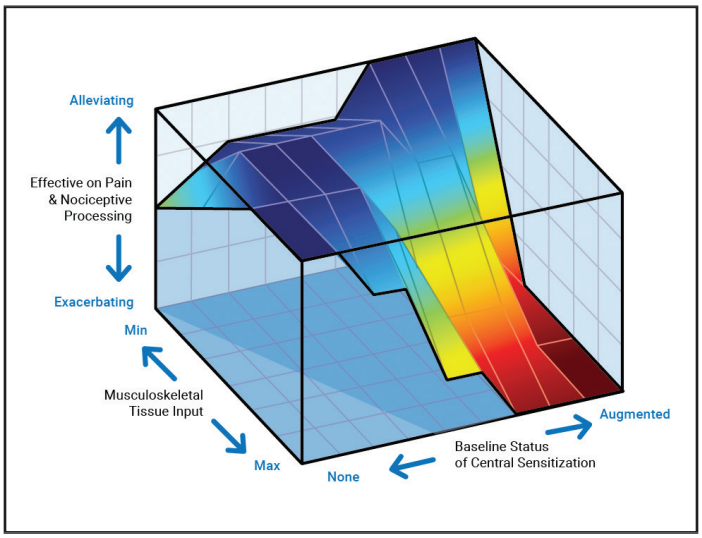
magnitude of conditioned pain modulation,[29-31] however, this notion has been questioned in a meta-analysis.[32] The capacity to inhibit pain is clearly dynamic in nature. Geva et al[33] found that facilitated anti-nociceptive processing was attenuated in situations of acute severe psychological stress, while Assa et al[29] 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]

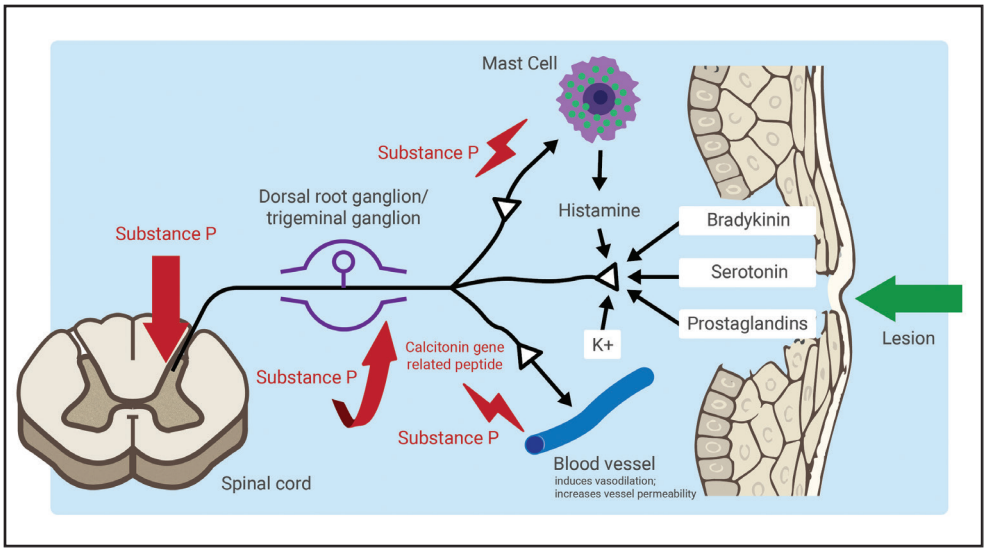
Figure 2. Potential Neurophysiological Effects of Manual Therapy Considering Baseline Nociplasticity[a]



[a]Illustration by Kinstler Design

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 3. Neurogenic Inflammation[a]



[a]Illustration by Kinstler Design

MECHANISMS OF MANUAL THERAPY INDUCED ANALGESIA

A model describing the neural structures activated by manual therapy interventions has been proposed[37] 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 al[39] 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 al[40] 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 al[42] 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