pain intensity[0 to 10] mean [95% confidence intervals]: *1 week = 0.6[-0.2, 1.4], 4 weeks = 0.5[-0.6, 1.5], 26 weeks = 0.2[-0.6, 1.0]* Disability[0 to 50] mean[95% confidence intervals]: *1 week = 3.5[-2.0, 9.0], 4 weeks = 1.5[-4.1, 7.1], 26 weeks = -0.9[-5.5:3.8]*	There were no between-group differences for the targets
Sutlive TG, 2009	Total = 60 IT = 30 (17/13) CT = 30 (14/16)	Not reported	Pain intensity[0 to 1] effect size: *2 days = 0.10* Disability[0 to 1] effect size: *2 days = 0.23*	There were no between-group differences for the targets
Martinéz-Segura R, 2012	Total = 62 IT = 29 (14/15) CT = 33 (17/16)	IT = 1 CT = 1	Pain intensity[0 to 1] effect size : *Immediately = 0.06*	There were no between-group differences for the targets
de Oliveira RF, 2013	Total = 148 IT = 74 (15/59) CT = 74 (24/50)	IT = 0 CT = 0	Pain intensity[0 to 10] mean [95% confidence intervals]: *Immediately = 0.5[-0.1:1.1]*	There were no between-group differences for the targets

Karas S, 2014	Total = 39 IT = 19 (6/13) CT = 20 (6/14)	Not reported	Pain intensity (cervical flexion)[0 to 10] mean [95% confidence intervals]: *Immediately = -1.2[-1.9:-0.5]**	A between-group difference was observed for pain intensity immediately following treatment favoring the IT.
Karas S, 2018	Total = 69 IT = 34 (8/26) CT = 35 (7/28)	Not reported	Pain intensity[0 to 1] effect size: *2 days = 0.25, 2 weeks = 0.14* Disability[0 to 1] effect size: *2 days = 0.33, 2 weeks = 0.18*	There were no between-group differences for the targets
Nim CG, 2020	*Total = 132* *IT = 66 (32/34)* *CT = 66 (40/26)*	*N = 85, no between-group difference reported*	*Pain intensity[0 to 10] mean [95% confidence intervals]:* *2 weeks = 0.1[−0.5:0.7], 4 weeks = −0.1[−0.7:0.5]*	*There were no between-group differences for the targets*
Romero Del Rey R, 2020	Total = 186 IT = 93 (29/64) CT = 93 (38/55)	Not reported	Pain intensity[0 to 1] effect size: 15 days = 0.00	There were no between-group differences for the targets
de Oliveira RF, 2020	Total = 148 IT = 74 (17/57) CT = 74 (16/58)	IT = 0 CT = 4	Pain intensity[0 to 10] mean [95% confidence intervals]: *4 weeks = 0.0[-0.9:0.9], 12 weeks = -0.1[-1.0:0.8], 26 weeks = -0.1[-1.0:0.8]* Disability[0 to 24] mean [95% confidence intervals]: *4 weeks = 0.1[-1.7:1.5], 12 weeks = 0.1[-1.6:1.7], 26 weeks = -0.9[-2.5:0.7]* Global perceived change[-5 to 5] mean [95% confidence intervals]: *4 weeks = -0.1[-1.0:0.8], 12 weeks = 0.3[-0.7:1.2], 26 weeks = 0.8[-0.2:1.7]*	There were no between-group differences for the targets

The outcome data has been modified to fit the systematic review.
Legend: IT = Intervention target, CT = Comparator target, PPT = Pressure pain detection threshold, * = reported as statistically significant

Different targets within the same vertebra

One studied compared two targets within the same vertebra (106). The study was of low quality, with only one low-risk domain. The study compared SMT applied at a clinically determined thoracic vertebra. The intervention targeted the restriction direction, and the comparator targeted the other direction. For instance, a flexion thrust (target) compared to an extension thrust (comparator). There was no between-group difference for neck pain intensity or neck pain-related disability.

Different specific targets within the same region

Two studies examined two targets within the same region. One of the studies was Manuscript I and has been reported in full detail in the thesis results section. This study was scored as overall high quality (six domains of low risk of bias) (111). The other study (100) compared neck SMT at a clinically determined target versus a comparator target at a randomly matched vertebra. This study was also of overall high quality (five domains of low risk of bias). This study did not find any between-group difference for neck pain intensity and subjective stiffness immediately following SMT and later the same day.

Specific targets versus generalized thrust in the same region

Three studies compared a specific thrust to a generalized thrust. Two examined LBP (101,102) and the other neck pain (105) but applied SMT at the thoracic spine. The two LBP studies were generally of high quality (five and six domains of low risk). These studies did not report any between-group difference for LBP intensity and disability. The neck pain study was of low quality (two domains of low risk of bias) and was also the study with the smallest sample size. However, this study did report a between-group difference of 1.2 points on an 11-point numeric rating scale for LBP.

Different regions

We included four studies that compared SMT delivered in different regions. Two studies examined lumbar SMT versus thoracic SMT for LBP (104,108), one study examined cervical SMT to thoracic SMT for neck pain (103), and the last study compared upper cervical SMT to multiple cervicothoracic SMTs for neck pain (107). All of the studies were scored as

having an overall low to moderate risk of bias with four, four, five, and five domains of low risk of bias, respectively. To summarize, none of the studies found any between-group differences for multiple outcomes: pain intensity, disability, and global perceived change.

Data synthesis

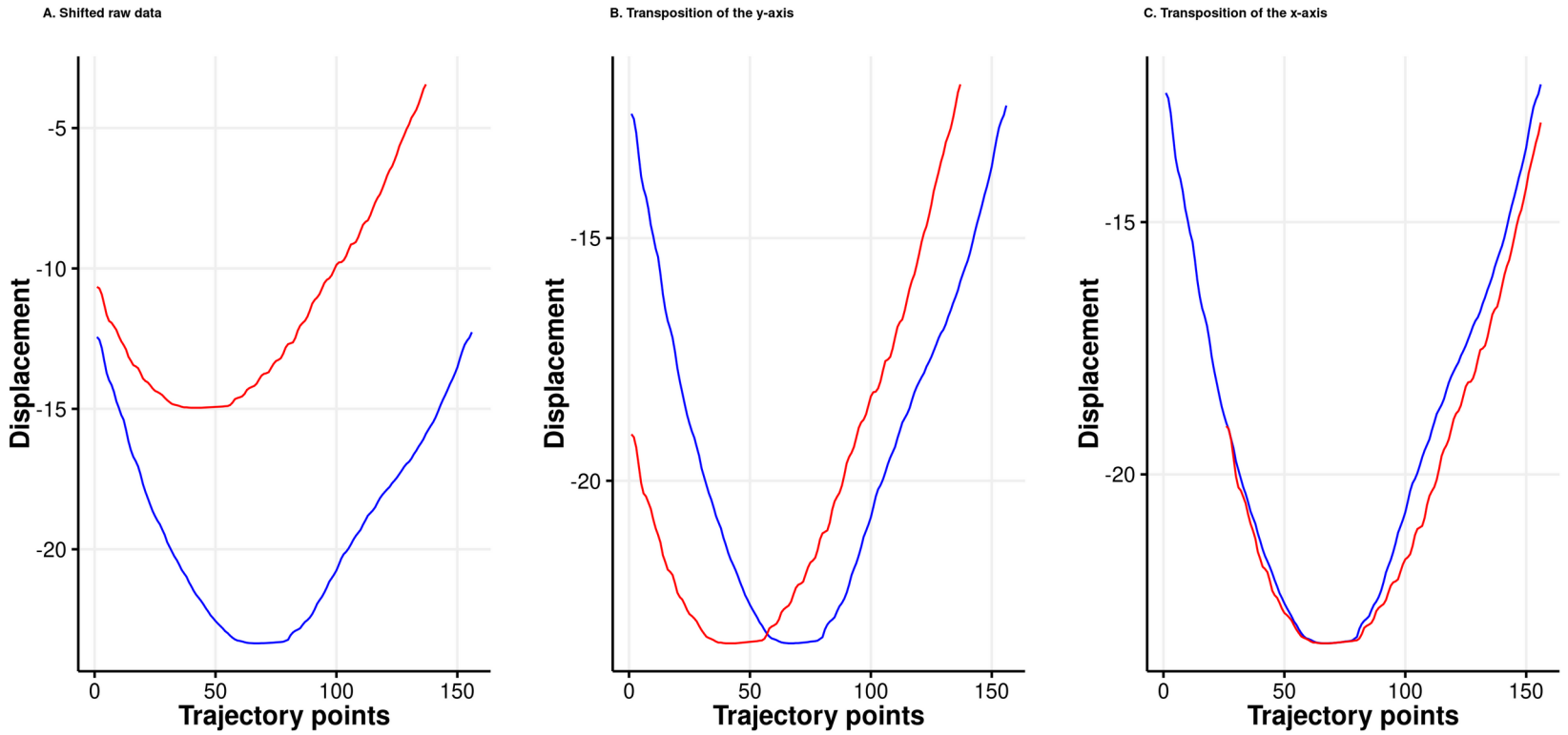
A total of 29 between-group difference/effect sizes were exported, and only *one* reported a statistically significant difference. Furthermore, when scrutinizing the 29 minor between-group differences, 10 favored the group where SMT was applied at a specific target, the remainder favored the comparator target or was 0.0.

Spatial synchronization method and implications

Due to shifted trajectories, we had to eliminate ~ 12% of the data containing the vertebral measures. While there is not much one can do concerning the QST parameters, the stiffness values are adjustable as data from the full trajectory (each mm from the *landing site* to the *lifting site*, e.g., S1 to T12) are available. Thus, to examine this, we reviewed another sample of VT data collected at the University of Alberta, Edmonton, Canada. This data set was used in a prospective randomized trial, investigating how LBP patients respond to different interventions following two SMT sessions (112). The data collection differed from the original cohort as they only applied palpation to locate the vertebrae, whereas we used ultrasound to ensure this identification. We attempted to determine the extent of spatial asynchrony of VT data and to demonstrate how a simple data transposition technique can generate spatial synchrony. Finally, we will suggest how it modifies the resulting measures of spinal stiffness.

We included data on 124 participants for this analysis (all of whom completed the first two SMT sessions). Using a newer version of the LabView analysis program, we extracted the displacement values for the full trajectory for each participant's load (displacement values per 1 mm). We visualized each displacement curve (trajectory/mm) to determine the extent of shift between trajectories. The reference data to which we synchronized the trajectory, were in all circumstances, the baseline data (Day 1 pre-SMT). The data collected at the subsequent trials were then transposed so that each trajectory's data points were overlapped with the baseline data. This synchronization followed three steps. Step 1: An automated mathematical translation of the x-axis until the greatest vertical displacement points were aligned. Step 2: A visual control. Initially, we also overlapped the y-axis, so the applied loads were completely visually overlapped. Step 3: CGN and two PhD students from Canada (PJ and MH) reviewed the automated process to ensure optimal synchronization. If the synchronization was not optimal, the data was further synchronized by manually transposing the x-axis of the subsequent trial. We had to come to a consensus before agreeing on a final shift. Figure 19 demonstrates an example of spatial synchronization that did not require manual post-processing.

Figure 19 Spatial synchronization of spinal stiffness data



Example of the vertebral effect of the data transposition. The baseline displacement data (blue line), and the displacement data from the assumed same trajectory measured at week 1 (red line). A) indicates the original data points, B) the overlapping of y-axis (visual purpose only) and, C) the resulting spatial synchronization. In the example the x-axis is transposed 15 mm

Table 8 lists mean transposition distances (mm) of displacement data needed to achieve spatial synchrony for each available session. In concordance with the data from this study, substantial shifts were observed throughout the intervention period. Also, despite using the same markings, a mean shift of ~5 mm was observed between the two measures obtained at the initial SMT session. The synchronization process also resulted in greater unmatched data points; this number increased gradually throughout the intervention period. The average distance between each vertebra's markings was 27 mm. The mean transposition distance of 12 mm represented approximately 50% of this value and corresponded to 7% of the total lumbar trajectory.

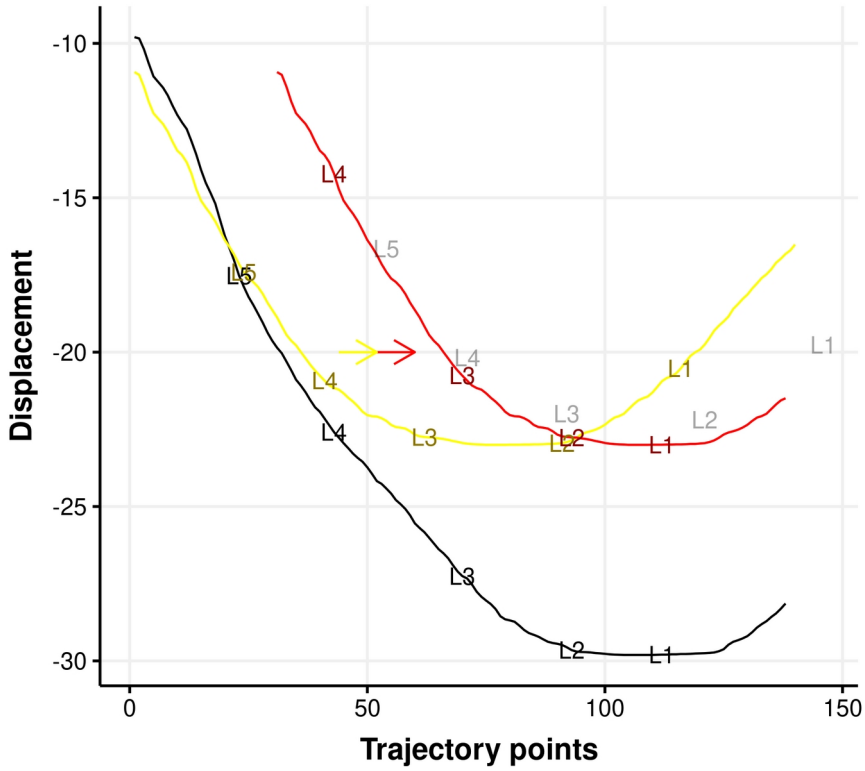
Table 8 Spatial transposition and the resulting unmatched data points

Test session	N	Spatial transposition (mm) compared to baseline - mean(SD)	% shift between spinous markings (% of the full spine(S1-T12))	Unmatched data points (mm) compared to baseline - mean(SD)
Day 1 Pre-SMT (Baseline)	124	0	0	0
Day 1 Post-SMT	123	4.6(4.8)	17(3)	5.1(5.4)
Day 4 Pre-SMT	123	12.4(11.6)	46(8)	13.4(14.3)
Day 4 Post-SMT	124	13.9(11.8)	52(9)	14.2(14.6)
Week 1	124	13.1(12.1)	49(8)	15.2(15.6)
Week 4	108	15.6(11.9)	57(10)	28.5(19.4)
Week 12	98	14.6(12.5)	54(9)	25.1(18.4)

SMT = Spinal manipulative therapy

To exemplify why transposing or removing the shifted trajectory points could be deemed necessary, we present a visual example of a participant with shifted data in Figure 20. Here, the transposition of the original data at week 1 (yellow) to the synchronized data (red), which was aligned with the baseline data (black), noted a misclassification of the vertebrae on the transposed data (red curve). For instance, what was erroneously palpated and marked as L5 at week 1 was located cranially to what was originally marked as L4 at baseline (shaded black spinous location). When synchronized, L5 appears to be an unmatched point and thus omitted in the week 1 trial. This was likely due to an error when placing the *landing site*, advancing the device to land cranially. Calculating L3's GS change for this participant from baseline to week 1 using the corrected, spatial synchronized data revealed a decrease of 1.39 N/mm. However, the raw data yield a decrease of 2.31 N/mm (i.e., the raw data overestimates a decrease in GS of 0.92 N/mm in this case).

Figure 20 The vertebral effect of spatial synchronization



Example of the vertebral effect of the data transposition. Baseline and week 1 trajectories are plotted with superimposed spinous process for each vertebra: black = baseline, yellow = shifted follow-up (raw data), red = spatial synchronized follow-up (transposed data)

Discussion

This thesis was the first to investigate whether patient-reported outcomes following SMT were affected by the target site, using quantifiable and reproducible measures. Furthermore, this was the first study to look at the variation in pain sensitivity using a comprehensive QST battery in persistent LBP patients treated with SMT. Also, we examined time and group dependent measures, using multiple dichotomized responder cut points. We added existing knowledge to the pain field by performing a latent class analysis, allowing us to understand baseline differences within a persistent pain population and extracting this information to examine changes following SMT. We also explore the linkage between biomechanical and neurophysiological measures.

Additionally, we conducted a systematic review, including the results from Manuscript I (Target site for NRS). We included ten studies and extracted a total of 29 between-group difference/effect sizes, where only one demonstrated a statistically significant effect favoring SMT at a specific target versus a comparator target.

Finally, we presented a technological aspect allowing future researchers to synchronize stiffness data spatially. Thus, overcoming the consistent returning issue of locating vertebrae through palpation (113,114).

Correlation between the regional experimental measures

We unexpectedly found that the correlation between vertebral stiffness and pain sensitivity was opposite to what we, a-priori, hypothesized. The participants with the highest degrees of stiffness also had the highest pain thresholds; this was clearer for mechanical deep pain sensitivity (*moderate correlation*) than superficial thermal pain sensitivity (*poor correlation*). These correlations were constant across all segments. There are multiple reasons why we found this result and why we perhaps should not have been as surprised as we were initially.

Lumbar stiffness might be an adaptive mechanical protective system (115) that could act in two distinct ways: i) as a neurophysiological response that decreases the nociceptive activity, and ii) as a physiological mediation where the participant perceives the spine as more resilient to external forces and vice versa for a less stiff spine. In both instances, this would

explain the correlation observed. While theoretically plausible, we are not aware of any research examining this. However, research in healthy volunteers suggests that a noxious stimulus to the lower back increases stiffness (116), but not PPT (117).

We also found a *good* correlation between PPT and HPT; this was expected and is congruent with similar research (118). Despite this correlation, the two parameters' peripheral processing theoretically differs, as PPT is related to deep tissue pain sensitivity, and HPT involves peripheral skin pain sensitivity (119). This suggests that there is a shared central modulation.

Differences between vertebrae

We found minor associations between the measured vertebra and vertebral stiffness and deep pain sensitivity, which reached statistical significance for stiffness. Here, the most caudal vertebrae differed from the most cranial. However, this difference was at a maximum of 11% (L5 and L2). This is only marginally higher than the mean manual detectable threshold at approximately 8% (120). Thus, it is likely difficult to differentiate between vertebrae of closer proximity. Another aspect that this analysis did not consider was the VT's standard error of measurement (65), which only further makes the differentiation between vertebrae more difficult to apprehend.

The QST scores were more constant and showed less variation between vertebrae. This is consistent with a previous study conducted at our lab (19). In comparison, this might be a phenomenon explicitly due to the enrolled participants' persistent pain state, where we would expect that the encompassed generalized hyperalgesia would limit between vertebra differences. However, this may differ for acute LBP patients or patients with radiculopathy, who could have a single vertebral level causing dismay. This is only speculative, and we are unaware of other topographic studies mapping QST procedures for the mentioned samples. The finding also appears to be consistent with healthy subjects (19,121). Although it is speculative, the lack of distinctions between vertebrae could be due to a substantial overlap of neural activity, as demonstrated when testing PPT at L1 and L5 in healthy subjects (122). This overlap would arguably increase due to perturbations in the somatosensory system's neurological mapping as the pain persists (123–126).

Latent class analysis

We split the sample using a latent class analysis approach between those with high and low pain sensitivity, i.e., generalized hyperalgesia or not. We expected this result a priori as the different QST parameters appear to correlate independently of the sensory input (118); further, similar findings are available in the literature (127).

Patient-reported outcomes

Overall, participants improved at a statistically significant level for both NRS and ODI at all time points, independent of how the sample was faceted. However, across analyses, there were no between-group differences. While we observed statistically significant mean changes within-group, these were most likely not clinically relevant. Further, when we dichotomized at different responder cut points, the minority improved by 50%, and as much as 24% had more pain at the final follow-up. These generally low scores could be due to the sample chosen. All participants were enrolled through a secondary care hospital specializing in persistent back pain syndromes.

Another potential was the intervention design, as it simply was not sufficient to induce a clinically relevant response. We limited the SMT sessions to four, as we wanted to examine the mechanistic effect of randomizing between different targets. The four sessions were applied from a prior study (128) to differentiate SMT responders and non-responders. Thus, we may not observe SMT's potential effects, but again, this was not the study's aim. Another reason could be that we limited the intervention to a single SMT thrust, excluding exercise, soft-tissue therapy, or other adjacent therapies. We did not adjust any of the models for cavitation, as this was achieved for most of the sessions. Noticeably, there was a discrepancy between cavitation and subjective success, a not surprising finding (129).

We also failed to report a between-group difference in the systematic review. Overall, this indicates that SMT's potential effect is not mediated by applying SMT at a specific target than a comparator target. This is interesting as much research is conducted on animal models that conclude the specificity as necessary for neurophysiological and biomechanical changes (76–78,130). Somehow these specific changes do not translate into either human tissue or the human perception of clinical improvement. A potential reason could be the non-specificity

associated with SMT; if cavitation is considered a proxy for mechanical affection, multiple vertebrae are influenced by a single SMT thrust (131–133). The non-specificity would, in part, explain why we did not observe any between-group differences for studies comparing SMT at the same vertebra, the same region, or even close distant regions, i.e., lower cervical and upper thoracic. However, it does not explain the lack of difference when applying SMT at the upper thoracic spine for LBP. This indicates that multiple factions play a role in clinical improvement following SMT. Contextual contributions are likely of more importance than actual biomechanical and neurophysiological changes (62,134–137). Additionally, the same findings are also present for a non-thrust mobilization, where a clinician-determined target is not superior to a random target (138) or a prescriptive target (139). Further supporting the notion of contextual contributions, as the cavitation aspect is eliminated for non-thrust mobilization while animal studies also indicate target specificity (140)

However, we should not view this as a limitation of SMT but rather as an opportunity. Suppose participants equally perceive pain relief at a distant target compared to targeting the suspected source of nociception. In that case, it may be the optimal way to apply manual therapy in the management of specific LBP, e.g., disc herniations and osteopathic compression fractures. Clinicians could simply deliver the thrust at a distant target, expecting to see clinical benefits.

Vertebral stiffness

We can safely estimate that this cohort did not have any tangible changes in stiffness. Thus, we failed to replicate the findings of Fritz et al. (45) and Wong et al. (46). Our results were comparable to Xia et al., who also performed SMT on a persistent LBP population (141) and Pagé et al., who also measured stiffness in a persistent pain population albeit thoracic back pain (142). Therefore, this raises the question of whether SMT actually modulates stiffness or if the measure, VT, is appropriate for the research in question. In contrast, animal studies indicate a definite effect that differs between vertebra target (43,76) and contact points (77,78,130). This non-invasive method of testing is not comparable to these rigorous, designed animal models – furthermore, we did not find any differences across vertebrae.

Possibly, other measures may be more appropriate in eligible human participants, such as disc-diffusion (46), electromyographic changes (143), or even range of motion (144).

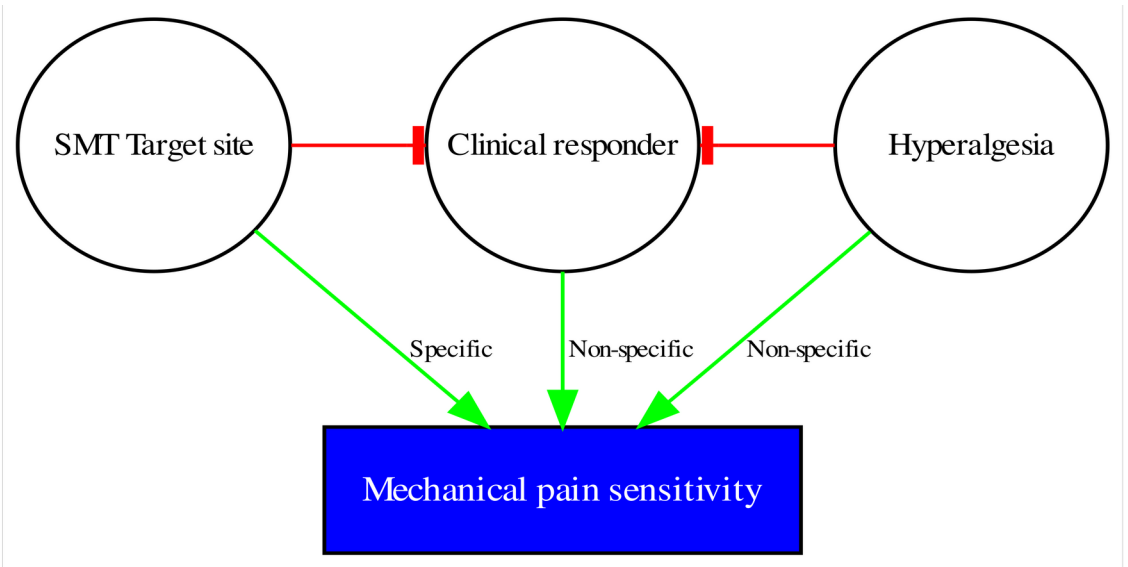
Another more clinical theory could be the pain persistence of this cohort. Arguably, the stiffness observed in this cohort could be due to more degenerative changes, intervertebral fibrosis, or muscle atrophy, while in a more acute or less affected pain population, it may be due to inflammation or muscle guarding. Despite this being theoretical, SMT responders appear to have a lower prevalence of disc degeneration and better disc diffusion (46,145,146); thereby, questioning whether SMT affects the complex paradigm surrounding the facet joints as an indirect measure of joint function. In other words, vertebral stiffness does not necessarily decrease upon clinical improvement. Instead, improvements could be inclined with changes in the intervertebral disc material. However, this is speculative, and we lack more research to answer this sufficiently.

Regional deep mechanical pain sensitivity

Figure 21, illustrates the three different instances we observed modulation of regional deep mechanical pain sensitivity. We do not know of any other studies that describe a causal vertebral effect on PPT when applying SMT in humans (I). The changes observed appear to be due to a vertebral neurophysiological reflex mediated normalization of deep mechanical pain sensitivity. However, this increase had no apparent clinical benefit, and we have to question whether the increase observed is of any relevance. Furthermore, this observation questions the importance of some mechanistic research conducted in healthy subjects. If, e.g., PPT can increase as a neurophysiological reflex, how do we know whether this increase is clinically relevant? This argument extends beyond the prior mentioned research conducted on QST changes following SMT (50–52), but also other aspects such as the hypoalgesic effect of exercise (147). However, and in contrast, we also saw a reversal of deep mechanical hyperalgesia as a non-specific effect through improvements in patient-reported outcomes (II) independent of the vertebra target. Two different theories could explain this: i) a curative effect on a mechanical vertebral dysfunction specific to the SMT. There is literature suggesting that inhibition of a nociceptive trigger induces decreased pain sensitivity (47,148), and ii) an overall reduction in patient-reported outcomes independent of SMT. Finally, we observed increases for the participants categorized with generalized hyperalgesia. At the

same time, this could be regression towards the mean. However, the substantial effect observed, which was much higher than the remaining QST scores, and the stagnation following treatment goes against this theory. Another cause could be, as we observed in (I), a neurophysiological reflex dependent on participants with either low PPT scores or generally low QST scores. As mentioned before, this change was independent of clinical improvement and is of questionable relevance. However, the changes were constant across all vertebrae and not dependent on the SMT targeted vertebra.

Figure 21 Three pathways for changes in pressure pain threshold following spinal manipulative therapy



I. A specific increase was observed for the group receiving SMT at the vertebra target with the lowest mechanical pain sensitivity (pain group), independent of responder status.
II. A non-specific increase was observed for the group who improved at follow-up (responder group), independent of the targeted vertebra.
III. A non-specific increase was observed for the group demonstrating generalized hyperalgesia (sensitive group), independent of the targeted vertebra.

The literature concerning regional deep mechanical pain sensitivity changes following SMT is, as stated, conflicting (50–53). However, this study supports that SMT can modify PPT in three different instances, potentially explaining the contradictory results. Another potential cause is the heterogeneous populations, whereas we used persistent LBP patients, most likely having impaired hyperalgesic modulation. While this limited the clinical benefit expected to

be observed, we found this inclusion appropriate as the study was partially aimed at investigating the mechanism related to pain sensitivity changes.

We also chose multiple SMT sessions as opposed to one. If the effect has to be clinically relevant or aimed at dysfunctional vertebra, multiple sessions are most likely needed. Four studies tried to aim SMT at a specific spinal dysfunction (149–152), and while PPT increased, it did not increase more substantially than a prescriptive target when the results were pooled (51). The difficulty in these studies is locating spinal dysfunction. The quantifiable assessment using a pressure algometer may be more superior to indicating a "tender" vertebrae instead of palpation.

Quantitative sensory pain testing

While we provide evidence for regional deep mechanical pain sensitivity changes following SMT, our study findings were limited to this parameter. No other clinically relevant changes occurred across the remaining QST parameters.

For regional heat pain threshold, small increases were observed for both vertebra targets independent of generalized hyperalgesia. Also, we could not link the changes to clinical responsiveness. Thus, we provide more evidence to the existing literature that SMT does not affect superficial thermal pain sensitivity (51,153). This is not surprising as we presume that LBP originates in deep spinal tissues, and secondly, SMT affects muscles and joints, thereby not providing a general neurophysiological change (154).

For wPPT and wPTT, minor increases were observed at follow-up, with the minority of the subgroups reaching statistical significance. However, this appears merely to be regression towards the mean as no changes were observed directly post-SMT. Consequently, it does not appear likely that SMT has a delayed effect on widespread pain sensitivity. The literature concerning whether SMT has widespread modifications to pain sensitivity is conflicting (50,51,53). Our results suggest that SMT does not have a widespread effect on generalized pain sensitivity.

Only minor changes occurred for TS, and they were only relevant to discuss when subgrouped by generalized hyperalgesia. Here, the sensitive group showed higher pain sensitivity degrees throughout the study period and vice versa for the Not-sensitized group.

This was opposite to what we found for PPT and indicates that the Sensitized group increases its perturbations of the somatosensory system after SMT instead of improving. This is likely due to i) normal variation when testing TS in a large sample, ii) few TS responders were enrolled, or iii) the CccA did not provide a sufficient stimulus to induce TS.

To the authors' knowledge, this is the first study that examined within-group changes of CPM following SMT of the lumbar spine (155). While an attenuated CPM response is most likely an important factor in persistent pain (156), SMT does not appear to affect this parameter.

Methodological limitations

Design

We did not conduct a placebo-controlled trial comparing SMT to a sham intervention. Hence, we cannot shed light on the causality between SMT and the different outcomes. However, this was not the aim of the study. Any mechanical input to the lumbar spine could potentially provide similar findings (155,157,158). Nonetheless, we did randomize between the vertebrae targeted. There was no precedent on how this would function, and we knew from our pilot trial that the stiffest and most pain-sensitive vertebra could overlap. Therefore, we chose a ratio that used absolute values (Eq. 1). We could not account for any anatomical distributions naturally occurring. However, in retrospect, this does not appear to be of importance. The most caudal lumbar spine might be slightly stiffer than the cranial lumbar spine, and adjusting for this would not have made a difference. However, when scrutinizing our results, there were minimal differences between vertebrae, and no specific effects were observed for the vertebra where SMT was targeted. Additionally, the presented results are only applicable to secondary care persistent non-specific LBP patients.

This randomized trial was erroneously set up as a superiority trial, despite that we did not have an, a-priori, best-guess estimate of whether one group was superior to the other. Nevertheless, we did have an understanding that the between-group differences would be small, as our sample size calculations applied an 80% beta to determine an effect size of 1 point in NRS, instead of the usual minimum clinically important difference. To fully answer whether the two SMT targets' effect was equal, we should have designed an equivalence

study (159). Finally, we did not register the trial prospectively but retrospectively. We did not have a thorough statistical analysis plan before the analysis, which was a potential risk for unmindful reporting bias. Nevertheless, we do not believe to be influenced in a direction guided by the data, and we did answer the objectives we initially set forth.

Spinal manipulative therapy

We assumed that the targeted vertebra was treated per-protocol and did not control for this. However, in reality, the markings sometimes disappeared between SMT sessions. Hence, the chiropractor had to apply palpation to determine the vertebral level resulting in a thrust that only approximated the predetermined vertebra. As with all studies concerning manual therapy, as mentioned earlier, there were some non-systematic errors. In general, cavitation occurs on multiple levels, not only on the targeted vertebra (131), and we cannot control for the thrust speed and direction. Finally, the contact point potentially covers more than the targeted vertebra.

Experimental measures

While we do present a way to synchronize the VT data using another cohort, we did not apply this method to our results. We observed minimal changes for stiffness, and it does not seem likely that moving the trajectories under half a vertebra and including the remaining ~12% would result in any differences. The VT also requires further validation in a persistent pain population; it is currently unknown if the same measurement properties that we see in healthy subjects are applicable for persistent pain cohorts.

For the QST, only PPT was affected by the rater; we limited this bias by only using one rater experienced with the procedure. The remaining were all automated or computer-controlled.

Systematic review

The overall high quality of the studies included and the large sample sizes further endorse our results. We were unable to perform a meta-analysis as the inclusion criteria were broad, the SMT targets were highly heterogeneous, and they differed significantly within the different trials. However, we do not find this as a limitation but rather a strength. Despite the methodological differences, we consistently saw the same pattern across the studies.

The included studies all scored high on the custom-defined risk of bias assessment concerning SMT's novelty for the participants. This is a potentially significant concern for the risks of bias assessment. It is not unlikely that participants familiar with SMT have a pre-defined definition of SMT and where it should be applied. Still, even with this potential risk for response bias (160), the studies still failed to report any between-group differences, further soliciting the results.

Conclusion

The thesis supports the following conclusions:

- Targeting a specific vertebra using quantifiable stiffness and pain sensitivity does not improve the clinical outcome following SMT in persistent LBP (α).
- When applying a broad QST battery to a persistent LBP cohort, it is possible to categorize the participants into i) low generalized hyperalgesia and ii) high generalized hyperalgesia (γ).
- Changes in deep mechanical pain sensitivity following SMT depend on i) a vertebral reflex mediated normalization, without clinical importance (α), ii) a non-specific improvement when improving clinically (β), and iii) a generalized hyperalgesia pain state pre-treatment (δ).
- Spinal manipulative therapy did not affect biomechanical measures of stiffness, superficial pain sensitivity, widespread pain sensitivity, or centrally modulated pain sensitivity (α, β, δ).
- Higher degrees of lumbar stiffness correlated with lower degrees of lumbar pain sensitivity (ε).
- There were minor differences between vertebrae for both biomechanical stiffness and neurophysiological pain measures of questionable clinical relevance (ζ).
- When using the VT to test for spinal stiffness repeatedly, data can easily be spatially synchronized to overcome the difficulty of locating vertebrae (**post-hoc**).

Finally, the findings from our randomized trial were consistent with the remaining literature. Thus, there is no added benefit of applying SMT at a specific target versus a comparator target for patient-reported outcomes.

Perspectives

This thesis's results indicate that targeting a specific vertebra is not of importance for achieving clinical benefits. Potentially, the limited time that clinicians have to assess pain patients could be more cautiously stratified and utilized in a more meaningful fashion. The same argument could be made about some educational institutions. Here, educators arguably spent much time teaching students how to palpate for spinal dysfunctions. Furthermore, they likely teach SMT as a highly specific biomechanical intervention (161–163) that cannot be attributed to the available human evidence.

When applying the VT for repeated measurements, we would strongly recommend that the researchers spatially synchronize the stiffness data before data analyses. Another benefit of this approach is the elimination of static palpation from the examination procedure. Instead, it just has to be ensured that enough trajectory is measured repeatedly. Another aspect could be to eliminate the rolling device altogether. Possibly, the single indentation device results in a better stiffness outcome. Here, the indentation typically occurs at L3 or the lowest point of the lumbar lordosis, ensuring a more direct posterior-anterior measure. Additionally, instead of using wheels that roll over the paravertebral muscles, a small probe pressed directly on top of the spinous process (164) might be superior. However, this is speculative, and our data cannot support this argument. We did notice minimal differences between vertebrae, and no specific changes transpired at distinct vertebrae. Hence, using a single indentation would most likely not miss relevant clinical data. However, we have to keep in mind that we did not see any stiffness changes for this persistent pain cohort.

We would suggest when conducting future research on changes in PPT following SMT to control for the relevant and distinct instances we present in this thesis and to provide multiple sessions.

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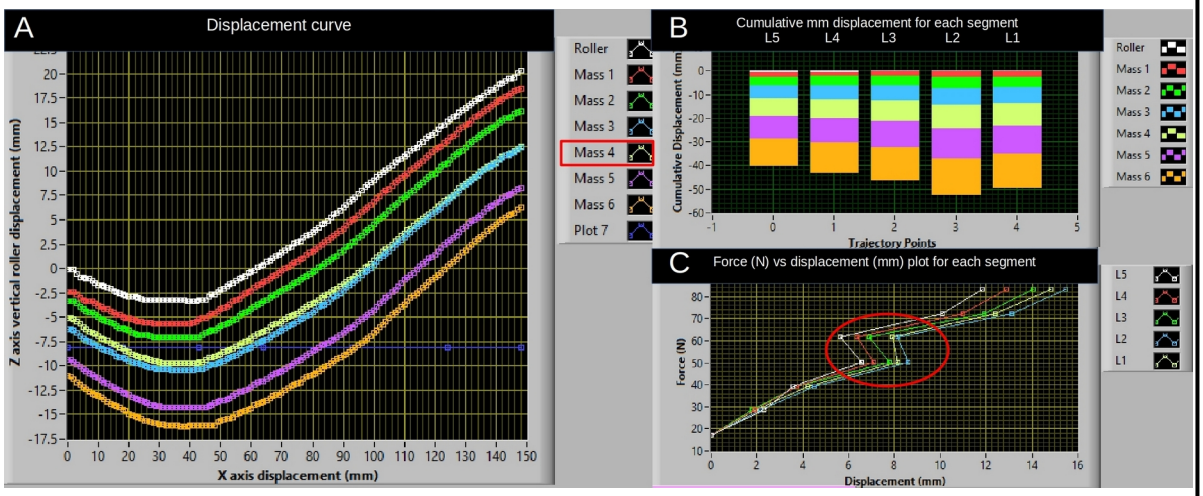
A. SUPPLEMENTARY MATERIAL

A1 Labview output



A) The displacement curve: y-axis vertical displacement for each trajectory point (x-axis), B) The cumulative displacement (mm) for each vertebra at different loads and C) The force-displacement (N/mm) curve for each vertebra. The light-yellow 40N line (mass 4) is being omitted as the displacement recorded was less than that recorded with 30N (mass 3), suggesting participant error. This is also illustrated by the skewness of the force-displacement curve in panel C (red circle).

A2 Literature search

Search string for the systematic review

PubMed

"Musculoskeletal Pain"[Mesh] OR “Musculoskeletal Pain” OR "neck pain"[MeSH Terms] OR “Neck Pain” OR "Back Pain"[Mesh] OR “Low Back Pain“ OR “Back Pain” OR “Thoracic pain” OR “spinal pain” AND
"Musculoskeletal Manipulations"[Mesh] OR manipu* OR "spinal adjust*" OR chiro* OR osteopath* AND
Segment OR level OR region OR specific OR site OR vertebra* OR clinic* OR direct* AND
gener* OR random OR nonspecific OR non-specific OR multiple OR prescript* OR non-region OR distant

Embase

musculoskeletal pain.mp. OR 'musculoskeletal pain'.ti,ab,kw. OR neck pain.mp. OR 'neck pain'.ti,ab,kw. OR low back pain.mp. OR 'low back pain'.ti,ab,kw. OR thorax pain.mp. OR 'thoracic pain'.ti,ab,kw. OR backache.mp. OR spinal pain.mp. OR 'back pain'.ti,ab,kw. OR 'spinal pain'.ti,ab,kw. AND
manipulative medicine.mp. OR 'manipulative medicine'.ti,ab,kw. OR manipu*.ti,ab,kw. OR 'spinal adjust*'.ti,ab,kw. OR chiro*.ti,ab,kw. OR osteopath*.ti,ab,kw. AND
Segment.ti,kw,ab. OR level.ti,ab,kw. OR specific.ti,ab,kw. OR site.ti,ab,kw. OR vertebra*.mp. OR vertebra*.ti,ab,kw. OR clinic*.ti,ab,kw. OR direct*.ti,ab,kw. AND
gener*.ti,ab,kw. OR random.ti,ab,kw. OR nonspecific.ti,ab,kw. OR non-specific.ti,ab,kw. OR multiple.ti,ab,kw. OR prescript*.ti,ab,kw. OR non-region.ti,ab,kw. OR distant.ti,ab,kw.

CINHAL

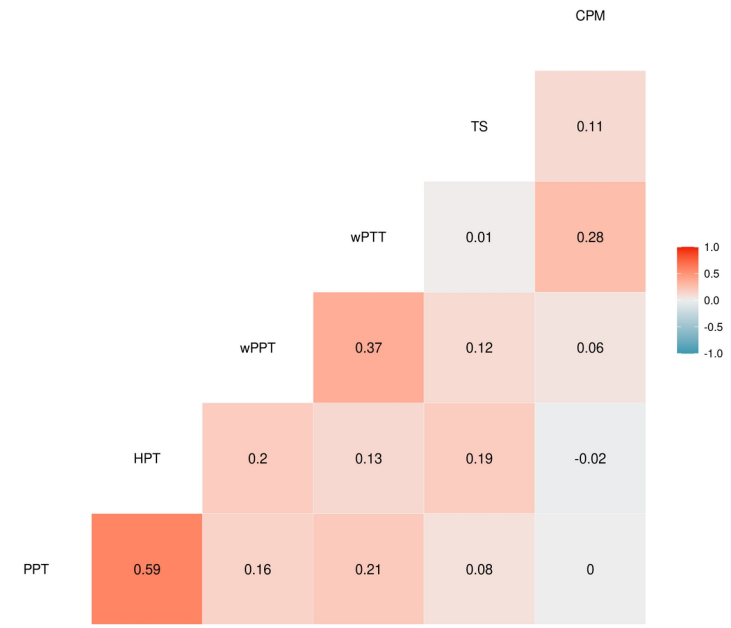
(MH "Muscle Pain") OR (MH "Low Back Pain") OR (MH “Back Pain”) OR (MH “Neck Pain”) OR “Low Back Pain“ OR “Back Pain” OR “Thoracic pain” OR “spinal pain” OR Neck pain AND
(MH "Manual Therapy") OR manipu* OR "spinal adjust*" OR chiro* OR osteopath* AND
(MH "Lumbar Vertebrae") OR (MH "Thoracic Vertebrae") OR (MH "Cervical Vertebrae") Segment OR level OR region OR specific OR site OR vertebra* OR clinic* OR direct* AND

Index to chiropractic literature

Subject:Musculoskeletal Pain OR All Fields:“Musculoskeletal Pain”, Peer Review only OR Subject:\"Neck Pain\", Peer Review only OR Subject:\\\"Low Back Pain\\\" OR Subject:\"Back Pain\", Peer Review only OR All Fields:Neck Pain OR All Fields:Back Pain OR All Fields:Low Back Pain OR All Fields:Thoracic pain OR All Fields:spinal pain AND
Subject:\\\"Musculoskeletal Manipulations\\\" OR Subject:\\\"Manipulation, Chiropractic\\\" OR All Fields:spinal adjust* OR All Fields:chiro* OR All Fields:osteopath* AND
All Fields:Segment OR All Fields:level OR All Fields:region OR All Fields:specific OR All Fields:site OR All Fields:vertebra* OR All Fields:clinic* OR All Fields:direct* OR Subject:\\\"Cervical Vertebrae\\\" OR Subject:\\\"Thoracic Vertebrae\\\" OR Subject:\\\"Lumbar Vertebrae\\\" AND
All Fields:gener* OR All Fields:nonspecific OR All Fields:non-specific OR All Fields:distant OR All Fields:distant OR All Fields:random OR All Fields:multiple OR All Fields:prescript* OR All Fields:non-region OR All Fields:distant

A3 Latent class analysis

Correlation matrix between the baseline QST scores



QST = Quantitative sensory pain test, PPT = Pressure pain threshold, HPT = Heat pain threshold, wPPT = Widespread pressure pain threshold, wPTT = Widespread pressure pain tolerance threshold, TS = Temporal summation, CPM = conditioned pain modulation

Latent class analysis, fitness and component cluster selection

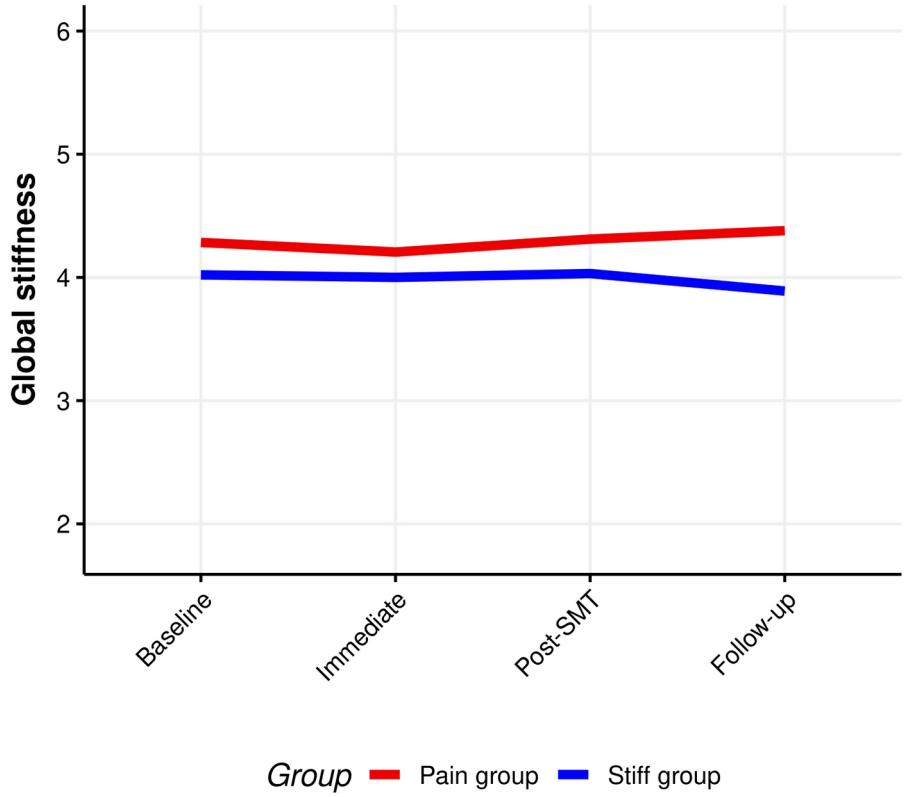
BIC	Probability of belonging to the cluster (>90%)	The Likelihood Ratio Test (p-value)	n in each cluster
-2152	85%	2 vs 3 groups: 22.2 (0.11)	1:38 2:89

BIC = Bayesian information criterion

A4 Global stiffness

Target site

Within-group changes and between-group differences in global stiffness (Target site)

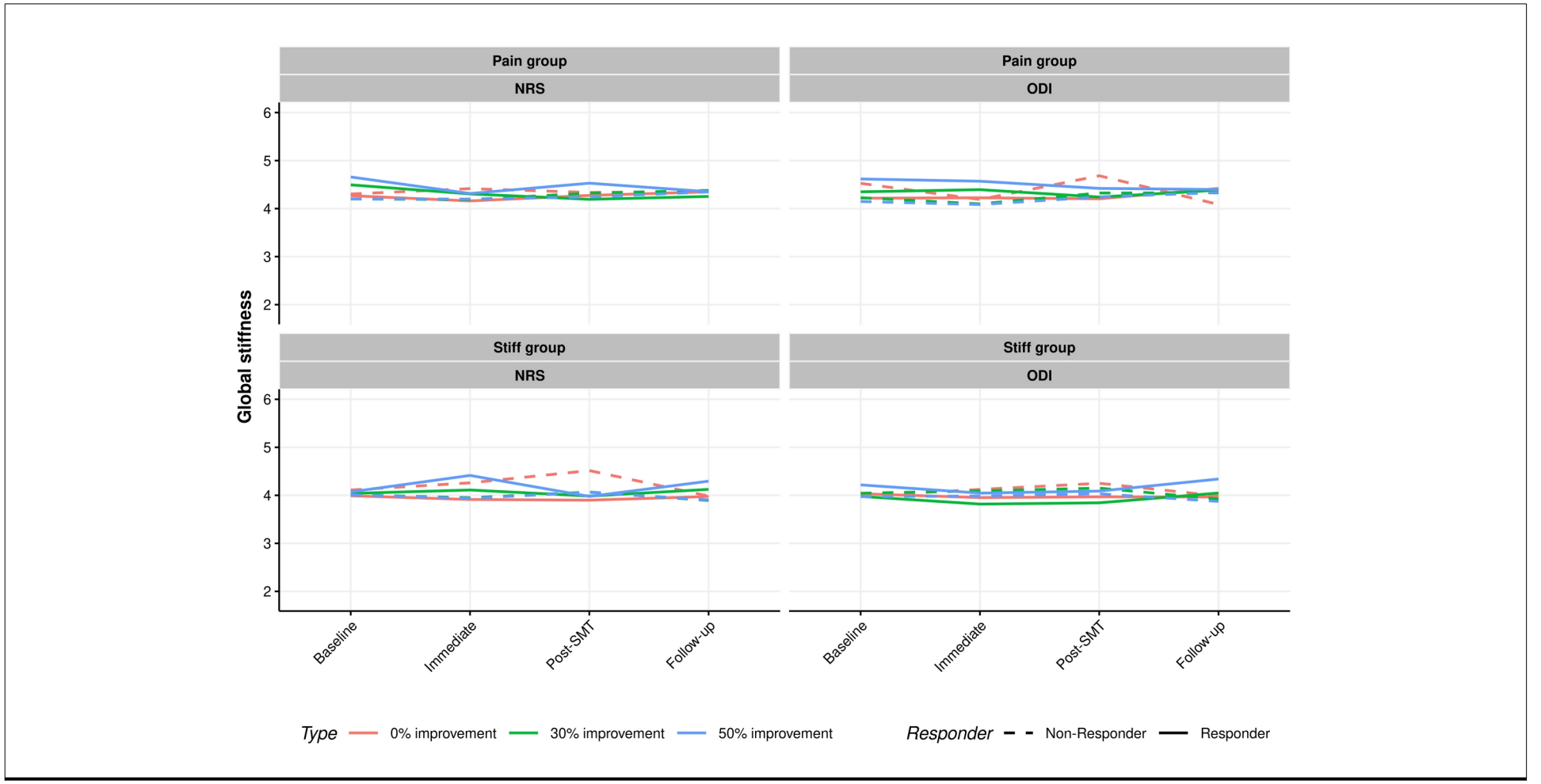


Time point	Mean difference (95 CI%)	P-value
Baseline - Immediate	0.1(-0.3 to 0.4)	0.91
Baseline - Post-SMT	0.0(-0.3 to 0.3)	~1
Baseline - Follow-up	-0.2(-0.6 to 0.1)	0.23

Within-group changes (figure) and between-group differences (table) in global stiffness [N/mm] following four sessions of SMT at either the stiffest vertebra (stiff group) or the most pain-sensitive segment (pain group). Presented as arithmetic means, 95% confidence intervals and the corresponding p-value
SMT = Spinal manipulative therapy, * = p-value < 0.05

Responder status

Within-group changes and between-group differences in global stiffness (Target site and responder status)



		Patient-reported LBP intensity		Disability	
		Pain group			
Time point	**Cut point**	**Mean difference (95 CI%)**	**P-value**	**Mean difference (95 CI%)**	**P-value**
Baseline - Immediate	0%	-0.2(-0.8 to 0.4)	0.86	0.3(-0.3 to 1.0)	0.57
Baseline - Post-SMT		-0.0(-0.7 to 0.6)	~1	-0.2(-0.9 to 0.5)	0.96
Baseline - Follow-up		0.0(-0.6 to 0.7)	~1	0.6(-0.1 to 1.3)	0.08
Baseline - Immediate	30%	-0.2(-0.8 to 0.4)	0.92	0.2(-0.4 to 0.7)	0.89
Baseline - Post-SMT		-0.4(-1.0 to 0.2)	0.33	-0.2(-0.8 to 0.4)	0.84
Baseline - Follow-up		-0.4(-1.1 to 0.2)	0.38	-0.1(-0.6 to 0.5)	~1
Baseline - Immediate	50%	-0.3(-1.0 to 0.4)	0.65	0.0(-0.6 to 0.6)	~1
Baseline - Post-SMT		-0.2(-0.9 to 0.6)	0.97	-0.3(-0.9 to 0.3)	0.65
Baseline - Follow-up		-0.5(-1.2 to 0.3)	0.45	-0.4(-1.0 to 0.2)	0.36

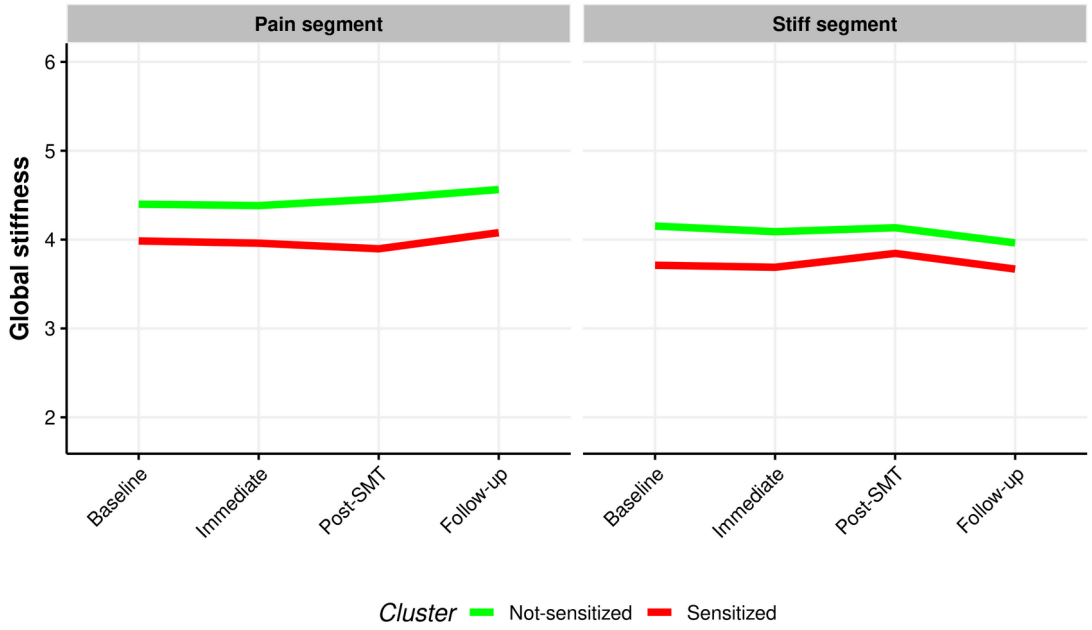
				Stiff group	
Baseline - Immediate		-0.2(-0.8 to 0.4)	0.57	-0.2(-0.8 to 0.4)	0.85
Baseline - Post-SMT	0%	-0.5(-1.1 to 0.2)	0.96	-0.3(-0.9 to 0.3)	0.58
Baseline - Follow-up		0.1(-0.5 to 0.8)	0.08	-0.1(-0.7 to 0.6)	~1
Baseline - Immediate		0.1(-0.5 to 0.7)	0.89	-0.2(-0.8 to 0.7)	0.84
Baseline – Post-SMT	30%	-0.1(-0.7 to 0.5)	0.84	-0.2(-0.8 to 0.4)	0.79
Baseline - Follow-up		0.2(-0.4 to 0.8)	~1	0.2(-0.4 to 0.8)	0.90
Baseline - Immediate		0.4(-0.4 to 1.2)	~1	-0.2(-0.9 to 0.5)	0.94
Baseline - Post-SMT	50%	-0.1(-0.9 to 0.6)	0.65	-0.2(-0.9 to 0.5)	0.95
Baseline - Follow-up		0.3(-0.4 to 1.1)	0.36	0.2(-0.5 to 0.9)	0.90

Within-group changes (figure) and between-group differences (table) in global stiffness [N/mm] for 50, 30 and 0% improvements in patient-reported low back pain intensity and disability following four sessions of SMT at either the stiffest vertebra (stiff group) or the most pain-sensitive segment (pain group). Presented as arithmetic means, 95% confidence intervals and the corresponding p-value.

NRS = Numerical rating scale, ODI = Oswestry disability index, SMT = Spinal manipulative therapy, * = Significant changes in responders from baseline to post-SMT. ** = Significant changes in responders from baseline to follow-up. # = Significant changes in non-responders from baseline to post-SMT. ## = Significant changes in non-responders from baseline to follow-up

General hyperalgesia

Within-group changes and between-group differences in global stiffness (Target site and pain hypersensitivity)

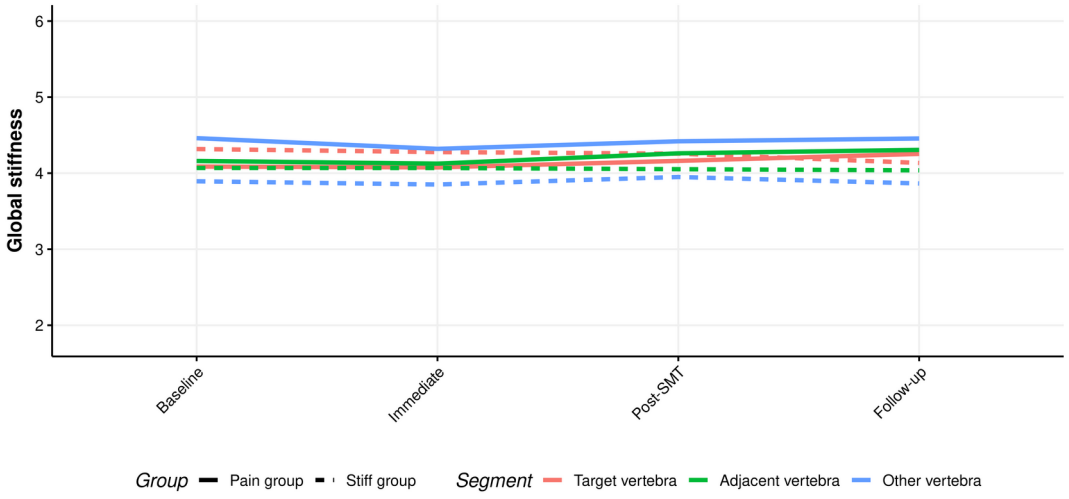


Time point	Target	Mean difference (95 CI%)	P-value
Baseline - Immediate	Pain group	0.0(-0.5 to 0.6)	~1
	Stiff group	-0.0(-0.7 to 0.6)	~1
Baseline - Post-SMT	Pain group	0.2(-0.4 to 0.7)	0.95
	Stiff group	-0.2(-0.8 to 0.5)	0.95
Baseline - Follow-up	Pain group	0.1(-0.5 to 0.6)	~1
	Stiff group	-0.2(-0.8 to 0.5)	0.96

Within-group changes (figure) and between-group differences (table) for the not-sensitized group and sensitized group in global stiffness [N/mm] following four sessions of SMT at either the stiffest vertebra (stiff group) or the most pain-sensitive segment (pain group). Presented as arithmetic means, 95% confidence intervals and the corresponding p-value.
SMT = Spinal manipulative therapy, * = p-value < 0.05

Target site by vertebra

Changes in global stiffness by vertebral target



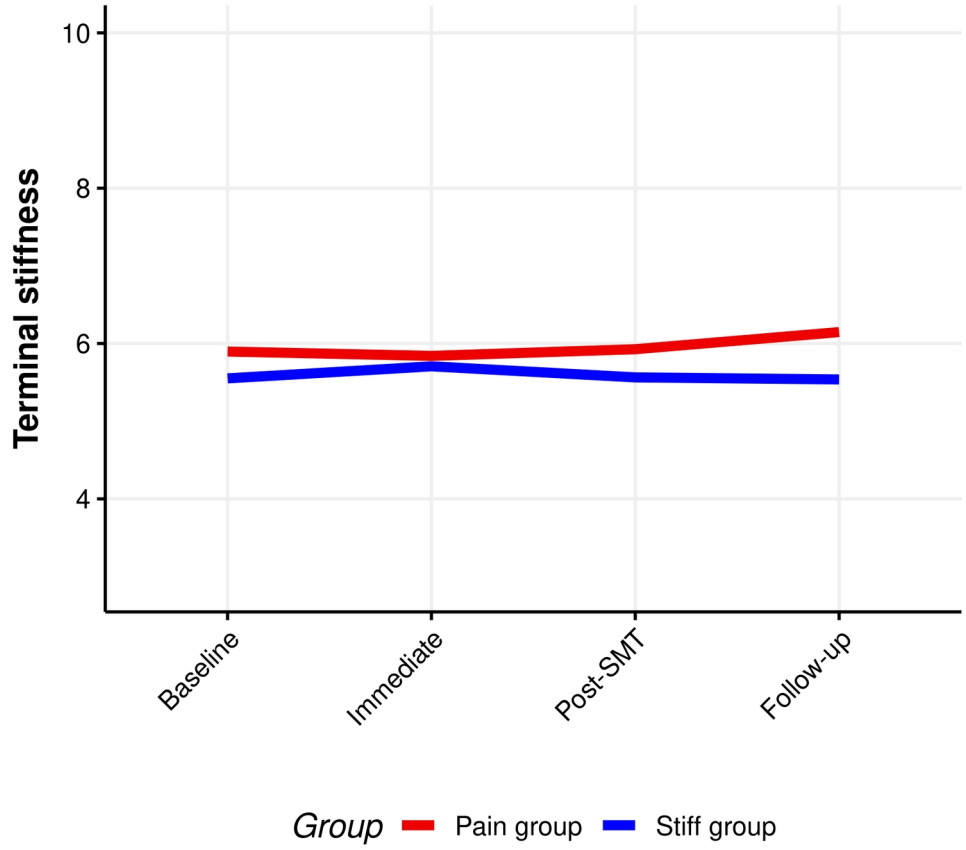
Arithmetic mean values for global stiffness [N/mm] following four sessions of SMT at either the stiffest vertebra (stiff group) or the most pain-sensitive segment (pain group). Vertebrae are categorized as the vertebra targeted, the adjacent vertebrae to the targeted and all other vertebrae

SMT = Spinal manipulative therapy

A5 Terminal stiffness

Target site

Within-group changes and between-group differences in terminal stiffness (Target site)



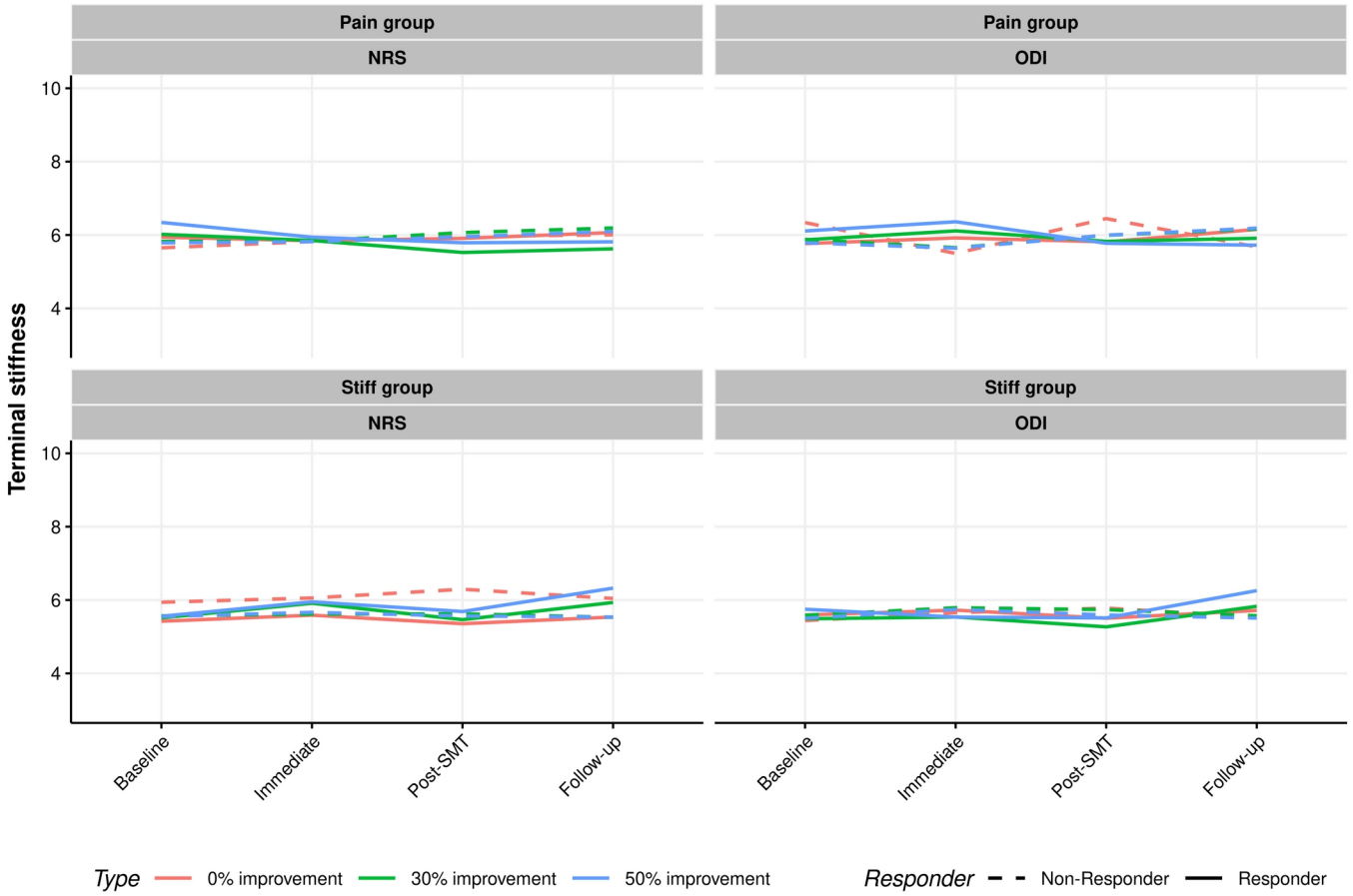
Time point	Mean difference (95 CI%)	P-value
Baseline - Immediate	0.2(-0.4 to 0.8)	0.67
Baseline - Post-SMT	0.0(-0.6 to 0.6)	~1
Baseline - Follow-up	-0.3(-0.8 to 0.3)	0.53

Within-group changes (figure) and between-group differences (table) in terminal stiffness [N/mm] following four sessions of SMT at either the stiffest vertebra (stiff group) or the most pain-sensitive segment (pain group). Presented as arithmetic means, 95% confidence intervals and the corresponding p-value

SMT = Spinal manipulative therapy, * = p-value < 0.05

Responder status

Within-group changes and between-group differences in terminal stiffness (Target site and responder status)



		Patient-reported LBP intensity		Disability	
		Pain group			
Time point	**Cut point**	**Mean difference (95 CI%)**	**P-value**	**Mean difference (95 CI%)**	**P-value**
Baseline - Immediate	0%	-0.3(-1.4 to 0.9)	0.96	1.0(-0.2 to 2.2)	0.14
Baseline - Post-SMT		-0.3(-1.5 to 0.8)	0.92	-0.1(-1.4 to 1.2)	~1
Baseline - Follow-up		-0.2(-1.4 to 1.0)	0.98	1.1(-0.2 to 2.3)	0.15
Baseline - Immediate	30%	-0.2(-1.3 to 0.9)	0.99	0.5(-0.5 to 1.4)	0.66
Baseline - Post-SMT		-0.7(-1.9 to 0.4)	0.38	-0.2(-1.2 to 0.9)	0.99
Baseline - Follow-up		-0.8(-1.9 to 0.4)	0.38	-0.2(-1.3 to 0.8)	0.97
Baseline - Immediate	50%	-0.4(-1.7 to 0.8)	0.88	0.4(-0.7 to 1.4)	0.82
Baseline - Post-SMT		-0.7(-2.0 to 0.6)	0.56	-0.5(-1.6 to 0.5)	0.63
Baseline - Follow-up		-0.8(-2.2 to 0.5)	0.43	-0.8(-1.9 to 0.3)	0.29

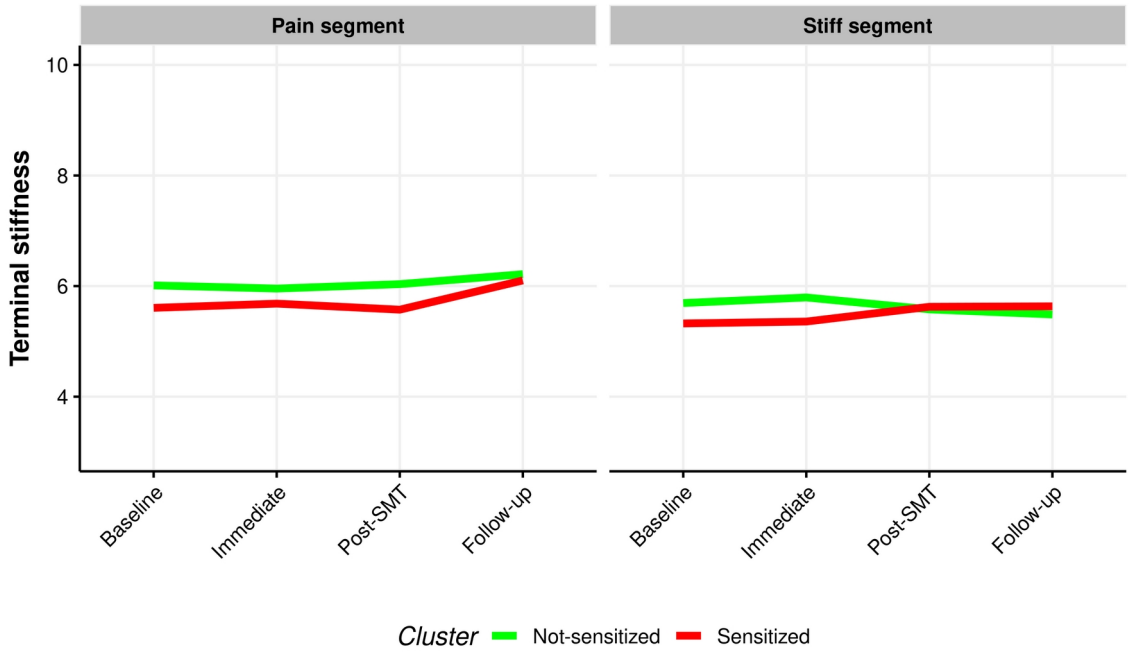
		Stiff group			
Baseline - Immediate	0%	0.1(-1.1 to 1.2)	~1	-0.1(-1.2 to 1.0)	~1
Baseline - Post-SMT		-0.4(-1.6 to 0.8)	0.86	-0.4(-1.6 to 0.7)	0.83
Baseline - Follow-up		0.01(-1.2 to 1.2)	~1	0.0(-1.1 to 1.2)	~1
Baseline - Immediate	30%	0.4(-0.7 to 1.4)	0.89	-0.2(-1.2 to 0.9)	0.99
Baseline – Post-SMT		-0.1(-1.2 to 1.0)	~1	-0.4(-1.5 to 0.7)	0.87
Baseline - Follow-up		0.5(-0.6 to 1.6)	0.77	0.4(-0.7 to 1.4)	0.89
Baseline - Immediate	50%	0.3(-1.2 to 1.7)	0.98	-0.5(-1.7 to 0.8)	0.83
Baseline - Post-SMT		0.1(-1.3 to 1.5)	~1	-0.3(-1.6 to 1.0)	0.95
Baseline - Follow-up		0.8(-0.6 to 2.2)	0.53	0.5(-0.8 to 1.8)	0.80

Within-group changes (figure) and between-group differences (table) in terminal stiffness [N/mm] for 50, 30 and 0% improvements in patient-reported low back pain intensity and disability following four sessions of SMT at either the stiffest vertebra (stiff group) or the most pain-sensitive segment (pain group). Presented as arithmetic means, 95% confidence intervals and the corresponding p-value.

NRS = Numerical rating scale, ODI = Oswestry disability index, SMT = Spinal manipulative therapy, * = Significant changes in responders from baseline to post-SMT. ** = Significant changes in responders from baseline to follow-up. # = Significant changes in non-responders from baseline to post-SMT. ## = Significant changes in non-responders from baseline to follow-up

General hyperalgesia

Within-group changes and between-group differences in terminal stiffness (Target site and pain hypersensitivity)



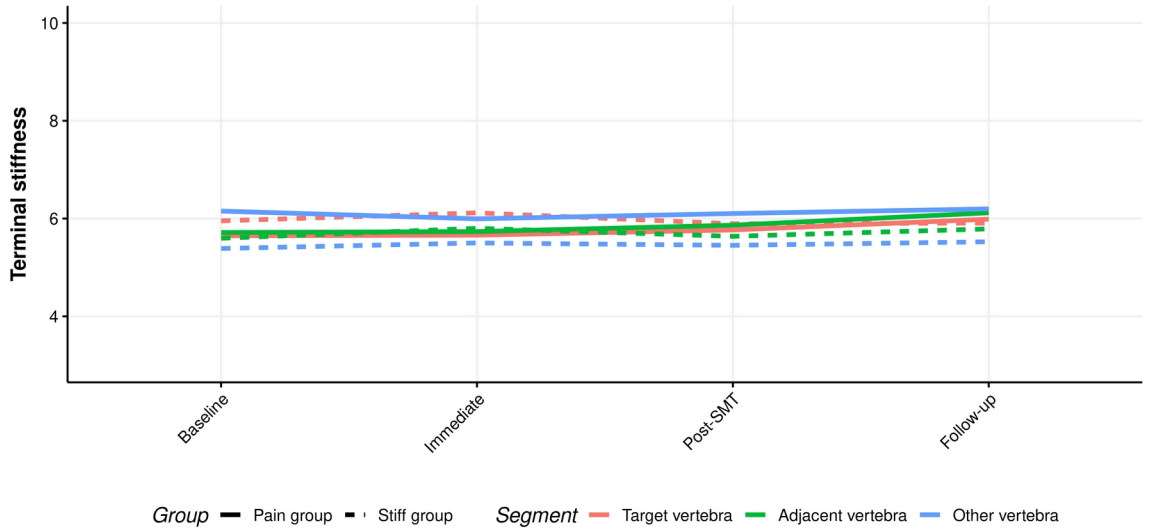
Time point	Target	Mean difference (95 CI%)	P-value
Baseline - Immediate	Pain group	-0.1(-1.1 to 0.8)	~1
	Stiff group	0.1(-1.0 to 1.2)	~1
Baseline - Post-SMT	Pain group	0.1(-0.9 to 1.1)	~1
	Stiff group	-0.4(-1.5 to 0.7)	0.82
Baseline - Follow-up	Pain group	-0.3(-1.3 to 0.7)	0.92
	Stiff group	-0.5(-1.6 to 0.6)	0.68

Within-group changes (figure) and between-group differences (table) for the not-sensitized group and sensitized group in terminal stiffness [N/mm] following four sessions of SMT at either the stiffest vertebra (stiff group) or the most pain-sensitive segment (pain group). Presented as arithmetic means, 95% confidence intervals and the corresponding p-value.

SMT = Spinal manipulative therapy, * = p-value < 0.05

Target site by vertebra

Changes in terminal stiffness by vertebral target



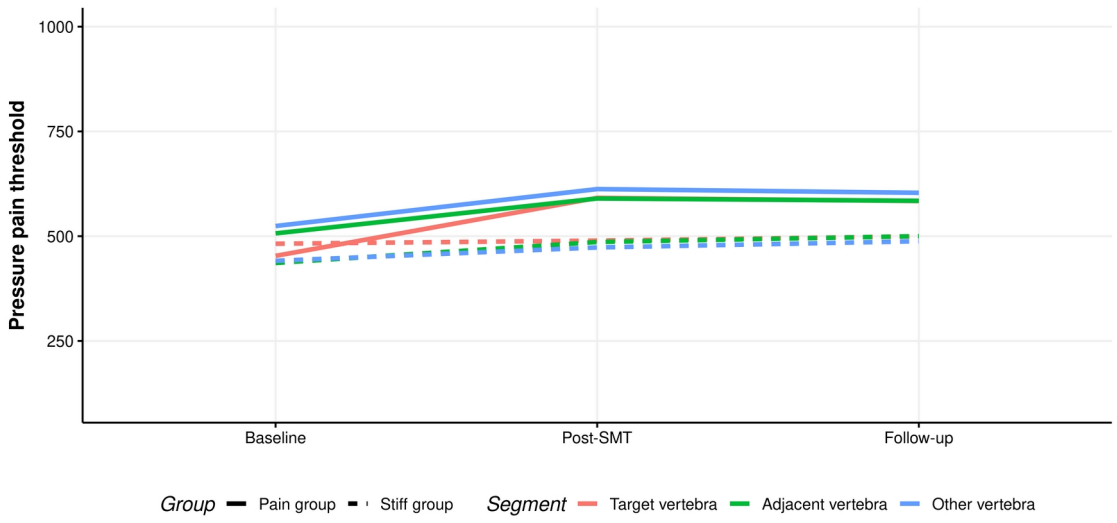
Arithmetic mean values for terminal stiffness [N/mm] following four sessions of SMT at either the stiffest vertebra (stiff group) or the most pain-sensitive segment (pain group). Vertebrae are categorized as the vertebra targeted, the adjacent vertebrae to the targeted and all other vertebrae

SMT = Spinal manipulative therapy

A6 Pressure pain threshold

Target site by vertebra

Changes in pressure pain threshold by vertebral target



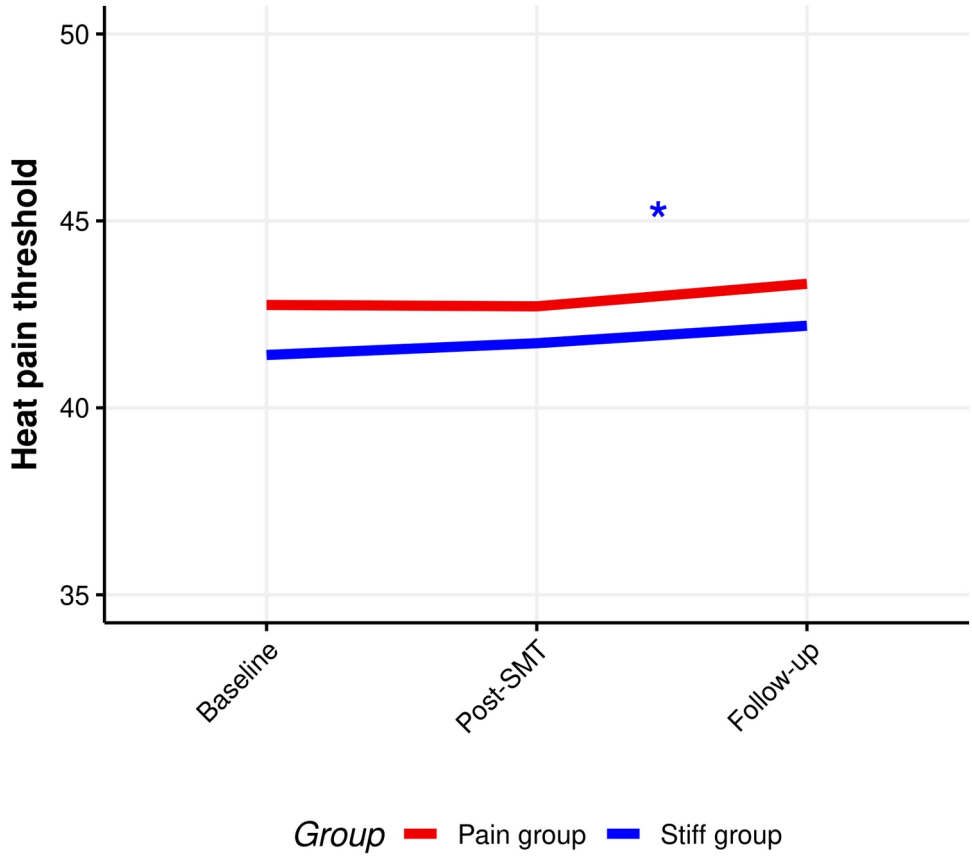
Arithmetic mean values for pressure pain threshold [kPa] following four sessions of SMT at either the stiffest vertebra (stiff group) or the most pain-sensitive segment (pain group). Vertebrae are categorized as the vertebra targeted, the adjacent vertebrae to the targeted and all other vertebrae

SMT = Spinal manipulative therapy

A7 Heat pain threshold

Target site

Within-group changes and between-group differences in heat pain threshold (Target site)



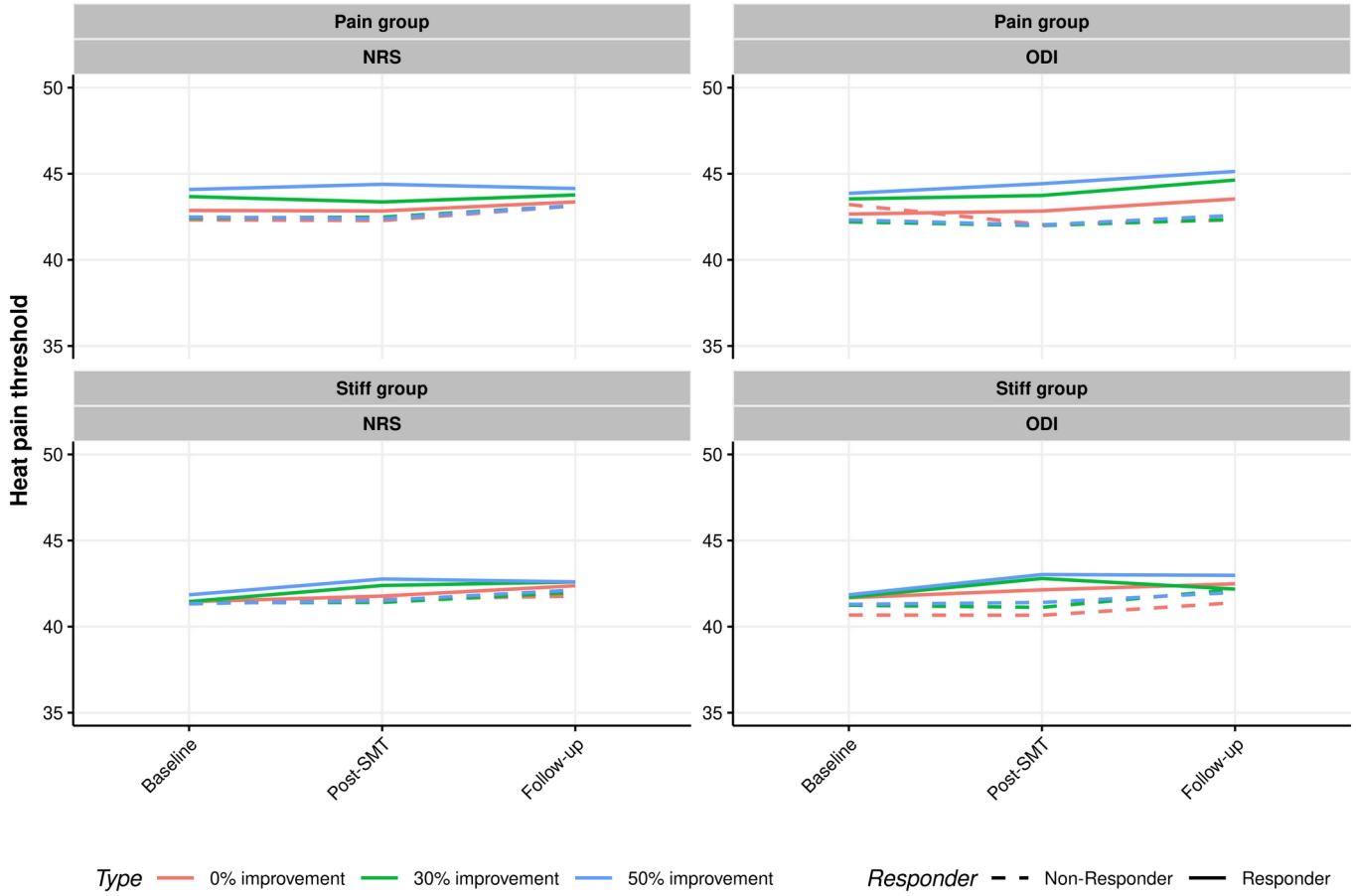
Time point	Mean difference (95 CI%)	P-value
Baseline - Post-SMT	0.4(-0.7 to 1.4)	0.69
Baseline - Follow-up	0.2(-0.8 to 1.3)	0.88

Within-group changes (figure) and between-group differences (table) in heat pain threshold [°C] following four sessions of SMT at either the stiffest vertebra (stiff group) or the most pain-sensitive segment (pain group). Presented as arithmetic means, 95% confidence intervals and the corresponding p-value

SMT = Spinal manipulative therapy, * = p-value < 0.05

Responder status

Within-group changes and between-group differences in heat pain threshold (Target site and responder status)



		Patient-reported LBP intensity		Disability	
		Pain group			
Time point	**Cut point**	**Mean difference (95 CI%)**	**P-value**	**Mean difference (95 CI%)**	**P-value**
Baseline - Post-SMT	0%	0.0(-1.9 to 2.0)	~1	1.3(-0.9 to 3.6)	0.44
Baseline - Follow-up		-0.3(-2.4 to 1.7)	0.99	1.8(-0.4 to 3.9)	0.16
Baseline - Post-SMT	30%	-0.4(-2.2 to 1.5)	0.98	0.4(-1.2 to 2.0)	0.96
Baseline - Follow-up		-0.6(-2.5 to 1.3)	0.89	0.9(-0.7 to 2.6)	0.51
Baseline - Post-SMT	50%	0.4(-1.8 to 2.6)	0.99	0.9(-0.9 to 2.6)	0.66
Baseline - Follow-up		-0.6(-2.8 to 1.6)	0.94	1(-0.8 to 2.8)	0.54
		Stiff group			
Baseline - Post-SMT	0%	0.1(-1.9 to 2.1)	~1	0.5(-1.4 to 2.3)	0.95
Baseline - Follow-up		0.5(-1.5 to 2.4)	0.96	0.1(-1.8 to 2.0)	~1
Baseline - Post-SMT	30%	0.9(-0.9 to 2.7)	0.63	1.2(-0.5 to 3.0)	0.31
Baseline - Follow-up		0.5(-1.3 to 2.4)	0.93	-0.4(-2.3 to 1.4)	0.96

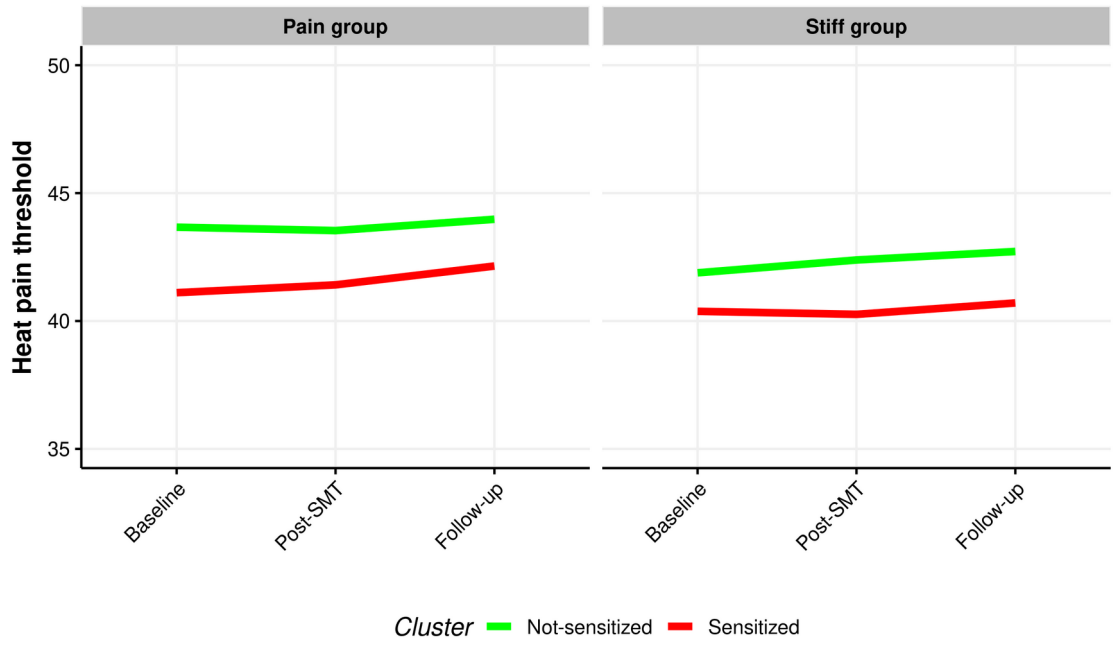
Baseline - Post-SMT	50%	0.7(-1.5 to 3.0)	0.90	1.1(-1.1 to 3.2)	0.63
Baseline - Follow-up		0.0(-2.4 to 2.3)	~1	0.4(-1.8 to 2.7)	0.98

Within-group changes (figure) and between-group differences (table) in heat pain threshold [°C] for 50, 30 and 0% improvements in patient-reported low back pain intensity and disability following four sessions of SMT at either the stiffest vertebra (stiff group) or the most pain-sensitive segment (pain group). Presented as arithmetic means, 95% confidence intervals and the corresponding p-value.

NRS = Numerical rating scale, ODI = Oswestry disability index, SMT = Spinal manipulative therapy, * = Significant changes in responders from baseline to post-SMT. ** = Significant changes in responders from baseline to follow-up. # = Significant changes in non-responders from baseline to post-SMT. ## = Significant changes in non-responders from baseline to follow-up

General hyperalgesia

Within-group changes and between-group differences in heat pain threshold (Target site and pain hypersensitivity)

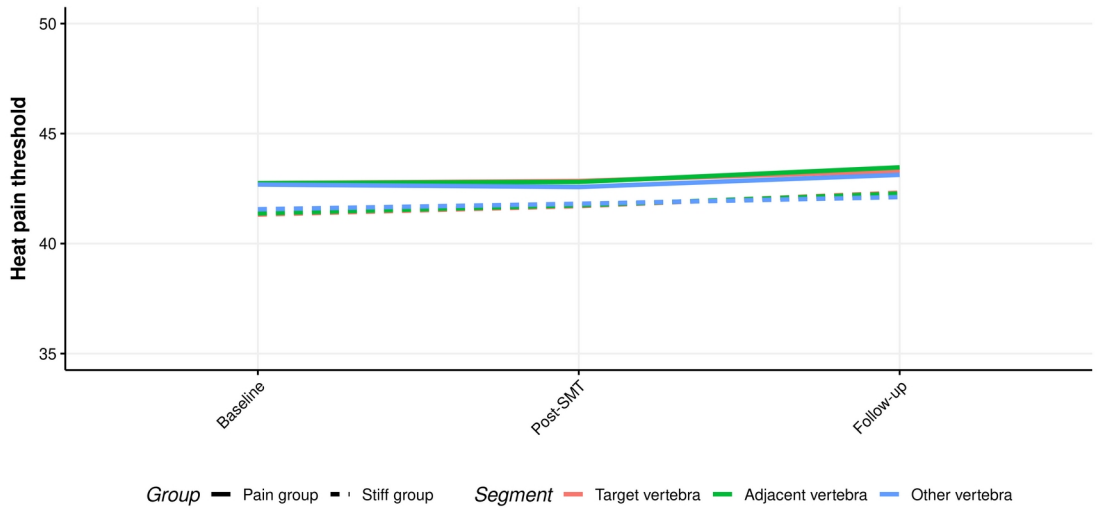


Time point	Target	Mean difference (95 CI%)	P-value
Baseline - Post-SMT	Pain group	-0.4(-2.0 to 1.1)	0.93
	Stiff group	0.6(-1.1 to 2.3)	0.85
Baseline - Follow-up	Pain group	-0.7(-2.3 to 0.8)	0.67
	Stiff group	0.5(-1.2 to 2.2)	0.92

Within-group changes (figure) and between-group differences (table) for the not-sensitized group and sensitized group in heat pain threshold [°C] following four sessions of SMT at either the stiffest vertebra (stiff group) or the most pain-sensitive segment (pain group). Presented as arithmetic means, 95% confidence intervals and the corresponding p-value.
SMT = Spinal manipulative therapy, * = p-value < 0.05

Target site by vertebra

Changes in heat pain threshold by vertebral target



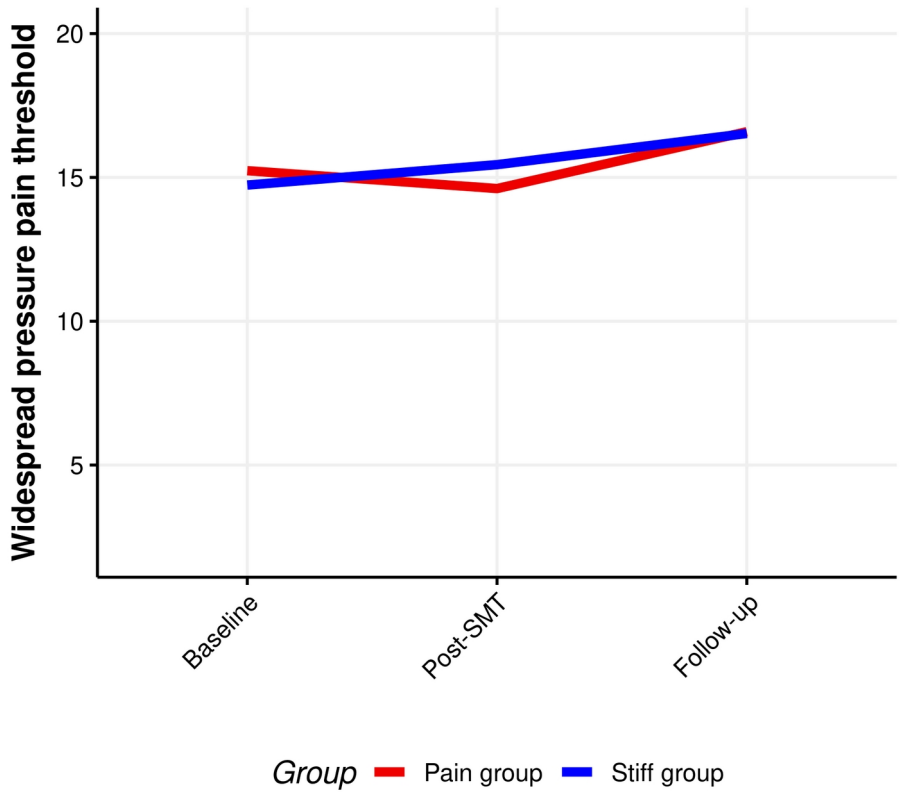
Arithmetic mean values for heat pain threshold [°C] following four sessions of SMT at either the stiffest vertebra (stiff group) or the most pain-sensitive segment (pain group). Vertebrae are categorized as the vertebra targeted, the adjacent vertebrae to the targeted and all other vertebrae

SMT = Spinal manipulative therapy

A8 Widespread pressure pain threshold

Target site

Within-group changes and between-group differences in widespread pressure pain threshold (Target site)

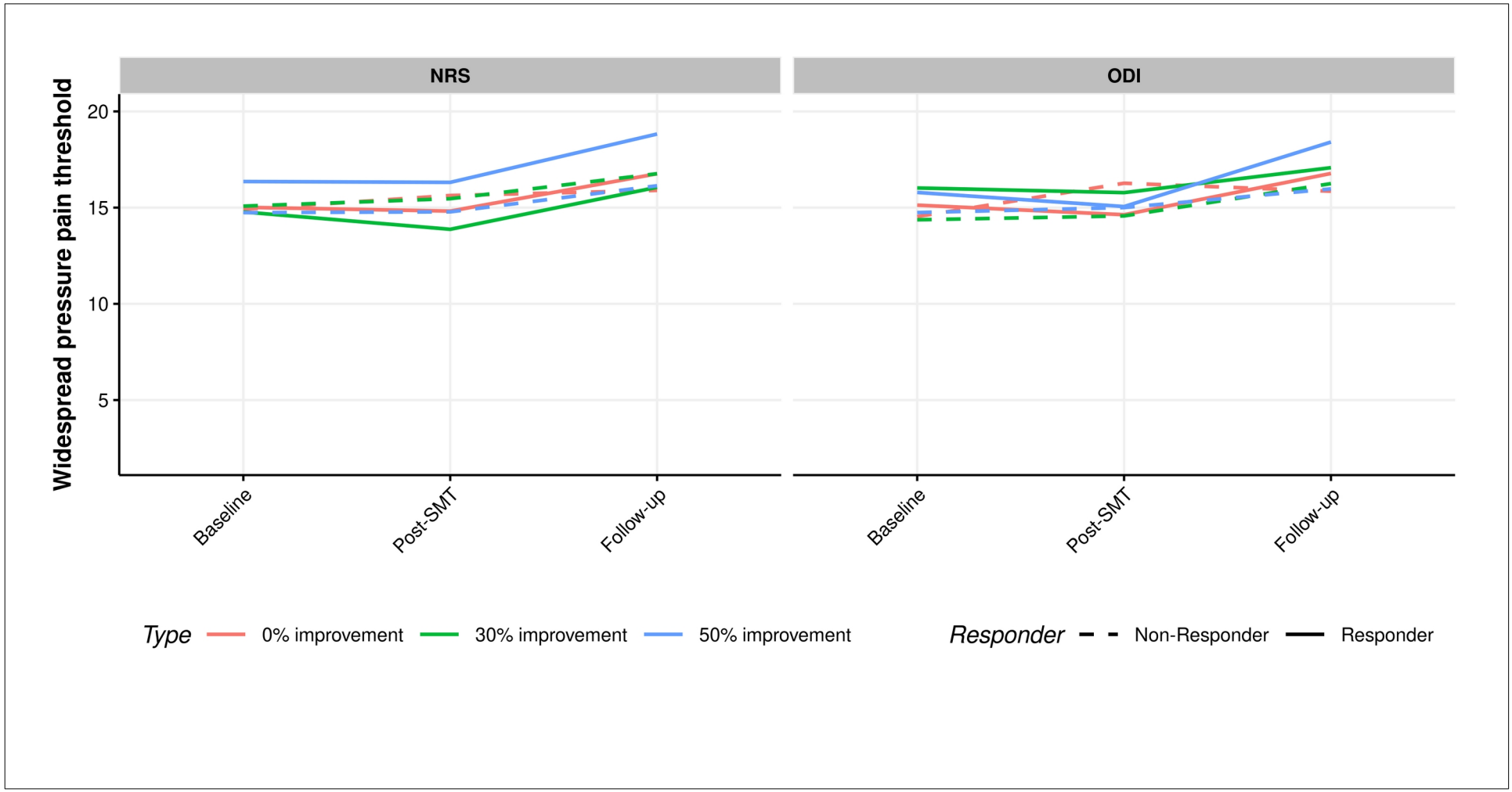


Time point	Mean difference (95 CI%)	P-value
Baseline - Post-SMT	1.3(-2.1 to 4.8)	0.63
Baseline - Follow-up	0.4(-3.0 to 3.9)	0.95

Within-group changes (figure) and between-group differences (table) in widespread pressure pain threshold [kPa] following four sessions of SMT at either the stiffest vertebra (stiff group) or the most pain-sensitive segment (pain group). Presented as arithmetic means, 95% confidence intervals and the corresponding p-value
SMT = Spinal manipulative therapy, * = p-value < 0.05

Responder status

Within-group changes and between-group differences in widespread pressure pain threshold (Responder status)



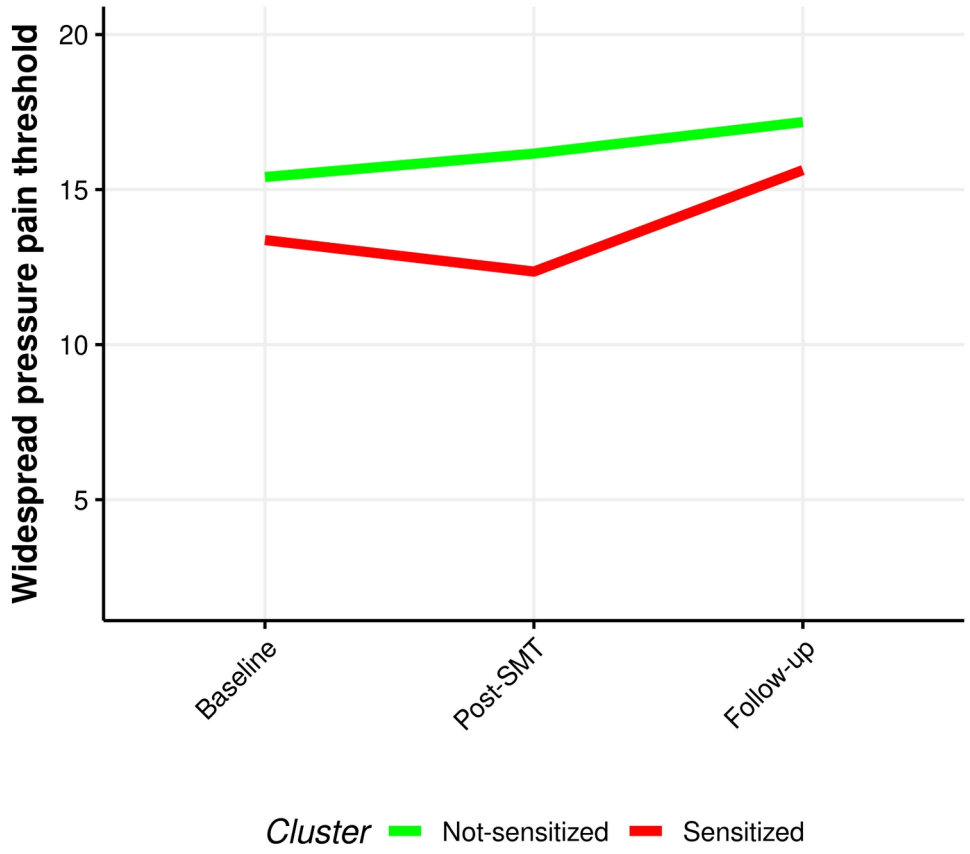
		Patient-reported LBP intensity		Disability	
Time point	**Cut point**	**Mean difference (95 CI%)**	**P-value**	**Mean difference (95 CI%)**	**P-value**
Baseline - Post-SMT	0%	-0.9(-4.9 to 3.1)	0.85	-2.2(-6.3 to 1.8)	0.39
Baseline - Follow-up		0.8(-3.3 to 4.8)	0.89	0.3(-3.9 to 4.3)	0.98
Baseline - Post-SMT	30%	-1.3(-5.1 to 2.5)	0.70	-0.4(-4.0 to 3.1)	0.95
Baseline - Follow-up		-0.4(-4.2 to 3.4)	0.96	-0.8(-4.4 to 2.7)	0.84
Baseline - Post-SMT	50%	-0.1(-4.9 to 4.7)	~1	-1.0(-5.0 to 3.0)	0.83
Baseline - Follow-up		1.1(-3.6 to 5.7)	0.85	1.4(-2.6 to 5.4)	0.68

Within-group changes (figure) and between-group differences (table) in widespread pressure pain threshold [kPa] for 50, 30 and 0% improvements in patient-reported low back pain intensity and disability following four sessions of SMT. Presented as arithmetic means, 95% confidence intervals and the corresponding p-value

NRS = Numerical rating scale, ODI = Oswestry disability index, SMT = Spinal manipulative therapy, * = Significant changes in responders from baseline to post-SMT. ** = Significant changes in responders from baseline to follow-up. # = Significant changes in non-responders from baseline to post-SMT. ## = Significant changes in non-responders from baseline to follow-up

General hyperalgesia

Within-group changes and between-group differences in widespread pressure pain threshold (Pain hypersensitivity)



Time point	Mean difference (95 CI%)	P-value
Baseline - Post-SMT	1.8(-2 to 5.5)	0.50
Baseline - Follow-up	-0.5(-4.2 to 3.2)	0.95

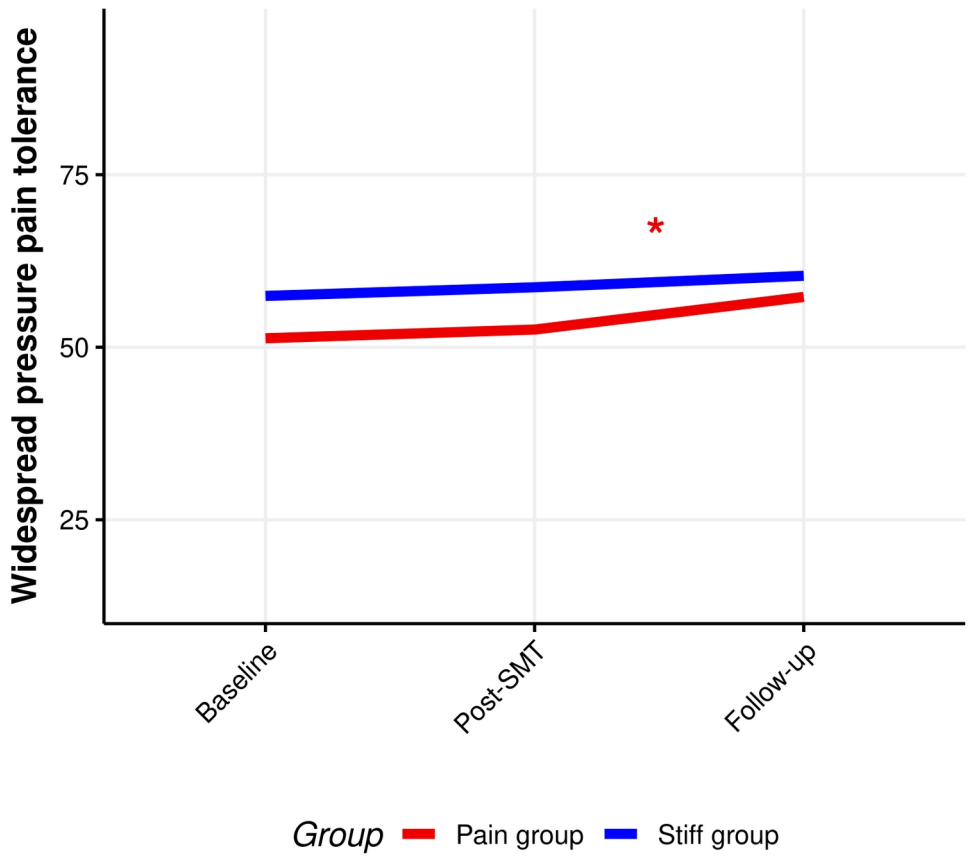
Within-group changes (figure) and between-group differences (table) for the not-sensitized group and sensitized group in widespread pressure pain threshold [kPa] following four sessions of SMT. Presented as arithmetic means, 95% confidence intervals and the corresponding p-value

SMT = Spinal manipulative therapy, * = p-value < 0.05

A9 Widespread pressure pain tolerance

Target site

Within-group changes and between-group differences in widespread pressure pain tolerance (Target site)

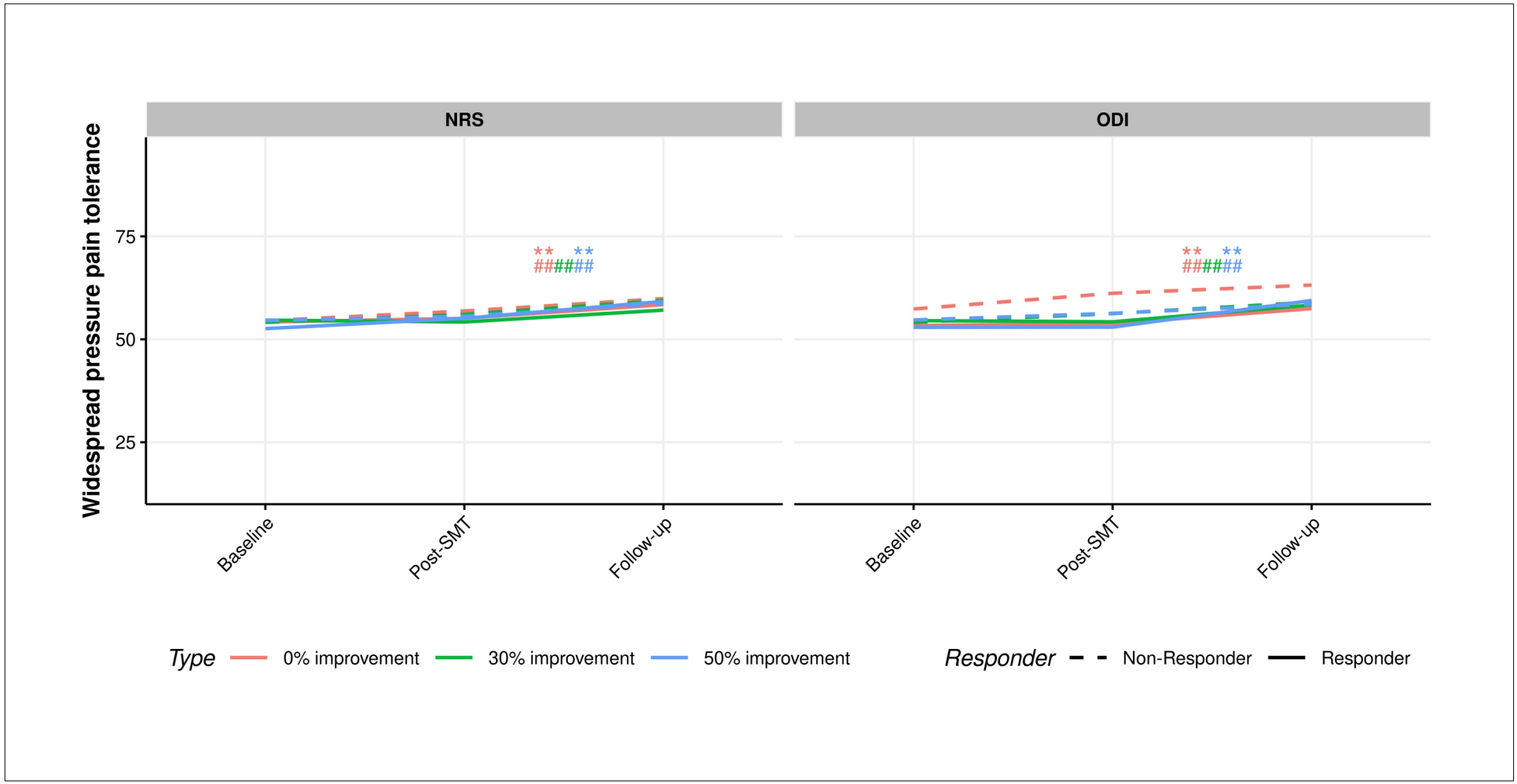


Time point	Mean difference (95 CI%)	P-value
Baseline - Post-SMT	0.0(-5.0 to 5.0)	~1
Baseline - Follow-up	-3.1(-8.1 to 1.9)	0.32

Within-group changes (figure) and between-group differences (table) in widespread pressure pain tolerance [kPa] following four sessions of SMT at either the stiffest vertebra (stiff group) or the most pain-sensitive segment (pain group). Presented as arithmetic means, 95% confidence intervals and the corresponding p-value
SMT = Spinal manipulative therapy, * = p-value < 0.05

Responder status

Within-group changes and between-group differences in widespread pressure pain tolerance (Responder status)



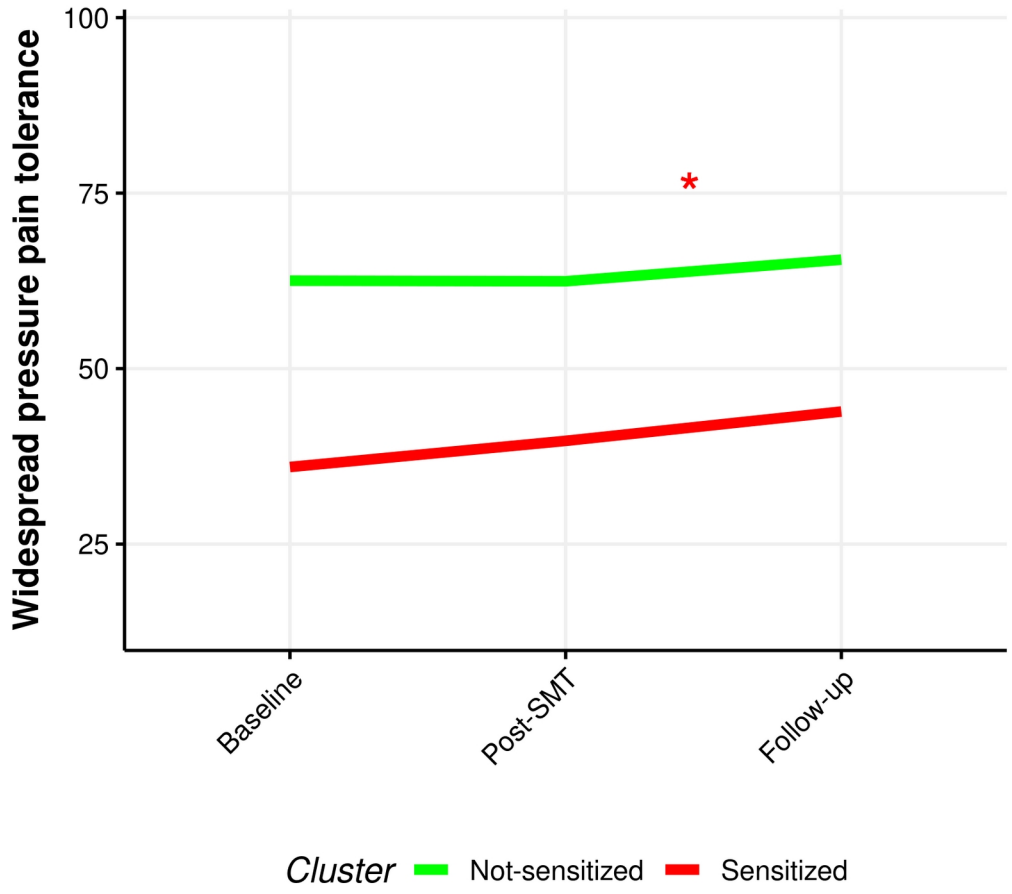
		Patient-reported LBP intensity		Disability	
Time point	**Cut point**	**Mean difference (95 CI%)**	**P-value**	**Mean difference (95 CI%)**	**P-value**
Baseline - Post-SMT	0%	-1.5(-7.3 to 4.4)	0.82	-3.3(-9.3 to 2.6)	0.38
Baseline - Follow-up		-1.2(-7.1 to 4.7)	0.89	-1.7(-7.6 to 4.2)	0.78
Baseline - Post-SMT	30%	-2.4(-8.0 to 3.2)	0.57	-2.4(-7.7 to 2.8)	0.51
Baseline - Follow-up		-2.9(-8.4 to 2.6)	0.42	-1.1(-6.3 to 4.1)	0.86
Baseline - Post-SMT	50%	1.5(-5.6 to 8.5)	0.87	-1.6(-7.5 to 4.3)	0.80
Baseline - Follow-up		2.5(-4.3 to 9.4)	0.66	2.7(-3.2 to 8.5)	0.52

Within-group changes (figure) and between-group differences (table) in widespread pressure pain tolerance [kPa] for 50, 30 and 0% improvements in patient-reported low back pain intensity and disability following four sessions of SMT. Presented as arithmetic means, 95% confidence intervals and the corresponding p-value

NRS = Numerical rating scale, ODI = Oswestry disability index, SMT = Spinal manipulative therapy, * = Significant changes in responders from baseline to post-SMT. ** = Significant changes in responders from baseline to follow-up. # = Significant changes in non-responders from baseline to post-SMT. ## = Significant changes in non-responders from baseline to follow-up

General hyperalgesia

Within-group changes and between-group differences in widespread pressure pain tolerance (Pain hypersensitivity)



Time point	Mean difference (95 CI%)	P-value
Baseline - Post-SMT	-3.8(-9.4 to 1.8)	0.24
Baseline - Follow-up	-4.9(-10.5 to 0.6)	0.10

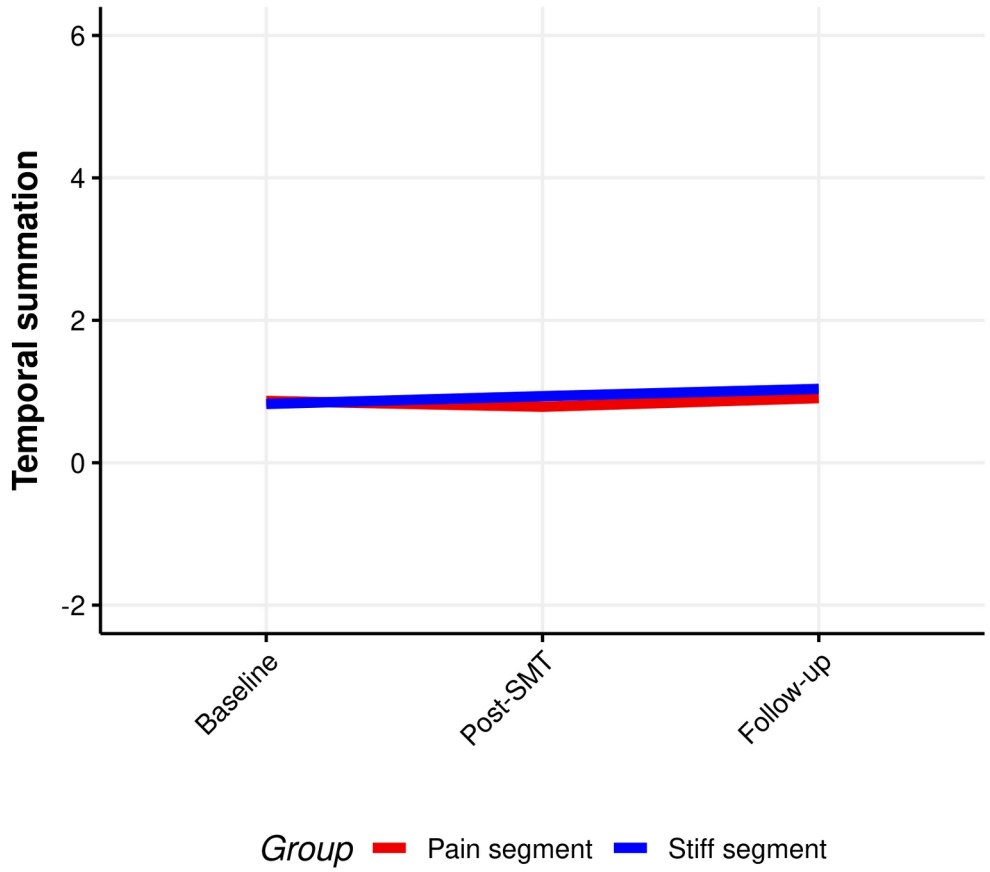
Within-group changes (figure) and between-group differences (table) for the not-sensitized group and sensitized group in widespread pressure pain tolerance [kPa] following four sessions of SMT. Presented as arithmetic means, 95% confidence intervals and the corresponding p-value

SMT = Spinal manipulative therapy, * = p-value < 0.05

A10 Temporal summation

Target site

Within-group changes and between-group differences in temporal summation (Target site)

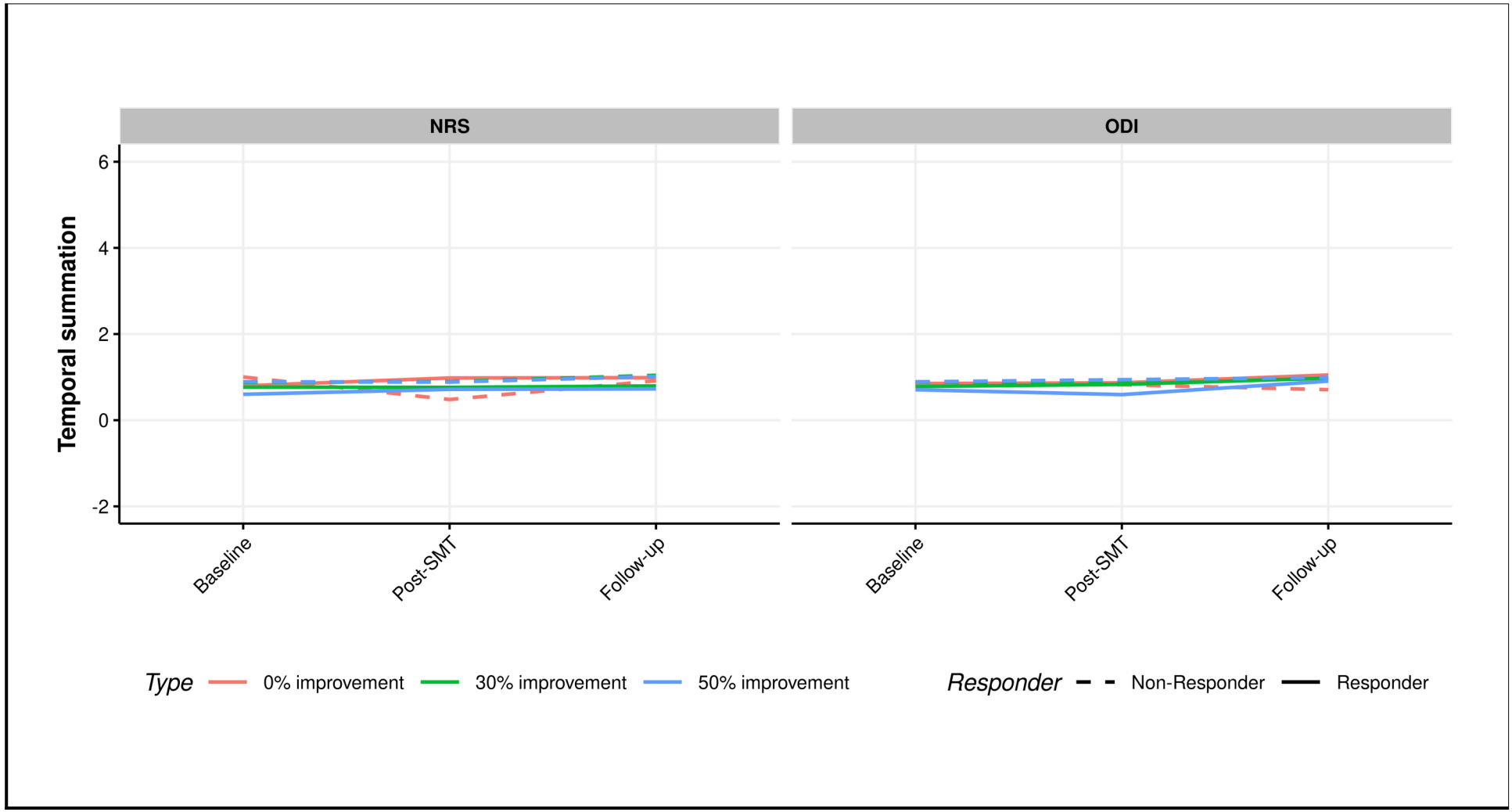


Time point	Mean difference (95 CI%)	P-value
Baseline - Post-SMT	0.2(-0.3 to 0.7)	0.66
Baseline - Follow-up	0.2(-0.3 to 0.7)	0.71

Within-group changes (figure) and between-group differences (table) in temporal summation [kPa] following four sessions of SMT at either the stiffest vertebra (stiff group) or the most pain-sensitive segment (pain group). Presented as arithmetic means, 95% confidence intervals and the corresponding adjusted p-value
SMT = Spinal manipulative therapy, * = p-value < 0.05

Responder status

Within-group changes and between-group differences in temporal summation (Responder status)



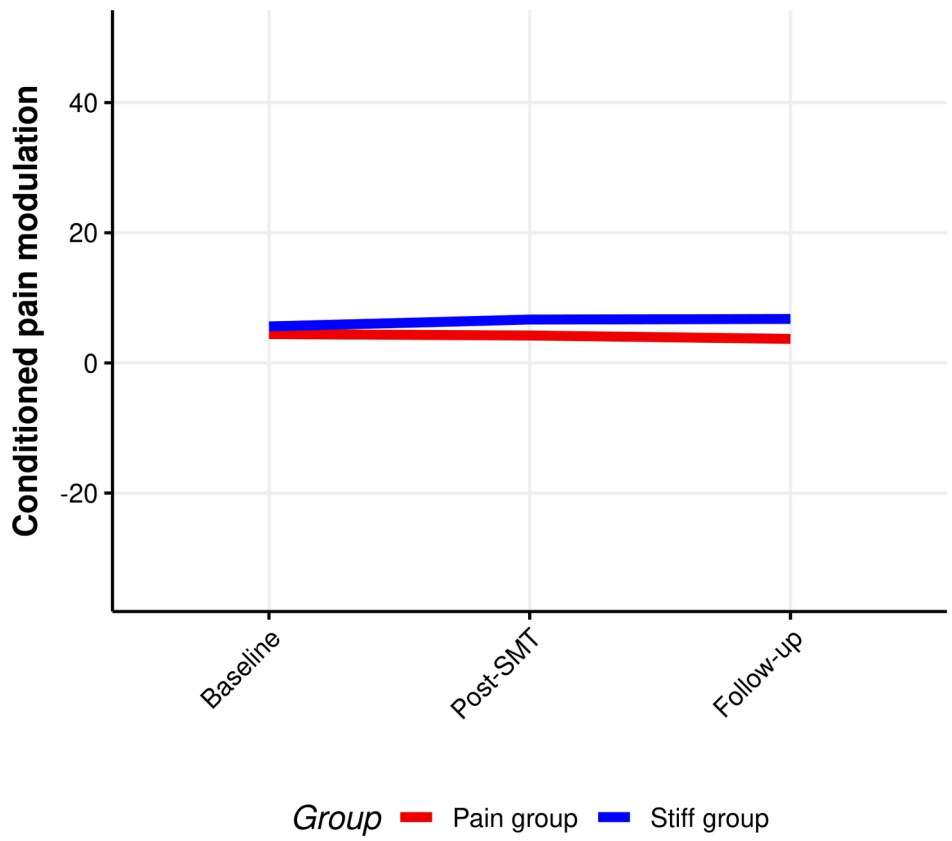
		Patient-reported LBP intensity		Disability	
Time point	**Cut point**	**Mean difference (95 CI%)**	**P-value**	**Mean difference (95 CI%)**	**P-value**
Baseline - Post-SMT	0%	0.7(0.1 to 1.3)	0.02	0.0(-0.6 to 0.6)	0.99
Baseline - Follow-up		0.3(-0.3 to 0.9)	0.52	0.3(-0.3 to 0.9)	0.42
Baseline - Post-SMT	30%	-0.0(-0.6 to 0.6)	~1	0.1(-0.5 to 0.6)	0.96
Baseline - Follow-up		-0.1(-0.7 to 0.4)	0.84	0.1(-0.4 to 0.7)	0.87
Baseline - Post-SMT	50%	0.1(-0.6 to 0.9)	0.92	-0.2(-0.8 to 0.5)	0.80
Baseline - Follow-up		0.0(-0.7 to 0.7)	~1	0.1(-0.5 to 0.7)	0.92

Within-group changes (figure) and between-group differences (table) in temporal summation [kPa] for 50, 30 and 0% improvements in patient-reported low back pain intensity and disability following four sessions of SMT. Presented as arithmetic means, 95% confidence intervals and the corresponding p-value.
NRS = Numerical rating scale, ODI = Oswestry disability index, SMT = Spinal manipulative therapy, * = Significant changes in responders from baseline to post-SMT. ** = Significant changes in responders from baseline to follow-up. # = Significant changes in non-responders from baseline to post-SMT. ## = Significant changes in non-responders from baseline to follow-up

A11 Conditioned pain modulation

Target site

Within-group changes and between-group differences in conditioned pain modulation (Target site)

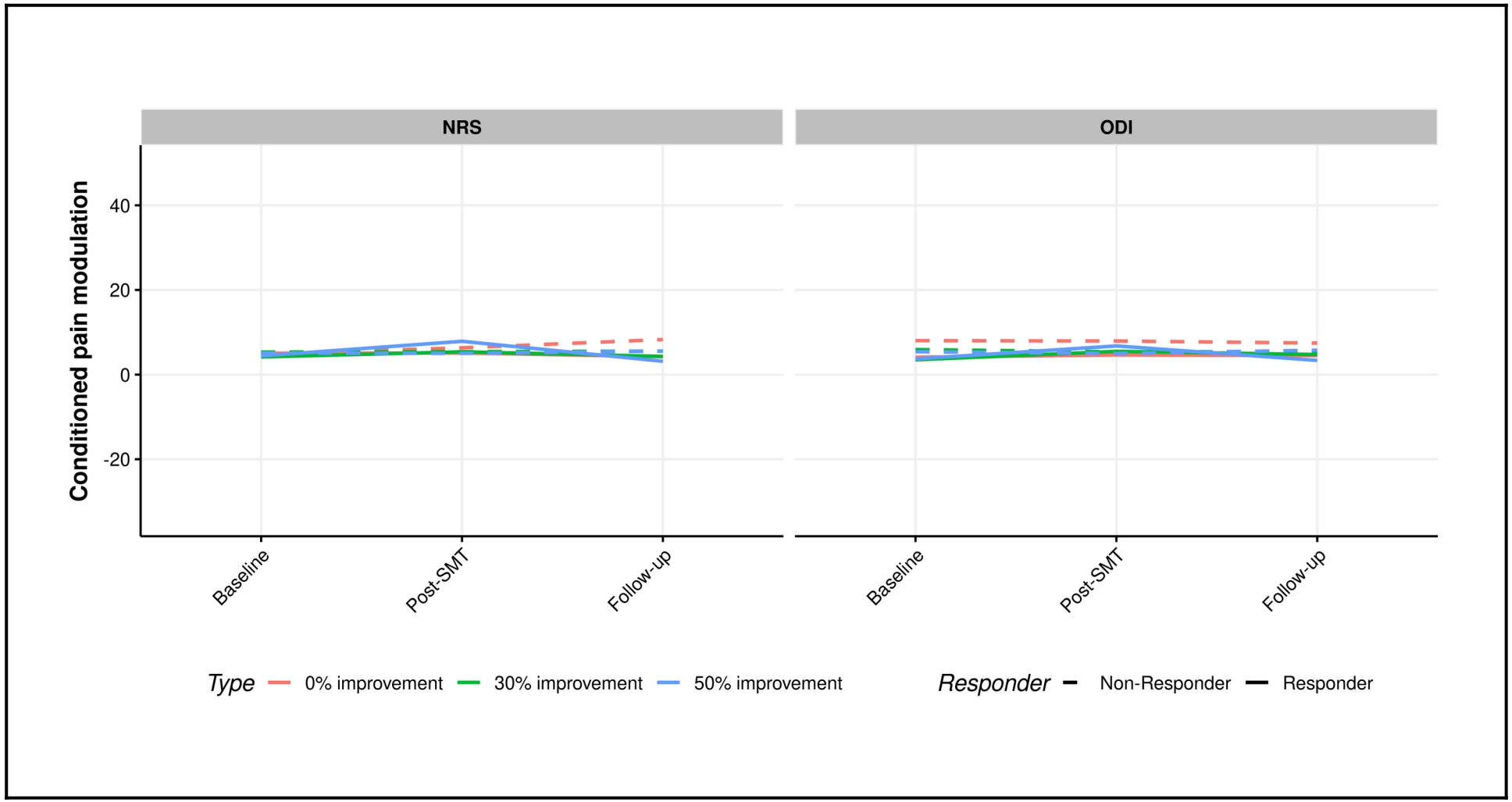


Time point	Mean difference (95 CI%)	P-value
Baseline - Post-SMT	1.3(-3.0 to 5.5)	0.76
Baseline - Follow-up	1.9(-2.3 to 6.1)	0.54

Within-group changes (figure) and between-group differences (table) in conditioned pain modulation [kPa] following four sessions of SMT at either the stiffest vertebra (stiff group) or the most pain-sensitive segment (pain group). Presented as arithmetic means, 95% confidence intervals and the corresponding p-value
SMT = Spinal manipulative therapy, * = p-value < 0.05

Responder status

Within-group changes and between-group differences in conditioned pain modulation (Responder status)



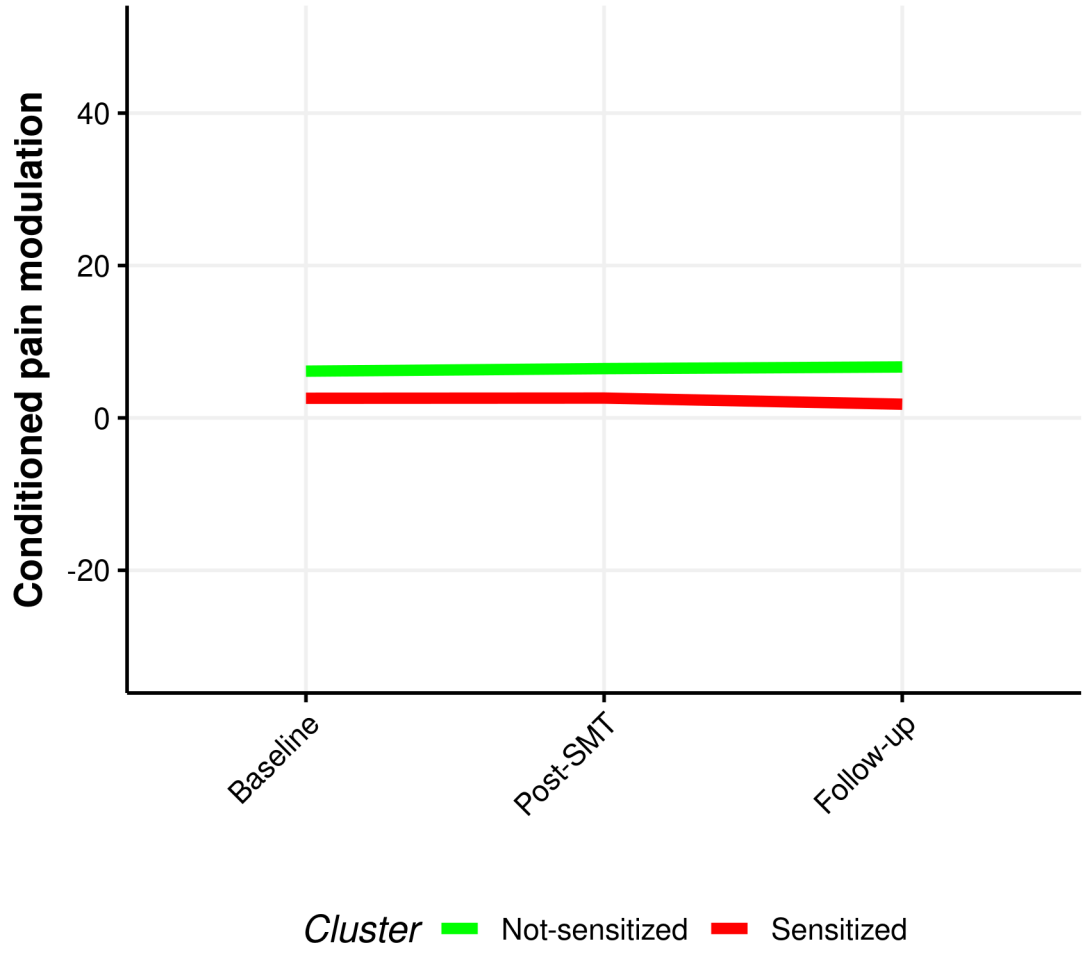
		Patient-reported LBP intensity		Disability	
Time point	**Cut point**	**Mean difference (95 CI%)**	**P-value**	**Mean difference (95 CI%)**	**P-value**
Baseline - Post-SMT	0%	-1.4(-6.3 to 3.5)	0.77	0.6(-4.4 to 5.6)	0.95
Baseline - Follow-up		-4.2(-9.2 to 0.7)	0.10	1.0(-4.1 to 6.0)	0.89
Baseline - Post-SMT	30%	1.1(-3.6 to 5.8)	0.84	2.5(-1.9 to 6.9)	0.36
Baseline - Follow-up		-0.1(-4.7 to 4.5)	~1	1.7(-2.6 to 6.0)	0.62
Baseline - Post-SMT	50%	3.5(-2.3 to 9.4)	0.33	3.5(-1.4 to 8.4)	0.21
Baseline - Follow-up		-1.7(-7.4 to 3.9)	0.75	-0.7(-5.6 to 4.2)	0.94

Within-group changes (figure) and between-group differences (table) in conditioned pain modulation [kPa] for 50, 30 and 0% improvements in patient-reported low back pain intensity and disability following four sessions of SMT. Presented as arithmetic means, 95% confidence intervals and the corresponding p-value

NRS = Numerical rating scale, ODI = Oswestry disability index, SMT = Spinal manipulative therapy, * = Significant changes in responders from baseline to post-SMT. ** = Significant changes in responders from baseline to follow-up. # = Significant changes in non-responders from baseline to post-SMT. ## = Significant changes in non-responders from baseline to follow-up

General hyperalgesia

Within-group changes and between-group differences in conditioned pain modulation (Pain hypersensitivity)



Time point	Mean difference (95 CI%)	P-value
Baseline - Post-SMT	0.3(-4.3 to 5.0)	0.99
Baseline - Follow-up	1.3(-3.3 to 5.9)	0.77

Within-group changes (figure) and between-group differences (table) for the not-sensitized group and sensitized group in conditioned pain modulation [kPa] following four sessions of SMT. Presented as arithmetic means, 95% confidence intervals and the corresponding p-value

SMT = Spinal manipulative therapy, * = p-value < 0.05

B. MANUSCRIPTS

Manuscript I

Nim CG, Kawchuk GN, Schiøttz-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, 10:14615

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The effect on clinical outcomes when targeting spinal manipulation at stiffness or pain sensitivity: a randomized trial

Casper Glissmann Nim[1]✉, Gregory Neil Kawchuk[2], Berit Schiøttz-Christensen[3] & Søren O'Neill[1]

The mechanisms underlying pain relief following spinal manipulative therapy (SMT) are not understood fully although biomechanical and neurophysiological processes have been proposed. As such, we designed this randomized trial to elucidate the contributions of biomechanical and neurophysiological processes. A total of 132 participants with low back pain were randomly assigned to receive SMT at either the lumbar segment measured as the stiffest or the segment measured as having the lowest pain threshold. The primary outcome was patient reported low back pain intensity following treatment. Secondary outcomes were biomechanical stiffness and neurophysiological pressure pain threshold. All outcomes were measured at baseline, after the fourth and final session and at 2-weeks follow-up. Data were analyzed using linear mixed models, and demonstrated that the SMT application site did not influence patient reported low back pain intensity or stiffness. However, a large and significant difference in pressure pain threshold was observed between groups. This study provides support that SMT impacts neurophysiological parameters through a segment-dependent neurological reflex pathway, although this do not seem to be a proxy for improvement. This study was limited by the assumption that the applied treatment was sufficient to impact the primary outcome.

Treatment of low back pain. Low back pain (LBP) is now the number one cause for years lived disability worldwide[1]. In most cases, a specific pathoanatomical cause of LBP cannot be identified[2]. Without a specific therapeutic target, a predictably large and diverse spectrum of interventions are available to clinicians that range from joint mobilization to spinal fusion surgery[3]. Given these almost endless possibilities, clinical guidelines rate education and exercise as first line therapy for low back pain often in combination with manual therapy[3]. Although, these guideline recommendations are generally clear and unambiguous, it is challenging for clinicians to implement them in practice (e.g. which exercises to recommend, how often, and which patients to offer manual therapy etc.).

Spinal manipulative therapy. Spinal manipulative therapy (SMT) is a manual therapy recommended as a second line intervention for LBP in most clinical guidelines[4]. However, like other conservative treatments, there is little evidence or consensus regarding the specifics of SMT application such as which patients are likely to respond, which type of SMT should be used, and which dose/frequency of SMT is optimal.

While the specific SMT technique does not seem to be important[5–7], there are at least two theoretical rationales for where to apply SMT: at the site of greatest biomechanical dysfunction or the site of greatest pain sensitivity. As the goal of SMT is to restore normal function to segments with biomechanical dysfunctions[8], it may be surprising to some that the evidence for identifying such dysfunction is sparse. A narrative review reported that clinicians use a variety of different ways to determine the application site of SMT, often consisting of palpation using patient reported pain when provoking specific segments, and a subjective assessment of lumbar stiffness[9].

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Biomechanical dysfunction as the site for SMT application. Spinal palpation used to identify biomechanical dysfunction in the spine has been thoroughly researched. While its intra-observer reproducibility is acceptable, the inter-observer reliability is, not surprisingly, less convincing[10]. Despite these conflicting results, palpating to identify hypomobile segments is included in a clinical prediction rule, and part of standard clinical examination prior to SMT[11]. As there is no universal agreement on the characteristics of a segmental dysfunction it is difficult to identify, quantify and thereby measure changes in these properties. While these manual methods of identifying dysfunction are problematic, a preliminary study using instrumentation found that patients with LBP who respond to SMT with improvements in self-reported disability had associated decreases in post-SMT stiffness[12]. The study by Wong et al.[12] measured stiffness at L3 with a single mechanical indentation[13]. A more recent version of this device, the VerteTrack (VT), has recently been developed. The VT has the ability to approximate mechanical indentation over a large spinal region, and, thereby, obtain a rapid measure of lumbar stiffness at each lumbar segment[14]. This potentially aids in quantifying segmental stiffness, and in turn, is thought to direct the application of SMT more accurately.

Lumbar pain sensitivity as the site for SMT application. Spinal manipulative therapy appears to have a hypoalgesic effect on pain sensitivity, both in the region where SMT is applied and more widespread[15]. This difference in pain sensitivity appears to manifest in both patients with musculoskeletal conditions[16] and healthy individuals alike[17], suggesting a short-term neurophysiological effect of SMT on pain sensitivity, irrespective of underlying pain conditions. In recent decades, pain sensitivity has been quantified reliably using quantitative sensory testing (QST)[18]. Pressure pain threshold (PPT) can quantify the amount of pressure needed to induce a perception of subjective pain[19,20], and be used to gain insight in local mechanical pain sensitivity at each lumbar segment. The authors, have no knowledge of any study using PPT to determine the site for SMT. This could potentially aid in identifying specific segmental pain sensitivity.

Study rationale. The clinical effect of SMT for persistent LBP (current LBP for more than 3 months) is comparable to other guideline recommended conservative treatments (e.g. exercise, education etc.) with regards to pain and disability[21]. However, the underlying mechanisms of the clinical effects of SMT remains unclear. A normalization of both segmental biomechanics and pain sensitivity could arguably be explanations for pain relief, and it is not known whether the effects of SMT can be improved by targeting spinal segments characterized by parameters such as segmental stiffness and pain sensitivity.

In this study, patients with persistent low back pain were enrolled. For each participant, the most stiff and most painful vertebral segments were identified. Spinal manipulative therapy was then provided at the same segment over four sessions. The segment was determined accordingly to the baseline randomization as either the most stiff or most painful segment.

Objectives. The primary aim of this study is to examine if spinal manipulation is more effective in regards to reducing patient reported low back pain intensity when directed at spinal segmental stiffness or segmental pain sensitivity in a cohort of persistent low back pain patients. The secondary aims were to measure between group mean changes in (i) lumbar stiffness and (ii) pressure pain threshold.

Methods

This trial was approved by the Regional Committees on Health Research Ethics for Southern Denmark (ID: S-20160201) and the Danish Data Protection Agency. The trial was registered at ClinicalTrials.gov 11/09/2019—identifier: NCT04086667. All participants provided informed, written and oral consent before entering the study. The project was conducted in accordance with the Helsinki-II declaration. The trial is reported according to the CONSORT 2010 statement[22].

Design. A randomized experimental trial comparing self-reported pain in persistent LBP patients following SMT applied to lumbar segments of high stiffness or low PPT.

Participants. Patients with LBP were recruited from the Spine Centre of Southern Denmark, a regional hospital that specializes in spinal pain syndromes referred by general medical practitioners, chiropractors, consultant rheumatologists, and other in-house clinicians. Participants were identified and invited to participate using two methods: (i) details of the project were included in the information sent to patients prior to their first appointment. (ii) Verbally at the clinical consultation.

All potential participants were diagnosed with persistent LBP by the clinician in charge before enrollment screening was conducted.

Inclusion criteria for the study were as follows: (a) persistent LBP for more than 3 months, without prior spinal surgery. (b) LBP of benign origin e.g. no malignancy or axial spondyloarthropathy. (c) Between 18 and 60 years of age. Exclusion criteria were (a) indications for surgical evaluation due to low back pain with/without leg pain. (b) History of SMT in the preceding 4 weeks. (c) Opioid use exceeding 40 mg of morphine or equivalent (oral intake) at the time of inclusion. (d) Comorbid conditions that could interfere with project methodology (e.g. BMI exceeding 35 and pregnancy). Further, exclusion for analysis were defined as: (a) failure to complete a minimum of 75% of the allocated intervention. (b) Received SMT or mobilization techniques to the lower back in other settings during the study. (c) Changes in pain medication during the study. The assessor in the study (CGN) recorded these parameters at each scheduled contact with the participant.

Variable name	Variable type	Data type	Description/transformation
Patient reported low back pain intensity/numerical rating scale [NRS]	Primary outcome	Continuous data [0:10]	The mean value of each NRS score in the low back pain rating scale (current, average and worst low back pain intensity)
Lumbar stiffness/global stiffness [GS]	Secondary outcome	Continuous data [0–∞]	The average slope of the force–displacement curve from the second lowest load to the second highest load allowed by protocol (~83 N) measured at each segment. For the analyses a mean sum score for all segments were applied
Pain sensitivity/pressure pain threshold [PPT]	Secondary outcome	Continuous data [0:1,000]	A mean score of the 3 trials (kPa) measured at each level, and for the analysis a mean sum score for all segments were applied

Table 1. An overview of the variables of interest for the analysis.

Study protocol. An overview of the study protocol is reported here, and an extended explanation for each point of interest is provided in the *data collection* section.

The baseline lab session. This session in the laboratory consisted of the following: (i) completion of the patient reported outcomes, (ii) segmental markings, (iii) VT testing, (iv) PPT testing and (v) the segmental randomization.

The initial SMT session. The initial SMT session immediately followed the baseline lab session.

SMT session two to four. The three additional SMT sessions, identical to the initial SMT session, were completed over the next 14 days.

The Post-SMT lab session. Immediately after the fourth and final SMT session, the participant repeated the items performed in the baseline lab session (i–iv).

The Follow-up lab session. Fourteen (14) days after the post-SMT lab sessions, the participant repeated the items performed in the baseline lab session (i–iv).

Data collection. *Demographic data.* Associated demographic data from each participant were extracted from the Danish SpineData questionnaire[23] with consent.

Pain intensity. Patient reported LBP intensity was captured by the validated Low Back Pain Rating Scale[24]. It consists of an 11-point numerical rating scale (NRS) of *current LBP*, *average* and *worst LBP* during the last 14 days.

Segmental markings. Each participant was placed in a prone position on a standard examination table and the spine process of T12-S1 were identified using ultrasonography (Sonosite Titan Linear, L38 probe)[25]. The participants were instructed not to wash off skin markings during the study period. This procedure was repeated at each lab visit and skin markings refreshed.

VerteTrack. The VT rolls a weighted indenter along the lumbar spine of a prone subject. The resulting vertical displacement in spinal tissues is measured continuously by a string potentiometer (TE Connectivity, USA). From this, tissue stiffness (N/mm) can be determined (applied mass/displacement) along the length of the lumbar spine. The trajectory of the roller follows pre-defined skin markings through a laser mounted guidance system to obtain stiffness values. The process is repeated with discrete incrementally increasing of 1 kg up to 6 kg with a sampling rate of 30 Hz.

The resulting data were graphically smoothed using a polynomial function, and visualized using LabView version 15.0f3 for windows 10, National Instruments, Texas, USA before being extracted to a spreadsheet (LibreOffice, vers. 6.0.7.3, for Ubuntu 18.04) for further analysis. Global Stiffness (GS) was calculated as the average of the slope with the first and terminal data points removed. The comfort and safety of VT has been evaluated previously[26] as has its reliability in an asymptomatic population[14].

Pressure algometry. Pressure pain threshold was measured with the participant in the prone position, at each segment from L1 to L5 using a pressure algometer (model 2, Somedic, Hørby, Sweden). Attached to the probe was a custom, 3D printed double-headed contact (2×1 cm^2, 3 cms apart), that allowed for a bilateral pressure to be applied to the skin surface at each side of the mid-line. The instrument was applied manually with a nominal rate of 50 kPa/s. A trial procedure consisting of 1–2 PPT tests were completed on the lower extremity and T12 to familiarize the participant with the procedure before spinal testing.

The PPT of each lumbar segment was measured three times with approximately 10 s rest intervals. If no pain has been elicited by 1,000 kPa, this was recorded as the PPT. If the first and second measurements were 1,000 kPa, a third would not be performed. All segments were tested in the same predetermined random order for each participant at each time point. Pressure pain threshold has excellent intra-rater reliability in a LBP cohort[27].

See Table 1 for an overview of collected variables.

Segment randomization procedure. The maximal force–displacement value (FD) from the VTs at the maximally applied load was used as an indicator of segmental stiffness, and the mean value of the three PPT measurements was used as an indicator of segmental pain sensitivity. The maximum VT displacement (FD) was used for the randomization to mimic a clinical examination. As the absolute maximum of these two parameters potentially could overlap, the identification of the 'most stiff' and 'most sensitive' segment was codified using a ratio that scored all segments between − 1 and + 1 (Eq. 1), where − 1 indicated the segment as characterized by the relatively highest degree of stiffness and lowest degree of pain sensitivity, while + 1 indicate the segment as characterized by the relatively highest degree of pain sensitivity and lowest degree of stiffness. The following algorithm was used to determine the ratio:

$$Segment_{NormalizedDifference} = \frac{(segment_{FD} - min_{FD})}{(max_{FD} - min_{FD})} - \frac{(segment_{PPT} - min_{PPT})}{(max_{PPT} - min_{PPT})} \quad (1)$$

The absolute lowest (− 1) and highest (+ 1) ratio score were chosen as the stiffest and the most pain sensitive segment, respectively. If the resulting segments were adjacent, the remaining ratio scores were scrutinized, and if another segment had a ratio score that differed by a ratio score of less than 0.1 compared to the ratio of the absolute '*most stiff*' or '*most sensitive*' segment, this segment was used for the allocation instead. If no such segment existed the two original adjacent segments were chosen for allocation.

For randomization, a computer-generated list was constructed, stratified in a list of A (indicating the *stiff group*) or B's (indicating the *pain group*) in a near 1:1 order for a total of 155 A or B characters corresponding to the maximum number of participants possible to include. The list further included a column indicating each ID number. In this fashion, each participant was given an a-priori assignment of either A or B indicating the group/segmental allocation.

Blinding. From baseline lab data, the assessor (CGN) identified the two specific spinal segments (L1–L5) that were the most *stiff* (segment A) and had the lowest pressure *pain* threshold (segment B). The assessor was thus aware of the meaning of segments 'A' and 'B', but was blinded to the randomization list (participant ID and A/B allocation). Conversely, the treating chiropractor used the randomization list to determine the specific spinal segment to treat, but was blinded to the meaning of 'A' and 'B' as *stiff* and *pain* group. The participant was blinded to both.

Spinal manipulative therapy. The SMT was provided in a standardized manner where the participant was placed in a side-lying position and the subsequent SMT was delivered with a high velocity, low amplitude technique[28] targeting the randomized segment[29,30] using a contact point at the spine process[31]. The direction of the SMT was applied in a posterior to anterior direction[32].

Up to 3 SMT attempts were allowed for a successful treatment. Whether the treatment was successful was determined by the chiropractor and independent of the common cavitation sounds that can accompany SMT[28]. Any adverse events that occurred were recorded for each SMT session.

Two chiropractors each with more than 12 years of clinical experience performed all SMT in this study. They were instructed not to discuss the project with the participants in order to avoid influencing their assessment of treatment outcomes. No further training was completed before initiating the trial[33].

No changes were made to the methodology after commencement of the trial.

Statistical considerations. *Power.* A power calculation based on a 10% mean group difference in patient reported low back pain intensity [numerical scale from 0 to 10] between the *stiff* and the *pain* group with an 80% beta and a 5% alpha level indicated group sizes of 62. The 10% group difference was chosen a-priori as we did not expect a large between group mean difference[34].

Descriptive data. Descriptive data is reported as means and standard deviations for normal distributed data, medians and interquartile ranges for non-normal distributed data or count and frequency for categorical data.

Stiffness data. Before extracting stiffness data a subjective analysis was completed in LabView. Some loads were affected by such factors as participant breathing, muscle guarding or technical errors and were subsequently removed from analysis.

Non-overlapping segment analysis. Both GS and PPT were obtained for each lumbar segment at three different time points (baseline, post-SMT and follow-up). As the location of these segments were repeated at each time point, it was possible that the trajectory used was not the same, this means that what was measured as L5 at baseline could have been measured as L4 at post-SMT. We inspected all the sagittal curvatures projecting the lordosis of the participants lower back, using the graphs presented by LabView and determined if the curvatures were comparable to the baseline curvature for each time point. If not, this time point was omitted for the mixed models concerning the outcomes of GS and PPT.

Repeated outcomes. Linear mixed models for the different outcome measures were used for the analyses, with group and time as fixed interacting effects, and subject as a random intercept using an unstructured variance–covariance all models. Model assumptions were tested for normal distribution of the residuals error using Q-Q plots and the homogeneity of variance was tested plotting the residuals vs the predicted values. All repeated out-

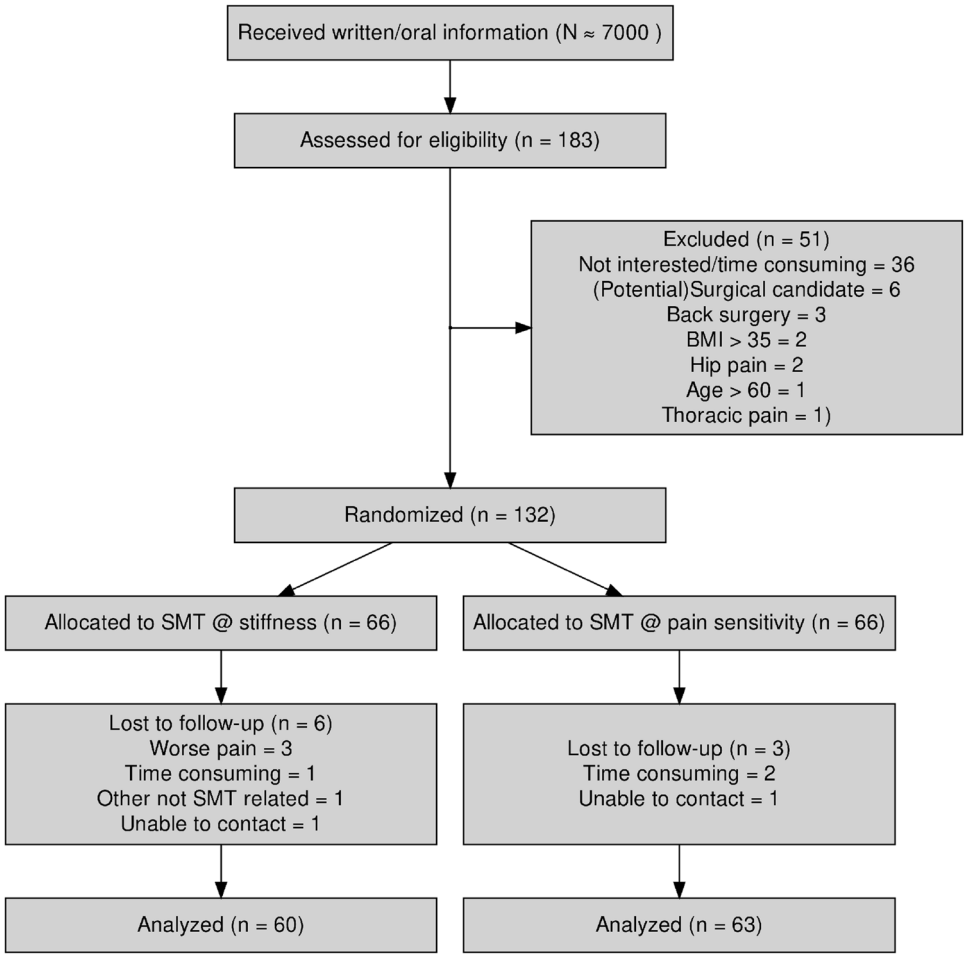

Figure 1. A CONSORT flow diagram of the participants enrollment, segment allocation and availability for follow-up and analysis. *SMT* spinal manipulative therapy.

comes are presented as mean baseline changes within group and mean differences between groups, along with 95% confidence interval and p-values, as well as a visual presentation of the mean scores and the standard errors.

A p-value < 0.05 was considered statistically significant.

Data were analyzed using R for linux (v. 3.6.0 with R-studio v. 1.1.456 and relevant add on packages from the Tidyverse[35]).

The statistical analysis plan was completed in collaboration with a biostatistician at the University of Southern Denmark.

Results

Participants. A total of 132 participants were enrolled in the study between November 2017 and January 2019. Of those 132, 7 did not complete the 2 week SMT intervention, and an additional 2 were unreachable for follow-up. The result was 123 participants completed the study. No participants were excluded after initiating the trial on the basis of the exclusion criteria. See Fig. 1 for a flowchart visualizing the participant inclusion.

Descriptive data. Table 2 shows a descriptive summary of the participant characteristics. The mean NRS score for the participants was 6 (SD = 2). The baseline GS was 4 (SD = 1) and the median value of PPT was 471 (IQR = 356). The participants were equally divided with 66 participants in each group.

Albeit the present cohort consisted of fewer women, it is comparable to the general patient population of our unit in terms of age, pain duration and intensity[23].

Non-overlapping segment analysis. The analysis concerning non-overlapping segments for repeated spinal measures resulted in the exclusion of 11.7% of the GS and PPT measures at different time points. These data points were omitted and not used in the final analysis. Furthermore, one baseline GS trial was faulty and therefore, omitted. As a result, the total data size (each subject measured three times) was reduced from 369 data points to 325 data points.

	Pain group, N = 66	Stiff group, N = 66
Patient reported low back pain intensity	5.64 (1.79)	5.55 (1.93)
Disability	27.42 (11.54)	28.19 (11.85)
Global stiffness	4.26 (0.75)	4.02 (0.86)
Pressure pain threshold	488.73 [330.95]	436.6 [364.9]
Age	46.74 (8.66)	43.47 (10.46)
Sex, male (%)	40 (61)	32 (48)
Low back pain duration (months)	14.10 [67.10]	17.50 [49.35]
Patient reported leg pain intensity	4.31 (2.67)	3.87 (2.77)
Overall progress since pain debut, worse (%)	34 (52)	38 (58)

Table 2. An overview of baseline characteristics for participants with persistent low back pain who entered a randomized experimental trial. Presented as mean (standard deviation), median [interquartile range] or categorical.

Within group					Between group	
	Within group mean change, estimate (95% CI)		p-value		Between group mean difference, estimate (95% CI)	p-value
Time	Pain	Stiffness	Pain	Stiffness	Pain–stiffness	Pain–stiffness
Patient reported low back pain intensity (numerical pain rating scale)						
Baseline to post-SMT	−0.70 (−1.12 to −0.28)	−0.60 (−1.03 to −0.17)	< 0.001	< 0.001	0.11 (−0.49 to 0.71)	0.68
Baseline to follow-up	−0.66 (−1.08 to −0.24)	−0.77 (−1.20 to −0.34)	< 0.001	< 0.001	−0.11 (−0.71 to 0.49)	0.67
Low back stiffness (global stiffness, N/mm)						
Baseline to post-SMT	0.03 (−0.22 to 0.29)	0.04 (−0.22 to 0.30)	0.76	0.74	0.00 (−0.36 to 0.37)	0.98
Baseline to follow-up	0.08 (−0.18 to 0.34)	−0.05 (−0.32 to 0.22)	0.48	0.66	−0.13 (−0.5 to 0.24)	0.42
Low back pain mechanical pain sensitivity (pressure pain threshold, kPa)						
Baseline to post-SMT	99.29 (56.78 to 141.8)	33.00 (−10.71 to 76.71)	< 0.001	0.08	−66.29 (−127.27 to −5.32)	0.01
Baseline to follow-up	90.02 (46.54 to 133.5)	48.51 (3.38 to 93.64)	< 0.001	0.01	−41.51 (−104.18 to 21.16)	0.12

Table 3. Changes in patient reported low back pain intensity, lumbar stiffness and pressure pain threshold in participants with persistent low back pain who are treated with spinal manipulative therapy over 4 sessions at either a *pain segment* or a *stiff segment*. Within mean changes and between group mean differences are presented as mean differences between baseline and post-SMT/follow-up and between group mean with 95% confidence intervals.

Spinal manipulative therapy. All four sessions were completed by 119 participants while 7 completed three. This was not adjusted for in the analysis. The average duration of the intervention period was 13 (SD = 6) days and follow-up occurred 14 (SD = 6) days afterwards.

Adverse events. Of the participants who completed the intervention, 69% reported minor side effects. This included a reporting of increased local muscle pain by 63%, 33% reported increased lumbar stiffness, 10% reported headaches and 8% reported worsening of leg pain, only 5% had other minor side effects such as nausea, dizziness etc. One participant reported continued anterior chest pain after the 4th session at follow-up.

Linear mixed model for group comparison over time. All models assumptions were upheld. See Table 3 for a summary of within mean changes and between group mean differences for the three outcome measures (i) NRS, (ii) GS and (iii) PPT.

Patient reported low back pain intensity. Both groups reported a significant decrease of NRS at post-SMT and follow-up, but there was no significant difference between the groups at any time point (group mean difference at: post-SMT of 0.11, p-value = 0.68, follow-up of 0.11, p-value = 0.67).

Global stiffness. There was no statistically significant within mean group changes for GS nor any between group differences. On average, a decrease in GS score was observed in the *stiff group* at follow-up. Conversely, the average GS score in the *pain group* increased.

Pressure pain threshold. The mean PPT scores increased over time for both groups. In the *pain group*, PPT increased significantly at both post-SMT and follow-up compared to baseline. The *stiff group* also demonstrated a significant increase in PPT, but only at follow-up. The *pain group* reported a significant higher mean PPT score compared to the *stiff group* of 66.29 kPa at post-SMT.

Discussion

This is the first trial that investigated whether clinical and experimental differences would be observed when randomly directing SMT at pre-targeted segments of increased stiffness or pain. Both groups responded to treatment with an overall decrease in the primary outcome patient reported LBP intensity, but there was no statistically or clinically significant difference between groups. Likewise for the secondary outcomes, stiffness did not change significantly throughout the study but PPT increased significantly in both groups at follow-up and a large between group difference in PPT was observed directly post-SMT, indicating that PPT increased at a much larger rate directly post-SMT for the *pain* group compared to the *stiff group*. However, PPT stagnates from post-SMT to follow-up for the *pain group*.

Patient reported low back pain intensity. Whether the reduction observed in patient reported LBP intensity is clinically significant is debatable and is overall lower compared to the majority of SMT trials on persistent LBP[21]. This result, could be explained by many different possibilities. The first possibility is that the intervention was not sufficient as the number of sessions was limited to four over 14 days; a number of treatments shown in the literature to predict overall improvement in primary care chiropractic patients[36]. The second possibility was that the participants were more likely to be complex[37] given their recruitment from a secondary treatment facility; they may have been more likely to be non-responders to SMT. Third, a longer follow-up period could have resulted in larger improvements[21]. Last, the planned intervention was experimental in nature and limited the SMT application to a single lumbar segment with no adjunct therapy.

Lumbar stiffness. Quantifying spinal stiffness is a relatively new field in spine research. Early experiments evaluating stiffness demonstrated a decrease in spinal stiffness in LBP patients who responded positively to SMT[38]. These results were subsequently repeated[12] although the duration of LBP in that cohort was not described in detail. Results since then have been mixed, as different studies have used the measure to evaluate associations with other outcomes[39] or in other parts of the spine[40].

As such, SMT may have a differential impact on stiffness in subgroups of LBP patients. Arguably, the stiffness associated with acute or trivial LBP could be due to inflammation or muscle guarding, whereas stiffness associated with chronic or non-trivial LBP could potentially be due to more degenerative changes, intervertebral fibrosis or muscle inhibition/atrophy. This is speculative, but is supported by an exploratory analysis reporting that SMT responders tends to have a lower prevalence of degeneration and a higher degree of disc diffusion[41]. The responder status of participants receiving SMT appears to modify the changes in stiffness[12,39]. The present study, did not take the inclusion of responders into account, and possibly the lack of stiffness change was due to the chronicity of cohort and the minor changes in patient reported LBP intensity.

Pain sensitivity. The literature concerning the hypoalgesic effect of SMT is conflicting[15–17]. This may be the result of differences in study populations as they often are heterogeneous, and includes asymptomatics participants[17] as well as participants with musculoskeletal conditions often found in the general public or primary care[16]. Further, these studies are experimental in nature, often using a single SMT session, followed by an immediate PPT reassessment[15–17].

The mechanism behind a hypoalgesic effect of SMT is unclear and two possible explanations exists: (i) SMT could have a neurologically mediated reflex independent of clinical improvement that would give rise to an immediate change in pain sensitivity or (ii) SMT has a curative effect on a mechanical relationship/segmental dysfunction. This in itself affects pain sensitivity, which arguably would give rise to a more profound and longer lasting effect on pain sensitivity. Multiple studies have measured different QST measurements before and after SMT at a "manipulative lesion" each finding an immediate decrease in the QST measurement[42–45]. However, when pooling the results in a systematic review, there was no greater hypoalgesic effect compared to a predetermined location[15]. An obvious weakness in these studies is the reliability of locating the "manipulative lesions".

Manual palpation has limited value in clinical practice, and appears to have no impact in modifying the hypoalgesic effect of a single SMT session[15]. As discussed, the hypoalgesic effect of SMT may be related to a presumed curative effect on underlying segmental dysfunctions which likely would require multiple sessions at the affected segment. In this scenario, the PPT change could progress gradually over time rather than immediately post-treatment. A recent two-armed trial[46] directed SMT at lumbopelvic region predetermined beforehand over multiple sessions in a chronic LBP population, a significant difference within group was found but none when compared to sham. This supports our finding that PPT change following SMT is a neurologically mediated reflex that is segment dependent (e.g. a segment with low PPT).

Neurological mediated effect of SMT. This neurological mediated reflex could depend upon sensitization of central pain mechanisms. This mechanism occurs as the pain persists[47] and typically the QST scores differs significantly in chronic versus acute pain[48] and versus asymptomatic subjects[49]. There is some evidence to suggest that such widespread hypersensitivity is rapidly reversible[50,51]. It is possible, albeit speculative that central hypersensitivity has to occur before a robust hypoalgesic effect of SMT can be observed.

Interestingly, the observed increase in PPT was not a proxy for clinical improvement of subjective pain relief. This suggests that multiple factors are important for locating the relevant segmental dysfunction or that multiple segments are responsible; SMT application should not be limited to pain provocation or stiffness assessment alone[52].

Limitations. The random allocation makes it possible to explore the effect between the 2 groups. All the tests were completed by one assessor thus eliminating inter-rater variability. Furthermore, the allocation was blinded for all involved. As we did not compare with a sham-SMT treatment, the present study does not shed light on whether SMT was responsible for the changes observed in outcome measures. It is possible that any mechanical sensory input could provide the same results. However, investigating the causality of SMT was not the overall purpose of the paper.

Although this was a randomized trial, numerous non-systematic errors could occur with respect to repeated SMT to the assigned segment. The present study tried to minimize this risk by using ultrasonography and skin-surface marking of vertebral location. Ultrasonography was, however, only completed at each lab visit, and some markings disappeared between visits meaning that static palpation was used to locate the indicated segment. The thrust used in SMT, albeit, directed at one segment, can result in cavitation on multiple segments[53] which further decreases the specificity of SMT application. However, this is the case for all studies investigating any manual therapy and cannot be controlled.

A significant and possible modifying factor was the randomization process. There was no prior research that had compared stiffness and pain sensitivity, Therefore, the study used absolute values for pain and stiffness. It is not evident whether the randomization actually represents the stiffest or most pain sensitive segments. It may be possible that a discrete anatomical distribution of lumbar stiffness exists that ought to be adjusted for, yet for PPT this does not appear to be the case[49]. The indexing was used to avoid a potential overlap between the stiffest and most pain sensitive segment. A pilot study was completed, before initiating the current study, that included 20 participants with persistent LBP and the overlap was approximately 25% (data unpublished).

In this study, the measurement techniques as well as the applied SMT likely differ from procedures used in clinical practice. Many techniques used here, although objectively quantifiable, are unidirectional, while both palpation and manual pressure can be directed at multidirectional planes. Further, the randomization procedure that guided the treatment in this study was only performed at baseline, it is possible that the ratio between stiffness and pain could change during the course of the experiment.

In this present study, no stratified analysis on responder/non-responder status was performed. It is possible, that such analysis could demonstrate important differences in secondary outcome measures between those with and without clinical improvement following SMT. This is the subject of a secondary analysis and future publication. Similarly, between-group differences in the secondary outcome measure (disability) is not presented here.

Finally, the primary objective of our study was patient reported LBP intensity and the sample size was calculated to be respondent for changes in this parameter. This leaves the possibility that the analyses of the secondary objectives were under powered. Further, some of the repeated data were omitted due to the non-overlapping spine trajectories, further increasing the risk of the analyses being under powered.

Conclusion

No difference between SMT applied to the most *stiff* vertebra or the most *painful* vertebra were found to improve the primary outcome, patient reported low back pain intensity or the secondary outcome, spinal stiffness. However, a large difference in the secondary outcome, pressure pain threshold was observed post-SMT.

This suggests that in the patient population studied, SMT appears to impact pain sensitivity in a specific segmental fashion and the effect is mediated by a neurological reflectory system. By comparison, the mechanical measure of spinal stiffness was not affected by the application site.

Data availability

Data is available upon request, please contact casper.nim@rsyd.dk.

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Author contributions

C.G.N. collected the data, completed the data analysis and wrote the initial draft of the manuscript. C.G.N., G.N.K., B.S.C. and S.O.N. all contributed to the design, interpretation of the data and approved the final manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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Manuscript II

Nim CG, Kawchuk GN, Schiøttz-Christensen B & O'Neill S

Changes in Pain Sensitivity and Spinal Stiffness in Relation to Responder Status following Spinal Manipulative Therapy in Chronic Low Back Pain: A secondary explorative analysis of a randomized trial

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Changes in Pain Sensitivity and Spinal Stiffness in Relation to Responder Status following Spinal Manipulative Therapy in Chronic Low Back Pain: A Secondary Explorative Analysis of a Randomized Trial

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Abstract

Background

In a prior randomized trial, we demonstrated that participants receiving spinal manipulative therapy at a pain-sensitive segment instead of a stiff segment experienced increased mechanical pressure pain thresholds. We hypothesized that the targeted segment mediated this increase through a segment-dependent neurophysiological reflective pathway. Presently, it is not known if this decrease in pain sensitivity is associated with clinical improvement. Therefore, we performed an explorative analysis to examine if changes in experimental pain sensitivity (mechanical and thermal) and lumbar stiffness were further dependent on clinical improvement in disability and patient-reported low back pain.

Methods

This study is a secondary explorative analysis of data from the randomized trial that compared 132 participants with chronic low back pain who received lumbar spinal manipulative therapy applied at either i) the stiffest segment or ii) the segment having the lowest pain threshold (i.e., the most pain-sensitive segment). We collected data at baseline, after the fourth session of spinal manipulation, and at 14-days follow-up. Participants were dichotomized into responders/non-responders using different clinical variables (disability and patient-reported low back pain) with varying threshold values (0, 30, and 50% improvement). Mixed models were used to assess changes in experimental outcomes (stiffness and pain sensitivity). The fixed interaction terms were time, segment allocation, and responder status.

Results

We observed a significant increase in mechanical pressure pain thresholds for the group, which received spinal manipulative therapy at the most pain-sensitive segment independent of whether they improved clinically or not. Those who received spinal manipulation at the stiffest segment also demonstrated increased mechanical pain sensitivity, but only in the subgroup with clinical improvement. We did not observe any changes in lumbar stiffness.

Conclusion

Our results suggest the existence of two different mechanistic pathways associated with the spinal manipulation target. i) A decrease of mechanical pain sensitivity independent of clinical outcome (neurophysiological) and ii) a decrease as a reflection of the clinical outcome. Together, these observations may provide a novel framework that improves our understanding of why some respond to spinal manipulative therapy while others do not.

Background

Spinal manipulative therapy

Clinical guidelines recommend spinal manipulative therapy (SMT) for chronic low back pain (LBP) (1), given its effect on pain and disability is comparable to that of other recommended conservative therapies (2). Toward optimizing SMT for chronic LBP, we recently published a randomized clinical trial (RCT) (3). In which, we experimentally categorized each segment as having either high stiffness or high mechanical pain sensitivity. In this trial, the participants received four SMT sessions directed at either the segment with the highest stiffness or highest pain sensitivity in a randomized manner. While significant within-group changes emerged in patient-reported LBP, the randomization did not yield any between-group differences. We also re-measured the experimental outcomes (stiffness and mechanical pain sensitivity) at each time point in the course of treatment. While we did not find differences in lumbar stiffness, mechanical pain sensitivity decreased significantly in the group that received SMT at segments characterized by high mechanical pain sensitivity (*pain segment group*), compared to the group that received treatment at segments characterized by high stiffness (*stiff segment group*). Interestingly, this increase did not imply clinical pain reduction. On this basis, we hypothesized that a segment-specific neurophysiological reflex most likely mediated the observed effect on mechanical pain sensitivity as opposed to a curative effect on a mechanical dysfunction (3).

Impact of being a responder

Our prior paper's analysis did not investigate the potential impact of being a clinical responder or non-responder within the allocated subgroups. For instance, preliminary research suggests decreases in lumbar stiffness following SMT, but only when this corresponded with improvements in disability (4,5). A similar pattern may emerge in this cohort when applying a responder threshold.

Notably, the finding that a segmental effect on mechanical pain sensitivity is not a proxy for clinical improvement appears inconsistent with previous studies that have found a hypoalgesic effect after overall clinical improvement (6,7). However, interpreting our novel finding of a modulating segmental impact of SMT requires a thorough responder analysis. Possible within-group differences in mechanical pain sensitivity could have affected our prior results. Besides, our previous study only included mechanical deep pressure pain sensitivity. Including other types of stimuli associated with chronic LBP (8), like peripheral heat pain sensitivity, may be helpful in an explorative and secondary analysis, as would be the impact of segmental versus regional measurements.

Objectives

In this explorative analysis, we used patient-reported disability and low back pain intensity to determine responder status and examine its relationship to various experimental outcome measures (changes in lumbar stiffness, mechanical pain sensitivity, and heat pain sensitivity).

Methods

Setting

A pre-planned secondary explorative analysis of data used for a primary analysis in an RCT (registered at Clinical.Trial.gov identifier: NCT04086667) (3). One-hundred-and-thirty-two participants enrolled in the study. All participants received lumbar spinal manipulative therapy directed randomly at either the segment of highest stiffness or the segment of highest mechanical pain sensitivity. Seven participants did not complete the study. Two others were lost to follow-up, leaving 123 participants with complete data sets.

We included participants from a regional Spine Centre in Denmark. The inclusion criteria were 18 to 60-year-old patients with LBP of benign or degenerative origin for more than three months. No prior spinal surgery and no indication for current spinal surgery. No history of SMT in the preceding four weeks. Body mass index had to be below 35. We limited the daily opioid intake to 40 mg of morphine at the time of inclusion.

Exclusion criteria were: failure to complete 75% of the allocated SMT interventions, receiving manual therapy of the lower back in another, non-project setting, or change pain medication during the study period. We excluded no patients after initiating the project based on these criteria.

All participants gave oral and written informed consent for the study approved by the regional research ethics board (S-20160201).

Procedure

The primary study protocol is described in full detail in the prior study (3). A short overview is provided here.

We extracted demographic data from the SpineData questionnaire, a clinical registry in use at The Spine Centre of Southern Denmark (9).

The *baseline* lab session consisted of i) completing patient-reported clinical outcomes, ii) identification and marking of each spinous process for each lumbar segment using ultrasonography (Sonosite Titan Linear, L38 probe) (10), iii) measures of lumbar stiffness and pain sensitivity (mechanical and heat), iv) segment randomization (high stiffness or high mechanical pain sensitivity) and v) initial SMT application.

Three additional SMT applications were provided over the following 14 days.

After the fourth SMT application, the *post-SMT* lab session followed in which we repeated items i - iii from the baseline lab session.

A final *follow-up* lab session took place approximately 14 days after the *post-SMT* session. Again, we repeated items i - iii. This concluded the study.

Spinal manipulative therapy

Two chiropractors (see acknowledgments), each with more than 12 years of clinical experience, performed the SMT, both blinded to the segment target allocation. Participants received standardized SMT that consisted of a side-lying posterior to anterior high velocity,

low amplitude thrust with contact point at the spinous process of the indicated segment. The protocol allowed up to three attempts for a successful treatment determined subjectively by the chiropractor and independently of the joint-related sounds that can accompany SMT (11).

Responder variables and responder thresholds

We conducted the responder analyses with two variables using three different responder thresholds. *Disability*, assessed by the Oswestry Disability Index (ODI) (version 2.1), was used to dichotomize responder status using three different responder thresholds: i) more than or equal to a 50% improvement to better be able to compare with similar literature (4,5,12), ii) more than or equal to a 30% improvement as consensus recommended (13), and iii) more than or equal to a 0% improvement indicating the absolute dichotomization between worsening and improving. The ODI has been translated to Danish and validated as a reliable instrument to measure LBP changes (14).

Similarly, we used *patient-reported low back pain* to set responder status at the same three different responder thresholds: i) a 50% improvement, ii) a 30% improvement, and iii) 0% improvement. The pain intensity score used a mean score (0-10) from the self-reported LBP numerical rating scale (NRS) (15), which consists of three scales: Current LBP, Worst LBP in the previous 14 days, and Average LBP in the last 14 days.

We only performed each dichotomization at the final follow-up time point.

Experimental measures

Lumbar stiffness

Lumbar stiffness was measured using the custom-manufactured research tool *VerteTrack* (VT). The apparatus consists of a pair of rollers, loaded by a fixed weight, which moves along the lumbar spine with one wheel on either side of the midline (3 cm apart). The movement is controlled in two axes (superior/inferior and medial/lateral) by computer-controlled stepper motors. Thus, reliably tracking a specific and pre-determined path (skin markings) along the spine. Displacement in the third axis (anterior/posterior) is measured continuously during movement by a string potentiometer (TE Connectivity, USA). Therefore, the VT generates a series of vertical displacement data for a given fixed weight in relation to the longitudinal and transverse positions. In the current study, VT measurements were performed with increasing weights, from 0 to 6 kg in steps of 1 kg. The VT has a sampling rate of 30 Hz. The participants were in a prone position during the procedure, and each indentation took approximately 8 seconds. Participants were guided to exhale and hold their breath while the rolling of the wheels transpired.

The VT has primarily been validated as safe and reliable in healthy volunteers (16,17). No study has yet examined the validity when applied to a back pain population. However, this has been achieved in a prior version using single indentation instead of rolling indentation (18). The bench-top performance indicates that the VT is accurate in-vivo both for rolling and single indentation (19). Thus, suggesting that the use of the VT was feasible in this cohort.

We measured stiffness for each segment as a global stiffness (GS) score, which denotes the force-displacement curve's average slope from the second load to the second heaviest load tolerated. Thus, GS was available i) for each segment (e.g., L5), and ii) each segment's GS

score was averaged as a single score indicating the GS score for the entire lumbar spine (L1 to L5).

Mechanical pain sensitivity

We assessed pressure pain threshold (PPT) using a pressure algometer (Somedic Model 2, Sweden). Attached to the probe was a custom, 3D printed double-headed probe (2x1 cm^2, 3 cm apart), which allowed for a bilateral pressure to be applied at either side of the midline corresponding to the point of indentation for the VT. The rate of increase in pressure was kept at a near-constant 50 kPa/s (indicator on the algometer). Each segment was measured three times in random order with 10-second rest intervals. The participant indicated when the pressure was perceived as painful by pressing an indicator button. We recorded this score as the PPT. If no pain had been elicited by 1000 kPa, this was recorded as the PPT. If the first and second measurements on a given segment were 1000 kPa, we did not perform a third. Pressure pain threshold has previously been shown to have excellent intra-rater reliability in a back pain population (20).

We averaged the PPT score (kPa) from each of the three trials for i) each segment (e.g., L5), and then for ii) all segments (i.e., L1 to L5).

Heat pain sensitivity

Heat pain threshold (HPT) was measured shortly after PPT. The thermode (Medoc TSA-II, Israel) used a single 3x3cm probe applied to the midline. The thermode baseline temperature was pre-set to 32 degrees Celsius. It was increased at a rate of 1 degree per second during testing until the participants indicated that the stimulation was perceived as painful by pressing an indicator button connected to the thermode controller. When the participant indicated the stimulation as painful, the probe was lifted off the skin without delay, and the temperature returned to the baseline temperature (10 degrees/second). Each segment was measured three times in random order with 10-second rest intervals. If no pain had been indicated at 50 degrees, this was recorded as the HPT, and the thermode returned automatically to baseline temperature. When applied to the spine, HPT has previously been found to have good-to-excellent intra-rater reliability in a healthy population (21).

We averaged the HPT score (C) from each of the three trials for i) each segment (e.g., L5), and then for ii) all segments (i.e., L1 to L5).

Before data collection, a trial run consisting of 1-2 tests on the lower extremity and at the T12 vertebra was performed for both PPT and HPT to familiarize the participant with the procedures.

Segmental randomization

The randomization process is described in full detail in the primary study (3). In short, segmental stiffness was determined using the raw force-displacement data (mm) from the VT's heaviest individual load (typically 6 kilograms), and segmental mechanical pain sensitivity was determined as the mean value of the three PPT measures. To resolve situations where the segments with the highest pain sensitivity and stiffness were identical or adjacent, a ratio ranging between -1 and +1 was calculated for each segment based on these two variables in combination. A ratio approximating -1 would indicate high stiffness and low

pain sensitivity, and correspondingly a ratio approaching +1 would indicate high pain sensitivity and low stiffness. SMT was directed at the segment with the highest (or lowest) ratio index.

Statistical analysis

Frequencies (count) are presented for responders/non-responders as defined by each threshold, and the cumulative proportion of responders is presented graphically for both ODI and NRS.

We performed a three-way mixed model analysis with subject as a random intercept using an unstructured variance-covariance structure. The interacting fixed effects were segment-allocation (target site), time, and responder status to determine within-group changes and between-group differences. For a concise description of the mixed model approach, see Bates et al. (22). Responder status consisted of six different predictor variables (minimum or equal to 50%, 30%, and 0% change in both ODI and NRS). The mixed model assumptions were upheld for the models. They evaluated: i) normal distribution of the residuals error using Q-Q plots, and ii) the homogeneity of variance by visually inspecting the residuals versus the predicted values.

We had to omit approximately 11% of the data points due to inaccuracies when identifying the segments at different time points. See the primary study for further detail (3).

The mixed models are presented as mean changes within-group from baseline to post-SMT and follow-up along with 95% confidence intervals. Where significant within-group changes are present in any outcomes, a table is present to further describe between-group mean differences (responder versus non-responder).

Segmental proximity analysis

In addition to the mixed model described above, we also categorized the lumbar segments into three groups: i) the specific SMT targeted segment (e.g., *L2*), ii) the adjacent segment(s) to the targeted (e.g., *L1* and *L3*), and iii) other segments (e.g., *L4* and *L5*). This segmental categorization was added as an interaction term to the original three-way models for the experimental outcomes (GS, PPT, and HPT) for ODI and NRS.

We completed the data analyses in R (23) (Linux, v. 3.6.0 with R-studio v. 1.1.456). Data wrangling was completed using the *Tidyverse* (24). The mixed models were fitted using the *lme4* package (22), p-values for the mixed models were calculated using the *multcomp* package (25). A p-value < 0.05 was considered significant, and repeated p-values were adjusted using the single-step method (25).

Results

Proportion of Responders

Table 1 present the responder/non-responder distribution of the 123 participants who completed the intervention.

Table 1

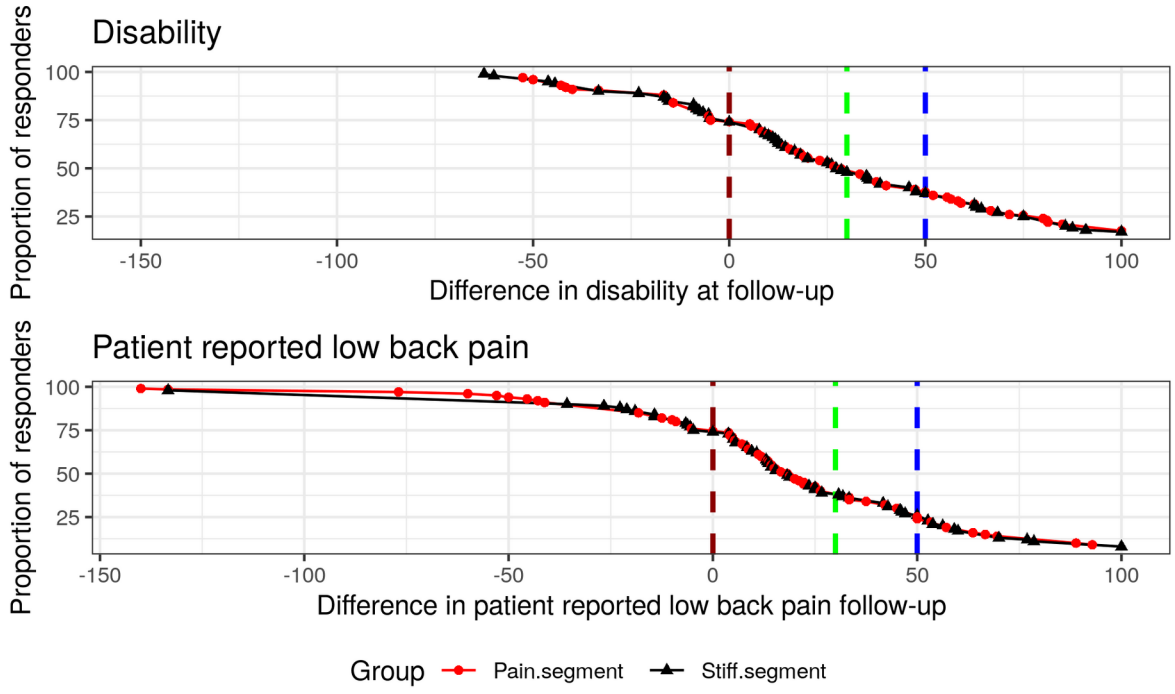
Proportion of responders/non-responders for ODI and NRS at all responder thresholds (0, 30 and 50%)

Parameter	≥0% improvement n(%)	≥30% improvement n(%)	≥50% improvement n(%)
ODI Responder	95(77)	46(37)	29(24)
ODI Non-Responder	28(23)	77(63)	94(76)
NRS Responder	94(76)	35(28)	19(15)
NRS Non-Responder	29(24)	88(72)	104(85)

ODI = Oswestry disability index, NRS = self-reported LBP numerical rating scale

Figure 1 illustrates the cumulative proportion of responders for ODI and NRS at follow-up. The vertical dashed lines represent thresholds for responder/non-responder at 50% (blue), 30% (green), and 0% (red). The line extends negatively beyond 0, indicating that 28 (23%) of the cohort experienced worsening of ODI at follow-up, and 29 (24%) demonstrated worsening of NRS. It also shows that the two groups respond at an equal rate. Furthermore, while an equal number of participants has increased (worsening) ODI and NRS, the variance is much greater in NRS changes, approximating 150% versus 50% for ODI.

Cumulative proportion of responders



A cumulative responder proportion graph for the participants treated with spinal manipulative therapy at either a *pain segment* or a *stiff segment*. The red line indicates a 0% improvement, the green line indicates a 30% improvement, and the blue line indicates a 50% improvement. Improvements are shown for disability and patient-reported low back pain. A negative value indicates worsening of the outcomes

Responder analysis

We present the results of the responder analysis in Tables 2 and 3. Table 2 lists changes in objective outcome measures (GS, PPT, and HPT) immediately post-SMT (4th session) and at follow-up for the two randomization groups (SMT at the stiffest segment and most pain-sensitive segment) and subgrouped by ODI responder status defined as 0%, 30%, and 50% improvement thresholds. Table 3 presents similar data for NRS.

Global stiffness

We observed no statistically significant changes within-group, nor were there any between-group differences, independent of responder status and randomization group. The minor differences observed appear to be spurious, with the largest differences seen in the subgroup with the lowest number of participants. A visual presentation can be found in Additional file 1.

Pressure pain threshold

Baseline PPT was not statistically significantly different between any of the responder thresholds.

Close examination of Tables 2 and 3 reveal that significant increases in PPT were observed in two contexts:

Pressure pain threshold increased for all 24 *responder* subgroups at both time points compared to baseline, independent of randomization groups ("pain" or "stiff"), clinical outcome measure (ODI and NRS), and responder threshold (0%, 30%, and 50%). This was statistically significant in 16 of the 24 comparisons. For the 24 *non-responder* subgroups, the findings were more discordant, and only statistically significant increases were observed in 9 of the 24 comparisons (8 for the *pain group*).

For the 24 *pain* subgroups, PPT again increased in all comparisons and statistically significant so in 21. The findings were also more discordant for the 24 *stiff* subgroups, and only statistically significant increases were observed in 5 instances (all *responders* subgroups).

In general, and for all responder thresholds, the change in PPT diminishes from post-SMT to follow-up. For further scrutiny of the between responder group differences, please see Table 4, and for ease of interpretation, the PPT changes are also presented visually in Figure 2.

Table 2

Changes for responders (ODI) in lumbar stiffness and pain sensitivity (mechanical and thermal) following SMT

Time	Status	Threshold	GS		PPT		HPT	
			Pain	Stiff	Pain	Stiff	Pain	Stiff
Post-SMT	Responder	50%	-0.20(-0.70:0.31)	-0.13(-0.77:0.52)	110(19:200)*	94(-24:211)	0.6(-0.9:2.0)	1.2(-0.7:3.1)
		30%	-0.11(-0.53:0.32)	-0.13(-0.61:0.34)	103(27:178)*	109(24:195)*	0.2(-1.1:1.4)	1.1(-0.3:2.5)
		0%	-0.01(-0.31:0.28)	-0.06(-0.38:0.26)	92(39:145)*	62(4:120)*	0.2(-0.7:1.1)	0.5(-0.5:1.4)
	Non-Responder	50%	0.10(-0.23:0.42)	0.06(-0.25:0.37)	95(37:153)*	19(-36:75)	-0.2(-1.1:0.8)	0.1(-0.8:1.0)
		30%	0.10(-0.26:0.45)	0.11(-0.24:0.45)	96(34:159)*	-6(-67:55)	-0.1(-1.1:0.9)	-0.1(-1.1:0.9)
		0%	0.16(-0.48:0.80)	0.26(-0.26:0.79)	135(17:253)*	-45(-141:50)	-0.7(-2.6:1.2)	0.0(-1.6:1.5)
Follow-up	Responder	50%	-0.22(-0.74:0.30)	0.12(-0.50:0.74)	143(48:237)*	91(-22:204)	1.3(-0.2:2.8)	1.1(-0.9:3.1)
		30%	0.04(-0.40:0.47)	0.07(-0.41:0.55)	105(28:182)*	125(40:211)*	1.1(-0.2:2.4)	0.5(-1.0:2.0)
		0%	0.20(0-0.10:0.51)	-0.07(-0.40:0.26)	87(32:142)*	75(15:135)*	0.9(-0.0:1.8)	0.8(-0.2:1.8)
	Non-Responder	50%	0.19(-0.14:0.51)	-0.10(-0.42:0.22)	70(11:128)*	38(-21:96)	0.3(-0.7:1.3)	0.7(-0.3:1.6)
		30%	0.10(-0.26:0.46)	-0.12(-0.48:0.24)	79(15:143)*	6(-57:70)	0.2(-0.9:1.3)	0.9(-0.2:2.0)
		0%	-0.44(-1.06:0.18)	0.00(-0.54:0.54)	103(-10:217)	-23(-121:75)	-0.6(-2.5:1.2)	0.7(-0.9:2.3)

Mean changes in GS (N/mm), PPT (kPa) and HPT (degrees Celsius) in groups randomized to SMT at the stiffest ('stiff') or most pain-sensitive ('pain') segment (columns). Subgrouped (rows) by responder status are defined as 0%, 30%, and 50% improvement thresholds in disability (ODI). Mean change refers to the difference in ODI between baseline and post-SMT, baseline, and follow-up, respectively, along with a 95% confidence interval. * = indicates a p-value < 0.05. SMT = Spinal manipulative therapy, GS = Global stiffness, PPT = Pressure pain threshold, HPT = Heat pain threshold, ODI = Oswestry disability index

Table 3

Changes for responders (NRS) in lumbar stiffness and pain sensitivity (mechanical and thermal) following SMT

Time	Status	Threshold	GS		PPT		HPT	
			Pain	Stiff	Pain	Stiff	Pain	Stiff
Post-SMT	Responder	50%	-0.13(-0.79:0.53)	-0.09(-0.80:0.61)	179(62:296)*	100(-25:225)	0.3(-1.7:2.3)	0.9(-1.1:3.0)
		30%	-0.30(-0.83:0.23)	-0.05(-0.56:0.45)	151(55:246)*	40(-51:132)	-0.3(-1.9:1.3)	0.9(-0.6:2.4)
		0%	0.01(-0.30:0.32)	-0.09(-0.41:0.23)	113(57:169)*	41(-17:98)	0.1(-0.9:1.0)	0.3(-0.6:1.3)
	Non-Responder	50%	0.04(-0.26:0.33)	0.05(-0.25:0.35)	83(31:135)*	21(-32:74)	0.0(-0.9:0.9)	0.2(-0.7:1.1)
		30%	0.12(-0.20:0.44)	0.06(-0.28:0.39)	81(25:138)*	30(-30:90)	0.1(-0.8:1.1)	0.0(-1.0:1.0)
		0%	0.03(-0.52:0.59)	0.40(-0.16:0.97)	52(-48:153)	9(-94:112)	0.0(-1.7:1.7)	0.3(-1.5:2.0)
Follow-up	Responder	50%	-0.31(-0.99:0.38)	0.22(-0.48:0.92)	214(91:336)*	91(-34:217)	0.1(-2.0:2.1)	0.8(-1.4:2.9)
		30%	-0.24(-0.80:0.32)	0.09(-0.41:0.58)	182(81:283)*	53(-36:142)	0.1(-1.6:1.7)	1.1(-0.4:2.7)
		0%	0.08(-0.24:0.40)	-0.01(-0.35:0.32)	103(46:160)*	69(8:130)*	0.5(-0.4:1.5)	0.9(-0.1:1.9)
	Non-Responder	50%	0.15(-0.16:0.45)	-0.11(-0.42:0.20)	66(13:120)*	41(-15:96)	0.7(-0.2:1.6)	0.8(-0.2:1.7)
		30%	0.18(-0.14:0.50)	-0.12(-0.47:0.23)	61(4:118)*	46(-18:109)	0.8(-0.2:1.7)	0.6(-0.5:1.6)
		0%	0.05(-0.52:0.62)	-0.13(-0.68:0.42)	45(-59:149)	-5(-105:95)	0.8(-1.0:2.6)	0.5(-1.2:2.1)

Mean changes in GS (N/mm), PPT (kPa) and HPT (degrees Celsius) in groups randomized to SMT at the stiffest ('stiff') or most pain-sensitive ('pain') segment (columns). Subgrouped (rows) by responder status are defined as 0%, 30%, and 50% improvement thresholds in patient-reported low back pain (NRS). Mean change refers to the difference in NRS between baseline and post-SMT, baseline, and follow-up, respectively, along with a 95% confidence interval. * = indicates a p-value < 0.05. SMT = Spinal manipulative therapy, GS = Global stiffness, PPT = Pressure pain threshold, HPT = Heat pain threshold, NRS = Patient-reported low back pain

Table 4

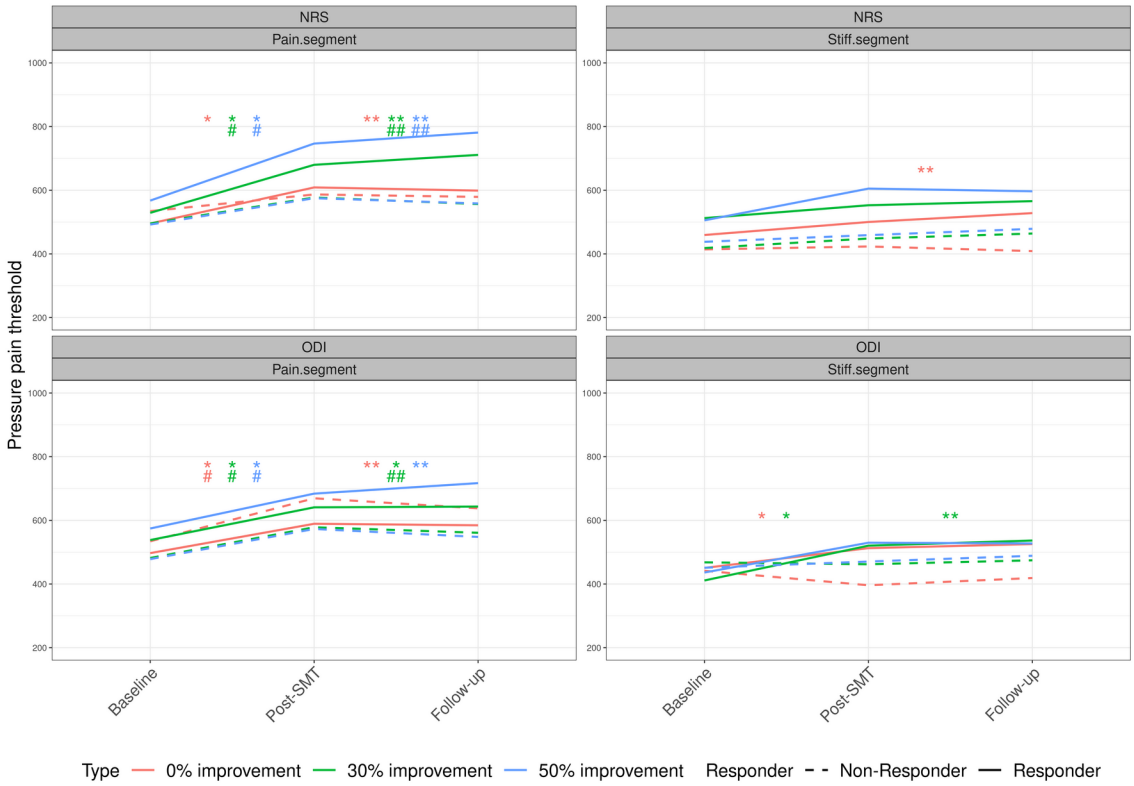
Between-group changes in pressure pain threshold for responder vs non-responders following SMT

Time	Improvement	ODI		NRS	
		Pain	Stiff	Pain	Stiff
Baseline	50%	96(-70:262)	-42(-232:148)	75(-124:275)	13(-195:222)
	30%	56(-96:209)	-71(-232:91)	33(-136:203)	17(-143:176)
	0%	-37(-226:152)	-84(-275:108)	-39(-217:140)	-75(-255:105)
Post-SMT	50%	15(-92:122)	74(-56:204)	96(-32:225)	79(-57:215)
	30%	6(-92:105)	115(10:220)*	69(-41:180)	11(-98:119)
	0%	-43(-172:86)	108(-4:219)	61(-54:176)	32(-86:150)
Follow-up	50%	73(-39:184)	54(-73:181)	147(14:281)*	51(-86:187)
	30%	26(-74:126)	119(12:226)*	121(5:237)*	8(-101:117)
	0%	-16(-142:110)	98(-17:213)	59(-60:177)	74(-43:191)

Between-group mean differences (responder vs non-responder) in pressure pain threshold (kPa) at varying thresholds for improvement in disability and patient-reported low back pain (0%, 30%, 50%) in groups randomized to SMT at the stiffest ('stiff') or most pain sensitive ('pain') segment (columns). Estimates are presented as between-group differences, 95% confidence interval, and "*" indicates a p-value < 0.05. ODI = Oswestry disability index, NRS = patient-reported low back pain

Figure 2

Changes in pressure pain threshold following SMT



Within-group mean changes in pressure pain threshold (kPa) for 50, 30, and 0% improvement in disability and patient-reported low back pain. Estimates are presented as means with 95% confidence intervals for each time-point and within-group significance level (p<0.05) - presented as: * = Significant changes in responders from baseline to post-SMT. ** = Significant changes in responders from baseline to follow-up. # = Significant changes in non-responders from baseline to post-SMT. ## = Significant changes in non-responders from baseline to follow-up. SMT = Spinal manipulative therapy

Heat pain threshold

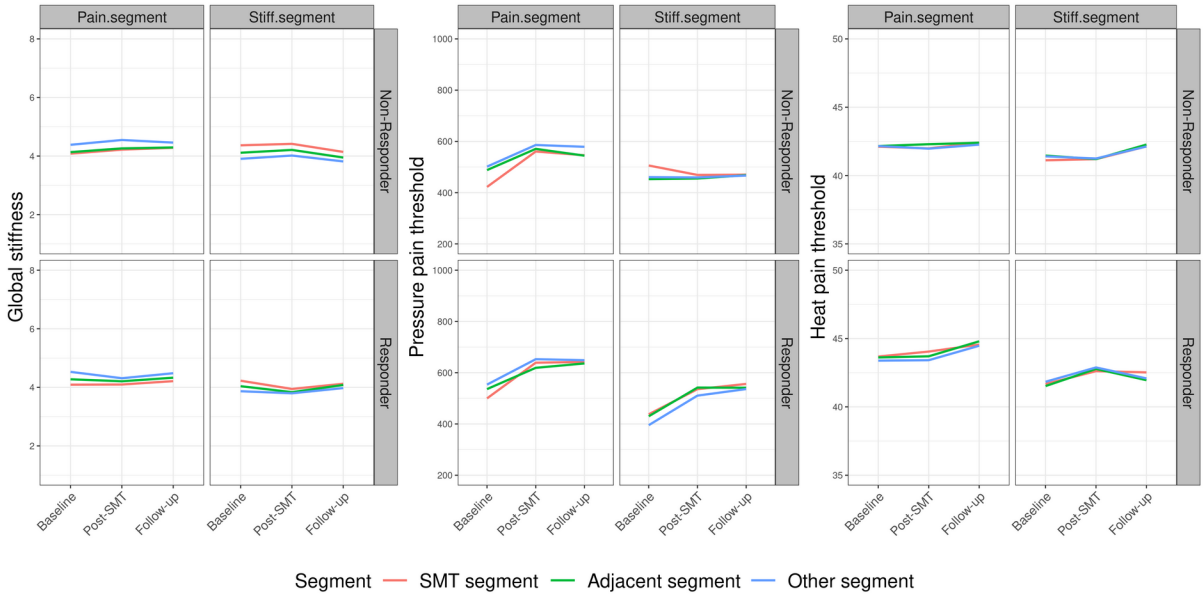
No statistically significant changes occurred for HPT. The data's direction indicates minor improvements for the responders compared to non-responders independent of treatment allocation, but these were minor and not statistically significant. A visual presentation can be found in Additional file 1.

Segmental proximity analysis

When categorizing segments into i) target, ii) adjacent, and iii) other, no significant within-group differences were observed, and no discernible patterns emerged (see Figure f.seg). The same pattern is present for all outcomes (GS, PPT, HPT) for each segment and each responder threshold in ODI and NRS. For simplicity, we illustrate 30% ODI improvement in Figure 3. The remaining figures are similar and can be found in Additional file 2.

Figure 3

Segmental changes in pain sensitivity (mechanical and thermal) and lumbar stiffness following SMT



The segmental changes in global stiffness (N/mm), pressure pain threshold (kPa), and heat pain threshold (degrees Celsius) presented for 30% improvement in disability. Estimates are presented as mean and 95% confidence intervals for each time-point. Segments are divided into the segment targeted, the adjacent segments to the targeted segment, and all other segments. SMT = spinal manipulative therapy

Discussion

The present analysis confirmed our previous results, namely that the segmental target impacted the increase of PPT, but added that responder status also had an isolated effect on PPT's increase. The observations were consistent across multiple thresholds for the definition of responder status, suggesting the finding can be interpreted as robust. Only deep mechanical pain sensitivity was affected by responder status and the segment of the SMT target. Neither lumbar stiffness nor thermal pain sensitivity was affected. The PPT change

appears to affect the whole lumbar spine as no obvious pattern emerged concerning the targeted, adjacent, and other segments.

This analysis presents new evidence regarding increases in PPT following SMT. More specifically, we observed an increase in two circumstances: i) when SMT was applied to the most pain-sensitive segment, in which case PPT increased irrespective of clinical response to treatment, and ii) in the clinical responder group, in which case PPT increased irrespective of where SMT was applied.

Multiple systematic reviews have indicated a non-specific decrease of mechanical pain sensitivity following SMT (26–29), and such an effect can explain the increase in PPT observed in the *pain segment group* irrespective of responder status (i). However, we did not observe such an effect in the *stiff segment group*. This may suggest that the analgesic effect may be greater when directed at pain-sensitive segments. In other words, this change in PPT may represent a localized, reflex-mediated reduction of pain sensitivity at a hyperalgesic segment.

Prior research also demonstrates that an experimental inhibition of a sensitized nociceptive trigger is followed by decreased experimental pain sensitivity (30,31). Our finding of increased PPT in the responder group independent of treatment allocation (ii) could be explained by such mechanism, i.e., a generalized decrease in experimental pain sensitivity following a successful reduction of clinical pain.

Therefore, the reduction of deep-tissue mechanical hyperalgesia in the present study could be explained by two parallel mechanisms: a *specific* neurophysiological effect of SMT on discrete hyperalgesic segments with no apparent clinical benefit, and a *non-specific*, general effect on pain sensitivity through successful treatment of a painful condition (Figure 4).

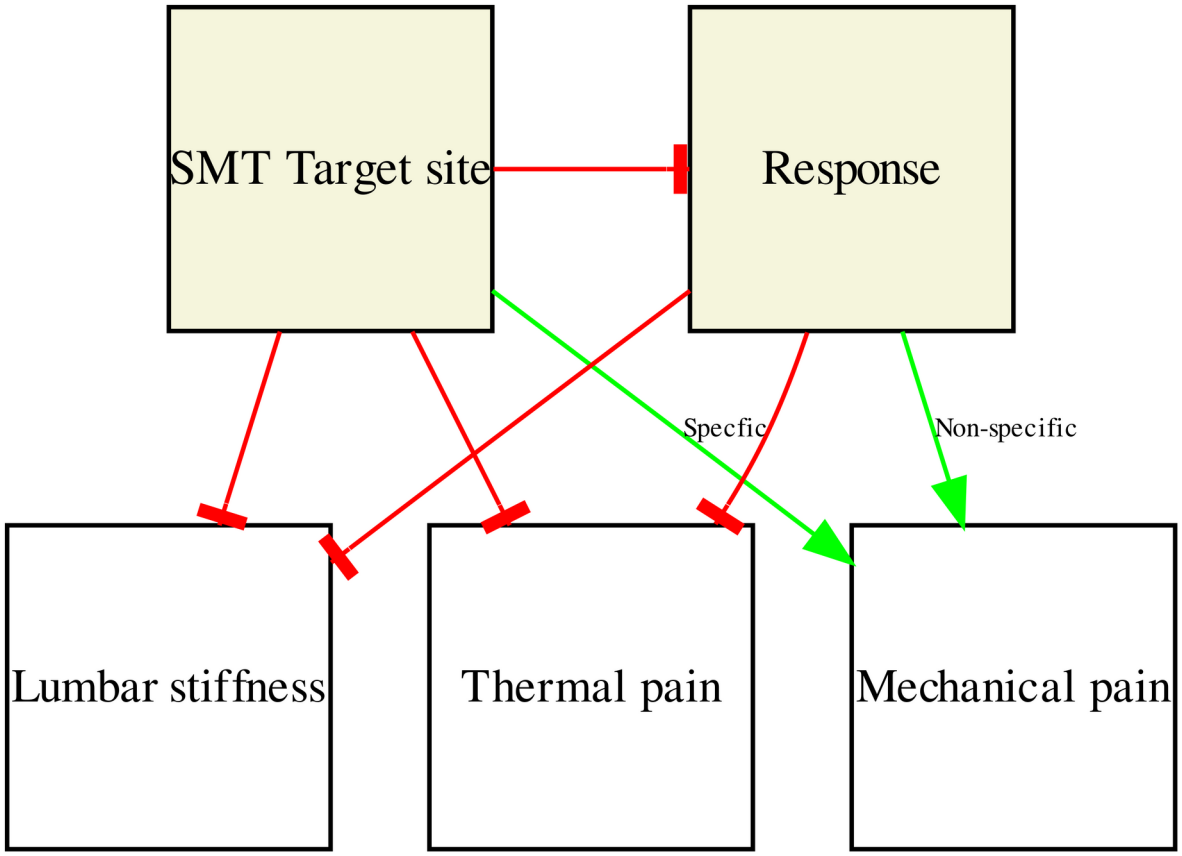
It is apparent that the outcome changes in pain sensitivity following SMT were strictly limited to deep-tissue mechanical pain sensitivity. Heat pain threshold quantifies superficial (skin) pain sensitivity. If one assumes that LBP originates in the deep spinal tissues, it is conceivable that no effect on superficial pain sensitivity was observed in contrast to deep PPT.

Another RCT by Aspinall et al. compared SMT to sham and also examined whether being a "rapid responder" following SMT increased PPT at a higher rate than being a non-responder. The authors noticed small and non-significant increases in lumbar PPT immediately following SMT (up to 30 minutes) for the responders, but not so for non-responders (32). The major differences between that and the current study were the intervention (1 vs. 4 sessions) and the follow-up time point (Immediately to 1 day vs. 2 to 4 weeks). While rapid responders may improve more clinically (33), it is questionable that clinically substantial changes in pain sensitivity would manifest so rapidly following a single treatment (3,6). Another observation by Aspinall et al. was that the responder group consisted of roughly equal numbers of actual and sham-SMT recipients (32), and there was no between-group difference in PPT increases following SMT or sham (34). This raises questions about whether an increase in PPT following SMT results from the intervention, simple touch, or the passage of time. Finally, we performed the QST on a cohort of participants with chronic LBP, whereas the other study used volunteers with LBP (32). Arguably chronicity presumes that this cohort had lower QST

scores. This could potentially impact how PPT varies over time and whether it is of clinical relevance.

Figure 4

The pathway of experimental changes following SMT in chronic low back pain patients



A pathway of changes following SMT in lumbar stiffness and pain sensitivity (mechanical and thermal), both in general and dependent on the target site (*pain* segment or a *stiff* segment). A green arrow indicates a positive specific/non-specific effect on the outcome, and a red blocked arrow indicates no effect on the outcome. SMT = Spinal manipulative therapy

In recent decades, a range of QST procedures with well-delineated methodology (stimulus type, intensity, rate of application, quantification method etc.) has been used to publish data on pain sensitivity (35). No such range of segmental spinal stiffness tests has been established (36), and it remains unclear which aspects of spinal stiffness are clinically relevant. Although the VT provides spinal stiffness measures, which are both standardized and objective, it is unknown to what extent these correlate to clinical procedures such as manual palpation (37). It is entirely possible that other measures of segmental biomechanical function are more relevant than those obtained from the VT.

The current findings do not suggest that the experimental outcomes change only at the targeted segment, but instead, changes were observed for all of the lumbar segments. This contrasts the literature, particularly when SMT is applied in a highly controlled condition in

animal models. Examining SMT in this fashion shows that the mechanistic outcomes are dependent on both the segmental target and the localized thrust on that segment (38,39).

Novel framework for SMT improvement

The underlying causes of low back pain are often obscure, and the connection to spinal stiffness is unclear. In degenerative joint and disc disease, spinal stiffness is likely affected, albeit pain is not always present. In other words, segmental spinal stiffness may be relevant to disability but potentially irrelevant to pain. Conversely, pain will tend to affect disability, irrespective of spinal stiffness.

Therefore, SMT may change pain perception through neurophysiological reflex mechanisms, thus changing both clinical pain and overall disability without actually improving segmental spinal stiffness. However, the difference in deep pressure pain sensitivity, which accompanies clinical improvement, may be unrelated to the SMT. Furthermore, SMT's reflex-mediated segmental effect on deep pressure pain sensitivity, which does not translate into a clinical improvement, is probably of limited relevance.

Methodological considerations

We observed a difference in the number of clinical responders when using disability compared to pain intensity. We consider the most likely reason for this difference to be that a reduction in pain intensity and improvement in disability does not necessarily correlate entirely (40). Furthermore, the responsiveness of the two scales varies. The numerical rating scale is restricted to one domain with scores between 0 and 10, whereas ODI spans a range of 0 to 50 and records ten different domains. The smaller resolution of the 11-item NRS could limit the responsiveness, thereby translating into a smaller number of responders. However, this is speculative, and the authors are not aware of any data to support this.

Participants in the present study were LBP patients referred for assessment in a hospital setting. One of the formal criteria for such referral in Denmark is the insufficient effect of conservative management in the primary care setting. In other words, we must assume that LBP patients who respond favorably to SMT are underrepresented in this cohort compared to LBP patients in general (2). The fact that around 23% of the participants experienced worsened disability after the intervention supports this assumption. This may further negatively impact the likelihood of positive clinical outcomes with SMT and affect the relationships between disability, pain, and experimental outcomes. This is speculative, however.

Another potential limitation is that we choose to dichotomize responder status at the final follow-up time point. We may miss some rapid responders directly following the fourth treatment to provide greater detail of the changes. However, the mean improvement at post-SMT and follow-up appears to be of equal size (3).

As stated in our previous paper (3), this was not a placebo-controlled study, and thus, the clinical improvement observed could be due to something other than the SMT. Therefore, the present findings do not speak to SMT's clinical efficacy but rather to the underlying mechanism of any such effect. Furthermore, these results are limited to the cohort in question, as different possible outcomes could be observed in a primary care setting. Finally, the pressure algometry was applied by a double-headed probe. It is unknown whether this

affects how the PPT scores change following SMT. Hence, caution should be taken when comparing our data to similar literature.

There are also strengths to consider; this was a relatively large cohort of chronic LBP patients seen in the secondary care sector. We measured the experimental outcomes both immediately following SMT and at 14-days follow-up and were able to correlate this with clinical improvements.

Conclusion

Spinal manipulative therapy appears to have a segment-specific neurophysiological reflex effect that decreases deep mechanical pain sensitivity when directed at hyperalgesic segments, irrespective of clinical outcome. Furthermore, a generalized decrease in deep mechanical pain sensitivity was observed when clinical outcomes improve irrespective of the SMT target site. Stiffness and heat pain sensitivity were not found to respond in specific ways to SMT or based on clinical improvement.

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Manuscript III

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Spinal Manipulation and Modulation of Pain Sensitivity in Persistent Low Back Pain: A Secondary Analysis of a Randomized Trial

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Spinal Manipulation and Modulation of Pain Sensitivity in Persistent Low Back Pain: A Secondary Analysis of a Randomized Trial

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Abstract

Background

Pain hypersensitivity can be assessed using Quantitative Sensory Testing (QST) and is associated with persistent low back pain. Changes in pain sensitivity following spinal manipulation have been reported in the literature, and this modulation of pain hypersensitivity could function as one mechanism leading to clinical improvements. In the current study, we applied a comprehensive QST battery to assess pain sensitivity in a cohort of low back pain patients before and after spinal manipulation to improve our understanding of the association between QST and clinical improvements. This study addresses two questions: Are clinical improvements following spinal manipulation in low back pain patients contingent on pain hypersensitivity, and does pain sensitivity change following spinal manipulation?

Methods

We performed a secondary analysis of data from a randomized clinical trial. One hundred and thirty-two participants with persistent LBP were treated with spinal manipulation four times over two weeks. Patient-reported outcomes and QST were assessed at baseline, after the fourth spinal manipulation session, and after 14 days. The clinical outcomes were changes in low back pain intensity and disability. Using latent class analysis, we categorized the participants into clusters depending on their baseline QST scores. We used linear mixed models to examine the association between clusters and changes in patient-reported outcomes and QST.

Results

Two clusters emerged: a *sensitive* and a *not sensitive* group. The former had significantly lower regional pressure and thermal pain thresholds, widespread pressure pain tolerance, and lower inhibitory conditioned pain modulation than the not sensitive group. However, we only found between-cluster differences for regional pressure pain threshold following spinal manipulation. Thus, the clusters were not associated with changes in patient-reported pain and disability or the remaining QST outcomes.

Conclusion

In line with previous findings, we report that the baseline QST profile was not associated with clinical improvements following spinal manipulation. We did observe a substantial change for regional pressure pain threshold, which suggests that any effect of spinal manipulation on pain sensitivity is most likely to be observed as changes in regional, mechanical pain threshold. Due to methodological caveats, we advise caution when interpreting the results.

Background

The conscious experience of pain is not a simple reflection of the stimulus, which caused it. A stimulus may initiate the conduction of a nociceptive signal, but the signal can be heavily modulated in the nervous system before reaching consciousness as pain. Long-lasting pain can cause disturbances in this system, resulting in pain hypersensitivity (1). Pain sensitivity and pain modulation can be examined using standardized psychophysical measures, collectively known as Quantitative Sensory Testing (QST) (2). Hence, we are able to quantify an individual's pain sensitivity using their pain perception elicited by a standardized stimulus (3). This allows us to describe different types of pain and treatment-induced changes within the same pain cohort.

Persistent low-back pain (LBP) patients appear to be affected by pain hypersensitivity and perturbations in pain modulation. When comparing persistent LBP patients to healthy individuals using QST, large differences are noted (4). While this arguably constitutes one process in developing persistent pain (5), the predictive value of baseline QST is unfortunately questionable and not sufficiently researched (6–8). Nonetheless, studies have reported QST changes following successful treatment in experimental (9,10) and clinical settings (11), arguably reflecting an underlying mechanistic explanation of pain relief.

Spinal manipulation (SM) is often used to treat low back pain and is historically theorized to effect clinical changes through neurophysiological mechanisms (12). The study of changes in pain sensitivity following SM has received considerable attention in the field. No less than four systematic reviews are available on the subject (13–16), and while there is an apparent disparity in the research, it appears that SM affects regional mechanical pain sensitivity across pain populations. To investigate this further, we recently published a randomized trial investigating whether the SM's application site (a stiff vs. a pain-sensitive segment) moderated the observed effect on regional pressure pain thresholds (17), and that study indicated a segmental effect. Namely, that regional pressure pain threshold increased for the group receiving SM at a pain-sensitive segment compared to the group receiving SM at a segment characterized by stiffness. We postulated that this was purely a segmental neurophysiological reflex phenomenon, as this effect was disconnected from a clinical pain reduction.

Objectives

Our previous study questioned the clinical benefit of increases in pressure pain thresholds. Furthermore, the findings have generated multiple questions concerning the association between baseline pain hypersensitivity and changes in i) patient-reported pain and disability and ii) QST outcomes following SM. Hence, this secondary analysis will re-analyze the longitudinal data used in the original randomized clinical trial (17) to answer the following specific research aims:

1 To cluster patients with persistent LBP cross-sectionally using a data-driven approach based on the baseline QST data.
2 To determine whether short-term changes in patient-reported pain and disability and QST outcomes differ between clusters.

Method

Setting

A secondary analysis using data from a randomized clinical trial (Clinical.Trial.gov identifier: NCT04086667, registered 11 September 2019 – Retrospectively registered, https://clinicaltrials.gov/ct2/show/NCT04086667) (17). The sample consisted of 132 participants with non-specific persistent LBP. All participants were recruited from a secondary-care hospital outpatient Spine Center in Southern Denmark between November 2017 and February 2019. The full description of participants, eligibility criteria, and study procedures are reported elsewhere (17). Here we provide a summary of the methods pertinent to the current analysis.

Inclusion criteria of the study included: benign and non-specific LBP (not malignant, infectious, inflammatory, or fracture) for more than three months, no prior spinal surgery, no current surgical indications due to radiculopathy, and age between 18 and 60 years. All participants gave oral and written informed consent for the study approved by the regional research ethics board (S-20160201).

Spinal manipulation

The SM was provided in a standardized manner with the participant in a side-lying position. A high velocity, low amplitude thrust targeted the randomized segment (the stiffest or the most pain-sensitive) in a posterior to anterior direction. The contact point was at the spinous process. We allowed up to three SM attempts for a successful treatment. The chiropractor who provided the SM determined subjectively and independent of cavitation whether the treatment was successful. Two chiropractors performed all SMT in this study, each with more than 12 years of clinical experience. A total of four SM sessions were provided over 14 days (17).

Procedure

The study design included three visits to the Human Experimental Pain Laboratory at the Spine Center of Southern Denmark:

- Before the first SM treatment session (baseline)
- Directly following the fourth and final SM treatment (post-SM)
- Two weeks after the end of SM treatment (follow-up)

We collected data on patient-reported pain and disability and QST at each of the laboratory visits. After enrollment, the participants were randomized to receive SM directed at either the segment of highest stiffness, measured using the VerteTrack (18), or the segment of lowest mechanical pain threshold measured using pressure algometry (19).

Data collection

Patient-reported outcomes

The Low Back Pain Rating Scale was used to assess low back pain intensity. Three 11-point numerical rating scales (NRS) quantified the current, worst, and average LBP over the last 14 days, and these scores were combined into a mean score. The scale is reliable for assessing LBP intensity (20).

The Oswestry Disability Index (ODI) version 2.1 (21) was used to measure disability. The ODI is a 10-item questionnaire with a five-point Likert rating scale, ranging from no disability to high disability. The items were combined and converted into percentages [0-100%]. This outcome measure has been translated into Danish and is responsive to clinical changes (22).

Quantitative sensory testing outcomes

The QST consisted of six different tests using three different methods. We measured pain sensitivity regionally (at the lower back), widespread (at the legs), and centrally modulated pain. The definition of the different QST procedures can be found in Table 1 (3,23,24):

Table 1

Definitions of the different QST procedures

QST procedure	Definition
Pain threshold	The minimum intensity of a stimulus that is perceived as painful
Pain tolerance	The maximum intensity of a pain-producing stimulus tolerated
Temporal summation	Increases in subjective pain response during repetitive pain-producing stimuli
Conditioned pain modulation	Decreases (inhibitory) or increases (facilitatory) of the pain response during the application of pain-producing conditioning stimulus

QST = Quantitative sensory testing

Manual pressure algometry (model 2, Somedic, Sweden) was used to assess regional pressure pain threshold at the lower back. With the patient placed in the prone position, we gradually increased the pressure perpendicular to the skin, simultaneously on both sides of each spinous process from L1 to L5 at a rate of 50 kPa/s using a custom made double-headed probe (Supplementary file 1). The participant indicated the onset of pain by pressing a button, which discontinued the pressure and recorded the pressure pain threshold. Each of the five segments was tested three times in random order. If no pain was elicited at 1000 kPa, we recorded 1000 kPA as the regional pressure pain threshold. Pressure algometry has excellent intra-rater reliability in LBP patients (25).

A thermode (Medoc TSA-II, Israel) with a single 3 cm × 3 cm probe was applied at the midline for each spine process (L1 to L5) to measure regional heat pain threshold. The thermode baseline temperature was pre-set to 32 °C. During testing, it increased at a rate of 1 °C/s until the participants indicated the stimulation as painful by pressing an indicator button. When indicated as painful, the probe was lifted off the skin, and the temperature returned to the baseline temperature (10 °C/s). If no pain was elicited at 50 °C, 50 °C was recorded as the regional heat pain threshold, and the thermode returned automatically to the baseline temperature. Regional heat pain threshold measured at the spine has good-to-excellent intra-rater reliability in a healthy population (26).

For both regional pressure pain threshold and regional heat pain threshold, we first completed a trial procedure consisting of 1-2 tests on the lower extremity and at the T12 spinal segment to familiarize the participant with the procedure before testing. We used a composite score

for each of the regional pressure pain threshold and regional heat pain threshold. The three tests at each segment were compounded into a single segment score, then the average between all segments was calculated and used for the analysis.

Computer-controlled cuff algometry (CCA) on the lower extremities was used to measure widespread pressure pain threshold, widespread pressure pain tolerance threshold, centrally modulated temporal summation, and conditioned pain modulation. The CCA procedure employed two 13-cm wide silicone tourniquet cuffs (VBM, Sulz, Germany). Each with two adjacent, equally sized proximal and distal chambers wrapped around the non-dominant and dominant gastrocnemius muscle 5 cm inferior to the tibial tuberosity. The pain intensity was assessed by increasing the inflation of the cuff.

We used the dominant leg as the experimental test site, which assessed deep-tissue pain sensitivity as a stimulus-response curve. The cuff pressure increased with one kPa/s in both chambers; the pressure limit was 100 kPa. Participants indicated their pain on a computerized electronic visual analog scale (VAS) ("No pain" = 0 cm to "Worst pain imaginable" = 10 cm). We instructed the participants to continuously rate the induced pressure pain intensity from the initial pain onset. The pressure at which the participant first perceived the stimulus as painful was noted as widespread pressure pain threshold. The pressure at the time of termination was recorded as widespread pressure pain tolerance threshold. If cuff pressure was tolerated to the limit of 100 kPa, 100 kPA was recorded as the widespread pressure pain tolerance threshold, and the pressure was instantly released.

Afterward, the CCA was programmed to apply a series of 10 pulses to the dominant leg of equal pressure to the individual's widespread pressure pain tolerance threshold at a rate of 1 Hz (i.e., 1 s of inflation to the target pressure and 1 s of deflation). The average pressure pain intensity of the first three stimuli was subtracted from the average of the last three stimuli and recorded as the temporal summation. We recorded Conditioned Pain Modulation as the difference in widespread pressure pain threshold at the dominant leg (test stimulus) before and during continuous conditioning pressure stimulus applied to the non-dominant leg (conditioning stimulus at 70% of the individual widespread pressure pain tolerance threshold). The CCA has previously been used to quantify temporal summation and conditioned pain modulation and is deemed reliable and sensitive for changes (27).

Statistical analysis

Latent class analysis

We used a data-driven latent class analysis to develop a clustering model with baseline QST variables for the participants with complete QST datasets (regional pressure pain threshold, regional heat pain threshold, widespread pressure pain threshold, widespread pressure pain tolerance threshold, temporal summation, and conditioned pain modulation). No generally accepted strategy exists to determine the sample size for such an analysis. However, 2^k participants have been suggested to be sufficient, where k denotes the number of variables included in the model (28). To assess the independence of the QST variables, we calculated correlation coefficients between each variable. *A priori*, we decided that if two variables were strongly correlated (coefficient >0.7), one of the variables would be omitted from the model (29). As the six variables were quantified using different continuous scales and limits, the variables were Z-transformed (mean-centered and normalized to one standard deviation). We reversed the temporal summation score to ease interpretation, as the meaning is the opposite of the remaining tests (a higher score indicating *higher pain sensitivity*).

We fitted the clustering models using the *Mclust package* for R (30). In addition to the number of clusters, *Mclust* uses different covariance structures to make the model as parsimonious as possible. A minimum of 2 clusters and a maximum of 6 clusters were investigated. We used the Bayesian Information Criterion (BIC) to evaluate the number of clusters, where the highest negative number indicates the best model fit (31). Another component cluster was only added if the BIC score improved by two units (32). Afterward, we performed the Bootstrap Likelihood Ratio Test, which compares model fit between different numbers of clusters, i.e., whether an increase in clusters increases fit (33). Finally, we present the fitted model using the following parameters: number of clusters, data structure, BIC, probability of belonging to a particular cluster, the results from the Bootstrap Likelihood Ratio Test, and individuals in each cluster. Any unexpected result of the latent class analysis would be examined in a posthoc test.

Patient-reported outcomes

We constructed two linear mixed models to investigate changes in patient-reported pain and disability (NRS and ODI). The model assumptions were normal distribution of the residuals errors and homogeneity of the variance, which were assessed using QQ-plots and by plotting the residuals versus the predicted values, respectively. We applied the final cluster model and time as interacting fixed effects, with the participant as the random intercept. We present baseline differences in NRS and ODI for each model as estimates of the between-cluster difference with 95% confidence intervals (95%CI). We also tabulate the within-cluster and between-cluster mean differences with 95%CI.

Quantitative sensory testing

We present the scaled means of each QST parameter per cluster. To describe the stability of the QST scores in groups at the different time points, the baseline fitted model was applied cross-sectionally to the additional time points (post-SM and follow-up) and presented as a horizontal process flowchart. To further investigate QSTs' variability over time, we attributed each outcome to a linear mixed model, using the before-mentioned approach. While we omitted the randomization process, we did previously observe changes in regional pressure pain threshold modified by the SM allocation site (17). Therefore, a posthoc test was planned should the clustering result in significant interactions for the QST outcomes. This posthoc test would apply a three-way analysis approach (cluster:time:SM allocation site). Again, we present baseline differences, tabulate the within-cluster and between-cluster mean differences with 95%CI.

We completed data cleaning and analyses in R (34) (Linux, v. 3.6 with R-studio v. 1.3), using the *Tidyverse* (35), 95%CI and p-values for the mixed models were calculated using the *LMERtest* package (36). A p-value of less than 0.05 indicated statistical significance for all statistical tests.

Results

Latent class analysis

Datasets from 5 participants were incomplete, consequently the sample size used for the analysis was 127. We found no strong correlations for any of the QST variables. Therefore, we included all six QST variables in the models (see Supplementary file 2). With six QST variables, a minimum of 64 (2^6) samples would be necessary, indicating that our sample size was sufficient for the model clustering.

Table 2 shows the top three BIC models. The model 2-VEE (rank #2) was the second most optimal model, but the difference in BIC score from the 3-VII model (rank #1) was -0.40, i.e., less than 2.00 (32). The Likelihood Ratio Test demonstrated a significantly better fit between 1 and 2 groups, but not between 2 and 3 (p-value of 0.11). Therefore, we chose the 2-VEE solution as the optimal and most parsimonious model. The 2-VEE data structure indicated the following: i) 2 clusters, ii) the distribution is ellipsoidal, iii) the volume is variable, iv) the shape is equal, and v) the orientation is equal (30).

Table 2

The top 3 models with the highest BIC score used to measure the fit of quantitative sensory tests derived by latent class analysis

Rank	Data structure	n clusters	BIC score	BIC Difference
1	VII	3	-2152	0
2	VEE	2	-2152	-0.4
3	VII	2	-2155	-2.6

For a detailed overview of the VEE,2 model, see Table 3. An acceptable rate of 85% of the participants had a probability of more than 90% of belonging to the specific cluster (37).

Table 3

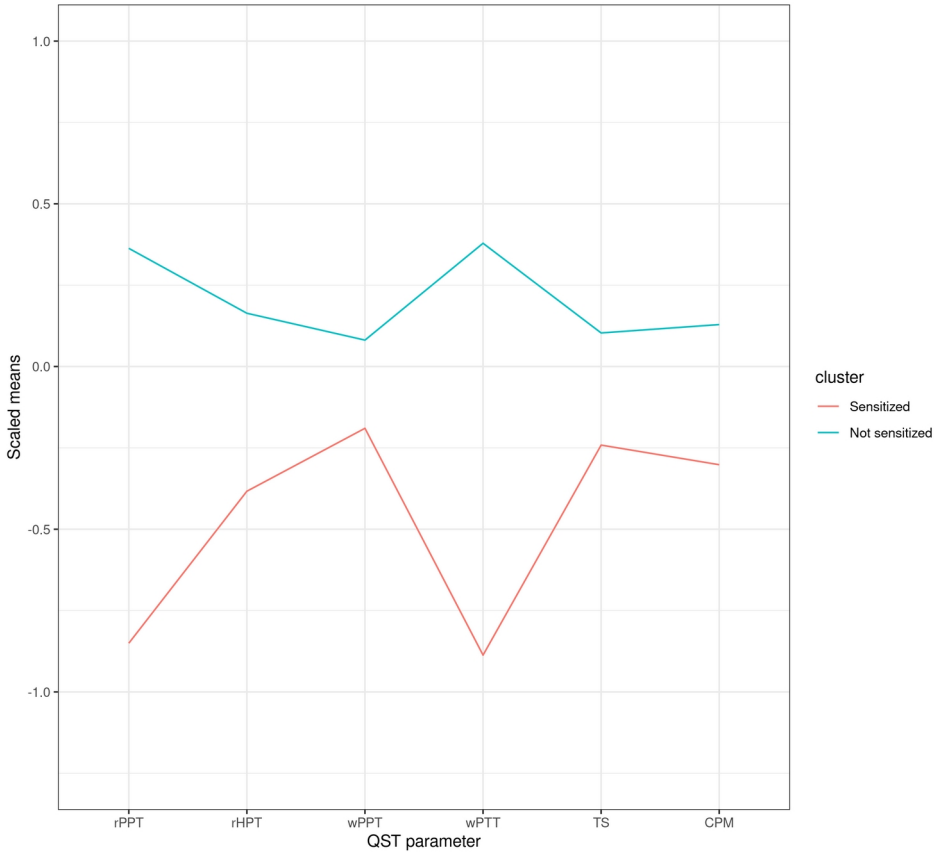
Latent class analysis measures of model fit and cluster probability for the chosen model, 2-VEE.

BIC	Probability (>90%)	The Likelihood Ratio Test (p-value)	n cluster
-2152	85%	2 vs 3 groups: 22.2 (0.11)	1:38/2:89

Based on the profile of the QST measures of each cluster, we designated the clusters as *Sensitized* and *Not sensitized* groups. The Sensitized group had lower regional pressure pain thresholds, regional heat pain thresholds, widespread pressure pain thresholds, and tolerances. They also had lower inhibitory conditioned pain modulation scores, indicating more pain hypersensitivity than the Not sensitized group. Temporal summation was scored opposite to our expectation, e.g., the Not sensitized group had a higher temporal summation score indicating lower pain hypersensitivity. See Figure 1 for a visual illustration of the distribution between clusters.

Figure 1

Quantitative sensory tests for the two groups derived from latent class analysis.



Scaled mean values for the different QST parameters [mean = 0, standard deviation = 1].QST: Quantitative sensory pain test. rPPT: Regional pressure pain threshold. rHPT: Regional heat pain threshold, wPPT: Widespread pressure pain threshold, wPTT: Widespread pressure pain tolerance threshold, TS: Temporal summation, CPM: Conditioned pain modulation.

Patient-reported outcomes

In general, the Sensitized group scored higher at baseline on NRS (Estimate = 0.66, 95%CI = -1.4 - 0.1) and ODI (Estimate = 3.75, 95%CI = -8.2 - 0.7). These results were not statistically significant, with a p-value ~ 0.1 for both parameters. Table 4 presents the changes from baseline to post-SM and follow-up, respectively, as the linear mixed model's coefficients with the dependent variable [Outcomes] and the following interacting fixed effects time:cluster, and subject as the random effect.

Table 4

Within- and between-group changes in low back pain intensity and disability for each latent class derived cluster after spinal manipulation

Outcomes		Baseline to Post-SM		Baseline to Follow up	
		Sensitized	Not sensitized	Sensitized	Not sensitized
Low back pain intensity (NRS)	Within-group changes	-0.59(-1.14 to -0.04)*	-0.75(-1.11 to -0.39)*	-0.92(-1.46 to -0.37)*	-0.75(-1.11 to -0.39)*
	Between-group differences	-0.16(-0.82 to 0.5)		0.21(-0.44 to 0.87)	
Disability (ODI)	Within-group changes	-5.67(-8.79 to -2.54)*	-5.57(-7.64 to -3.49)*	-7.88(-10.98 to -4.77)*	-5.57(-7.64 to -3.49)*
	Between-group differences	0.1(-3.65 to 3.85)		2.26(-1.48 to 5.99)	

Mean within-group changes (95% Confidence intervals) and mean between-group differences (95% confidence intervals) from baseline to post-SM and follow up, respectively, in the two groups derived from latent class analysis. NRS = Numerical pain rating score [0 - 10], ODI = Oswestry disability index [0 - 100], * = p-value < 0.05

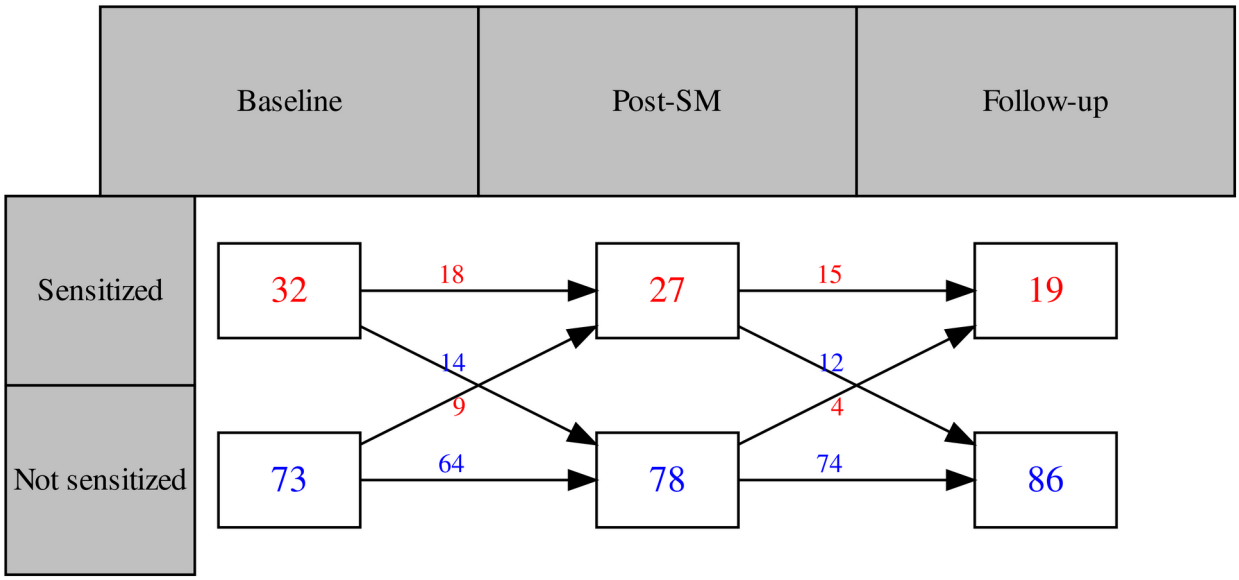
Although no between-group mean differences were found, both groups displayed statistically significant within-group mean changes, but not clinically important reductions in ODI and NRS.

Quantitative sensory testing

Of the participants with complete QST data at follow-up (n=105), 73 were Not sensitized at baseline, and 32 were noted as Sensitized. However, at follow-up, the number of Sensitized participants dropped to 19, as indicated by increases in the scaled QST scores (approximating 1). Figure 2 illustrates this relation.

Figure 2

Stability patterns of quantitative sensory tests for two groups at three different time points.



An overview of the cluster stability pattern in the latent class analysis following spinal manipulation in persistent low back pain patients. The numbers above the arrows indicate the transition of patients over time. A red number indicates the transition to *sensitized*, and a blue number indicates the transition to *Not sensitized*.

Using linear mixed models for each QST outcome, we examined the baseline differences for the different QST parameters between the clusters. There were statistically significant differences between the clusters in regional pressure pain threshold (Estimate = 266, 95%CI = 188 - 343), regional heat pain threshold (Estimate = 1.93, 95%CI = 0.5 - 3.3), widespread pressure pain tolerance (Estimate = 26.5, 95%CI = 19.6 - 33.5), and conditioned pain modulation (Estimate = 3.56, 95%CI = 0.04 - 7.08). Thus, there were no statistically significant difference for the clusters in widespread pressure pain threshold (Estimate = 2.03, 95%CI = -1.1 - 5.2) and temporal summation (Estimate = 0.32, 95%CI = -0.06 - 0.70).

Table 5 presents the within-group mean changes and between-group mean differences for the different parameters. For regional pressure pain threshold, both groups at both time points demonstrated an increase. However, at a much larger rate in the Sensitized group, resulting in a significant between-group difference post-SM. Widespread pain tolerance also improved for the Sensitized group and regional heat pain threshold for the Not sensitized group. However, this only reached statistical significance at follow-up. In contrast, the temporal summation score increased (indicating more sensitization) for the Sensitized group at both time points – showing statistically significant between-group mean differences. All other parameters stayed consistent.

Table 5

Within and between changes in quantitative sensory tests for each latent class derived cluster after spinal manipulation

Quantitative sensory testing		Baseline to Post-SM		Baseline to Follow up	
		Sensitized	Not sensitized	Sensitized	Not sensitized
Regional pressure pain threshold	Within-group changes	123(72 to 174)*	52(18 to 86)*	103(52 to 155)*	52(18 to 87)*
	Between-group differences	-71(-132 to -9)*		-51(-113 to 11)	
Regional heat pain threshold	Within-group changes	0.1(-0.7 to 0.9)	0.2(-0.3 to 0.7)	0.8(-0.1 to 1.6)	0.6(0 to 1.1)*
	Between-group differences	0.1(-0.9 to 1)		-0.2(-1.1 to 0.8)	
Widespread pressure pain threshold	Within-group changes	-1(-4.1 to 2.1)	0.8(-1.3 to 2.8)	2.3(-0.8 to 5.3)	1.8(-0.3 to 3.8)
	Between-group differences	1.8(-2 to 5.5)		-0.5(-4.2 to 3.2)	
Widespread pressure pain tolerance	Within-group changes	3.7(-1 to 8.4)	-0.1(-3.1 to 3)	7.9(3.3 to 12.5)*	3(-0.1 to 6.1)
	Between-group differences	-3.8(-9.4 to 1.8)		-4.9(-10.4 to 0.7)	
Temporal summation	Within-group changes	0.6(0.1 to 1)*	-0.3(-0.6 to 0)	0.6(0.2 to 1.1)*	-0.2(-0.5 to 0.1)
	Between-group differences	-0.8(-1.3 to -0.3)*		-0.8(-1.4 to -0.3)*	
Conditioned pain modulation	Within-group changes	0(-3.9 to 3.9)	0.3(-2.2 to 2.9)	-0.8(-4.6 to 3.1)	0.6(-2 to 3.1)
	Between-group differences	0.3(-4.3 to 5)		1.3(-3.3 to 5.9)	

Mean within-group changes (95% Confidence intervals) and mean between-group differences (95% confidence intervals) from baseline to post-SM and follow up, respectively, in the two groups derived from latent class analysis. rPPT: Regional pressure pain threshold [kPa, 0 - 1000]. rHPT: Regional heat pain threshold [Degrees celsius, 32 - 50], wPPT: Widespread pressure pain threshold [kPa, 0 - 100], wPTT: Widespread pressure pain tolerance threshold [kPa, 0 - 100], TS: Temporal summation [visual analog scale, 0 - 10], CPM: Conditioned pain modulation [visual analog scale, 0 - 10]. * = p-value < 0.05

Posthoc analysis

Segment randomization

A posthoc analysis (cluster:segment:SM allocation site) showed consistency with our prior findings (17). We observed increases of regional pressure pain threshold in two instances i) the group receiving SM at a pain-sensitive segment independent of cluster classification and ii) the Sensitized group independent of allocation site. See Table 6

Table 6

Within changes in regional pressure pain threshold for each latent class derived cluster faceted by segment allocation after spinal manipulation

Cluster group	Treatment allocation	Baseline to Post-SM	Baseline to Follow-up
Sensitized	Pain segment group	146(68:224)*	118(40:196)*
	Stiff segment group	93(3:183)*	84(-6:174)
Not Sensitized	Pain segment group	87(31:143)*	78(22:135)*
	Stiff segment group	18(-37:73)	26(-30:81)

Within mean changes (95% confidence intervals) from baseline to post-SM and follow up, respectively, in the two groups derived from latent class analysis for each allocated SMT segment group. rPPT: Regional pressure pain threshold [kPa, 0 - 1000]. rHPT: Regional heat pain threshold [Degrees celsius, 32 - 50], wPPT: Widespread pressure pain threshold [kPa, 0 - 100], wPTT: Widespread pressure pain tolerance threshold [kPa, 0 - 100], TS: Temporal summation [visual analog scale, 0 - 10], CPM: Conditioned pain modulation [visual analog scale, 0 - 10]. * = p-value < 0.05

Temporal summation

We examined whether the reverse relation observed between temporal summation and sensitivity status was due to range-of-instrument constraints. We examined the distribution of the pressure pain intensity score from which temporal summation was calculated. Potentially, very low or very high pressure pain intensity scores could have resulted in ceiling or flooring effects, thus obfuscating any temporal summation effect. However, the Sensitized group scores were located at the center of the VAS-scale, and the pressure pain intensity ranged from a mean VAS-score of 3.75 (pulse 1 to 3) to 4.40 (pulse 8 to 10). Similarly, for the Not sensitized group, the range was 4.09 to 5.06. We also ran the latent class analysis reversing the temporal summation score to the original score. Unsurprisingly, this did not result in any differences.

Discussion

To our knowledge, this was the first study to investigate variations in pain sensitivity using a comprehensive QST battery in a large cohort of persistent LBP patients receiving SM. The latent class analysis clustered two groups: a *Sensitized* and a *Not sensitized*. This division is not surprising as QST scores often correlate independent of the pain domain (38), and similar findings have been reported previously (39).

The categorization into clusters was not associated with overall clinical improvement, which confirms previous publications concerning the predictive value of QST in LBP (7). In general, we observed only minor clinical improvements, which could be due to an inefficient treatment paradigm for the select patient cohort under study. We have no data to support that assertion directly. However, we included participants from a patient population seen at a secondary care hospital Spine Center, for which referral criteria stipulate that relevant conservative treatment has already been undertaken in a primary care setting but proven unsuccessful.

Despite the limited clinical improvements, we found substantial regional pressure pain threshold increases, and while consistent with the literature (16), the Sensitized group's changes were surprisingly large. Arguably, two parallel mechanisms can explain this increase in regional pressure pain threshold: (I) A change following SM on pain sensitivity in those with generalized high pain sensitivity, and (II) a segmental reflex effect of SM when directed at a sensitized segment (independent of generalized high pain sensitivity). While mechanism II appears to be a causal effect due to the application site's randomization, we cannot state the same about mechanism I. This could solely be due to regression towards the mean. However, the observation that the Sensitized group scored significantly lower in several pain measures at baseline, whereas only regional pressure pain threshold changed in such an extensive and systematic manner following SM, speaks against regression towards the mean.

Regional mechanical pain sensitivity

Arguably, this provides new evidence that generalized sensitization appears to be a modifier for changes in regional pressure pain threshold following SM. However, if we attribute such an effect to SM, it appears strictly limited to regional mechanical pain sensitivity rather than a systemic or widespread effect. The minor but statistically significant increase in regional heat pain threshold is simply a testament to the larger group size in the Not sensitized group. This decrease was only slightly lower than for the Sensitized group (Δ 0.2 degrees difference). This supports the literature, namely that thermal pain threshold is not affected by SM (14,40).

We did find a heterotopic effect of SM concerning widespread pressure pain threshold, but this was only observed at follow-up two weeks later and not in the immediate post-SM period. It seems unlikely that this should reflect a delayed widespread effect of SM when we did not observe any differences in patient-reported pain and disability.

We observed a systematic inverse difference in temporal summation for both groups, indicating higher degrees of pain sensitization in the Sensitized group and vice versa in the not sensitive group. While not due to any constraint introduced by the VAS-scale, arguably, the widespread pressure pain tolerance thresholds were so low in the Sensitized group that the repeated stimuli did not provide sufficient input to facilitate a wind-up phenomenon. Thereby not inducing an observable temporal summation effect (41). This analysis and a recent randomized trial comparing SM to sham treatment found no effect on temporal summation (42). Thus, SM appears not to affect temporal summation.

To the authors' knowledge, this is the first study to examine within-group changes of conditioned pain modulation following SM of the lower back. An attenuated conditioned pain modulation response has been suggested to be a central component in the development of persistent pain (43), and our latent class analysis supports this. However, as administered in this study setting, SM did not affect the conditioned pain modulation response, but as with temporal summation, we saw limited scores for conditioned pain modulation. The low widespread pressure pain tolerance resulted in a very low conditioning stimulus (70% of tolerance) and, thus, potentially did not sufficiently activate the central inhibition needed to modulate the subsequent pain stimuli.

To summarize, the limited changes in temporal summation and conditioned pain modulation following SM could be a limitation of the CCA protocol. Potentially, the protocol did not adequately facilitate these phenomena.

Methodological considerations

A strength of the current study was the large number of participants with persistent LBP. We found the inclusion of persistent LBP patients appropriate, as this study aimed to investigate the mechanism related to changes in pain sensitivity. Perturbed pain modulation is likely more prevalent in our cohort of persistent pain patients seen at a hospital than primary care patients. Nevertheless, it is unclear whether to expect higher or lower effects of SM in a population with more pronounced perturbation of pain modulation. Conversely, the study cohort was drawn from a patient population that had failed to respond to conservative treatment and was probably less likely to respond to the SM intervention than a primary care patient group.

We choose to use the absolute values for the latent class analysis in our regression models. The participants' probability of belonging to that particular group was high, and four of the six QST parameters differed statistically significantly between the groups, despite substantial variation for each measure.

We used a large QST battery that covered multiple techniques, stimuli, and pain domains, all tested by the same rater. By contrast, many, if not most studies investigating changes in pain sensitivity, apply only a single QST (13–16). The SM's standardization was arguably a weakness of the intervention due to the simplicity and dissimilarity with clinical practice, i.e., poor external validity. However, it did optimize the underlying hypothesis of investigating the SM's mechanism, increasing the reproducibility. As stated previously, this was not a placebo-controlled trial, so we cannot state whether the observed changes were causally linked.

Conclusion

Distinct subgroups (Sensitized and Not sensitized) were identified from the latent class analysis. However, they were not associated with differences in patient-reported pain and disability or changes in regional thermal pain thresholds, widespread pressure pain threshold and tolerance, temporal summation, or conditioned pain modulation.

The cluster affiliation and application site of SM was related to the observed change on regional mechanical pain sensitivity by two parallel mechanisms. I) Changes following SM specific to participants with generalized high pain sensitivity, and II) local effects of SM application when applied at a sensitized segment independent of general high pain sensitivity. These results are only specific to this cohort of persistent LBP patients sampled from a hospital and should not be generalized to a primary care setting.

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Manuscript IV

Nim CG, O'Neill S, Geltoft AG, Jensen LK, Schiøttz-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

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A Cross-sectional Analysis of Persistent Low Back Pain, Using Correlations Between Biomechanical Stiffness, Pressure Pain Threshold, and Heat Pain Threshold

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Abstract

Objectives

Little is known about the underlying causes of low back pain (LBP). Recently, technological advances have made it possible to quantify biomechanical and neurophysiological measures, which are seen as potentially relevant factors in understanding LBP etiology. While several studies have been conducted in each of these domains, few studies have explored the relation between these factors. The specific aims of this study are to i) quantify the correlation between biomechanical and neurophysiological outcome measures in LBP patients, and ii) examine whether these correlations differ when considered regionally vs. segmentally.

Methods

A cross-sectional analysis of 132 patients with persistent non-specific LBP. Primary biomechanical data included spinal stiffness (global stiffness) measured by a rolling indenter. Primary neurophysiological data included pain sensitivity (pressure pain threshold and heat pain threshold) measured by a pressure algometer and a thermode. Correlations were tested using Pearson's product-moment correlation or Spearman's rank correlation as appropriate. The association between these outcomes and the segmental level was tested using ANOVA with post-hoc Tukey corrected comparisons.

Results

A moderate positive correlation was found between spinal stiffness and pressure pain threshold i.e. high degrees of stiffness were associated with high pressure pain thresholds. The correlation between spinal stiffness and heat pain threshold was poor and not statistically significant. Aside from a statistically significant minor association between the lower and the upper lumbar segments and stiffness, no other segmental relation was significant.

Conclusions

The moderate correlation between spinal stiffness and mechanical pain sensitivity was opposite than expected, meaning higher degrees of stiffness was associated with lower pressure pain threshold. No clinically relevant segmental association existed.

Introduction

The lumbar spine is a complex anatomical structure, the chief function of which is biomechanical – to bear loads through various static and dynamic functions and provide protection for soft neural tissues[1]. However, it is not apparent when perturbations in biomechanical function are causal factors for developing low back pain (LBP), when they result from LBP, and when they are simply irrelevant normal variants[2]. Hence, LBP is often termed non-specific LBP. We can only attribute around 5-10% of LBP to an explicit patho-anatomical issue. In the remaining 90-95%, there is no apparent structural issue[3]. In a clinical setting among manual therapy providers, it is common to attribute such non-specific LBP to permutations in biomechanical function, i.e., as a causal factor, although the evidence is lacking[2,4,5].

Much research has been conducted to understand LBP's etiology better, but so far, progress has been limited[6–8]. Arguably, this is the result of limitations in measurement, methodology, and population sampling. In the area of measurement, recent technological advances have made it possible to collect data in new areas, which could shed light on LBP's underlying causes. In particular, the development of new technologies to quantify spinal stiffness non-invasively[9], thus better quantifying what is thought to be an influential clinical factor in LBP[10]. Spinal stiffness has shown promise in that it may be associated with treatment-induced disability improvements. E.g., in patients with LBP, those who have immediate reductions in spinal stiffness after spinal manipulation have improvements in disability, and this change in stiffness does not occur for those who do not have improvements in disability[11,12].

In parallel to the exploration of the mechanical aspect of LBP, researchers are also exploring the underlying mechanisms of the pain experience itself. This includes quantitative sensory pain testing (QST), which quantifies individual pain perception in response to controlled noxious stimuli[13]. Such experimental tests can differentiate LBP patients from healthy controls, and perturbations in pain modulation (sensitization) appear to manifest in the sub-acute stage as pain turns persistent[14]. It is of interest that these perturbations, in a commonly noted mechanical syndrome such as LBP, extend beyond deep muscle mechanical pain sensitivity, i.e., pressure pain, to superficial skin measures, e.g., heat pain. Nevertheless, apparent differences have previously been reported for both these measures between LBP patients and healthy controls[15,16], and they also seem to correlate with each other[17].

Furthermore, each of these new technologies also allows researchers to explore these properties at the segmental level[9,15] an important consideration given that back pain is often thought to be localized to specific anatomic areas pertaining to a given segmental level. While biomechanical testing has been used to evaluate the spine's primary biomechanical function, and experimental QST has done the same for neurophysiological function, it seems unlikely that the two are not interconnected. We put forward that another factor that may hinder our understanding of LBP etiology is artificial segregation of biomechanics and neurophysiology. These two aspects of LBP are often discussed, studied, and treated in research and clinical settings as if they are distinct phenomena, when in reality, they may well be interconnected[18]. Studying biomechanical and neurophysiological systems together may provide important information to understand the etiology of LBP better. This is particularly important in the field of manual therapy, where the treatment site is often determined using a mixture of stiffness and pain locations[18]. However, we know little about

the segmental interplay between stiffness and pain sensitivity, yet both are frequent complaints for patients with LBP[19].

Hence, this study will use an experimental test setup that mimics clinical practice to investigate the relation between specific biomechanical measures, i.e., spinal stiffness, and different pain measures, mechanical and non-mechanical (thermal). Perturbations in both are known to be associated with hyperalgesia in persistent LBP[15,16]. Yet, whether a correlation also exists with mechanical spinal stiffness is unknown.

Therefore, the specific aims of this investigation are, to i) quantify the correlation between biomechanical and neurophysiological measures (global stiffness, pressure pain threshold, and heat pain threshold) in LBP patients, and ii) examine if these correlations differ when considered regionally (the lumbar back) or segmentally (e.g. L4).

We hypothesize that stiffness and pain sensitivity are negatively associated, i.e., high degrees of stiffness and low pain threshold are correlated and that this relation may be greater when considered segmentally versus regionally.

Methods

Study design

Our study design was a secondary observational cross-sectional analysis of baseline data from a randomized trial of participants with persistent non-specific LBP[20]. The study was approved by the Regional Committees on Health Research Ethics for Southern Denmark (ID: S-20160201) and the Danish Data Protection Agency. The manuscript was prepared in reference to the STROBE format.

Setting

A population sample of patients seen at *the SpineCenter of Southern Denmark*, a large, public, regional hospital department specializing in spinal pain syndromes, were recruited consecutively between November 2017 and February 2019.

Participants

Participants were included based on a diagnosis of non-specific LBP from a clinician at the SpineCenter. A total of 132 participants were included using the following criteria:

- Persistent LBP of more than three months duration, defined as dorsal pain in the area between the gluteal folds and lower rib cage with no known specific pathology (disk herniation, spondyloarthritis, fractures, etc.).
- No surgical indication or previous spinal surgery.
- Daily oral opioid intake was limited to 40 mg of morphine at the time of inclusion.
- Body mass index under 35 kg/m^2
- Age between 18 and 60 years old.

Variables

All testing was done at the SpineCenter by one rater (CGN) who gained experience with the test procedures through practical laboratory training, including pilot testing on 20 participants with persistent LBP not included in the present study.

The baseline test session was initiated by identifying each lumbar segment. With the participant in the prone position, each spine process from S1 to T12 was marked superficially with a marker. The segment identification was confirmed using ultrasonography (Sonosite Titan Linear, L38 probe)[21].

Spinal stiffness

Spinal stiffness was tested using the VerteTrack (VT). The device consists of weighted probe wheels that roll along the lumbar spine of a prone subject using the surface markings of spinous process locations. The resulting displacement during rolling is measured by a string potentiometer, which can then be quantified as stiffness (applied mass/displacement or N/mm). This process is then repeated with increasing loads of 10N up to a maximum of 60N. Before testing, each participant was instructed to exhale and hold their breath at around the residual air volume while completely relaxing their muscle until the trial was complete. If pain or discomfort were elicited, the procedure would be repeated one more time, and if the trial continued to produce discomfort, the procedure was discontinued. Only trials where no discomfort was felt were used for the analysis. The VT is a novel experimental device reported as comfortable and safe[22] with good reliability in asymptomatic subjects[9].

Deep mechanical pain sensitivity

Deep mechanical pain sensitivity was determined using a pressure algometer (Model 2, Somedic, Sweden) with a custom made double-headed probe (2x1cm^2, 3 cm apart), which allowed for bilateral pressure at either side of the mid-line for each lumbar segment. The pressure was increased gradually with an approximate rate of 50 kPa/s until the participant reported the pressure as painful by pressing an indicator button. If no pain had been elicited by 1000 kPa, the test was discontinued, and 1000 kPa was recorded as the pressure pain threshold (PPT). The pressure algometer has excellent intra-rater reliability for patients with LBP[23].

Superficial thermal pain sensitivity

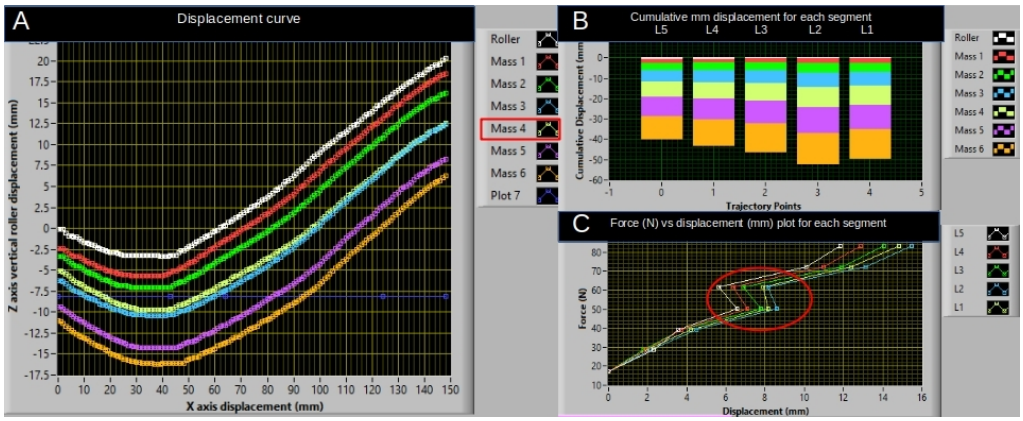
Superficial thermal pain sensitivity was assessed using a handheld thermode (Medoc TSA-II, Israel) with a single 30x30mm probe placed in the midline for each lumbar segment centered at the spinous process, ensuring full contact between skin surface and probe. The baseline temperature was pre-set to 32 degrees Celsius (C). During testing, the temperature increased at a rate of 1 C/s until the participant reported the temperature as painful by pressing an indicator button. Maximum temperature was pre-set at 50 C, and if no pain had been elicited by then, this was recorded as the heat pain threshold (HPT). Using the thermode to indicate the HPT has good-to-excellent intra-rater reliability when tested at the spine of asymptomatic volunteers[24].

All QST tests (PPT and HPT) were performed, with the patient in the prone position, at each spinal segment three times. The segments were tested in a pre-determined, computer-generated, random order with 10-second rest intervals between each test. If no pain had been elicited by 1000 kPa after the first two trials, a third trial was not performed for PPT. Before data collection, one or two test trials of each pain threshold assessment were performed at the lower extremity and one test at the T12 segment to familiarize participants with the procedure.

Variables of interest

Lumbar stiffness: The VT data were smoothed and visualized (Labview 15.0f3 for Windows 10, National Instruments, Texas, USA) before being exported to a spreadsheet (LibreOffice, vers. 6.0.7.3, for Ubuntu 18.04) for further analysis. Global lumbar stiffness (GS) was calculated as the slope from the second load to the second highest load (force/total displacement (N/mm)). As part of the data analysis, a subjective inspection was completed before extracting the data. Some loads within the participant trial were affected by factors such as breathing, muscle guarding, or technical errors and were omitted. This process was guided by visual inspection of the displacement curve corresponding to each load. See Figure 1 for a LabView output and an example of a removed trial. Global stiffness is a continuous parameter ranging from 0-∞ and was recorded for each segment [L1-L5].

Figure 1



An example of the LabView output, illustrating: A) The displacement curve, the y-axis represent vertical displacement for each trajectory point along the lumbar lordosis (x-axis), each load trajectory is presented as a unique color. B) The cumulative displacement (mm) for each segment across loads. C) The force (N) versus displacement curve (mm) for each segment. In this example, we would omit the light-yellow 40N line (mass 4) as the displacement recorded was less than that recorded with 30N (mass 3), suggesting muscle guarding. This is also illustrated by the skewness of the plot in panel C (red circle). After data cleaning, the stiffest segment was L5 with a global stiffness score of 5.5, and the least stiff segment was L2 with a global stiffness score of 4.2 (panel B)

Deep muscle pain sensitivity: Pressure pain threshold is a continuous parameter ranging from 0-1000 kPa and was calculated for each segment [L1-L5] as the average of three trials.

Superficial skin pain sensitivity: Heat pain threshold is a continuous parameter ranging from 32-50 C and was calculated for each segment [L1-L5] as the average of three trials.

Statistical analysis

Descriptive statistics

Descriptive data, including the demographics and all outcomes, are presented as mean, median, standard deviation, and interquartile range for a complete overview. Normal distribution for each outcome was visualized using density plots, QQ-plots, and tested with the Shapiro-Wilks test. Visual inspection for skewness and data shape was further conducted[25].

Correlation

The correlation between the three outcomes is presented visually as Loess slopes[26] plotted for each segment. Pearson's product-moment correlation (ρ) was used for parametric data, and Spearman's rank correlation (R_s) was used for non-parametric data. We omitted individual participants if they did not have data for both the parameters in question. The strength of the correlations was evaluated as *poor* (< 0.30), *moderate* (0.31 ≤ 0.50), *good* (0.51 ≤ 0.70) and *strong* (> 0.70)[27]. All correlations are presented as the correlation coefficient and the corresponding p-value. All correlations were examined as a single summarized value for all segments for each participant and individually for each segment. A p-value < 0.05 was considered to be significant.

Segmental statistics

Segmental data are depicted as means and 95% confidence intervals. The association between outcomes was tested using a one-way analysis with the outcomes as the dependent variable and segment as the independent variable. The assumptions for the ANOVA were tested for i) normality by plotting the residuals against predicted values and ii) homogeneity of variances using Levene's test. A p-value of less than 0.1 would indicate further post-hoc testing using Tukey multiple pairwise-comparisons to investigate within segment differences. The results for each outcome are presented as F scores, within segment difference and adjusted p-values.

Data analyses were completed using R[28], for Linux, v. 3.6.0 with R-studio v. 1.1.456. Data cleaning were performed using the Tidyverse[29].

Results

Participants characteristics

Of the 132 participants included, complete experimental baseline data were available for 128 (3 participants had missing HPT data, 1 participant had incomplete GS data). The sample consisted of 72 (55%) males. Complete demographic data are presented in Table 1.

Table 1

Parameter	Mean	SD	Median	IQR
Age	45.1	9.7	46.0	14.2
Body mass index (kg/m^2)	26.2	3.9	25.6	4.9
Disability (ODI, 0-100)	27.8	11.6	27.3	18.5
Low back pain intensity (0-10)	5.6	1.8	5.5	2.7
Pain duration (Months)	48.2	78.1	14.8	53.9

The participant's demographics, n=132, ODI = Oswestry disability index

All data were normally distributed except for PPT. None of the variables were visually skewed and overall had consistent data shape across outcomes. All experimental outcome measures are presented in Table 2 as a single average score for all segments and each segment.

Table 2

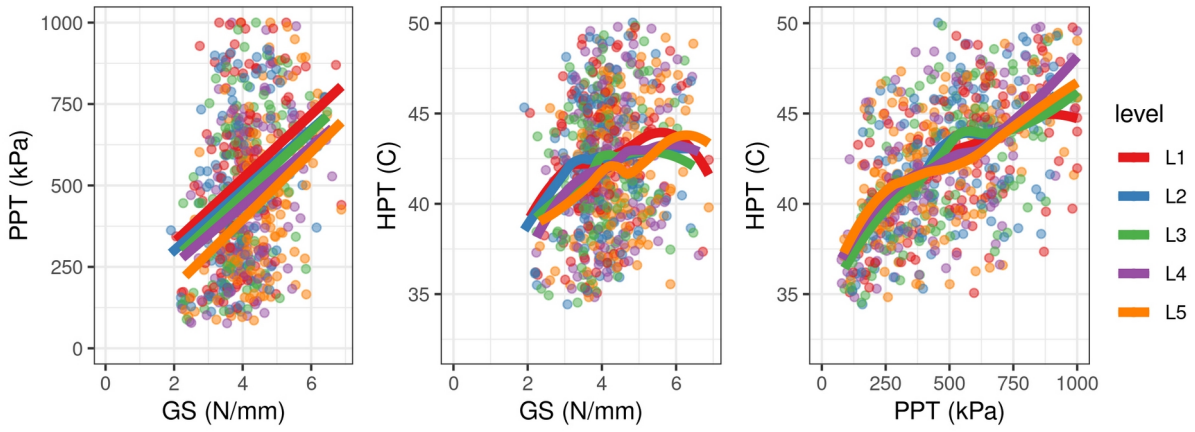
Outcome	Segment	Mean	SD	Median	IQR
Global stiffness	All	4.14	0.88	4.05	1.13
	L1	4.01	0.88	3.89	0.94
	L2	3.97	0.86	3.90	0.97
	L3	4.03	0.84	3.93	0.92
	L4	4.20	0.85	4.11	1.06
	L5	4.48	0.90	4.40	1.07
Pressure pain threshold	All	475	231	446	363
	L1	522	244	523	369
	L2	482	228	465	357
	L3	472	225	452	376
	L4	455	225	437	346
	L5	445	229	401	338
Heat pain threshold	All	42.2	3.7	42.0	5.6
	L1	42.5	3.6	42.4	5.3
	L2	42.3	3.8	42.4	6.3
	L3	42.0	3.6	41.3	5.3
	L4	42.1	3.8	41.6	5.6
	L5	42.0	3.6	41.8	5.7

The participant's regional experimental outcome measures, n=132

Correlation data

The relationship between segment and each outcome is depicted in Figure 2. Visually the correlation does not differentiate between segments.

Figure 2



Correlation between lumbar stiffness, mechanical pain sensitivity, and superficial pain sensitivity, presented as Loess slopes for each segment. GS = Global stiffness, PPT = Pressure pain threshold, HPT = Heat pain threshold

Table 3 lists the correlations and p-values for all outcomes. All correlations were statistically significant, except for the correlation between GS and HPT at the L2 segment (p-value=0.12). All correlations had a positive direction. The correlation between GS and PPT for all segments was moderate (ρ=0.38). Conversely, the correlation between GS and HPT was poor (R_s=0.23) and not significant. The correlations between PPT and HPT were good for all segments (ρ=0.53).

Table 3

	Global stiffness vs Pressure pain threshold		Global stiffness vs Heat pain threshold		Pressure pain threshold vs Heat pain threshold	
Segment	R_s	P-value	ρ	P-value	R_s	P-value
All	0.38	<0.01	0.23	<0.05	0.58	<0.01
L1	0.36	<0.01	0.19	0.03	0.53	<0.01
L2	0.33	<0.01	0.14	0.12	0.55	<0.01
L3	0.34	<0.01	0.21	<0.05	0.57	<0.01
L4	0.33	<0.01	0.22	<0.05	0.56	<0.01
L5	0.38	<0.01	0.28	<0.01	0.50	<0.01

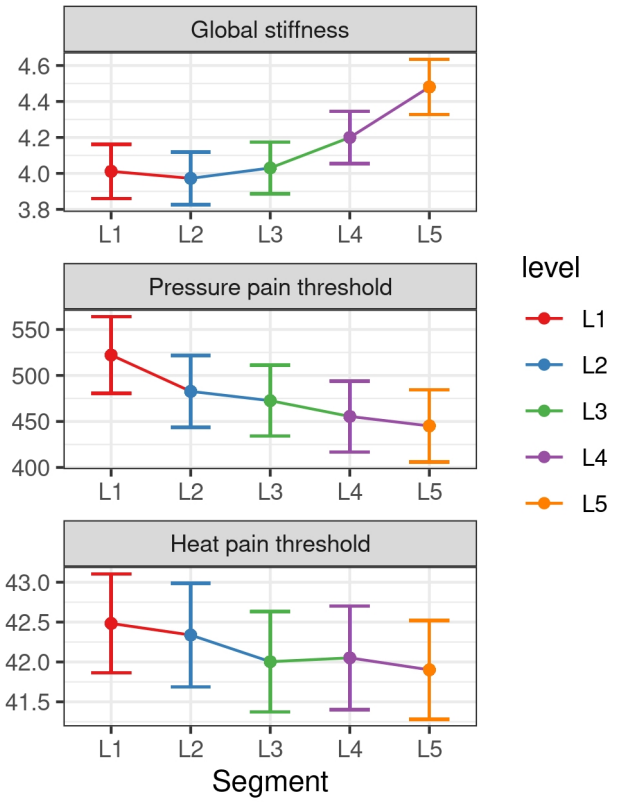
Correlation for all and every segment between mechanical lumbar stiffness, pressure pain and superficial pain sensitivity. Presented as chi² scores and p-values. R_s = Spearman's rank correlation, ρ = Pearson's product-moment correlation

Segmental data

All outcomes are presented visually in Figure 3. A segmental pattern can be observed from L1 to L5. Global stiffness increased while PPT and HPT decreased caudally. This indicates that L5 is the stiffest segment but also the most sensitive segment for both pressure and heat pain thresholds. The within-segment difference in GS and HPT for the upper segments are almost negligible. All model assumptions were upheld for the ANOVA. The ANOVA revealed the following: There was a statistically significant effect of spinal segmental level on GS ($F_{4,650}$=7.7, p<0.01). Whereas, we found no significant effect on PPT ($F_{4,655}$=2.2, p=0.07) or HPT ($F_{4,640}$=7.7, p =0.68). This indicates that a statistically significant association was apparent for GS, while PPT had a p-value of just above 0.05. Heat pain threshold was clearly not significant and exceeded the cut point (p-value = 0.1). Post-hoc testing of GS and PPT were, consequently, indicated.

For GS, a significant adjusted difference was observed in the Tukey multiple comparisons for L5 against L1, L2, and L3. No segments differed significantly for the PPT scores when considering the adjusted scores. However, as Figure 3 demonstrates, L5 and L4 have the lowest PPT scores compared to L1. All values are available in Table 4.

Figure 3



The segmental value for lumbar stiffness (Global stiffness - N/mm), deep pressure pain (Pressure pain threshold - kPa), and superficial pain (Heat pain threshold - degrees Celsius). Connected means with error bars indicating the 95% confidence interval

Table 4

	Global stiffness		Pressure pain threshold	
Segment	Difference (95% CI)	Adj. p-value	Difference (95% CI)	Adj. p-value
L2-L1	-0.04 (-0.33 to 0.25)	1	-39.5 (-117.2 to 38.3)	0.63
L3-L1	0.02 (-0.27 to 0.31)	1	-49.6 (-127.3 to 28.2)	0.41
L4-L1	0.19 (-0.10 to 0.48)	0.40	-66.7 (-144.5 to 11.0)	0.13
L5-L1	**0.47 (0.18 to 0.76)**	**<0.01**	-77.0 (-154.8 to 0.7)	0.05
L3-L2	0.06 (-0.23 to 0.35)	0.98	-10.10 (-87.9 to 67.7)	1
L4-L2	0.23 (-0.06 to 0.52)	0.21	-27.24 (-105.0 to 50.5)	0.87
L5-L2	**0.51 (0.22 to 0.80)**	**<0.01**	-37.6 (-115.3 to 40.2)	0.68
L4-L3	0.17 (-0.12 to 0.46)	0.50	-17.14 (-94.9 to 60.6)	0.97
L5-L3	**0.45 (0.16 to 0.74)**	**<0.01**	-27.46 (-105.2 to 50.3)	0.87
L5-L4	0.28 (-0.01 to 0.57)	0.07	-10.32 (-88.1 to 67.4)	1

Post hoc Tukey comparison after ANOVA testing of lumbar stiffness and pressure pain threshold between each segment. Bold indicates a significant difference between segments

Discussion

Summary of the results

Our results demonstrated a *moderate* positive correlation between GS and PPT; higher stiffness scores were associated with higher deep mechanical pain thresholds. In contrast, the correlation between GS and HPT was poor, while, as expected, a good correlation was observed between deep and superficial pain thresholds. When examining stiffness and pain sensitivity across segments, we only observed a statistically significant difference in stiffness between higher and lower lumbar segments.

Correlation findings

Surprisingly, the correlation observed between spinal stiffness and pressure pain threshold was opposite than expected: Participants with higher degrees of spinal stiffness also had higher pressure pain thresholds (i.e., lower pain sensitivity). Three different postulations could view this relation: i) The increased lumbar stiffness might be explained as part of an adaptive mechanical protection system[30] that decreases nociceptive activity in the lumbar region and therefore increases PPT. This is consistent with similar research. When inducing pain at the low back in two asymptomatic populations, higher degrees of stiffness were observed[31], whereas the PPT score did not change[32]. Possibly, and opposed to pain sensitivity, stiffness could be viewed as a continuum where high degrees of stiffness can be advantageous for the locomotor system. ii) This could be reversed so higher pain thresholds increase stiffness again as a protective adaption. iii) Possibly, as a perceptual influence. A stiffer spine may be perceived as more resilient to applied forces. Given pain is considered a protective response, a stiffer spine might require less protection, resulting in an increased ability to tolerate force (i.e., higher PPTs). In contrast, in a less stiff spine, the spine may be perceived as less resilient to applied forces, with the PPT decreased through psychological mediation (increased protection needed). However, the authors are not aware of any research that has investigated this previously for LBP. Nevertheless, there is evidence on this connection between mind and body in prior work from other fields[33].

A *good* correlation observed between PPT and HPT is congruent with previous findings[17]. This correlation may simply reflect shared modulation of both central as well as peripheral pain mechanisms. This is an interesting finding as these measures differ within the aspect of pain processing. A mechanical pressure involves the activation of deep tissue afferent fibers and thermal stimuli involving peripheral skin activation[34].

Segmental findings

Figure 3 reveals an apparent minor association between all the outcomes, which reached statistical significance for lumbar stiffness. When comparing within-segments, a difference in mean stiffness was observed between the higher and the lower lumbar segments. However, the largest mean difference in stiffness observed was between L5 and L2 and corresponded to 11%, which is only marginally higher than the mean manual detectable threshold of change in stiffness at 8%[35]. The small difference between the largest values suggests it is nearly impossible to palpate differences in stiffness between closer or adjacent segments. Furthermore, this difference is possibly even smaller as the current analysis did not consider the standard error of measurement for the VT[36].

For the QST measures, no differences were found within-segment. This is consistent with a prior study conducted at our laboratory[15]. Arguably, this is due to the sample's chronicity, indicating that the original nociceptive input has developed into a generalized peripheral

sensitization[37]. Furthermore, changes at the supra-spinal level could potentially also lead to the generalized effect observed for both thresholds. Current research indicates that persistent LBP patients often have perturbations in neurological mapping of the somatosensory system and cortical homunculus or "*cortical smudging"*[38]. Potentially, such cortical smudging could lead to difficulty identifying the different stimuli at the nearby segments, which is supported by previous findings of distorted body images[39] and difficulty in identifying the midline of the trunk under painful sensorimotor manipulation in persistent LBP patients[40]. This is further highlighted by a study investigating the neural activity of the hemisphere. When testing PPT at L1 and L5 segments in healthy subjects, an activity overlap of 76% was observed at the right hemisphere and 59% at the left hemisphere[41]. Theoretically, this area of activity is likely to increase with pain chronicity, as persistent LBP patients also have difficulty extending beyond 2-point-discrimination to decreased graphesthesia at the lower back compared to healthy controls[42]. It is also possible that the spatial resolution of painful sensory input is too poor in the lumbar region to differentiate one segment from another.

The previously described cortical smudging could also affect movement behaviors such as postural control[43], lumbopelvic motor control[44], and thoracolumbar dissociation[38]. This indicates that patients with persistent LBP are probably less able to perceive lumbar stiffness reliably. This is highlighted by the findings of Stanton et al., who reported that patients with persistent LBP felt significantly stiffer compared to healthy controls. However, when measuring lumbar stiffness using mechanical indentation, no between-group difference was observed[45]. Whether this finding is present in acute LBP is unknown.

Methodological considerations

A strength of the study was a large sample size compared to our previous topography study[15], albeit the measures were limited to the midline. All tests were conducted by the same rater limiting the intra-rater variability. While the VT is computer-controlled, further minimizing the risk of rater based errors, this was not the case for the QST measures. We endeavored to reduce the risk of bias through multiple training sessions, allowing the participants up to three test stimuli to familiarize them with the procedures. Furthermore, both QST measures are commonly used and thus, vigorously described and tested in the literature[13,46,47].

In addition, the stiffness measure was a single plane indentation and possibly not a clinically relevant way to measure stiffness. It is not yet known if mechanical measures of stiffness are clinically relevant beyond a few studies[11,12]. Manual palpation has some benefits over the experimental testing used in this study. It is possible to direct the pressure for stiffness and pain in multiple planes, examine trophic changes of the skin and muscles, perform joint-play, locate non-verbal reflectory muscle guarding and tender points using verbal feedback. The evidence for these factors is arguably sparse, and manual palpation carries with a considerable risk of bias[48]. Other biomechanical factors may better reflect spinal biomechanics such as local muscle activity[49], multifidus thickness, or disc diffusion[12]. Finally, the VT has only been deemed reliable in an asymptomatic population, and we currently do not have evidence that demonstrates the same measurement properties apply to LBP patients. However, the reliability score is consistent with single indentation, a similar technique examined on LBP patients[36].

Another limitation is the lack of data on the most symptomatic clinical segment. While not apparent in this analysis, this localized point could potentially provide a more meaningful correlation, which we currently miss in the averaged data. Finally, this was a cross-sectional study that did not compare to other LBP groups or healthy controls. Thus the results are, therefore, only applicable for secondary care persistent non-specific LBP patients.

Conclusion

The a-priori hypothesis could not be confirmed. We found moderate correlations between spinal stiffness and mechanical pain sensitivity to be the opposite of what we expected; higher degrees of stiffness was associated with lower pressure pain threshold. As suspected, mechanical and heat pain threshold had a good correlation, while stiffness and heat sensitivity were poorly correlated. We observed no clinical relevant lumbar within-segment association for any of the outcomes in this population sample of persistent non-specific low back pain patients.

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Manuscript V

Nim CG, Downie A, Kawchuk GN, Perle S, Leboeuf-Yde C & O'Neill S

Spinal manipulative therapy applied at a specific target versus spinal manipulative therapy applied at a comparator target in the treatment of spinal pain: A systematic review

Manuscript in preparation

Spinal manipulative therapy applied at a specific target versus spinal manipulative therapy applied at a comparator target in the treatment of spinal pain: A systematic review

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Abstract

Background

Spinal manipulative therapy (SMT) is a popular treatment for spinal conditions. However, it is being applied and taught as a specific intervention targeting specific spinal structures. Numerous in-vivo animal studies support the notion that SMT is target-dependent. However, three systematic reviews indicate that thoracic SMT is effective for neck pain. Furthermore, spinal non-thrust mobilization is not superior when applied to a specific target compared to a random target. Whether the same applies to SMT is currently unknown. Our purpose was to investigate whether SMT is more effective when applied to a specific target versus a comparator target.

Methods

In this systematic review, we searched the literature in four databases (origin to September 15th, 2020). We included randomized controlled trials comparing SMT at a specific target versus a comparator target. Two authors independently reviewed the literature and assessed the quality using a modified Cochrane risk of bias tool. We extracted any between-group difference reported or calculated effect sizes from the within-group changes. We sub-grouped the analysis by target comparison.

Results

Eleven (11) of 3288 identified studies were assessed. Risks of bias were mostly low for random sequence generation, allocation concealment, assessor blinding, complete outcome data reporting. At the same time, the studies potentially introduced response bias and participant and personnel blinding bias. We sub-grouped the studies into i) different targets within the same vertebral level (1 study), ii) different specific targets within the same region (2 studies), iii) specific targets versus generalized thrust in the same region (3 studies), and iv) targets in different regions (5 studies). Only one study reported a statistically significant between-group difference, and this study was of overall poor quality. We extracted a total of 40 between-group differences, two were statistically significant, and only 12 favored the intervention target.

Conclusions

There is considerable good quality evidence that target specificity in SMT does not confer superior clinical results. This is in stark contrast to clinical practice and educational programs, emphasizing the importance of SMT specificity.

Background

Spinal pain syndromes are associated with significant disability and pain (1), which in part is a reflection of the limited effect of treatment (2–4). Available clinical guidelines make only very broad recommendations regarding treatment and do not provide specific details such as exercise type and dose, spinal manipulative therapy (SMT) targets and type (5–7). In clinical practice, however, treatment specificity is often regarded as meaningful and essential for clinical outcomes.

Practitioners of SMT typically consider target specificity paramount to clinical success (8): Firstly, the clinician must deliver the intervention as a high-velocity, low amplitude thrust within the para-physiological space of joint movement (9). It takes time and practice to acquire the necessary motor skills to master such techniques (10–12), and secondly, the intervention has to be targeted at a specific spinal vertebra or joint complex deemed to be dysfunctional and thus a relevant target for SMT. Identifying such spinal dysfunction is another challenging skill to acquire.

Laboratory animal research indicates that indeed SMT has precise implications on the tissues and cell structures that are, in part, dependent on the thrust, the target site, and the technique applied (13–16). In a clinical setting, a multitude of methods have been described to identify such targets for SMT (8,18), but the validity of these is questionable, with limited inter-rater and intra-rater reliability (19). Accordingly, clinical guidelines only make very general recommendations on the application of SMT. Thus, it seems there is a disparity in the importance placed on SMT specificity between basic sciences, clinical practice, and clinical guidelines, and the clinical importance of being specific in targeting SMT is unresolved.

These issues are further compounded by the difficulty in accurately identifying anatomical landmarks (20), diagnosing spinal dysfunction reliably, and targeting specific vertebrae with SMT (21–23).

Objectives

We conducted the present literature review to explore SMT's effectiveness when explicitly applied to a *specific target* versus SMT applied to a *comparator target*. Our primary outcome was between-group differences in patient-reported outcomes (e.g., pain intensity or disability), and secondary outcomes were objective measures (e.g., pressure pain detection threshold (PPT) or range of motion).

Methods

Design and setting

This systematic review was submitted to and is currently under review by the international prospective register of systematic reviews (PROSPERO) (submission data November 16th, 2020, searches completed, ID = 202598). Only minor changes were made to the protocol since PROSPERO registration for consistency before we proceeded with data extraction. We prepared the manuscript according to the *Preferred Reporting Items for Systematic reviews and Meta-Analyses* (PRISMA) statement (24).

Eligibility criteria

We defined *specific target* as i) targets for SMT based on clinical indication or ii) as pre-specified by the study protocol. We defined *comparator target* as i) targets for SMT not based on clinical indication or ii) as pre-specified by the study protocol. For instance, a study comparing: i) a specific vertebra versus a generalized regional thrust, ii) specific vertebra in a painful region versus a specific vertebra in a non-painful region, iii) a vertebra versus another vertebra in the same region, as pre-specified by protocol, and iv) a specific clinical directed target versus a specific non-clinical directed target.

We included only randomized controlled study designs on humans with spinal pain, where the between-group effect size was estimable, and groups were defined by the targeting criteria for SMT.

Intervention could be any SMT, including instrumented devices, but had to be thrust techniques, i.e., studies of non-thrust mobilization (Maitland grade I to IV (25)) were excluded. Studies comparing instrumented versus manual SMT were excluded. Studies comparing SMT directed at different targets based on clinical indications were also excluded.

Controls had to be one or more groups receiving *comparator targeted* SMT. Studies in which the control group(s) received SMT as the intervention plus some other concomitant treatment were excluded. Concomitant therapy administered independently of the allocation group was allowed.

We did not restrict the inclusion to any specific outcome, publication date, or written language. However, non-English studies had to be translated sufficiently before inclusion.

Search for literature

We conducted a systematic literature search in four electronic databases: PubMed, Embase, Index to chiropractic literature, and CINAHL from the point of origin to September 15th, 2020. The search strategy was initially developed for PubMed (Supplementary file 1) and afterward adopted to the three other databases in collaboration with a research librarian from the University of Southern Denmark. The search contained terms relating to i) spinal pain and ii) The SMT specifying both the target and the comparator. MeSH terms and truncation (*) were elected as appropriate.

Study selection

We managed the review process systematically using Covidence (26). Titles and abstracts for all identified studies were reviewed independently by two authors (CGN and AD) until consensus was reached. If consensus could not be reached, a third author would arbitrate the decision (CLY). After screening, the same two authors reviewed the relevant full texts until consensus was reached. If consensus could not be reached, the same third author would arbitrate the decision. Finally, CGN reviewed the included text reference lists to identify additional studies.

Data extraction

One author (CGN) extracted the data initially. Afterward, another author (SON) checked the results, and consensus was achieved in a systematic face to face comparison (CGN and SON). AD refereed any disagreement. We extracted information concerning the characteristics of the study, participants, interventions, and the allocation groups (definition of the specific target and comparator target). We extracted the between-group differences for

all outcomes reported at all available time points for the groups, comparing specific target SMT to comparator target SMT. If no between-group difference was reported, we calculated a Cohen's effect size for within-group estimates (mean_specific-mean_comparator/SD_pooled) (27). If this approach was applied, we only extracted the outcome concerning our primary objective (patient-reported differences). Finally, if a study presented multiple different outcomes for the same domain, e.g., PPT at multiple regions, we only extracted the initial reporting, e.g., PPT at the lower back.

We defined patient-reported outcomes as a subjective measurement not influenced by any external factors (28). In comparison, we defined objective measurements as a subjective measure reported by the patient but while being influenced by the assessor or as an unaffected outcome, e.g., disc-diffusion on advanced imaging. If an included full text, with an appropriate protocol concerning our research question, did not report any data that allowed for data synthesis, we contacted the lead author and requested the data. If we did not receive a response, the study was excluded.

Risk of bias assessment

We assessed the quality and potential for risk of bias for each included study using the Cochrane Risk of Bias tool (RoB) (28). The RoB contains the following items to judge for different risks of bias: *Selection bias* (Sequence generation, allocation concealment), *performance bias* (blinding of participants and personnel), *detection bias* (blinding of outcome assessors), *attrition bias* (incomplete outcome data), *reporting bias* (selective outcome reporting), and *other sources of bias*. We qualified the final domain by extending it to three items: i) An *undefined risk of bias*, ii) *intervention bias*, a transparent and reproducible description of the SMT, if this information was not provided thoroughly, it was estimated as a high risk of bias, and iii) *response bias*, this concerns the participant's naivety to SMT, i.e., whether the treatment was novel for the participant, as familiarity with SMT, was considered a high risk of bias. We applied the revised Cochrane assessment for selective reporting. Thus, if we could not locate an a-priori statistical analyses plan, this was scored as unsure (29). Each study was assessed for risk of bias by two authors independently (CGN and AD). If consensus could not be reached, a third author (SON) would arbitrate the decision.

Data Synthesis

The synthesis is reported according to the *Synthesis without meta-analysis in systematic reporting guideline* (SWiM) (30), as it was not possible to pool the results for meta-analysis due to heterogeneity in the SMT targets and participant profiles. We tabulated extracted data from each study into a narrative report describing the study, participants, intervention, comparator, and outcomes.

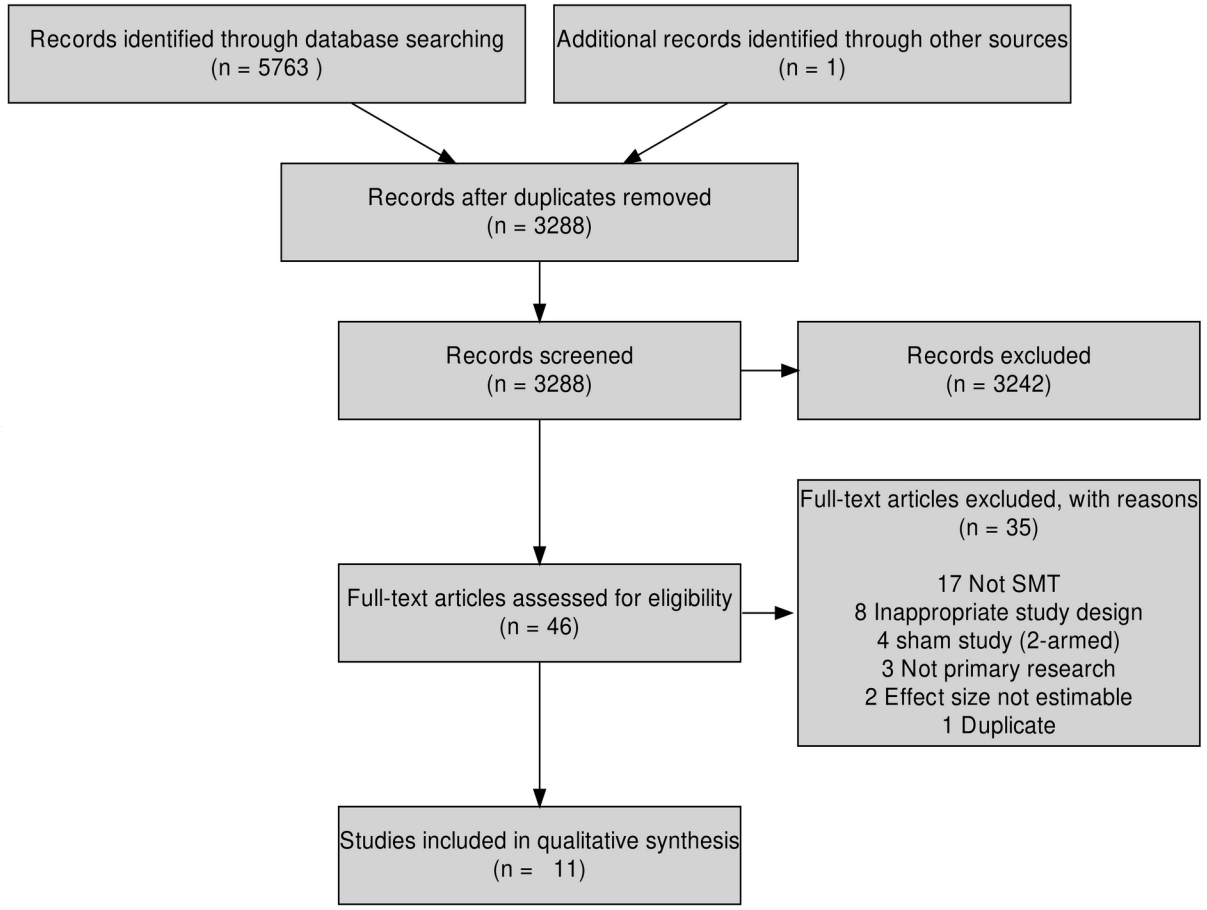
For synthesis, we subgrouped each study by the SMT target: i) Different targets within the same vertebra, ii) different targets within the same region, iii) specific target versus generalized thrust in the same region, and iv) targeting different regions. If needed, this was further subgrouped by the SMT target, i.e., as clinically indicated or pre-specified by study protocol. We report a narrative synthesis by providing a count of statistically significant between-group differences and estimates favoring the specific target. We prioritized the results by the risk of bias assessment and the sample size.

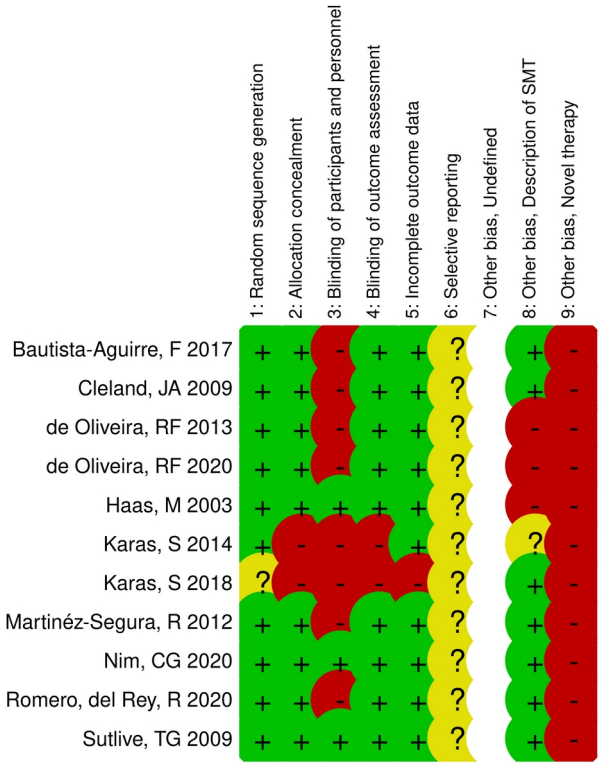
Results

Figure 1 illustrates a PRISMA flowchart. We initially screened 3288 studies, from which 11 were included (31–41). All the studies were in English and published between 2003 and 2020. All but 3(33–35) studies reported *no conflicts of interest*. A total of 6 studies reported that they received funding (31,32,38,39,41). One study was found through searching the reference lists (36). We excluded two studies as we could not calculate an effect size, and the author did not respond to our request (42,43).

Figure 1

PRISMA flow-diagram of the literature search and study inclusion in a systematic review on the effect of spinal manipulative therapy at a specific target versus a comparator target





Risk of bias was assessed using the Cochrane Risk of Bias Tool for Randomized Controlled Trials. A green + indicates low risk of bias, a red - indicates high quality, a yellow *?* indicates and unclear risk of bias, and a *white field* indicates missing information.

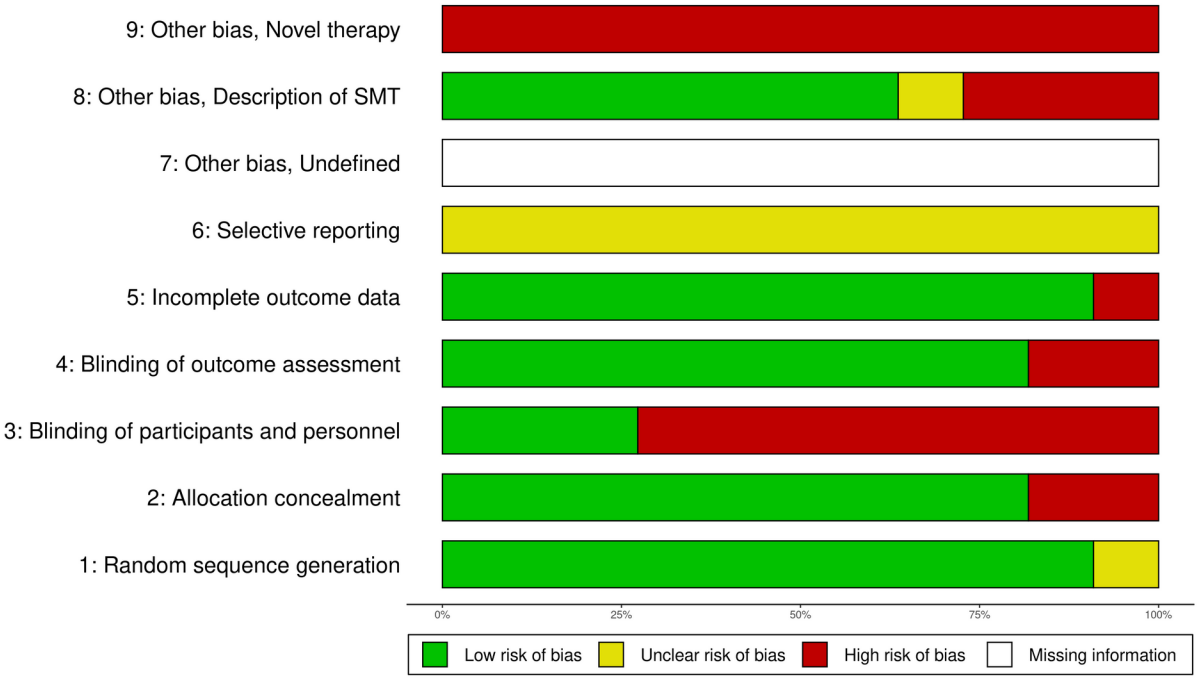
Table 3 highlights the extracted findings from different studies. The SMT intervention target was determined from hands-on clinical examination in seven studies and the study protocol in two studies. Finally, two studies combined these approaches. All but one of the SMT comparator targets were determined by the study protocol, and the one study applied an SMT target not based on a clinical indication (38).

Different targets within the same level

Only one study examined whether SMT outcomes differed when applied at different targets within the same vertebra (38). This study was rated as low quality (one low-risk domain). The intervention target was determined clinically at a thoracic vertebra by palpating for movement restriction, i.e., a flexion thrust (specific target) or an extension thrust (comparator target) or vice versa. Outcomes were measured immediately following 2 SMT sessions and at two weeks follow-up. The study reported that there were no between-group differences in pain or disability.

Figure 3

Risk of bias across studies included in a systematic review on the effect of spinal manipulative therapy at a specific target versus a comparator target



Risk of bias was assessed using the Cochrane Risk of Bias Tool for Randomized Controlled Trials

Different specific targets within the same region

We included two studies examining SMT applied to the same region with two different targets (31,39). Both studies were assessed as high quality (5 and 6 domains of low-risk, respectively). One study specified the specific SMT target using clinical assessment (31), and the other was pre-specified by the study protocol. The comparator target was pre-specified by the study protocol for both studies. Both studies measured outcomes immediately following SMT, first session (31) and fourth sessions (39). The latter also re-measured at four weeks follow-up. None of the studies found any between-group differences for the patient-reported outcomes (pain or disability) at any time point.

Furthermore, both studies measured stiffness, one as a self-reported estimate (31), and the other objectively using mechanical indentation (39). However, this also did not differ between groups at any time point. Finally, one study also measured PPT and found a statistically significant difference when targeting SMT at the most tender vertebra versus the stiffest vertebra immediately following the 4th treatment (39).

Table 1

Description of 11 studies included in a systematic review on the effect of SMT at a specific target versus a comparator target

1st author, year	Country, setting	Study aim (IT vs CT)	N (Male/Female)	Participants	Age, mean (SD)
Haas M, 2003	United States of America, Chiropractic college outpatient clinic	To compare specific cervical SMT to a matched random target for pain intensity and subjective stiffness	Total = 99 IT = 47 (19/28) CT = 52 (17/35)	Adult neck pain patients recruited from referral or advertisement	IT = 42 (13) CT = 43 (14)
Cleland JA, 2009	United States of America, Military Health System, and out-patient physical therapy	To compare SMT targeted a specific lumbar vertebra to a generalized thrust for pain intensity and disability	Total = 75 IT = 38 (17/21) CT = 37 (20/17)	Adult low back pain patients who fit an SMT clinical prediction rule recruited from the Military Health System and out-patient practice	IT = 37 (12) CT = 44 (10)
Sutlive TG, 2009	United States of America, Military hospital	To compare SMT targeted a specific lumbar vertebra to a generalized thrust for pain intensity and disability	Total = 60 IT = 30 (17/13) CT = 30 (14/16)	Adult low back pain patients who fit an SMT clinical prediction rule recruited from the military hospital	IT = 26 (9) CT = 25 (10)
Martinéz-Segura R, 2012	Spain, private physiotherapy practice	To compare SMT targeting the right cervical spine to thoracic SMT for pain intensity, cervical range of	Total = 62 IT = 29 (14/15) CT = 33 (17/16)	Adult bilateral chronic mechanical neck pain patients	IT = 35 (8) CT = 38 (7)

		motion and pressure pain threshold		recruited from private practice.	
de Oliveira RF, 2013	Brazil, private physiotherapy practice	To compare SMT targeting a specific lumbar vertebra to thoracic SMT for pain intensity and pressure pain threshold	Total = 148 IT = 74 (15/59) CT = 74 (24/50)	Adult non-specific chronic low back pain patients recruited from private practice.	IT = 46 (10 CT = 46 (12)
Karas S, 2014	United States of America, Hospital orthopedic department	To compare SMT targeting a specific thoracic vertebra to a generalized thrust for pain intensity and cervical range of motion	Total = 39 IT = 19 (6/13) CT = 20 (6/14)	Adult with neck pain recruited from an out-patient hospital	IT = 42 (10) CT = 39 (12)
Bautista-Aguirre F, 2017	Spain, private physiotherapy practice	To compare cervical SMT to thoracic SMT for pressure pain threshold and grip strength	Total = 58 IT = 28 (7/21) CT = 30 (8/22)	Adult chronic mechanical neck pain patients recruited from private practice.	IT = 32 (6) CT = 31 (6)
Karas S, 2018	United States of America and Germany, private physiotherapy practice	To compare SMT targeting a thoracic restriction to thoracic SMT targeting the counter restriction for pain intensity and disability	Total = 69 IT = 34 (8/26) CT = 35 (7/28)	Adult mechanical neck pain patients recruited from out-patient practice	IT = 40 (2) CT = 38 (2)
Nim CG, 2020	Denmark, Hospital spine center	To compare SMT targeting lumbar stiffness to SMT targeting lumbar pain sensitivity for pain intensity, stiffness and pressure pain threshold.	Total = 132 IT = 66 (32/34) CT = 66 (40/26)	Adult non-specific chronic low back pain patients recruited from a hospital spine center	IT = 44 (10) CT = 47 (9)

Romero Del Rey R, 2020	Spain, private physiotherapy practice	To compare upper cervical SMT to cervicothoracic SMT for pain intensity	Total = 186 IT = 93 (29/64) CT = 93 (38/55)	Adult chronic mechanical neck pain patients recruited from private practice.	IT = 34 (11) CT = 32 (10)
de Oliveira RF, 2020	Brazil, private physiotherapy practice	To compare SMT targeting a specific lumbar vertebra to thoracic SMT for pain intensity, disability, global perceived change, and pressure pain threshold	Total = 148 IT = 74 (17/57) CT = 74 (16/58)	Adult non-specific chronic low back pain patients recruited from private practice	IT = 45 (13) CT = 45 (14)

The descriptive data has been modified to fit the systematic review. SMT = Spinal manipulative therapy, IT = Intervention target, CT = Comparator target

Table 2

Description of the SMT in 11 studies included in a systematic review on the effect of SMT at a specific target versus a comparator target

1st author, year	SMT provider	Intervention target determined by	Comparator target determined by	SMT sessions	Add-on intervention
Haas M, 2003	Chiropractor	Clinically: SMT targeting a cervical vertebrae according to cervical endplay assessment Technique: Unknown	Study protocol: SMT targeting a random computer-generated matched target Technique: Unknown	1	-
Cleland JA, 2009	Physiotherapist	Clinically: SMT targeting a clinician selected lumbar vertebra Technique: Side-lying thrust	Study protocol: Generalized SMT targeting the lumbar spine Technique: Supine thrust	2	Daily: Range of motion exercise program and stretching
Sutlive TG, 2009	Physiotherapist	Clinically: SMT targeting a clinician selected lumbar vertebra Technique: Side-lying thrust	Study protocol: Generalized SMT targeting the lumbar spine Technique: Supine thrust	1	Twice a day for 30 seconds: The pelvic tilt range of motion exercise
Martinéz-Segura R, 2012	Physiotherapist	Clinically, by study protocol: SMT targeting a clinician selected	Study protocol: SMT targeting the midthoracic spine	1	-

		cervical vertebra on the right side Technique: Supine ipsilateral rotational thrust	Technique: Supine thrust		
de Oliveira RF, 2013	Physiotherapist	Clinically: SMT targeting a clinician selected lumbar vertebra (L2-L5) Technique: Side-lying thrust	Study protocol: SMT targeting the thoracic region (T1 and T5) Technique: Supine thrust	1	-
Karas S, 2014	Physiotherapist	SMT targeting a clinician selected thoracic vertebra Technique: Supine thrust	Study protocol: Generalized SMT targeting the thoracic spine Technique: Seated thrust	1	-
Bautista-Aguirre F, 2017	Physiotherapist	Clinically, by study protocol: SMT targeting C7, side was determined by the clinician Technique: Supine thumb-move	Study protocol: SMT targeting T3 Technique: Supine thrust	1	-
Karas S, 2018	Physiotherapist	Clinically: SMT targeting a clinician selected thoracic vertebra either in flexion or extension Technique: Supine thrust	Not clinically: SMT targeting a clinician selected thoracic vertebra in the opposite restriction vector as the intervention target Technique: Supine thrust	2	Daily: a series of home exercises - restriction specific
Nim CG, 2020	Chiropractor	Study protocol: SMT targeting the stiffest lumbar vertebra measured using the VerteTrack Technique: Side-lying thrust	Study protocol: SMT targeting the most tender lumbar vertebra measured using a pressure algometer Technique: Side-lying thrust	4	-
Romero Del Rey R, 2020	Physiotherapist	Study protocol: SMT targeting C1-C2 Technique: Supine thrust	Study protocol: SMT targeting C3-C4, C7-T1, and T5-T6 Technique: Multiple setups	1	-
de Oliveira RF, 2020	Physiotherapist	Clinically: SMT targeting a clinician selected lumbar vertebra Technique: Unknown	Study protocol: SMT targeting T5/T6 Technique: Unknown	10	-

Table 3

Results from 11 studies included in a systematic review on the effect of SMT at a specific target versus a comparator target

1st author, year	Side effects	Between group differences extracted/calculated	Summary of results
Haas M, 2003	No between-group differences reported	Pain intensity[0 to 100] mean(SD): *Immediately = 0.9(3.5), Later same day = 2.2(3.5)* Subjective stiffness[0 to 100] mean (SD): *Immediately = 1.3(3.4), Later same day = 4(3.6)*	There were no between-group differences for the targets
Cleland JA, 2009	IT =9 CT =9	Pain intensity[0 to 10] mean [95% confidence intervals]: *1 week = 0.6[-0.2, 1.4], 4 weeks = 0.5[-0.6, 1.5], 26 weeks = 0.2[-0.6, 1.0]* Disability[0 to 50] mean[95% confidence intervals]: *1 week = 3.5[-2.0, 9.0], 4 weeks = 1.5[-4.1, 7.1], 26 weeks = -0.9[-5.5:3.8]*	There were no between-group differences for the targets
Sutlive TG, 2009	Not reported	Pain intensity[0 to 1] effect size: *2 days = 0.10* Disability[0 to 1] effect size: *2 days = 0.23*	There were no between-group differences for the targets
Martinéz-Segura R, 2012	IT =1 CT =1	Pain intensity[0 to 1] effect size : *Immediately = 0.06*	There were no between-group differences for the targets
de Oliveira RF, 2013	IT =0 CT =0	Pain intensity[0 to 10] mean [95% confidence intervals]: *Immediately = 0.5[-0.1:1.1]* PPT lumbar[0:100] mean [95% confidence intervals]: *Immediately = -1.8[-6.4:2.8]*	There were no between-group differences for the targets
Karas S, 2014	Not reported	Pain intensity during cervical flexion[0 to 10] mean [95% confidence intervals]: *Immediately = -1.2[-1.9:-0.5]** Cervical range of motion, flexion[0 to inf]: *Immediately = 2.1[-1.8:6.1]*	A between-group difference was observed for pain intensity immediately following treatment favoring the IT.
Bautista-	Not	PPT wrist, right[0 to inf] mean [95% confidence intervals]:	There were no between-group

Aguirre F, 2017	reported	*Immediately = 0.0[-1.4 to 1.8]* Grip strength, right[0 to inf] mean [95% confidence intervals]: *Immediately = 0.1[-1.1 to 1.3]*	differences for the targets
Karas S, 2018	Not reported	Pain intensity[0 to 1] effect size: *2 days = 0.25, 2 weeks = 0.14* Disability[0 to 1] effect size: *2 days = 0.33, 2 weeks = 0.18*	There were no between-group differences for the targets
Nim CG, 2020	N = 85, no between-group difference reported	Pain intensity[0 to 10] mean [95% confidence intervals]: *2 weeks = 0.1[−0.5:0.7], 4 weeks = −0.1[−0.7:0.5]* PPT lumbar[0 to 1000] mean [95% confidence intervals]: *2 weeks = −66[−127:− 5]*, 4 weeks = −42[−104:21]* Stiffness[0 to inf] mean [95% confidence intervals]: *2 weeks = 0.0[−0.4:0.4], 4 weeks = −0.1[−0.5:0.2]*	There were no between-group differences for the targets for pain intensity or stiffness. A between-group difference was observed for PPT at 2 weeks favoring the CT.
Romero Del Rey R, 2020	Not reported	Pain intensity[0 to 1] effect size: 15 days = 0.00	There were no between-group differences for the targets
de Oliveira RF, 2020	IT =0 CT =4	Pain intensity[0 to 10] mean [95% confidence intervals]: *4 weeks = 0.0[-0.9:0.9], 12 weeks = -0.1[-1.0:0.8], 26 weeks = -0.1[-1.0:0.8]* Disability[0 to 24] mean [95% confidence intervals]: *4 weeks = 0.1[-1.7:1.5], 12 weeks = 0.1[-1.6:1.7], 26 weeks = -0.9[-2.5:0.7]* Global perceived change[-5 to 5] mean [95% confidence intervals]: *4 weeks = -0.1[-1.0:0.8], 12 weeks = 0.3[-0.7:1.2], 26 weeks = 0.8[-0.2:1.7]* PPT lumbar[0 to 2000] mean [95% confidence intervals]: *4 weeks = 6[-88:101]*	There were no between-group differences for the targets

IT = Intervention target, CT = Comparator target, PPT = Pressure pain detection threshold, * = reported as statistically significant

Specific targets versus generalized thrust in the same region

Three studies examined SMT targeting a specific vertebra versus a generalized thrust in the same region. Two studies examined LBP (32,33) and the other neck pain (36). The two low back pain studies compared a targeted thrust to a generalized thrust at the lower back, whereas the neck pain study compared targeted versus generalized SMT at the thoracic spine. All outcomes were measured immediately after the first and only SMT session. In addition, one study provided two sessions and repeated the measurements immediately following the second SMT session, at four weeks and 26 weeks (32). One study found a statistically significant between-group difference immediately following a targeted SMT at the thoracic spine for neck pain. The same study also found larger improvements for neck range of motion, but this was not statistically significant. This study was assessed as low quality for multiple domains (two domains with low-risk of bias). Also, it was the study with the fewest included participants (36). The two other studies were generally of high quality (five and six domains of low risk of bias) and did not find any between-group differences for neither pain nor disability (32,33). None of these studies reported any objective measures.

Different regions

Finally, we included five studies comparing SMT delivered in different regions (34,35,37,40,41). However, these studies varied considerably. Two investigated low back pain and compared targeted SMT at the lumbar spine versus thoracic spine (35,41). Two compared cervical to thoracic SMT for neck pain (34,37), and one study examined upper cervical SMT to a series of lower cervical, cervicothoracic, and mid-thoracic SMT (40).

Two studies identified the specific target from clinically indication (35,41), one as per study protocol (40), and two as a composite of clinical and study protocol (34,37). Due to the randomization between regions, blinding of the participants and personnel was not possible.

Clinically determined target

The two studies using clinically determined specific targets (35,41) were scored as moderate quality (four domains of low risk). The initial study examined immediate changes following a single SMT session and found no between-group difference for patient-reported low back pain or PPT at the lumbar spine (35). The second study (41) provided the participants with ten SMT sessions and measured changes in low back pain, disability, global perceived change, and PPT at four, 12, and 26 weeks. All between-group differences were close to 0 with narrow confidence intervals, and none were statistically significant.

By study protocol determined target

The study using a pre-specified by protocol specific target (40) compared a single SMT session of the upper cervical vertebrae to multiple SMTs in neck pain participants. The study was scored as high quality (five domains of low risk) and reported a minor between-group difference that was not statistically significant.

Composite of clinical and study protocol

One study (34) employed a three-arm allocation, comparing cervical SMT at both the right and left side to thoracic SMT. After reviewing their results and concluding that there was no difference between the right and left side, we decided to only extract the results from the right side (specific target) compared to thoracic SMT (comparator target). The study was also assessed as high quality (five domains of low risk) and reported no between-group difference in neck pain immediately following one SMT session.

The other study (37) compared a specific target of C7 to a comparator target of T3 for neck pain participants. The study was assessed as high quality (five domains of low risk). However, this study did not present any patient-reported outcomes but reported multiple PPTs across both upper limbs and bilateral grip strength immediately following one SMT session. We only extracted the initial PPT assessment (right wrist) and grip strength for the right hand. The between-group changes were minimal and not statistically significant. When scrutinizing the original study (37), none of the other measures were statistically significant (10 outcomes reported, all unadjusted p-values).

Data synthesis

We extracted a total of 40 statistical analyses, of which only 12 favored the group receiving SMT at a specific target. Only two were reported as statistically significant, and one favored the specific target, and one favored the comparator target.

Discussion

Summary of our findings

This review included 11 studies that compared SMT at different targets, differing within the same vertebra, the same spinal region, and across spinal regions. Despite the common difficulties in manual therapy trials concerning blinding (44), the studies were scored mostly as high quality. The reporting of multiple SMT targets and the quality assessment allows us to make a confident conclusion from the data synthesis. To summarize, despite the heterogeneity and differences across the included studies, none, but one study, found a statistically significant difference in a patient-reported outcome. However, this finding's clinical meaning was questionable (i.e., 1.2 points on an eleven-point numerical pain rating scale). The minor observed between-group differences mostly favored the comparator target and not the specific target. That one study that did find a difference had the smallest sample size of the included studies and was scored as low quality (36).

Excluded studies

We excluded two studies that applied a design appropriate to our research question. However, we were unable to extract any between-group differences or within-group differences, allowing us to calculate an effect size. We requested data from the authors but did not receive a response.

Contrary to our findings, one study (42) reported significant between-group differences in clinical improvement with the specific target SMT directed at the cervical spine, compared to the comparator target, multiple SMTs, in the thoracic spine. Furthermore, several issues in this study of acute neck pain should be considered carefully. For instance, side-effects were highly prevalent in the comparator target group, but not the specific target group. By contrast, only two SMT sessions in the specific target group were reported to significantly improve outcomes for as long as six months. The effects of natural history and side effects were difficult to disentangle in this study of 24 participants (45).

The other excluded study reported in line with the current findings (43) based on a randomized trial comparing a specifically targeted SMT to a comparator target of generalized SMT for low back pain. Sixty-one participants were included and underwent three SMT sessions. Outcomes were assessed before and after each session.

Clinical interpretation

When considering the body of available evidence on this topic, the SMT target does not appear to be essential for clinical improvements in low back or neck pain. With the literature in mind, that is perhaps not surprising: First of all, SMT is not a very specific treatment. It has been documented on several occasions that cavitation is induced at several vertebrae following a single targeted SMT thrust (21–23). Therefore, targeting a specific vertebra may affect multiple other locations in the proximity of the intended target. We would argue that this is undoubtedly one of the possible reasons why a generalized thrust is reported to be as effective as a specifically targeted thrust. Additionally, this non-specificity could explain the lack of difference between targets within the vertebra, the region, or even between regions, e.g., low cervical versus upper thoracic SMT. Furthermore, speculations concerning the biomechanical chain and the spinal regional interdependence could explain why thoracic SMT affects changes in cervical pain (46).

Considerations about SMT's non-specificity and biomechanical arguments aside, it is difficult to provide a simple mechanistic explanation for improvements in lumbar pain from SMT of the upper thoracic region. Such explanations would have to rely on understanding the spinal column as a complex integrated biomechanical unit. Even so, it is difficult to see how SMT would effect immediate changes in pain of distant areas of the target.

While animal research suggests that target specificity is important for SMT and non-thrust mobilization, some differences are also noted between the two (47); despite these differences in animal research, the clinical effects of SMT and non-thrust mobilization are comparable (48–50). Interestingly, in a clinical setting, the target specificity seems less critical in SMT and non-thrust mobilization alike (51–53).

Thus, while SMT appears to be an efficient intervention strategy for treating spinal pain (54,55), the intervention target does not appear to modify this effect. Likely a more nuanced theory has to be forwarded. The likelihood of improvement is arguably contingent on other factors such as contextual contributions (56), e.g., patient expectations (57–59) and the therapeutic alliance (60,61).

A potential benefit of our results is the inclusion of SMT in the management of specific spinal pain syndromes. The implications of not targeting the SMT to address a clinical issue extend SMT's reach to, e.g., disc herniation or compression fracture. Here, clinicians could merely provide the SMT at a distant vertebra and expect to see improvements, possibly even in the short term.

Additionally, we have to acknowledge that stroke of the vertebral arteries sometimes occurs following SMT. Despite a considerable amount of high-quality epidemiological and experimental research indicating that this relation is more likely due to associations between visiting a physician for neck and head pain instead of a causal link between SMT and dissection (62–65). There are limited clinical benefits of opting for cervical SMT as opposed to thoracic SMT. These results are further supported by three systematic reviews that examine thoracic SMT for neck pain (66–68). However, none of the included studies in the other reviews compare thoracic SMT to cervical SMT. Thus, this study adds some vital additions to the literature and provides further evidence that thoracic SMT is as likely to improve neck pain as cervical SMT, without the potential adverse events sometimes described to cervical SMT.

Quality assessment of the included studies

The included studies generally scored low on important potential biases related to this type of research. It is important to notice that the blinding of participants and personnel is difficult in manual therapy trials. Hence only a few studies scored low on this domain. The therapist has to know what type of SMT to administer and where to direct it. Only the study by Karas et al. from 2018 (38) had the possibility of blinding the therapist, but this was not clear if done appropriately from the manuscript. Only one study of low quality and sample size found a between-group difference for the targets (36). Among others, that study potentially introduced bias by not sufficiently concealing the allocation. In particular, this domain is critical for a study that compares a highly specific technique to a non-specific technique without a specific target (44).

All of the included studies scored high on the custom-defined risk of bias assessment of whether SMT was novel to the participant. This potentially introduces response bias (69), as the subjects could have a pre-defined definition of what SMT is and, importantly, where it should be targeted. This point is crucial for the studies comparing SMT at different spinal regions. Nevertheless, despite this high risk of response bias, the studies generally did not find any between-group changes, further confirming our conclusion.

Methodological considerations

Our literature search was based on four different databases, but obviously, we can not exclude the possibility that other relevant publications have been missed. The manual perusal of the reference lists only provided one additional study, which suggests that our search was probably relatively comprehensive.

Many of the included studies did not provide between-group mean differences, and we had to calculate effect sizes from the mean within-group changes. Therefore, we had no means of confirming the underlying statistical assumptions for such calculations (27). For that reason, we opted not to extract more information than that concerning our primary outcome. Alternatively, we could have excluded all studies that failed to report a between-group difference, but this would have considerably limited the data material. We also extracted information concerning objective outcomes such as PPT. However, as different studies had different methodologies (e.g., test sites), we cannot conclude anything definite on whether the target site affects experimental outcomes.

The systematic search was intentionally set up with broad inclusion terms. This made meta-analysis impossible, as we included studies that i) compared SMT in multiple ways, ii) using different techniques, and iii) included different pain populations. However, we would argue that this is a strength of the review as all the outcomes follow the same pattern. Another strength of the review was the careful selection process, data extraction, and risk of bias assessment.

This review did not focus on or assess whether other SMT aspects are needed for clinical improvements. For instance, technique, thrust direction, and speed. Also, no study examined thoracic pain. Therefore, our results only apply to low back and neck pain.

Recommendations

Future research

We acknowledge further research attempting to determine the underlying mechanism of SMT to be of importance. However, there appears to be limited knowledge gained by conducting further trials striving to optimize SMT by comparing specific targets as an intervention for spinal pain. This is an important aspect considering that five out of 11 studies were published within the last four years (37–41).

Educational institutions

This review does not change that universities should continue to teach SMT. However, the teachings have to align with the best available evidence. Animal studies may supply evidence for specific biomechanical and neurophysiological effects following SMT (13–16). However, this specificity does not appear to translate into clinical improvements. Thus, instead of teaching specificity for different targets, we recommend teaching how to implement SMT in an evidence-based and guidelines recommended manner.

Conclusions

Despite the lack of a high quality randomized controlled equivalence trial examining whether applying SMT at two different targets exist, judging from these studies spread across the spine, using different techniques with different targets. We can assuredly estimate that the target site of SMT is not of importance for improvements in patient-reported outcomes. However, whether SMT's target site affects objective outcomes are not as rigorously researched, and the research varies between outcomes. Thus, further and more standardized studies are needed to provide an answer.

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Manuscript VI

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Spatial Synchronization of Spine Stiffness Data

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Spatial Synchronization of Spine Stiffness Data

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Abstract

Background

A novel device that measures spinal stiffness has made it possibly to conduct a quantifiable assessment of applied force and resulting displacement throughout the lumbar spine. However, in order to acquire this data, the process is dependent on surface marking of spinal landmarks; a difficult and challenging task. If these markings are incorrect, or the data is not collected at the same starting point, the result can be spatially shifted data. We present a simple solution to this by transposing data collected at multiple days to create spatial synchronization.

Methods

To test this approach, we analyzed stiffness data previously collected from a prospective trial of low back pain patients. As expected, transpositions were needed between trials to synchronize data for the same participant to correct for spatially shifted data.

Results

The resulting stiffness measures from the synchronized data were different from the unsynchronized data.

Conclusions

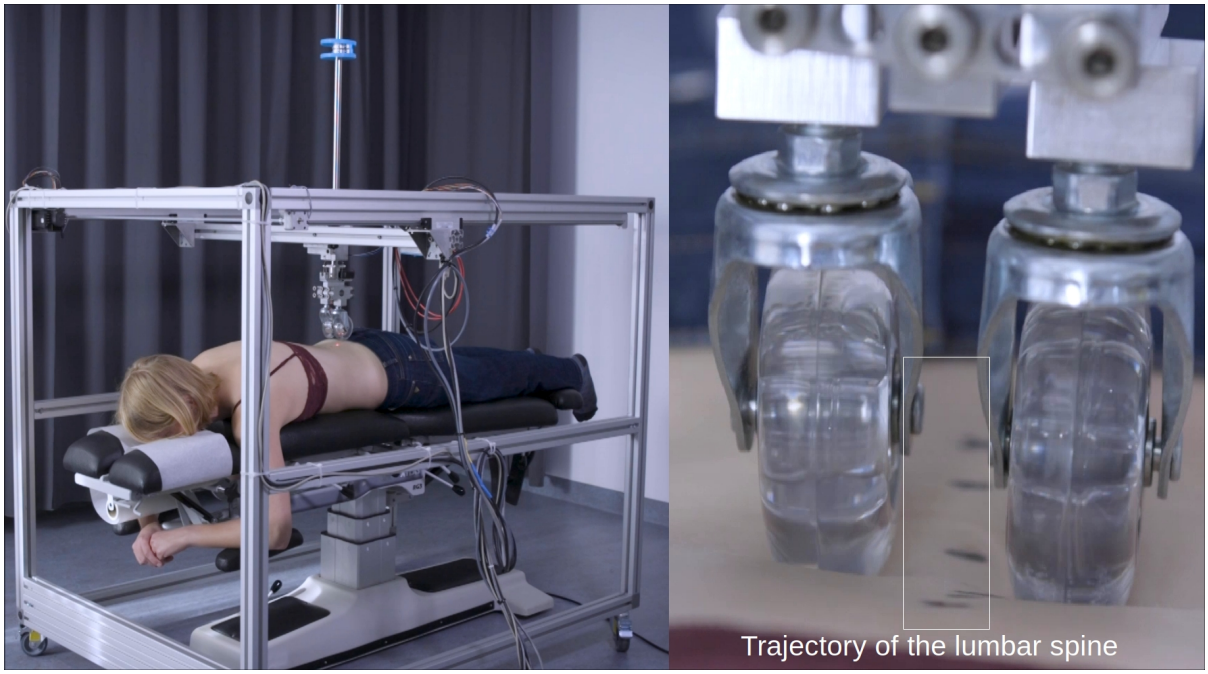
Given these results, we recommend that studies using data obtained by this method utilize spatial synchronization of within-subject data to correct for this potential confounder.

Background

The lumbar spine provides a biomechanical foundation for human kinetics and protection of the sensitive nerve structures housed within the spinal column [1]. Given these functions, it is a common observation that low back pain often is associated with excessive lumbar spine rigidity [2]. Multiple attempts have been made to quantify spinal stiffness, often by applying indentation at a single spinal point and measuring the resulting displacement [3]. More recently, this approach has been expanded from single test location to encompass the entire lumbar spine (VerteTrack (VT)) using laser steered wheels that pass over the spinous processes of all five lumbar segments [4]. The result is a spatial representation of spinal posterior-anterior displacement as a function of the applied load which can then be used to calculate spinal stiffness anywhere along the lumbar spine (Figure 1).

Figure 1

An illustration of the VerteTrack setup



To acquire this data, investigators must not only identify and mark the locations of the lumbar spinous processes, but then also position the device correctly in relation to these markings [5,6]. When collecting data on multiple occasions, the reliability of these procedures is critical for accurate comparison of data. Indeed, in recent clinical trials employing the VT [7], we have noticed that data collected on multiple occasions from the same participant may not be spatially aligned.

Objective

Therefore, the objective of this paper is to determine the extent of spatial asynchrony in an existing VT data set, and determine whether a simple data transposition technique that creates spatial synchrony would have an impact on resulting measures of spinal stiffness.

Methods

Setting

VerteTrack data were collected in a previous prospective randomized trial, of low back pain patients to investigate the effect of different interventions following two sessions of lumbar manual therapy (MT) within one week [8] (see Table 1 for all test sessions). All participants who completed the first week of this study were included.

Ethics approval for primary data collection was granted by the Institutional Review Board at the University of Alberta (Pro00067152). Informed, written consent was obtained for all.

Data collection

In the prior data collection, each participant was placed in the prone position on an examination table. The location of the lumbar spinous processes (S1 - T12) were identified using palpation by an experienced clinician [8] and marked superficially with a felt-tip pen. The wheels of the VT were then aligned to each spinous location, and the resulting coordinates were used to create a continuous rolling trajectory for the wheels to follow cranially. Using applied mass in increments of ~10N (loads from 17N to 83N) [9], the resulting vertical displacement of spinal tissues during wheel movement was measured continuously by a string potentiometer (TE Connectivity, USA). From these measures, lumbar stiffness (N/mm) was then calculated throughout the trajectory. The process is illustrated in Figure 1 and virtually in Supplementary file A.

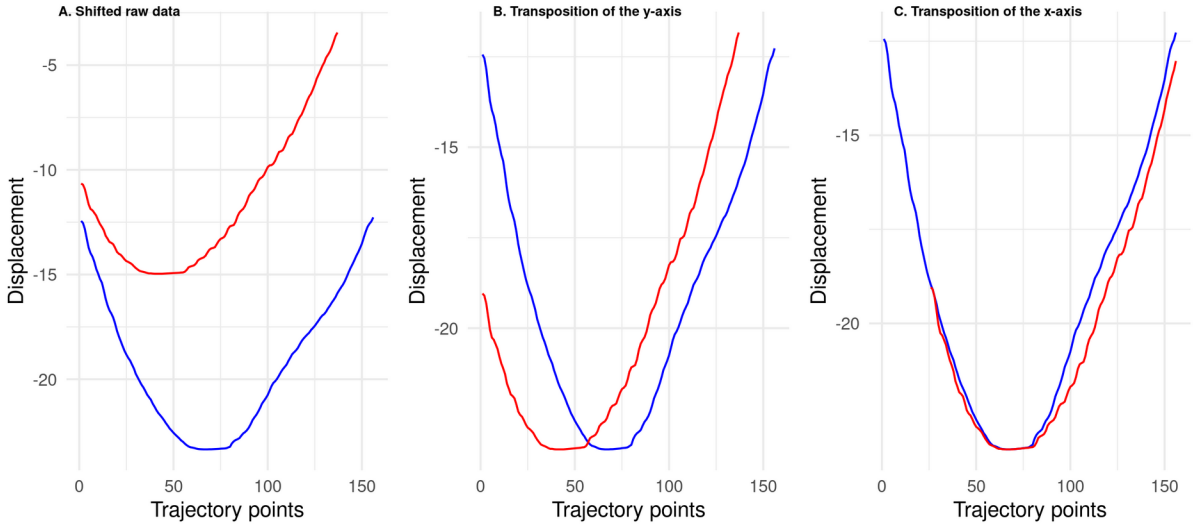
Spatial synchronization

Displacement data collected by a customized LabVIEW program (version 15, National Instruments, USA) were smoothed using a 2-factor polynomial and each trial scrutinized visually in order to identify and exclude errors (participant breathing, movement, voluntary muscle contraction or any technical errors). The LabVIEW program then calculated measures of stiffness (displacement as a function of load) at each sampling point in the rolling trajectory. The formatted data were imported into *R* (v. 3.6, Austria) [10] and the displacement curves visualized using *ggplot* [11]. Baseline displacement data were used in all cases as the *reference* data (day 1 pre MT). Data collected from subsequent trials (using the highest available load for both trials) were then transposed so that the data points were synchronized with the reference data. Synchronization was achieved mathematically by translating the x-axis until the points of greatest vertical displacement were aligned. The magnitude of transposition needed to achieve synchrony was then quantified. To better inspect the resulting transposition on the x-axis, the y-axis of the plot was also transposed so applied loads were equalized (Figure 2). Finally, three authors (CGN, PJ, MH) reviewed the results to inspect whether optimal synchronization was achieved. If agreement was not achieved, the data were further manually transposed and visualized until agreement was reached. Figure 2 demonstrates an example of spatial synchronization.

Furthermore, we calculated the average distance between markings of each spinous process.

Figure 2

Spatial synchronization process



The blue line indicates the *baseline* displacement data, and the red line the displacement data from the assumed same trajectory measured at week 1. Figure 2.A is the original data points, Figure 2.B shows the overlapping of y-axis (visual purpose only) and, Figure 2.C shows the resulting spatial synchronization. In the example provided the transposition at the x-axis equals 15 mm

Outcome measures

The resulting spatial synchronization of the x-axis was evaluated using two outcomes calculated via the *geiger* package [12]: 1) Within-trial cumulative total lumbar displacement and 2) Between trial cumulative change in stiffness.

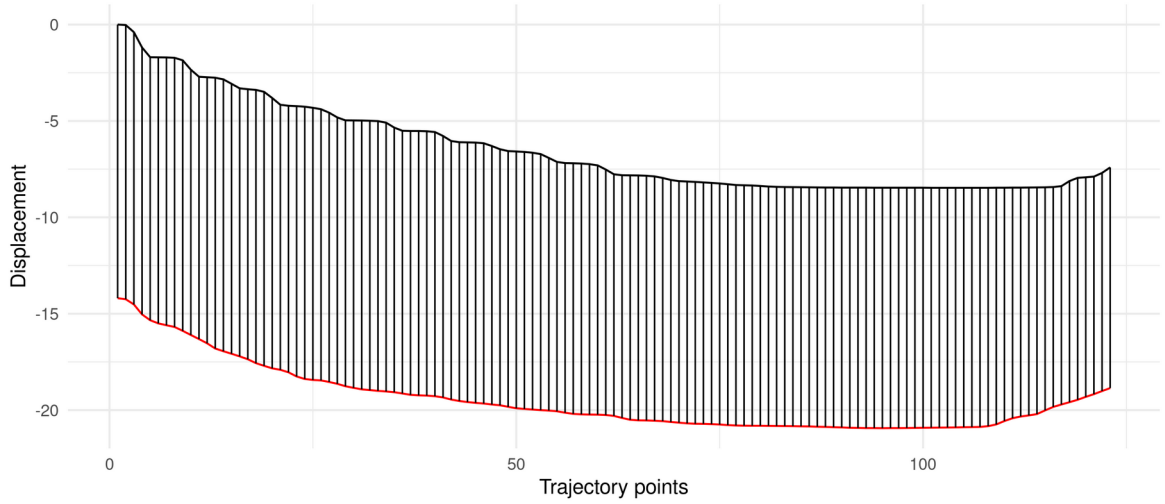
1) Within-trial cumulative total lumbar displacement: This outcome was calculated as the cumulative displacement between the lowest and the highest applied loading within the same trial. Figure 3 illustrates an example of within-trial cumulative total lumbar displacement.

2) Between trial cumulative change in stiffness: This outcome was calculated by first determining the stiffness at each point along each displacement curve then determining the change in stiffness between trials on different days using the baseline and highest common load available for the same participant. Figure 4 illustrates two examples of between trial cumulative change in stiffness.

Finally, to determine the effect of spatial synchronization on single point stiffness measures, a comparison of stiffness change at L3 was conducted between the synchronized data and the raw shifted data.

Figure 3

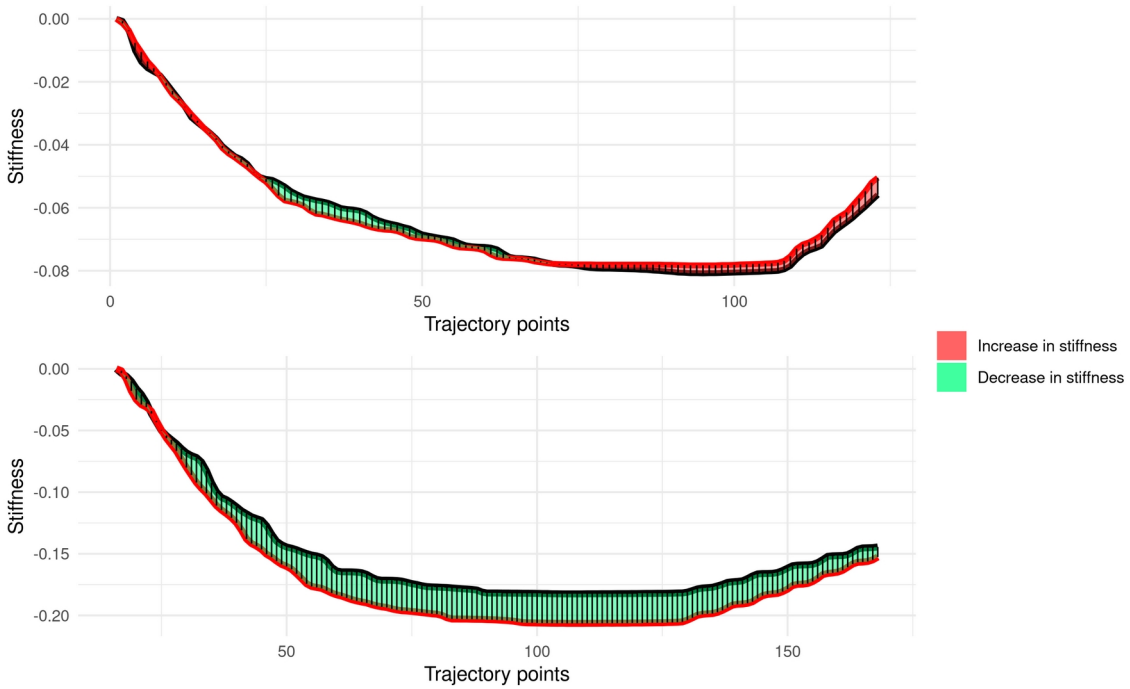
An example of a total cumulative lumbar displacement score within a single trial.



The cumulative displacement marked corresponds to 1590 mm.

Figure 4

Between trial cumulative change in stiffness



Two examples of differences in cumulative stiffness data between baseline and week 1, the black line illustrates the max displacement at baseline, and the red line the max displacement for week 1 (common load = 83N). Shaded red area indicates more stiffness at follow-up, while the shaded green area indicates less stiffness at follow-up. The first example illustrates, a minor increase of stiffness in the caudal part of the lumbar spine whereas the cranial section had a minor decrease (upper panel). In total, the complete lumbar stiffness changed 0.03 N/mm, indicating a minor increase in stiffness. The second example (lower panel) illustrates a substantial decrease in stiffness of 2.7 N/mm.

Results

Spatial synchronization of the displacement data

A total of 124 participants had complete VT data at week 1 with one VT trial omitted from analysis as it was incomplete. At week 12, 97 participants with applicable VT data remained, see Table 1.

Table 1 lists mean transposition distances (mm) of displacement data needed to achieve spatial synchrony for each available trial. Notably, a mean shift of ~5 mm was observed between the two measures obtained on day 1. On average, an even larger shift was observed at day 4 which then remained consistent throughout the intervention period. The synchronization process resulted in unmatched data points at either end of the trajectory that are listed in Table 1. Notably, more data were gradually unmatched throughout the intervention period.

The average distance between the markings of each spinous process was 27 mm. The mean transposition distance of 12 mm represented ~ 50% of this value and corresponded to 7% of the total lumbar spine (trajectory points between S1 and T12).

Table 1

The mean spatial transposition and the resulting unmatched data points

Test session	N	Spatial transposition (mm) compared to baseline - mean(SD)	% shift between spinous markings (% of the full spine(S1-T12))	Unmatched data points (mm) compared to baseline - mean(SD)
Day 1 Pre MT (baseline)	124	0(0)	0(0)	0(0)
Day 1 Post MT	123	4.6(4.8)	17(3)	5.1(5.4)
Day 4 Pre MT	123	12.4(11.6)	46(8)	13.4(14.3)
Day 4 Post MT	124	13.9(11.8)	52(9)	14.2(14.6)
Week 1	124	13.1(12.1)	49(8)	15.2(15.6)
Week 4	106	15.4(12.1)	57(10)	19.7(18.1)
Week 12	97	14.4(12.3)	53(9)	16.5(15.1)

The mean spatial transposition and the resulting unmatched data points for each test session compared to the baseline/reference data. SD = Standard deviation, MT = Manual therapy

Outcomes

Table 2 displays results for within-trial cumulative total lumbar displacement and between trial cumulative change in stiffness.

The within-trial cumulative total lumbar displacement indicated that the average displacement per participant decreased, over time, from 2290 mm to 1750 mm. Only minor differences were observed between trial for cumulative changes in stiffness, however, the resulting standard deviations were substantial.

Table 2

Within-trial cumulative total lumbar displacement, and between trial cumulative change in stiffness

Test session	N	Cumulative total displacement (mm), mean(sd)	Cumulative changes in stiffness (N/mm), mean(sd)
Day 1 Pre MT (baseline)	124	2290(639)	0(0)
Day 1 Post MT	123	2234(559)	0.4(3.9)
Day 4 Pre MT	123	2061(572)	-0.2(3.8)
Day 4 Post MT	124	2083(582)	0.1(4.1)
Week 1	124	2093(594)	-0.1(3.6)
Week 4	106	1832(575)	-0.2(4.4)
Week 12	97	1750(521)	0.3(4.9)

Within-trial cumulative total lumbar displacement for each trial, and between trial cumulative change in stiffness between baseline and additional trials. SD = Standard deviation, MT = Manual therapy

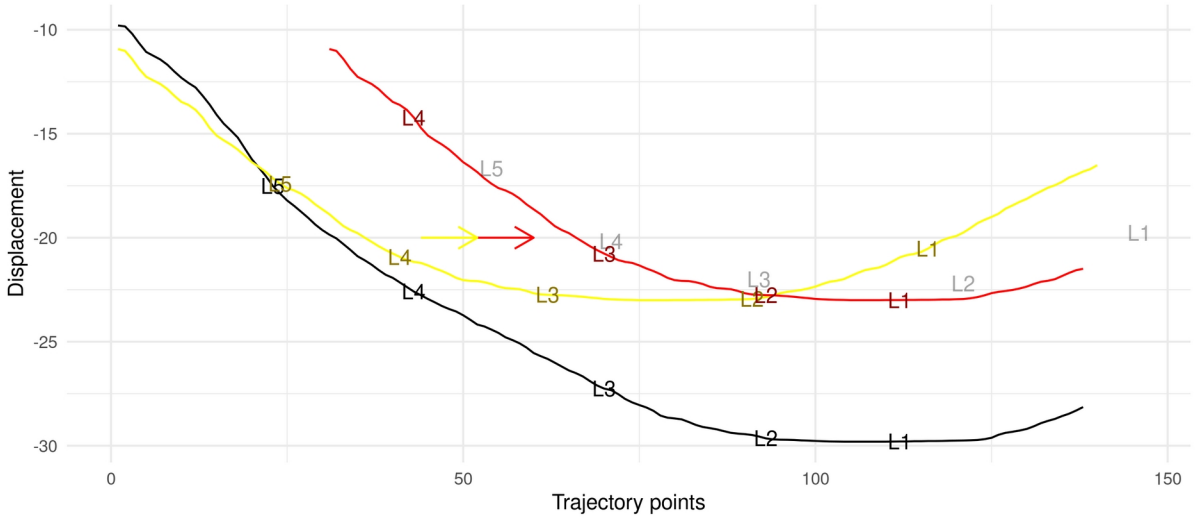
The effect of spatial synchronization

We present changes in single point stiffness measures at L3 between baseline and week 1. Using the original raw data, the difference in stiffness would indicate a minimal positive mean change of 0.07(range=-3.19 to 5.02) while the transposed data resulted in a minimal mean negative change of -0.02 (range=-4.58 - 3.65). Only minor changes in stiffness were observed for this cohort, this difference being -0.09 (range=-3.38 to 4.06). However, this range appears to be important.

To clarify this point we present a visual example of a participant with a potential important difference due to shifted data. Figure 5 illustrates the transposition of the raw data at week 1 (yellow curve) to corrected data (red curve) which was aligned with the baseline data (black curve). This transposition revealed a misclassification of spinous locations on the transposed data (red curve). For instance, what was erroneously denoted L5 appears to be located cranially to L4 (shaded black spinous location). Also, when synchronized, L5 appears to have been missed in the subsequent trial likely due to an error in placing the starting point of data collection. Calculating the change in stiffness for the participant at L3 from baseline to week 1 using the corrected, spatial synchronized data revealed a decrease of 1.39 N/mm. However, the raw data would yield a decrease of 2.31 N/mm (i.e. using the raw data would overestimate a decrease in stiffness of 0.92 N/mm).

Figure 5

Effects of the data transposition on specific spinous locations



An example of the effects of the data transposition on a specific spinous location. Baseline and week 1 trajectories are plotted with superimposed spinous locations for each lumbar segment: black = baseline, yellow = shifted follow-up (raw data), red = spatial synchronized follow-up (transposed data)

Discussion

We present i) a simple method of transposing displacement data collected at different trials, ii) examples of new displacement and stiffness outcomes and iii) provide data on how the resulting synchronization can effect measures of stiffness.

The validity of the method rests on the rational assumption, that observed discrepancies in displacement trajectories actually reflect mistakes in surface marking of anatomical landmarks, and not a gross anatomical change in lumbar curvature. Arguably, changes could occur due to participant breathing, muscle contraction or because of the manual treatment itself, as experimental research indicates that stiffness does change more rapidly at the therapeutic application site compared to adjacent locations [13]. Overall, these effects could result in modifications of the lumbar curvature, potentially appearing as if the data was asynchronized. However, this does not seem likely, nor appear to be the case, as the total number of unmatched data points increased at a slightly higher rate than the calculated shifts.

We thus postulate that the spatial length increases over time due to erroneous measurements as opposed to anatomical changes in the lumbar spine. Whether the synchronization process described here has a statistically significant impact on the stiffness outcome when using the cumulative displacement or total stiffness change was not the focus of this report.

While the cumulative stiffness changes were minor, the standard deviations were substantial, likely due an increase (positive value) or a decrease (negative value) of stiffness. The minor mean difference between stiffness changes at L3 is a testament to the power of this sample, however the reported range should give caution about interpretation especially in more modest cohort sizes [14].

This method of synchronization has some caveats: i) As illustrated in Figure 4 bidirectional changes can be missed if the full trajectory is not visually inspected. ii) We restricted our comparison to the baseline trial and maximum loading which means we do not know how our outcome measures performed between these extremes. iii) The reliability of palpation potentially increases over time and the operator could become more experienced using the VT for each participant, thereby transposing to other trials could maintain more of the unmatched terminal data points. This is a clear limitation of spatial synchronization as up to 10% of the lumbar spine data may be transposed leading to ~20 mm of unmatched points.

We suggest that all future investigations using the VT as an outcome measure should assess displacement data and synchronize accordingly. This is an important point as there are currently eleven VTs installed at different research institutions globally, and some are used for repeated outcome measures. It is possibly that more efficient methods than the one described here could be developed to synchronize data points, but the issue needs to be addressed in any case. Finally, spatial synchronization allows for standardization of the dataset and workflow which ought to establish more reproducible results, and importantly limit the variation in the analysis [15].

Conclusion

This spatial synchronization of lumbar displacement data corrects for variability in the current technique inherent to spinous process identification and/or starting point location. This method has limitations which requires careful assessment and interpretation. Whether synchronization has a significant impact on clinical outcomes are currently unknown. We highly recommend that future reports using repeated VT data transposition the displacement data before concluding on the results.

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