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Unraveling the Mechanisms of Manual Therapy: Modeling an Approach

Manual therapy (MT) interventions are a preferred treatment for both health care professionals from a variety of disciplines[14,36,77,82] and patients with musculoskeletal pain conditions.[2,12,53,70] Despite the popularity of MT, systematic reviews only find small to modest effect sizes[43,73] or fail to recommend these interventions.[39,68] In fact, individual clinical practice guidelines for low back pain include differing recommendations for the use of spinal manipulation, indicating conflicting research support.[60] Such findings are not dissimilar to those for other interventions for pain and are attributed to substantial individual variability in treatment response.[32] Subsequently, the clinical decision-making process that guides the use of MT may be best directed at the individual patient on the provider level, rather than using a "one-size-fits-all" approach.[32]

Mechanistic-based approaches to treating individuals presenting with musculoskeletal pain conditions represent a rational targeted approach for personalizing treatment.[26,32,45] There are 2 prerequisites needed to properly implement this approach: first, a mechanism contributing to a clinical population or subpopulation (ie, a homogeneous subgroup) must be identified; second, the biological effects of a treatment should be established. When these 2 prerequisites are met, patients can be matched to an appropriate treatment, allowing for the targeted application of a specific intervention of known mechanisms to patients with presentations amenable to these mechanisms.[15,45] Mechanistic-based treatment approaches for MT necessitate identification of the key mechanisms through which MT works; however, the current understanding of these mechanisms is lacking, requiring additional and more optimally designed studies to answer this important question.

SYNOPSIS: Manual therapy interventions are popular among individual health care providers and their patients; however, systematic reviews do not strongly support their effectiveness. Small treatment effect sizes of manual therapy interventions may result from a "one-size-fits-all" approach to treatment. Mechanistic-based treatment approaches to manual therapy offer an intriguing alternative for identifying patients likely to respond to manual therapy. However, the current lack of knowledge of the mechanisms through which manual therapy interventions inhibit pain limits such an approach. The nature of manual therapy interventions further confounds such an approach, as the related mechanisms are likely a complex interaction of factors related to the patient, the provider, and the environment in which the intervention occurs. Therefore, a model to guide both study design and the interpretation of findings is necessary. We have previously proposed a model suggesting that the mechanical force from a manual therapy intervention results in systemic neurophysiological responses leading to pain inhibition. In this clinical commentary, we provide a narrative appraisal of the model and recommendations to advance the study of manual therapy mechanisms. *J Orthop Sports Phys Ther 2018;48(1):8-18. doi:10.2519/jospt.2018.7476*

KEY WORDS: *manipulation, mobilization, neurophysiology, pain, theory*

The Need for a Model of the Mechanisms of MT

The mechanistic approach to MT is complicated by the complex nature of MT interventions. While drug effects are often attributed to a specific and well-defined active ingredient, the mechanisms underlying complex interventions, such as those used for MT, are multifaceted and comprise specific and nonspecific factors related to the intervention, the patient, the provider, and the environment in which the intervention is provided. Subsequently, a single, well-defined mechanism of an MT intervention is unlikely, and resulting outcomes are probably related to varying inherent elements and contextual factors.[13,25,74] We believe that research focusing on individual mechanisms in isolation will always fall short of providing meaningful insight, because MT is a complex intervention involving

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multiple interactions of complementary mechanisms. As with other complex interventions, MT providers and researchers benefit from a theoretical model to both guide the design and assist in interpreting the results of mechanistic studies.

We published a model to begin to account for the multiple pain inhibitory mechanisms of MT.[6] The model postulates that the mechanical stimulus from an MT intervention results in neurophysiological responses within the peripheral and central nervous systems responsible for pain inhibition (**FIGURE 1**). Importantly, the model is applicable to different MT approaches (ie, joint mobilization, massage, neurodynamic interventions) and not intended to emphasize any single or specific approach. The model was designed to comprehensively account for the interacting mechanisms behind a complex MT intervention. Importantly, the model allows researchers (1) to consider and account for competing mechanisms when designing studies (ie, mechanisms related to biomechanical effects, peripherally mediated effects, spinal cord–mediated effects, and supraspinally mediated effects), and (2) to acknowledge the potential for alternative plausible explanations to their findings should the study not account for competing mechanisms.

This clinical commentary will address the current state of the MT mechanistic literature within the context of our model, as well as highlight key areas for advancing this area of research. For the model to continue to be relevant, specific issues related to its future application are considered. Importantly, this commentary is not intended to be a systematic review or complete appraisal of the original model. Rather, the commentary highlights areas that we believe are important considerations for progressing clinical and research perspectives.

Advancing the Understanding Through Appropriate Study Design

Mechanistic studies of MT are often performed in humans, which, unlike animal models, prohibit direct observation of the

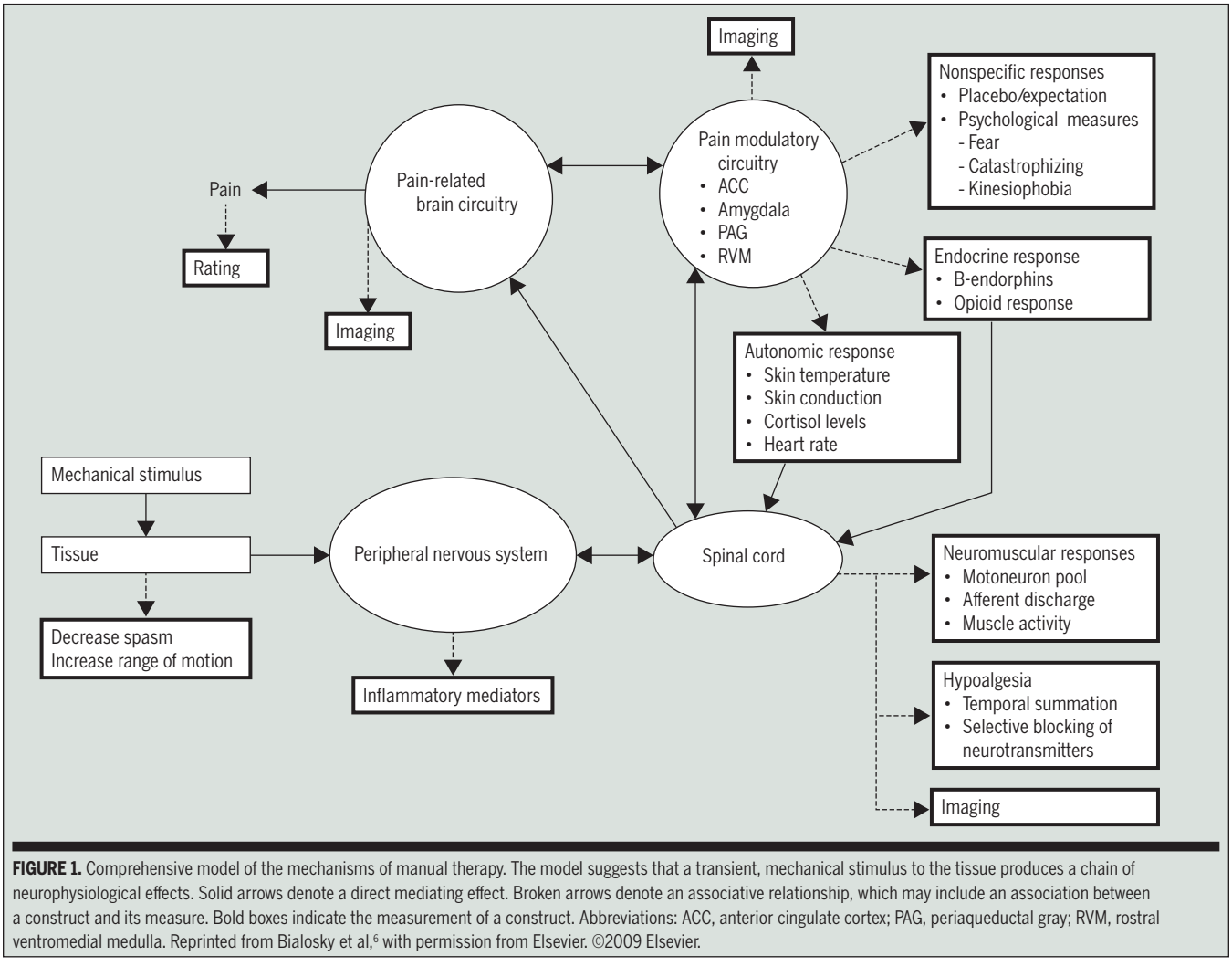

FIGURE 1. Comprehensive model of the mechanisms of manual therapy. The model suggests that a transient, mechanical stimulus to the tissue produces a chain of neurophysiological effects. Solid arrows denote a direct mediating effect. Broken arrows denote an associative relationship, which may include an association between a construct and its measure. Bold boxes indicate the measurement of a construct. Abbreviations: ACC, anterior cingulate cortex; PAG, periaqueductal gray; RVM, rostral ventromedial medulla. Reprinted from Bialosky et al,[6] with permission from Elsevier. ©2009 Elsevier.

nervous system. Our model based the assessment of nervous system responses to MT in humans on associated responses serving as behavioral correlates (ie, proxy measures) of underlying mechanisms. For example, changes in skin blood flow represent an indirect correlate of the sympathetic nervous system responses to MT,[104] while changes in the flexor withdrawal reflex may represent a spinal cord–mediated response to MT.[24] Numerous studies have provided evidence of immediate neurophysiological responses following MT; however, while serving as proof-of-concept work for more complex designs, single pre/post randomized controlled trials are not designed to determine the individual or combined influential factors of clinical improvement. Future studies must establish a link between these associated responses and clinical symptoms, as well as establish covariance of improvements between associated responses and clinical outcomes. Evaluating these multifactorial relationships requires complex study designs that are not always feasible to conduct in clinical settings. Cook[18] has highlighted the limitations of reliance on immediate assessment of either mechanistic or clinical outcomes, including similar findings in response to numerous interventions and the failure to relate these to long-term clinical outcomes. One strategy to address these concerns and to advance this line of research in future studies is to attempt to distinguish these immediate associated responses as treatment mediators and moderators. Mediators are variables measured during the course of treatment to evaluate for change and subsequent impact on outcome.[62,76] Mediators have been described as process variables that implicate possible mechanisms by which an intervention may be effective, especially when these variables represent a plausible construct that the treatment is intended to modify. Potential mediators of change establish how or why treatment effects occur and should be identified a priori and measured before, during, and after treatment to establish temporal precedence with an outcome. For example, spinal stiffness and lumbar multifidus recruitment were assessed at baseline and immediately following a spinal manipulative therapy intervention over 2 sessions, and then a week following the second session, in participants with low back pain.[38] Improvements in the Oswestry Disability Index were mediated by improved lumbar multifidus recruitment and decreases in stiffness.[38] Moderators are variables measured prior to treatment that interact with a specific intervention and influence an outcome of interest often identified in a randomized clinical trial.[62,76] For example, secondary analysis of the UK BEAM trial found that, although several baseline factors predicted overall outcome, none were predictive of response to a specific treatment (ie, spinal manipulation, exercise, or spinal manipulation followed by exercise), with only trends identified for the role of positive treatment expectations for those receiving combined treatment.[93] Identifying treatment-effect moderators provides information to establish "for whom and under what conditions" treatment is effective.[76]

Advancing the Understanding of the Mechanical Force

Clinical use of MT is traditionally driven by the assumption of a peripherally acting, mechanical mechanism,[10,33,52] for example, the application of a specific MT technique applied to a perceived dysfunctional vertebral segment identified through passive movement assessment or imaging. Our model acknowledges a mechanical force as an inherent element of any MT intervention and directs studies to account for mechanical force as a potential contributing mechanism. Based on the literature at the time, the model theorized that clinical outcomes were related to corresponding neurophysiological responses and occurred independent of the specific mechanical parameters of the force. Little has changed to support a mechanism related to the specific biomechanical parameters of the interventions since the model was originally published, and, in fact, more recent studies continue to refute a specific biomechanical mechanism. The clinical examination process for determining biomechanical dysfunction continues to be unreliable,[97] relates poorly to clinical outcomes,[85] and demonstrates a poor association with reliable and accurate mechanical measures[61] as well as with magnetic resonance imaging.[63]

Specific to clinical outcomes, significant within-group improvements are observed in response to MT interventions; however, between-group differences are not observed, confirming similar responses to techniques of varying mechanical parameters.[19,55,100] Furthermore, the clinical outcomes of MT interventions, whether based on clinical presentation or random allocation, are similar.[31,59] Collectively, this body of literature continues to support our initial assertion against an isolated and specific mechanical mechanism accounting for clinical outcomes in response to complex MT interventions.[6] Despite this evidence to the contrary, the clinical approach to MT based on a theorized specific biomechanical mechanism persists.[1,29,30,42,95] We believe that this perpetuation of dated modes of action for MT is both unsubstantiated and counterproductive.

Advancing the Understanding of MT-Related Pain Inhibition

Our model was designed to account for the mechanism of MT on pain inhibition.[6] Psychophysical testing, such as the application of standardized noxious thermal or mechanical forces, allows for the study of mechanisms related to changes in pain processing. Systematic reviews support a transient pain inhibitory effect of MT[21,40,69] on psychophysical measures, occurring both locally and remotely. Higher pain sensitivity, as determined by a lower pain threshold at the site of injury or pain, may reflect local sensitization in the peripheral (reduced receptor threshold) or central nervous system (specific somatosensory

regions), while higher pain sensitivity at sites distant from the site of injury may reflect more general sensitization of the central nervous system. Changes in pain sensitivity are observed in response to MT both at the site of application and at distal sites, indicating the presence of a central mediating effect.[22,64,81] The approach of such studies is often limited to assessment of static measures of mechanical and thermal pain thresholds, providing little insight into individual pain modulation capacity.

Psychophysical testing protocols allow for the assessment of in vivo pain modulatory capacities and profiling of individuals based on response to nociceptive input. For example, conditioned pain modulation is characterized by a reduction of pain sensitivity at one site in response to nociceptive input at another site and reflects descending inhibition of pain through the spino-bulbar-spinal loop, representing a pain inhibitory process.[78,101] Temporal summation, characterized by an increase in pain sensitivity in response to repeated noxious stimulation, represents increased dorsal horn excitability[27,47] and reflects a pain facilitatory process.[45,102] Dynamic psychophysical testing allows for profiling of individuals. For example, those with augmented temporal summation or inefficient conditioned pain modulation are considered at risk for developing a pain condition, experiencing greater pain severity when a pain condition develops, and progressing from acute pain to chronic pain.[102] Conversely, those with blunted temporal summation or augmented conditioned pain modulation may be less likely to develop a pain condition, experience less pain severity when a pain condition develops, and be less likely to progress from acute to chronic pain.[102] Subsequently, pain modulatory profiles may be useful in identifying more homogeneous groups of patients.

Pain modulatory capacities are responsive to MT. For example, we have shown that temporal summation of heat pain is reduced immediately after the application of spinal manipulative therapy, and that these reductions are greater than those following exercise or carefully constructed sham interventions.[7-9,11] Improved pain modulatory capacity, as observed through changes in conditioned pain modulation, has been found to correspond to joint mobilization to the knee in participants with knee osteoarthritis.[23] Subsequently, favorable changes in pain modulatory capacity represent a potential biological effect of MT, possibly informing mechanistic-based treatment approaches. Such approaches have been undertaken in drug trials. For example, duloxetine, a drug that enhances descending inhibition of pain, is more effective in individuals who demonstrate diminished conditioned pain modulation.[103] Furthermore, ketamine, which inhibits temporal summation, is more effective for individuals presenting with heightened temporal summation.[46] A similar approach has not been adequately considered in the field of MT, necessitating further study and a future direction of studies of pain inhibition in response to MT.

Movement-evoked pain offers an alternative pain modulatory measure that should be considered in future mechanistic-focused MT studies. Movement-evoked pain often has a greater association with physical function decline and decreased quality of life than does resting/spontaneous pain.[87,89] For example, pain in response to a repeated lifting task accounted for significant and unique variance in disability beyond a measure of spontaneous pain in participants with whiplash-associated disorder.[66] Differences in magnitude and influence of pain types suggest that different mechanisms and MT effects may also differ between spontaneous and movement-evoked pain. Considering movement-evoked pain may better characterize the pain-relieving properties of interventions providing episodic relief. The literature on transcutaneous electrical nerve stimulation has incorporated paradigms that determine differential pain-relieving effects on movement-evoked pain.[83,94] Movement-evoked pain lessens following an MT intervention,[4,56,57] which suggests that future investigation should differentiate these findings from spontaneous pain, in terms of the magnitude of response as well as the relationship to clinical outcomes of importance to patients.

Advancing the Understanding of Supraspinally Mediated Mechanisms

Previous mechanistic models of MT incorporating nervous system responses took a "reflexive" route, meaning that neurological responses to MT were limited to physiologic or autonomic outputs.[75] Our model acknowledged such processes but advanced the pathway into regions of the nervous system not typically considered as having a "direct" response to MT. The timing of this focus was vital, because when the model was first proposed, limited evidence from human and animal research supported the assumption of MT altering sensory processing in supraspinal structures.[48,65,84]

The understanding of supraspinally mediated mechanisms of MT has progressed greatly since the model was originally published, including studies of MT-associated measures of cortical function through somatosensory-evoked potentials,[48,49] as well as neuroimaging advances through positron emission tomography[72] and functional magnetic resonance imaging (fMRI). Findings from these approaches have significantly advanced the understanding of MT-related changes in cortical function. For example, fMRI has been used to study the effects of MT in several complementary ways. First, fMRI has been used to investigate cortical responses during MT. For example, during the posterior-to-anterior mechanical force produced by MT, activation is observed in medial parts of the postcentral gyrus (S1) bilaterally, the secondary somatosensory cortex (S2), posterior parts of the insular cortex, different

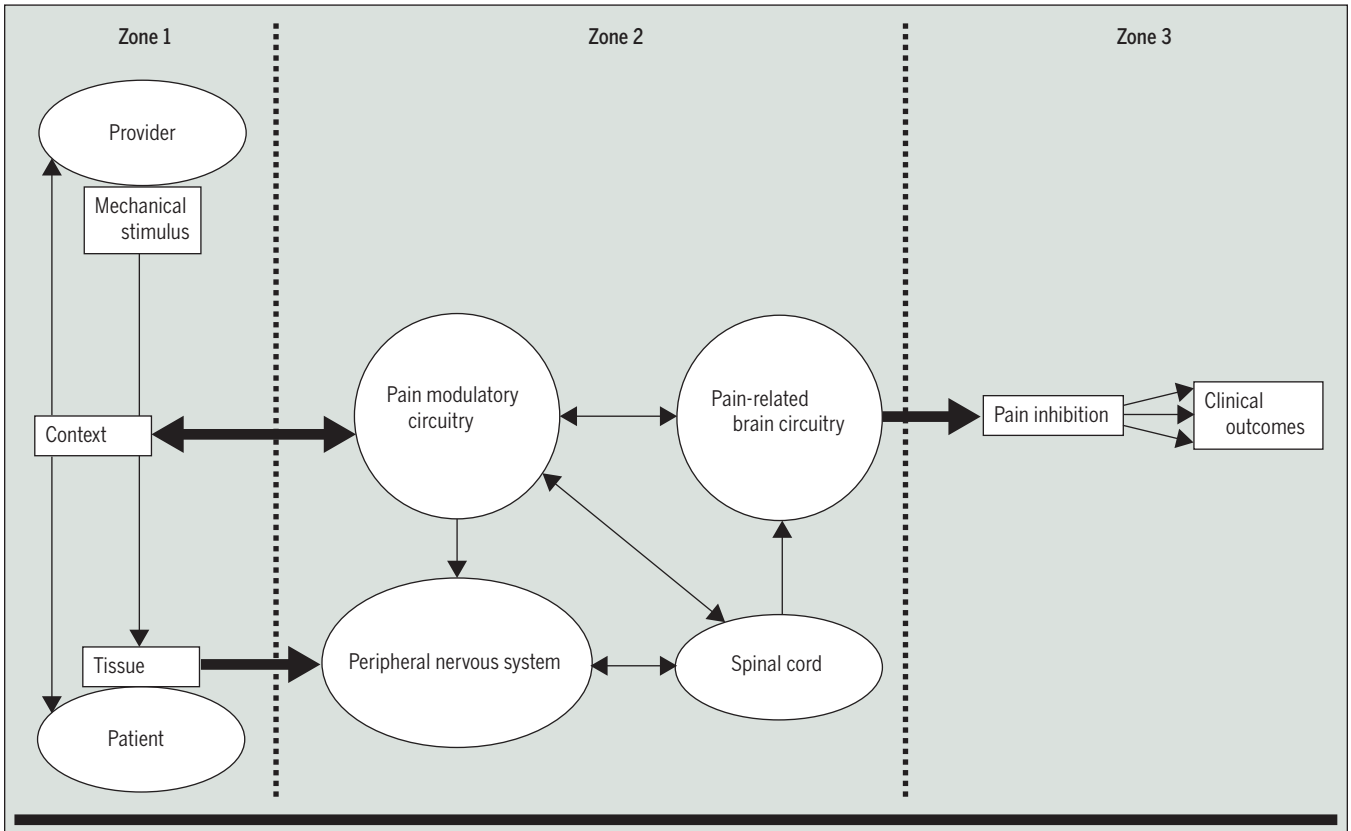

FIGURE 2. Updated comprehensive model of the mechanisms of manual therapy. The model suggests that a transient, mechanical stimulus to the tissue produces a chain of neurophysiological effects. Zone 1 represents the mechanical stimulus from the provider to the tissue, as well as the interaction between the patient and provider. Zone 2 represents potential nervous system responses to the mechanical stimulus, as well as the patient-provider interaction. Zone 3 represents the potential outcomes.

parts of the cingulate cortex, and the cerebellum.[67] Second, fMRI has been used to assess how MT alters the central nervous system responses to a noxious stimulus. For example, healthy volunteers underwent fMRI scanning while receiving noxious stimuli applied to the cuticle of the index finger. Participants then received a supine thrust manipulation directed to the mid thoracic spine and were immediately returned to the scanner for reimaging with a second delivery of noxious stimuli. The thrust joint manipulation was associated with hypoalgesia, as well as a significant reduction in activity in the sensory-motor cortices S1, S2, anterior cingulate cortex, cerebellum, and insular cortices, with reduction of cortical activity correlated to decreased pain perception.[86] Third, resting-state fMRI assessed the coupling of cortical activity between brain regions involved in the processing of nociception before and after MT. Healthy volunteers, who completed an exercise-injury protocol to induce low back pain, underwent resting-state fMRI. They were then randomized into 1 of 3 MT interventions: spinal thrust manipulation, spinal nonthrust mobilization, or therapeutic touch, and then underwent a second resting-state fMRI. Following MT, there was a reduction in experimentally induced low back pain, with no differences observed between types of MT. Common to all MT interventions, the coupling of cortical activity decreased between sensory discriminant and affective regions (primary somatosensory cortex and posterior insular cortex), while increases were observed between affective regions (posterior cingulate and anterior insular cortices) and affective and descending pain modulatory regions (insular cortex and periaqueductal gray).[41] The results of this study suggest that MT alters cortical interactions within nociceptive processing networks at rest, such that subsequent stimuli are received within the cortex in an altered state. Future studies should attempt to further clarify how MT disrupts maladaptive cortical patterns and functional connectivity associated with chronic pain.

Limitations

Methodological approaches to measurement are one of the primary limitations to the study of MT mechanisms, as many techniques described in the model to evaluate nervous system processing are not direct or are isolated measures of nervous system activity. The model is based on associated neurophysiological responses and not direct observation of nervous system activity. Subsequently,

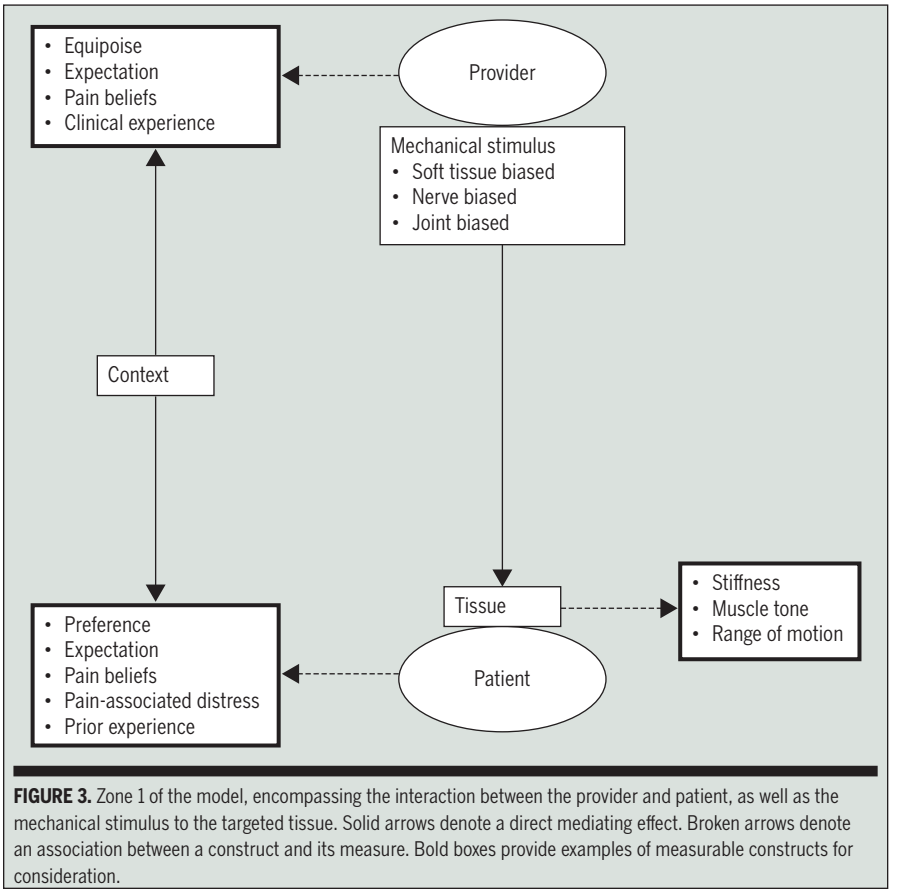

FIGURE 3. Zone 1 of the model, encompassing the interaction between the provider and patient, as well as the mechanical stimulus to the targeted tissue. Solid arrows denote a direct mediating effect. Broken arrows denote an association between a construct and its measure. Bold boxes provide examples of measurable constructs for consideration.

the observed responses are suggestive of specific nervous system activity (generally based on findings from animal studies); however, these assumptions are not directly confirmable in humans, as conducting such studies would introduce valid ethical concerns. The model considers associated neurophysiological responses and attempts to provide direct relationships to clinical outcomes. Importantly, neurophysiological responses to MT are beneficial in furthering our understanding of why MT is effective; however, the gold standard for determining whether MT is effective is patient self-report.[80] The model can be used to guide and account for nervous system responses to MT as a plausible explanation for observed clinical outcomes; however, neurophysiological responses must be linked to patient self-report outcomes and should not be interpreted as a replacement for determining clinically effective interventions.

Advancing the Model

We have modified the model since its initial development to represent some of the key changes in understanding MT mechanisms. For simplicity, we present the revised model in its entirety (**FIGURE 2**) and by individual zones, with zone 1 (**FIGURE 3**) representing the provider, mechanical force, and targeted tissue; zone 2 (**FIGURE 4**) representing patient nervous system responses; and zone 3 (**FIGURE 5**) representing clinical outcomes. The personal attributes of the MT provider (ie, the clinician) comprise one element omitted from the original model. Clinical equipoise is the lack of a preference for an intervention. Equipoise is desirable in clinical trials to avoid bias[20]; however, a lack of equipoise may be desirable in practice, as provider preferences for an intervention have been associated with clinical outcomes. For example, a study comparing the use of spinal thrust manipulation to nonthrust mobilization for participants with low back pain observed no group-dependent differences in pain, disability, total visits, days in care, or rate of recovery; however, a significant association was observed between the treating therapist's lack of equipoise (ie, preference for thrust versus nonthrust mobilization) and subsequent outcomes.[19] Moreover, provider expectations can also influence patient outcomes. For example, baseline physician expectations are predictive of changes in pain and physical function in response to acupuncture in individuals with chronic pain[99] and in return to work following an acute episode of low back pain.[58] Furthermore, pain relief in response to a placebo intervention was significantly greater for a group of individuals following third molar surgery when the provider was aware of the chance of administering an active medication, as compared to when the provider knew that no active drug would be administered.[44] Collectively, provider preference and expectations have strong potential to influence MT outcomes; therefore, we have revised the model to account for both the potential role of provider characteristics in the mechanical force, as well as the potential influence on patient-reported outcomes through a supraspinally mediated effect.

Finally, the model was designed to account for the mechanisms of MT in pain inhibition. However, complete reliance on this aspect of MT may result in limited conclusions and failure to acknowledge overall clinical effectiveness, which is yet another multifactorial construct. More recently, reliance on the sensory aspect of pain as a primary outcome has been discouraged in the case of chronic pain conditions.[90] Core outcome domains for pain have been suggested, including factors such as physical function, emotional function, sleep, and satisfaction with treatment.[91,92] Patients seeking physical therapy care attach importance to improvement in constructs

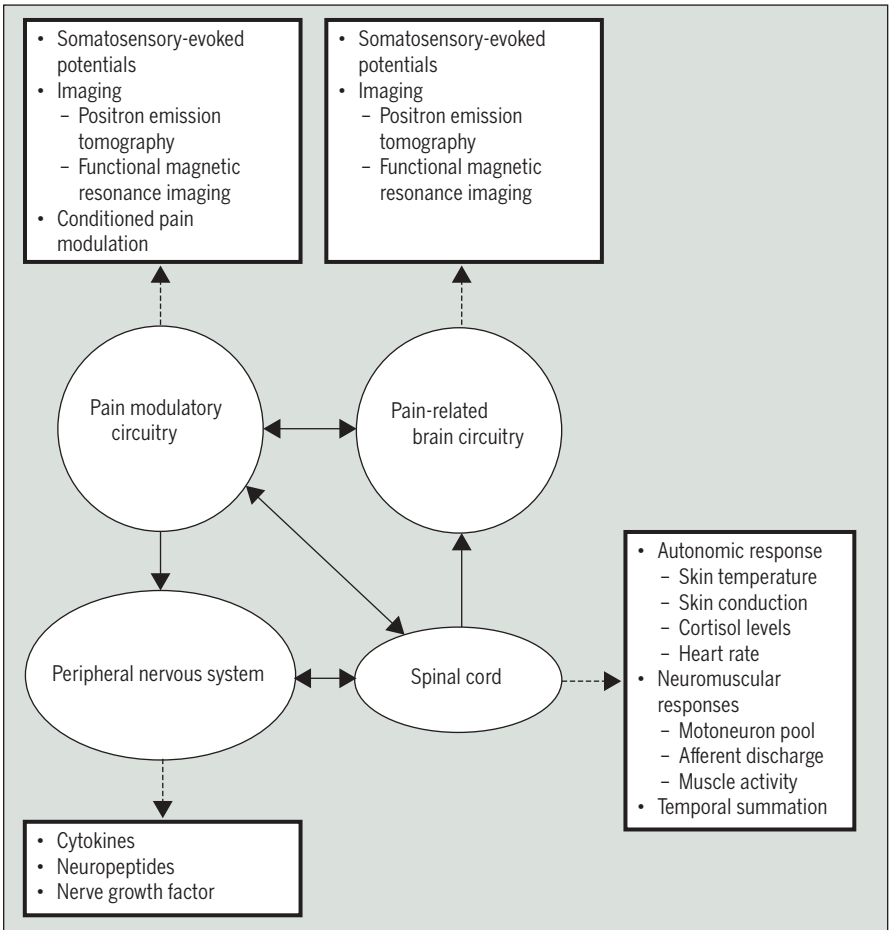

FIGURE 4. Zone 2 of the model, encompassing the nervous system response of the patient to receiving a manual therapy intervention. Solid arrows denote a direct mediating effect. Broken arrows denote an association between a construct and its measure. Bold boxes provide examples of measurable associated responses suggestive of a direct nervous system response.

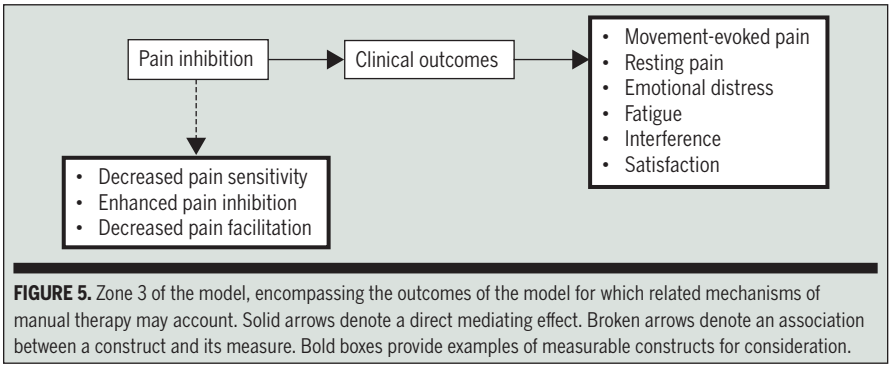

FIGURE 5. Zone 3 of the model, encompassing the outcomes of the model for which related mechanisms of manual therapy may account. Solid arrows denote a direct mediating effect. Broken arrows denote an association between a construct and its measure. Bold boxes provide examples of measurable constructs for consideration.

beyond the sensory aspect of pain,[105] and MT is effective in altering outcomes beyond the sensory aspect of pain.[53,98] We believe that a continued emphasis of the model of the mechanisms of MT in pain inhibition is warranted, because (1) other domains are not mechanistic, precluding a similar approach to study; and (2) pain inhibition is an important precursor to the other domains. However, mechanistic studies should be designed to link MT-related pain inhibition to core outcome domains that are valued from a patient perspective.

CONCLUSION

The implementation of effective MT depends on many factors, including a thorough understanding of the underlying multifactorial mechanisms through which these interventions exert their effectiveness. Determining the mechanisms of MT would both strengthen the best available research and enhance clinical practice through a personalized treatment approach, perhaps resulting in better agreement between clinical judgment, patient preferences, and the available literature. Clinical prediction rules are one approach to stratification initially embraced by MT providers and researchers. Many clinical prediction rules purported to identify key signs and symptoms suggestive of patients with musculoskeletal pain who are likely to benefit from MT.[3,16,28,34,37,54,71,79,96] Despite the initial enthusiasm, the methodology of these approaches has been questioned and cautious interpretation recommended, as initial results may represent spurious findings or a generally favorable prognosis rather than one specific to the effects of MT.[5,51,88] Furthermore, derivation studies require validation, and the vast majority of derived clinical prediction rules lack additional study or have failed attempted validation studies.[17,35,50] While a noble effort, the current state of clinical prediction rules suggests that this approach may not be optimal for identifying MT responders. Subsequently, a different approach is necessary, and mechanistic-based approaches may provide a more robust method.

Study of the mechanisms of MT is made difficult by the complex nature of these interventions, resulting in the interaction of multiple complementary mechanisms. We have published a model that served as the basis for studies to further our understanding of aspects of modulation of pain sensitivity, as well as to guide studies of supraspinal effects of

MT. Recent work suggests limitations to the original model that can be improved by the inclusion of provider factors, the inclusion of movement-evoked pain, and linking findings to a broader spectrum of pain-related outcome domains. Moving forward, we believe that the traditional emphasis on solely biomechanical mechanisms of MT is misguided in focus and limited in scope. Subsequent efforts should focus on a broader understanding of how MT alters processing of nociception to impact the entire pain experience. Specifically, greater consideration of pain modulatory capacity, as determined by dynamic measures of psychophysical testing, consideration of neurophysiological responses to MT, and studies better designed to account for potential mediators and moderators of treatment outcomes will better inform knowledge of this important topic. ◉

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