

Manual Therapy for Chronic Conditions: A Mechanistic Approach to Modern Manual Therapy

Carol A. Courtney, PT, PhD, ATC, FAAOMPT^{1,2}
Cesar Fernández-de-las-Peñas, PT, PhD, DrMedSci^{3,4}

¹Department of Physical Therapy and Human Movement Science, Northwestern University, Chicago IL, USA

²College of Health Sciences, Rush University, Chicago IL, USA

³Department of Physical Therapy, Occupational Therapy, Physical Medicine and Rehabilitation, Universidad Rey Juan Carlos, Alcorcón, Spain

⁴Department of Health Science and Technology, Aalborg University, Aalborg, Denmark

ABSTRACT

In recent decades, there has been a change from a purely biomechanical model to a neurophysiological model explaining the effects of manual therapy interventions in individuals with musculoskeletal pain. This monograph describes the similarities and differences in how joint-biased, soft tissue-biased, and nerve-biased forms of manual therapy may mediate pain through neurophysiological mechanisms. We propose that understanding underlying mechanisms of manual therapy interventions and identifying the presence of altered nociceptive pain processing in patients with chronic pain will lead to better clinical outcomes. Clinically, physical therapists often attempt to make judgements about the irritability of a patient's condition and from that, determine both spatial (how vigorous) and temporal (how long) parameters of their manual therapy intervention to be applied. The use of quantitative sensory testing measures as an objective means to augment decision-making is discussed. This monograph reviews the animal model and human research describing the neurophysiologic mechanisms of manual therapy induced analgesia and the research literature relating to joint-biased, soft tissue-biased, and nerve-biased manual therapies is presented. A model is proposed on how the presence of nociplasticity alters physical therapy management of the patient. Finally, case studies relating to patients with chronic pain are provided. Therapeutic management of chronic pain should focus on nociceptive pain processing mechanisms instead of biomechanical models. It is clear that manual therapies should be integrated into a multimodal approach, and never as an isolated intervention.

Key Words: biomechanics, central sensitization, manipulation, mechanisms, mobilization, neurophysiological, nociplasticity, pain

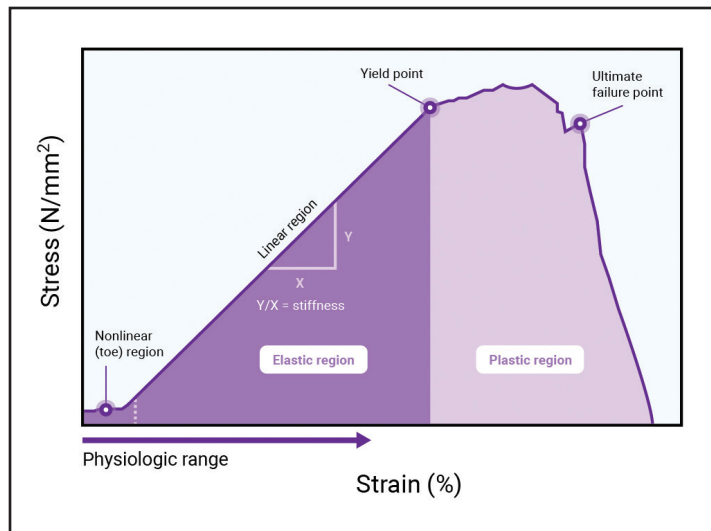
LEARNING OBJECTIVES

1. Differentiate biomechanical versus neurophysiological effects of manual therapy in individuals with musculoskeletal pain.
2. Understand the effects of manual therapy on physical impairments and function in individuals with chronic musculoskeletal pain.
3. Identify interacting mechanisms through which manual therapy may inhibit pain and design interventions accordingly.
4. Describe how nociplastic pain presentations may alter manual therapy outcomes.
5. Analyze the relationship between dynamic quantitative sensory measures of temporal summation and conditioned pain modulation with neurophysiological mechanisms of wind-up and descending inhibition.
6. Compare and contrast the effects of manual therapy versus other physical therapy interventions on opioidergic and non-opioidergic pain inhibitory mechanisms.
7. Describe similarities in how joint-biased, soft tissue-biased, and nerve-biased forms of manual therapy may mediate pain in terms of neural mechanisms.
8. Recognize the role of the sympathetic nervous system and the hypothalamic pituitary adrenal axis on stress and how stress may influence chronic pain.
9. Apply decision-making to determine dosage of manual therapy in the patient with and without nociplastic pain.
10. Distinguish the role of manual therapy in modern physical therapy management approaches to patients with chronic musculoskeletal pain conditions.

INTRODUCTION

Manual therapy, defined as the passive application of mechanical input to neuromusculoskeletal tissues, is arguably one of oldest known medical interventions in history.¹ It is comprised of a large number of techniques including passive joint-biased interventions (non-thrust [static and oscillatory accessory and physiological joint mobilization] or thrust manipulation), soft tissue-biased interventions (massage or trigger point pressure release), nerve-biased interventions, and active joint/muscle mobilizations.² Traditionally, manual interventions have been used to impart tissue stretch or mobilization for the explicit purpose of regaining connective tissue mobility. The stress-strain curve (**Figure 1**) depicts how increasing forces applied to connective tissues eventually results in plastic deformation, and when applied therapeutically, may result in increased tissue extensibility. However, the implicit rationale for the application of manual therapies has been pain relief and improved function. Over the years, both practitioners and patients tacitly accepted the notion that mechanical input to areas of pain, through massage, stretching, oscillatory joint non-thrust mobilization, or thrust manipulation would relieve symptoms.

Figure 1. Stress Strain Curve Applied to Human Tissues^a



^aIllustration by Kinstler Design

With some exceptions, the physical application of manual therapies has not changed drastically over the millennia. What has evolved is our growing understanding of manual therapy effects on human tissue mobility and even more so its effects on neuroplasticity. Previous theories on the underlying mechanisms of manual therapy were primarily based on biomechanical models, where a specific tissue dysfunction was the target of the intervention.³ Modern thinking has led to a paradigm shift, moving from biomechanical to more neurophysiological models based on pain neuroscience.⁴

Improved function and diminished pain are the typical outcomes clinical studies use to examine the effectiveness of manual therapy interventions; however, other effects have been investigated. A recent meta-analysis found low evidence supporting manual therapy when compared to other treatments for improving fear-avoidance, kinesiophobia, and pain catastrophizing in individuals with musculoskeletal pain.⁵ It is generally recommended that manual therapies should be integrated into a multimodal approach, and never used as an isolated intervention.

While manual therapy has been most associated with physical therapists, osteopaths, chiropractors, and massage therapists, in reality, the use of passive movement as an intervention is much more ubiquitous. A number of neuroscience research studies have observed alterations in spinal excitability following a bout of rhythmic passive movement performed with the purpose of understanding the effect of passive movement on motor control and function.⁶⁻⁸ In contrast, other mechanistic studies in manual therapy have examined

the effects of passive techniques on nociceptive processing. Passive movement may cause activation of muscle spindles and joint afferents (**Table 1**) including Group II, III, and IV fibers. In an animal model, Group III and IV joint afferents have been found to respond to both noxious and non-noxious stimuli in various ranges of joint motion,⁹ and these responses were facilitated in the presence of joint inflammation.¹⁰ These heightened responses in the presence of joint insult/inflammation may mediate the differences found between healthy individuals and patient populations in reaction to manual therapy interventions.

As the clinician hypothesizes on the pathophysiology of a patient's specific condition, questions naturally arise as to which manual intervention would produce the best effects. The parameters of how manual therapy should be applied are not well-defined. A continuing challenge for clinicians is the decision-making on symptom reproduction (eg, should the intervention reproduce symptoms) and symptom modification (eg, choosing the best intervention to reduce a particular painful movement).

THE IMPORTANCE OF DETERMINING BASELINE: DECISION-MAKING IN MANUAL THERAPY

Studies examining the efficacy of manual therapy have been equivocal when applied in certain patient populations.¹¹⁻¹⁵ If the purpose of manual therapy is to induce a neurophysiological effect, and as a consequence, pain relief, then a critical step in gauging its effectiveness would be establishing a patient's baseline neurophysiological status. In this neurophysiological paradigm, the clinician must consider pro-nociceptive and anti-nociceptive mechanisms,¹⁶ which can drastically alter the desired effect of a manual therapy intervention, requiring the clinician to alter the intensity or timeframe (dosage) of the applied technique. To consider this mathematically, the outcome of an applied manual therapy technique is dependent upon dosage. Specifically, it is a function of the degree of mechanical input (degree of tissue stretch and duration of treatment) and the extent of central nociplasticity where:

$$\text{Outcome} = \text{Manual Therapy Dosage} * \text{Nociplasticity}$$

The International Association for the Study of Pain defines nociplastic pain as pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain. Establishing such a baseline would entail determining if signs of peripheral and more specifically, central nociplasticity are present. Few if any clinical trials examining outcomes of

Table 1. Sensory Fiber Types

Type	Erlanger-Gasser Classification	Diameter (mm)	Myelin	Conduction Velocity
Ia	Aa	13-20	Yes	80-120 m/s
Ib	Aa	13-20	Yes	80-120 m/s
II	Ab	6-12	Yes	33-75 m/s
III	Ad	1-5	Thin	3-30 m/s
IV	C	0.2-1.5	No	0.5-2 m/s

manual therapy have captured this information as a part of their protocols. Failure to identify this information may alter outcomes of manual therapy interventions. Quantitative sensory testing (QST) is slowly gaining attention in clinical settings. These tests (eg, temporal summation) can be used as dynamic, albeit indirect, measures of nociplasticity, capturing how the central nervous system responds to specific noxious and non-noxious stimuli in separate but related ways.

Temporal summation¹⁷ is considered a clinical correlate of the wind-up phenomenon¹⁸ and captures the rate of change in excitability of spinal and potentially supraspinal pathways. It has been referred to as a pro-nociceptive mechanism,¹⁶ and when elevated has been associated with non-response to physical therapy interventions.¹⁹ This simple test (temporal summation) is performed by applying a stimulus (cutaneous pinprick or heat is commonly used) repetitively at a rate of 1 Hz for 30 seconds (or at times continuously), typically in an area of hyperalgesia, and analyzing the rate of pain increase over the time period.¹⁷ With hyperexcitability of nociceptive pathways, pain is amplified up at a heightened rate and to a greater intensity. This hyperexcitability is characteristic of central nociplasticity and when present, over-vigorous application of oscillatory non-thrust manual therapy into hyperalgesic joint tissues may actually accentuate pain rather than down-modulate it, resulting in a flare-up of patient signs and symptoms. For the clinician it may be possible to use a functional test as a measure of temporal summation – this is illustrated in one of the case studies at the end of this monograph.

Alternately, the assessment of conditioned pain modulation may help determine an individual's ability (or lack of ability) to down modulate pain via endogenous inhibitory mechanisms. Conditioned pain modulation is measured by determining a baseline pain level (the test stimulus) and then applying a painful conditioning stimulus, typically at a distant limb, to determine the extent to which the central nervous system will inhibit the painful input. Reassessment of the test stimulus provides an objective measure. Physical therapy interventions

such as transcutaneous electrical nerve stimulation (TENS), exercise, and manual therapy are thought to modulate pain via facilitating descending inhibitory pathways.²⁰⁻²² Studies have shown that individuals with certain chronic pain conditions, including fibromyalgia,²³ irritable bowel syndrome,²⁴ and knee osteoarthritis (OA),²¹ demonstrate impairment in this anti-nociceptive mechanism, identified in the clinical setting by QST measures of conditioned pain modulation.²⁵ This impairment represents a central nociplastic change in neural processing, and while certain physical therapy interventions may facilitate mechanisms of pain inhibition in individuals with impaired or unimpaired inhibitory mechanisms, the inappropriate technique may have the opposite of the desired effect, specifically resulting in a flare up of the patient's signs and symptoms.

Why does this flare response occur? Sensory afferents in musculoskeletal tissues perceive mechanical stimuli, such as tissue stretch and compression, and transmit this information to the central nervous system. When tissues are hyperalgesic, excessive stretch or compression of these structures causes activation of nociceptors producing further facilitation of spinal and supraspinal nociceptive hyperexcitability, and potentially a poorer clinical outcome (**Figure 2**). Secondly, over-vigorous manual therapy may activate mechanisms of neurogenic inflammation, where inflammatory mediators such as Substance P and Calcitonin Gene Related Peptide (CGRP) are released efferently from the nerve into the periphery, promoting pain and chronic inflammation,²⁶ and facilitating central nociplasticity at the dorsal horn²⁷ (**Figure 3**), and thereby a heightened intensity and spread of pain distribution. Interestingly, a recent meta-analysis found that physical therapy can produce a small improvement in these 2 related outcomes of nociplasticity, a decrease in temporal summation and an increase of conditioned pain modulation, in musculoskeletal chronic pain conditions.²⁸

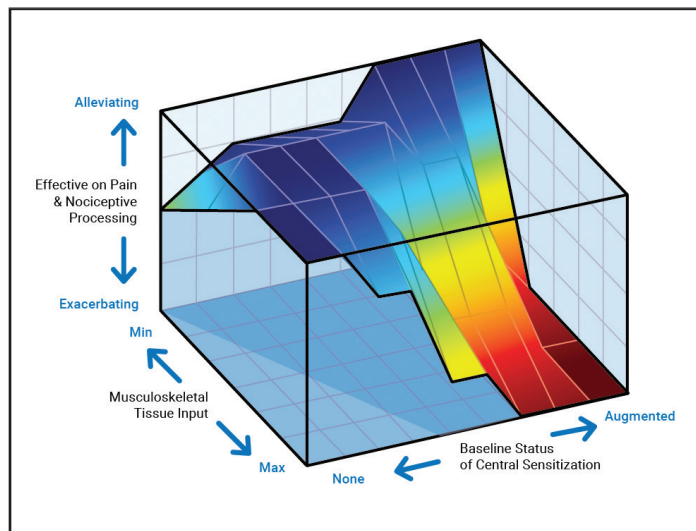
The concept of facilitated anti-nociceptive processing should also be considered. Some studies have suggested that athletes may demonstrate higher pain tolerance and greater

magnitude of conditioned pain modulation,^{29,31} however, this notion has been questioned in a meta-analysis.³² The capacity to inhibit pain is clearly dynamic in nature. Geva et al³³ found that facilitated anti-nociceptive processing was attenuated in situations of acute severe psychological stress,

while Assa et al²⁹ found that endurance athletes demonstrated greater pain inhibition than strength athletes when measured by conditioned pain modulation. Consequently, superior outcomes from manual therapy and exercise may depend on the athlete's exercise/sport dosage. However, this is clearly an area of future research, particularly considering the fact that chronic pain and depression are prevalent in retired professional athletes.³⁴

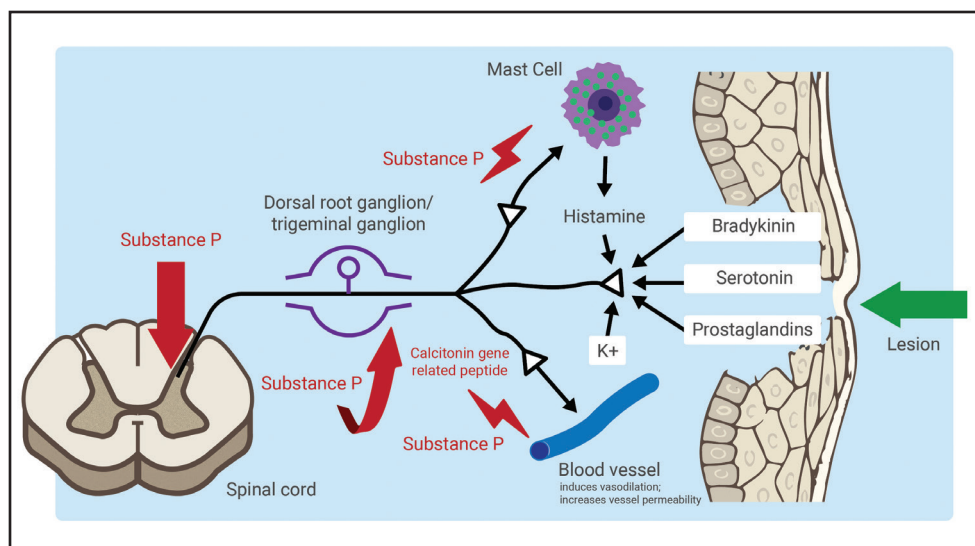
Previously physical therapists have often attempted to subjectively determine baseline status of nociplasticity by making judgements about the irritability of a patient's condition. From that, they would determine both spatial (how vigorous) and temporal (how long) components of their intervention. While self-reported outcomes of central irritability or sensitization such as the Central Sensitization Inventory (CSI)³⁵ may help with clinical decision-making, selecting the proper dosage and intensity of an intervention for the patient with chronic pain who is likely to present with a unique clinical presentation remains a challenge for clinicians. Quantitative sensory testing can be a clinically relevant tool to aid this decision-making and determining baseline status of nociplasticity. Clinicians may wish to use temporal summation to identify patients with hyperexcitable nociceptive processing and conditioned pain modulation to identify patients with impaired inhibitory mechanisms.

Figure 2. Potential Neurophysiological Effects of Manual Therapy Considering Baseline Nociplasticity^a



^aIllustration by Kinstler Design

Figure 3. Neurogenic Inflammation^a



^aIllustration by Kinstler Design

MECHANISMS OF MANUAL THERAPY INDUCED ANALGESIA

A model describing the neural structures activated by manual therapy interventions has been proposed³⁷ and more recently a similar model has been proposed for dry needling as an intervention.³⁸ These models provide an important potential framework for mechanistic studies, however, neither model accounted for the effect baseline status of nociplasticity may have on clinical outcomes and nociceptive processing. A large and diverse number of mechanistic

studies have recently been performed in both animal model and human patient populations. The diversity and breadth of these findings can be confusing for the clinician making decisions on manual therapy interventions. **Table 2** describes examples of neurophysiological findings that have been reported in manual therapy studies and the potential nociceptive mechanism associated with them.

In a recent scoping review of animal model studies on manual therapy, Lima et al³⁹ described findings of diminished inflammatory profiles (potentially due to decreases in neurogenic inflammation), changes in gene, neurotransmitter release, and protein expression, and reduction in nociceptive excitability (potentially due to facilitation of descending inhibition) in studies using joint mobilization (ie, non-thrust manipulation) as a manual therapy intervention. The ability to study neurogenic inflammation directly in the animal model is valuable as this mechanism can facilitate release of neuropeptides such as Substance P and CGRP both in the periphery and at the dorsal horn,²⁷ and can occur with heightened nociceptive processing. In the periphery, neurogenic inflammation may promote vascular permeability and cause vasodilation of blood vessels, producing a flare response.

Animal model studies on thrust manipulation reported changes in muscle spindle activation, nociceptive excitability, and immunologic response, while animal model studies on massage resulted in changes in autonomic and circulatory functions, lymphatic and immune functions, and gene expression, among other findings.³⁹ Importantly, Skyba et al⁴⁰ demonstrated that joint-biased manual therapy likely induces analgesia via non-opioidergic inhibitory pathways. Clinically, this may be critical

as the physical therapist may use multimodal approaches where interventions are chosen to facilitate different inhibitory mechanisms, such as manual therapy (non-opioidergic) and TENS (opioidergic).⁴¹

In human studies, the effects of joint manual therapy have often been dichotomized into thrust versus non-thrust techniques and spinal versus peripheral joint application, however the delineation may be artificial, as similar neurophysiological effects have been found in studies from each category. A finding seemingly specific to thrust manipulation was reported in a review by Gyer et al,⁴² suggesting that spinal thrust manipulation alters the myotatic stretch reflex properties in a segmental manner (ie, localized to the spinal segment) potentially reducing spasm and pain, and as a consequence, improving pain-free motion at that spinal segment. The myotatic reflex can be modulated by central input so these effects may not be solely due to high-velocity stretch of muscle tissues around the joint. Gyer et al⁴² theorized that stretch of joint or local muscle tissues would mediate the positive effects that occurred with thrust techniques via spinal mechanisms and that these effects would be specific to the site of application (or segmental level) rather than a generalized systemic effect.

Mechanisms of Joint-biased Manual Therapy Induced Analgesia

It has recently been suggested that physical therapists should employ a ‘pain-mechanisms’ approach to pain management, however, the myriad of altered neurophysiological mechanisms that may occur in acute and chronic pain can make this challenging. Studies on manual therapy have focused on specific

Table 2. Physical Therapy Interventions for Chronic Pain and Targeted Neurophysiologic Mechanisms

Physical Therapy Intervention	Neurophysiologic Mechanism
Manual interventions	
Joint-biased manual therapy	Decreases central sensitization
Soft tissue-biased manual therapy	Promotes descending inhibition of pain
Nerve-biased manual therapy	Unclear
Active interventions	
Promote quality sleep	Disturbed sleep can result in impaired pain inhibition
Aerobic exercise	Promotes descending inhibition of pain
Isometric exercise	Systemic and local inhibitory mechanisms
Educational – cognitive interventions	
Pain science education	Diminishes psychological (top down) drivers of pain
Graded approach to increased functional activity	Promotes pain relief and well-being without triggering inflammatory flare thought to occur via neurogenic inflammation
TENS	Promotes descending inhibition of pain
Noxious electrical stimulation	Promotes descending inhibition of pain