MECHANISMS OF MANUAL THERAPY

By

JOEL ERIC BIALOSKY

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To Laurie, Justin, and Walter whose lives were turned upside down so that I could pursue my Ph.D. You not only supported this endeavor, but also served as an inspiration for me to succeed. This would not have been possible without your love and encouragement during these past four years. What an adventure it has been. I loved sharing it with you and look forward to our next adventure.

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LIST OF ABBREVIATIONS

ACC	Anterior cingular cortex
ASI	Anxiety sensitivity index
CAM	Complimentary and alternative medicine
CSI	Combined sensory index
CSQ-R	Coping strategies questionnaire revised
CTS	Carpal tunnel syndrome
DASH	Disability of arm, shoulder, and hand questionnaire
EMG	Electromyographic
FPQ	Fear of pain questionnaire
H- Reflex	Hoffman reflex
LBP	Low back pain
MRI	Magnetic resonance imaging
MT	Manual therapy
MVAS	Mechanical visual analog scale
NCS	Nerve conduction study
NDI	Neurodynamic intervention
NIH	National Institutes of Health
NRS	Numerical rating scale
PAG	Periaquaductal gray
PASS	Pain anxiety sensitivity scale
PCOQ	Patient centered outcome questionnaire
PCS	Pain catastrophizing scale
QST	Quantitative sensory testing
ROM	Range of motion

RVM	Rostral ventromedial medulla
STAI	State trait anxiety inventory
TSK	Tampa scale for kinesiophobia
ULTT	Upper limb tension test
VAS	Visual analog scale

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Joel Eric Bialosky

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Musculoskeletal pain is a common complaint requring billions of dollars in medical care and lost work time. Manual therapy (MT) is an effective form of treatment for musculoskeletal pain; however, the mechanisms though which MT works are undetermined.

Biomechanical and neurophysiological effects are associated with MT and are suggested as potentially pertinent mechanisms. A shortcoming of the literature is that studies have considered individual mechanisms without thought to the potential collaboration between mechanisms. We present a model for the mechanistic study of MT to provide a framework for the design of future studies and allow better interpretation of past studies. Additionally, we present the results of 3 pilot studies and a dissertation study which have assessed components of the model.

The three pilot studies explored potential mechanisms of a MT force applied to the low back of both healthy participants and those experiencing low back pain. In the first two studies, we observed c- fiber mediated hypoalgesia to standard thermal stimuli which was attributed to a spinal cord mediated effect of MT. As indicated by the model, a shortcoming of these studies was the failure to account for potential supraspinal mediated mechanisms. Subsequently, we manipulated participant expectation for experimental pain in the third study and observed a significant hyperalgesic effect of MT in individuals whose expectations were altered to expect

greater pain. The findings of the three pilot studies suggest a consistent c- fiber mediated effect of MT at the dorsal horn of the spinal cord with the potential for a supraspinal effect (expectation) to further influence outcomes.

Our dissertation study explored potential mechanisms of a specific MT technique to the upper extremity of individuals experiencing carpal tunnel syndrome (CTS). Participants were randomly assigned to receive a direct MT technique known to stress the median nerve or an indirect technique designed to minimize stress to the median nerve and underwent up to six sessions of MT over three weeks. Group differences were not observed in expectation for pain in response to treatment or in perception of which technique was received suggesting the indirect MT technique provides similar expectation and believability as the direct MT. Group differences were present in experimental pain perception with changes in c- fiber mediated pain observed in participants receiving the direct MT technique but not the indirect MT technique. An immediate hypoalgesic effect was observed in clinical pain in response to the MT which was independent of group assignment. Neither group dependent changes nor main treatment effects in clinical pain were reported over the 3 week period of the study. A small improvement in function was observed over the 3 week period of the study independent of group assignment. While controlling for baseline pain, both baseline immediate clinical pain hypoalgesic response to MT and baseline expectation for pain following the study were predictive of pain at the completion of the study.

We present a model for the mechanistic study of MT along with 4 studies which have been guided by the model and assess specific parts of the model.

CHAPTER 1
INTRODUCTION

Musculoskeletal pain is a common complaint. For example, greater than two percent of physician's visits in the United States are due to low back pain (Deyo et al., 2006). Additionally, prevalence rates of up to twenty- six percent for low back pain,(Deyo et al., 2006;Strine & Hootman, 2007) fourteen percent for neck pain,(Deyo et al., 2006;Strine & Hootman, 2007) and fifty- two percent for upper extremity pain have been reported (Walker-Bone et al., 2004).

The financial burden of musculoskeletal pain is substantial. The cost of medical care for musculoskeletal pain was estimated at 193 billion dollars in 1996 (Yelin et al., 2001) and loss of work production has been estimated at 61 billion dollars (Stewart et al., 2003). Specific to low back pain, loss of production has been estimated at 7.4 billion dollars in workers in the United States between the ages of forty and sixty- five (Ricci et al., 2006). The prevalence and cost of musculoskeletal pain suggest a significant public health problem. Subsequently, treatments effective in the resolution of musculoskeletal pain are desirable.

Manual therapy (MT) is a complimentary and alternative medicine (CAM), classified by the National Institutes of Health (NIH) under manipulative and body based practice. MT is a general term encompassing numerous techniques which are similar in the application of a force to given structures of the body. Generally, MT may be categorized into techniques directed at the joints (mobilization and manipulation), the soft tissue (massage), or the nerves (neural dynamic interventions). MT is effective in the treatment of musculoskeletal disorders including low back pain (Childs et al., 2004;Cleland et al., 2006b;Cleland et al., 2006a;Licciardone et al., 2003), carpal tunnel syndrome(Akalin et al., 2002;Rozmaryn et al., 1998), knee osteoarthritis(Deyle et al., 2000), and hip osteoarthritis (MacDonald et al., 2006). Furthermore, individuals with musculoskeletal pain are seeking complimentary and alternative treatments such

as MT at an increasing rate. For example, a survey from 2002 estimated that sixty- two percent of adults used a form of CAM over the previous year (Barnes et al., 2004). Despite the apparent clinical effectiveness and increasing usage, the mechanisms through which MT works are not established. The purposes of this manuscript are to first, review the current literature regarding the potential mechanisms behind MT. Second, present a model to guide future studies of MT. Finally, present the findings of three prior studies and the current dissertation study which have focused on specific aspects of the model to assess the potential mechanisms of MT.

CHAPTER 2
LITERATURE REVIEW OF MECHANISMS OF MANUAL THERAPY

MT likely works through biomechanical and/or neurophysiological mechanisms. A biomechanical mechanism is suggested by common clinical practice in which evaluation techniques are directed at locating mal- aligned or hypo mobile tissue or joints followed by the application of MT to reposition or restore mobility. Neurophysiological mechanisms include changes in the nervous system which are associated with MT and have a potential role in the clinical outcomes. .

Biomechanical Mechanisms

Biomechanical effects are associated with MT as force and movement have been quantified with these techniques (Colloca et al., 2006;Coppieters & Butler, 2007;Coppieters & Alshami, 2007;Gal et al., 1997) Despite the empirical and clinical support of a biomechanical mechanism, the implications for clinical outcomes are questionable. A biomechanical mechanism implies a specific dysfunction requiring MT is identified and treated using a precisely applied technique to produce a lasting change in the biomechanical properties of the target site. While movement accompanies MT (Colloca et al., 2006;Coppieters & Butler, 2007;Coppieters & Alshami, 2007;Gal et al., 1997), the literature does not support a sole biomechanical mechanism of action. First, biomechanical assessment is not reliable. Palpation for positional faults and hypomobility has demonstrated poor reliability (Seffinger et al., 2004;Troyanovich et al., 1998) and this suggests an inability to accurately determine a specific location requiring MT. Second, MT interventions lack precision as techniques are not specific to a given location (Herzog et al., 2001;Kleinrensink et al., 2000;Ross et al., 2004) and different kinetic parameters are observed between clinicians in the performance of the same technique (Hessell et al., 1990;Ngan et al., 2005). Finally, only transient biomechanical effects are

supported by studies which quantify motion and not a lasting positional change (Hsieh et al., 2002;Tullberg et al., 1998). *The clinical effectiveness of MT despite the inconsistencies in the biomechanical evaluation and application suggests other mechanisms may be more influential.*

Neurophysiological Mechanisms

The musculoskeletal pain experience includes complex interactions of both the peripheral and central nervous system. Neurophysiological effects are associated with MT and suggest a mechanism of action originating from specific points of the nervous system. We will categorize neurophysiological mechanisms as those likely originating from a peripheral mechanism, spinal cord mechanisms, and/or supraspinal mechanisms.

Peripheral Mechanisms

MT has been suggested to exert an effect on the peripheral nervous system. For example, (Teodorczyk-Injeyan et al., 2006) observed a significant reduction of blood level cytokines in individuals receiving MT which was not observed in those receiving sham MT or in a control group. Additionally, changes of blood levels of β-endorphin, anandamide, N-palmitoylethanolamide, serotonin, (Degenhardt et al., 2007) and endogenous cannabinoids (McPartland et al., 2005) have been observed following MT. Finally, soft tissue biased MT has been shown to alter acute inflammation in response to exercise (Smith et al., 1994) and substance P levels in individuals with fibromyalgia (Field et al., 2002). Collectively, these studies suggest a mechanism of action of MT on musculoskeletal pain mediated by the peripheral nervous system.

Spinal Cord Mechanisms

MT may influence musculoskeletal pain through action at the level of the spinal cord. Direct evidence for such an effect comes from a study in which MT was applied to the lower extremity of rats following capsaicin injection (Malisza et al., 2003b). A spinal cord response

was quantified by functional magnetic resonance imaging (MRI) during light touch to the hind paw following the injection. A trend was noted towards decreased activation of the dorsal horn of the spinal cord following the MT. Associated neuromuscular responses following MT provide indirect evidence for a spinal cord mediated mechanism. For example, MT is associated with changes in pain perception (George et al., 2006;Mohammadian et al., 2004;Vicenzino et al., 2001), afferent discharge (Colloca et al., 2000;Colloca et al., 2003), motoneuron pool activity (Bulbulian et al., 2002;Dishman & Burke, 2003), and muscle activity (Herzog et al., 1999;Symons et al., 2000).

Pain perception

Studies have observed an immediate decrease in pain perception (hypoalgesia) associated with MT to the lumbar spine (George et al., 2006), cervical spine (Sterling et al., 2001), thoracic spine (Mohammadian et al., 2004), and extremities (Paungmali et al., 2004;Vicenzino et al., 2001). Hypoalgesia associated with MT has been attributed to the dorsal horn of the spinal cord in two studies due to the associated finding of a lessening of temporal summation (George et al., 2006;Bialosky et al., 2008). Additionally, Skyba et al., (2003) performed MT to the knee joint of rats following capsaicin injection into the ankle joint. A hypoalgesic behavioral response was associated with MT; however, eliminated with blocking of the serotonin receptors in the spinal cord and lessened with blocking of the α2-adrenergic receptors in the spinal cord. The hypoalgesic response was not affected by blocking of the GABA receptors and opioid receptors. These findings suggest a mechanism of MT upon the neurotransmitters at the level of the spinal cord.

Afferent discharge

Increased afferent discharge of lumbar paraspinal mechanoreceptors (Pickar & Wheeler, 2001;Pickar & Kang, 2006;Sung et al., 2005) has been observed in the cat model in response to

MT type loads. Similar observations have been made in human studies. For example, a series of studies (Colloca et al., 2000;Colloca et al., 2003;Colloca et al., 2004) have recorded positive action potentials at the S1 nerve root in response to MT in anesthetized subjects undergoing spinal surgery. Subsequently, MT may stimulate afferent discharge with a corresponding lessening of pain due to modulation at the spinal cord (Pickar & Wheeler, 2001).

Motoneuron pool excitability

A lessening of the alpha motoneuron pool excitability has been associated with MT. A decrease in the Hoffman reflex (H- reflex) is associated with MT has been observed following MT in the lumbar (Bulbulian et al., 2002;Dishman & Burke, 2003) and cervical spine (Dishman & Burke, 2003) and to the lower extremity (Morelli et al., 1998;Sullivan et al., 1991) These findings suggest inhibition of the motoneuron pool and indicate a spinal cord mediated effect of MT with the potential to produce associated outcomes such as decreased pain and muscle spasm. In contrast one study has assessed motoneuron pool activity supraspinally using transcranial magnetic stimulation and measured the change in motor evoked potentials in the gastrocnemius following MT to the lumbar spine (Dishman et al., 2002). An excitatory effect on the motoneuron pool was observed and suggests central motor facilitation. The authors theorize MT may provide sensory input to the CNS which alleviates the gain in motoneuron pool excitability (Dishman et al., 2002).

Muscle activity

A reflex link exists between the lumbar joint capsule and the paraspinal musculature (Indahl et al., 1997;Solomonow et al., 1998). Specifically, paraspinal muscle activity has been elicited with stimulation of the lumbar disc (Indahl et al., 1997) and multifidus activity with stimulation of the supraspinous ligament (Solomonow et al., 1998). Additionally, saline injected into the facet joint has been shown to inhibit this response (Indahl et al., 1997). Subsequently,

MT is postulated to alter muscle activity through the stimulation of this reflex link (Indahl et al., 1997). Further support for this theory comes from studies reporting transient increases in electromyographic (EMG) activity associated with MT (Colloca & Keller, 2001;Colloca et al., 2003). The transient increases in EMG activity is then be followed by a decrease in resting EMG (DeVocht et al., 2005;Lehman et al., 2001) suggesting a possible mechanism for the clinical outcomes of decreased pain and muscle spasm. Furthermore, clinical studies have noted both a decrease in muscle inhibition (Suter et al., 1999;Suter et al., 2000) and decreased EMG activity in the superficial neck flexors (Sterling et al., 2001) suggesting MT may have a longer lasting effect on motor function. Collectively, the literature suggests both transient and lasting effects of MT on muscle activity potentially mediated through the spinal cord. Clinically, decreased pain, decreased muscle spasm, and improved motor function may result.

Supraspinal Mechanisms

Finally, MT may influence musculoskeletal pain through supraspinal structures. Direct support for a supraspinal mechanism of action of MT comes from Malisza et al., (2003a) who applied MT to the lower extremity of rats following capsaicin injection. Functional MRI of the supraspinal region quantified the response of the hind paw to light touch following the injection. A trend was noted towards decreased activation of the supraspinal regions responsible for central pain processing. Indirect support for a supraspinal mechanism comes from studies indicating a role for non- specific mechanisms such as placebo and expectation, sympathetic responses, and opioid mechanisms.

Non- specific mechanisms

Non-specific mechanisms are seemingly inert; however, may produce outcomes greater than those observed due to natural history and include potential mechanisms such as placebo, expectation, and psychological constructs such as fear and catastrophizing. For this manuscript,

we categorize non- specific mechanisms as neurophysiological effects related to associated changes in the opioid system (Sauro & Greenberg, 2005), dopamine production (Fuente-Fernandez et al., 2006), and central nervous system (Matre et al., 2006;Petrovic et al., 2002;Wager et al., 2004) which have been observed in studies unrelated to MT. Non- specific mechanisms have a postulated involvement in the clinical effectiveness of MT (Ernst, 2000;Kaptchuk, 2002). For example, (Kalauokalani et al., 2001) reports on a secondary analysis of participants with low back pain randomized to receive either acupuncture or MT. Subjects with higher expectations for their assigned treatments demonstrated significantly greater improvement in function. Additionally, a recent systematic review of the literature has noted that MT is associated with improved psychological outomes (Williams et al., 2007).

Sympathetic response

An increase in sympathetic activity has been associated with MT (Moulson & Watson, 2006;Sterling et al., 2001;Vicenzino et al., 1998) and suggests a potential supraspinal mechanism of action. For example, clinical studies report an association between MT and changes in skin temperature, skin conduction (Sterling et al., 2001;Vicenzino et al., 1998), and local blood flow (Vicenzino et al., 1998). Cortisol levels have been measured following MT as an indicator of stress and sympathetic function and do not appear to increase (Christian et al., 1988;Whelan et al., 2002). In fact some evidence suggests a decrease following MT (Ouchi et al., 2006). Collectively, the literature suggests a sympathetic effect of MT; however, the direction of such an effect may vary.

Opioid response

Opioids have a potent analgesic effect and may work centrally or peripherally. Studies of (Vernon et al., 1986;Kaada & Torsteinbo, 1989) suggest an increase in β- endorphin levels following MT; however, follow up studies of have not supported this finding (Christian et al.,

1988). Additionally, the effects of MT have been found to not change following injection of the opioid antagonist, Naloxone (Paungmali et al., 2004). Subsequently, an opioid mechanism of action of MT is not currently supported by the literature.

Limitations of the Current Mechanistic Literature

A limitation of the current literature is the failure to acknowledge the potential for a combined effect of the proposed mechanisms. Biomechanical effects and multiple neurophysiological effects are associated with MT and have the potential to work together to influence clinical outcomes. Prior studies have observed individual effects associated with MT without full consideration of the potential for multiple effects or interaction of individual effects. Only recently are studies beginning to quantify biomechanical and neurophysiological effects in relationship to each other (Colloca et al., 2006;McLean et al., 2002;Sung et al., 2005;Pickar et al., 2007). For example, (McLean et al., 2002) assessed hypoalgesia, in response to varying levels of force application during MT and observed larger neurophysiological response with forces greater than 1.9 N/cm. A consideration of the potential interaction between biomechanical and multiple neurophysiological effects is lacking in many prior studies and necessitates a comprehensive model to synthesize the current literature and direct future research.

A second limitation of the current mechanistic literature is the failure to adequately account for non- specific effects of MT. Subsequently, the magnitude of non- specific effects in outcomes associated with MT is currently not known. A primary limitation in the determination of the magnitude of non- specific effects in MT is that a validated model of placebo for MT does not currently exist. The lack of a consensus has led to multiple unsubstantiated MT placebos including joint biased MT without cavitation (Hoiriis et al., 2004;Suter et al., 2005;Teodorczyk-Injeyan et al., 2006), sham laser (Preyde, 2000), and sham ultrasound (Deyle et al., 2000).

Additionally, in prior studies which have attempted to validate an MT placebo (Hawk et al., 2005;Vernon et al., 2005), a pre- requisite is an inert placebo which does not significantly affect the outcome of interest. Such requirements may be unreasonable when the magnitude of the placebo effect on pain in other studies is considered (Price et al., 1999;Vase et al., 2003). Subsequently, an adequate model of placebo for MT is lacking which produces similar expectations as "active" MT and has a known treatment effect size.

CHAPTER 3
COMPREHANSIVE MODEL OF THE MECHANISMS OF MANUAL THERAPY

Overview of Model

We propose a model as a framework for conducting research into the mechanisms of MT which provides a compilation of the existing literature as to how MT likely exerts its effects (Figure 3-1). Prior studies have focused on individual biomechanical or neurophysiological effects and the model encourages consideration of multiple mechanisms. The model suggests the effects of MT are initiated by a mechanical stimulus to a given tissue. As previously noted, the MT literature suggests a mechanical force is associated with MT; however, likely not causative of outcomes. Subsequently, the model suggests a mechanical stimulus initiates a cascade of neurophysiological responses in the periphery or in the CNS which are then responsible for clinical outcomes. Specific mechanisms within the nervous system are frequently not directly measurable in human studies. Subsequently, the mechanistic literature is based primarily upon inferences from associated responses rather than direct measurements. For example, MT is suggested to exert an effect at the periaquaductal gray (PAG) due to associated hypoalgesia and sympathetic responses (Wright, 1995) and at the dorsal horn of the spinal cord due to lessening of temporal summation (George et al., 2006). The model provides implications of specific mechanisms through the reporting of measurable associated relationships when direct measures are not possible.

As indicated in figure 3-1, MT may exert its effect at the peripheral level (as measured by associated responses such as changes in inflammatory mediators), at the spinal cord (as indicated by associated responses such as neuromuscular changes), and at the supraspinal level (as indicated by associated responses such as autonomic or endocrine changes). The model further recognizes that associated relationships may occur between neural and psychological constructs.

For example, placebo has a postulated role in the outcomes associated with MT (Astin & Ernst, 2002;Ernst, 2000). A relationship may be observed between the neural construct (pain modulatory circuitry) and a psychological construct (expectation) as measured by an associated response (measure of expectation) and suggest a non- specific supraspinal effect of MT.

Finally, Figure 3-1 clearly shows how the model addresses a specific limitation of the current literature by encouraging the consideration of multiple potential mechanisms and their potential interaction. For example, placebo studies of experimental pain have noted a conditioning response. If a painful stimulus is surreptitiously lessened immediately following the suggestion of a placebo, upon returning the stimulus to its prior intensity, a more robust hypoalgesic effect is noted (Colloca & Benedetti, 2006;Price et al., 1999). Similar events could occur following MT. Specifically, the mechanical stimulus associated with MT may produce an afferent discharge with subsequent transient hypoalgesia through a spinal cord mediated effect. The resultant hypoalgesia could then strengthen a non- specific supraspinal mediating effect (placebo) due to expectation of lessening of pain perception. The model encourages the measurement of different mediating effects so that their individual contributions to the overall mechanisms may be determined.

Limitations of Proposed Model

The model is intended to be applicable to all forms of MT. MT may be categorized into specific techniques which are theorized to affect the joints, soft tissue, or individual nerves. While the forces associated with individual techqniques may differ, the current literature does not support the specificity of biomechanical mechanism with regards to pain relief. Subsequently, the related neurophysiological responses are similar and adequately encompassed within the model given the current state of knowledge. The proposed model provides a

framework, currently lacking in the literature, to empirically test hypotheses related to different neurophysiological effects specific to types of MT.

The proposed comprehensive model is intended to guide methodology in studies specific to the mechanisms of MT on musculoskeletal pain. MT has a postulated role in the treatment of disorders of other body systems such as asthma (Balon & Mior, 2004) and high blood pressure (Plaugher & Bachman, 1993); however, those effects are beyond the scope of the current model.

Finally, the model is strictly intended to guide research questions regarding the mechanisms of MT. A body of literature already exists suggesting the effectiveness of MT (Childs et al., 2004;Deyle et al., 2000;MacDonald et al., 2006). The model is intended to compliment this line of clinical research and provide underlying explanations for the effectiveness of MT.

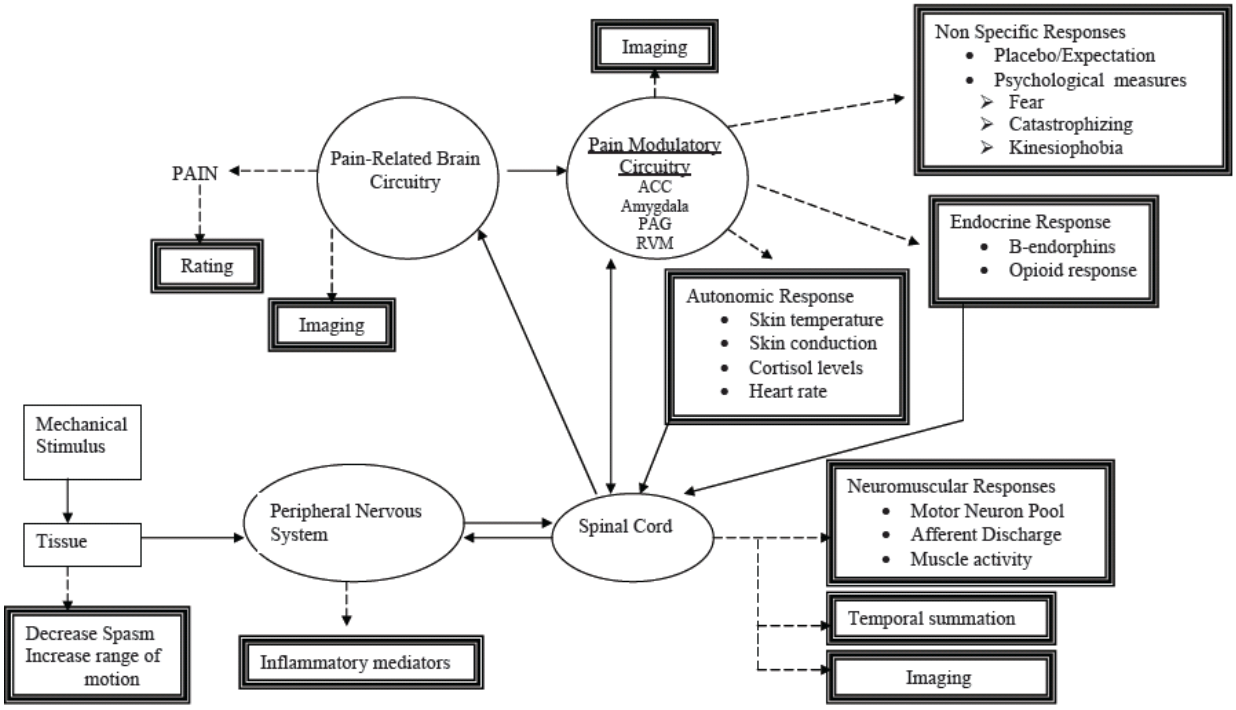


Figure 3-1. Comprehensive model for the study of the mechanisms of manual therapy. The model suggests a transient, mechanical stimulus to the tissue produces a cascade of neurophysiological effects. Solid arrows denote a direct mediating effect. Broken arrows denote an associative relationship. Bold boxes indicate the measurement of a construct. ACC = anterior cingular cortex; PAG = periaqueductal gray; RVM = rostral ventromedial medulla

CHAPTER 4
IMPLEMENTATION OF COMPREHENSIVE MODEL

The model provides a framework for mechanistic studies of MT through which researchers may clearly identify domains that have been previously studied, as well as domains that have been understudied. Perhaps most importantly, the model elucidates multiple interactions between different body systems and outlines how these factors may inhibit pain, and how these factors can be measured. Studies designed to evaluate potential mechanisms currently lacking adequate consideration or account for the complex interactions involved in pain inhibition are of future interest. We have performed three pilot studies leading up to a dissertation proposal which have tested limited domains of the model.

Pilot Study 1: Effect of MT on Experimental Pain in Healthy Participants

Our first study assessed the effect of MT on thermal pain sensitivity in pain free participants (George et al., 2006). Inclusion criteria were ages 18 to 60 years old and English speaking. Exclusion criteria were systemic medical conditions (e.g. diabetes, hypertension), psychiatric illness, pregnant women, and regular use of prescription medication for management of pain. Baseline quantitative sensory testing (QST) was performed using protocols specific to Aδ and c- fiber mediated pain perception (Price et al., 2002;Staud et al., 2001). Participants were then randomly assigned to ride a stationary bike, perform low back range of motion exercises, or receive MT. Immediately following the intervention, QST was repeated. 60 individuals agreed to participate and signed an informed consent form. Table 4-1 indicates the baseline characteristics of the groups. A group × time interactions was not observed for Aδ fiber mediated pain in the lower extremity at 47°C ($F_{(1,57)} = 2.40$, $p = 0.10$, partial $\eta^2 = 0.08$) or at 49°C ($F_{(1,57)} = 1.30$, $p = 0.27$, partial $\eta^2 = 0.05$). However, a significant treatment effect in the lower extremity at each temperature was observed (Table 4-2). A significant group × time

interaction for c- fiber mediated pain was observed in the lower extremity ($F_{(1,57)} = 3.70$, p = 0.03, partial $\eta^2 = 0.12$) (Figure 4-1). Post-hoc testing revealed that MT had a larger hypoalgesic effect in the lower extremity than riding a stationary bicycle (p = 0.04), but similar as lumbar extension exercise (p = 0.11).

Pilot Study 2: Effect of MT on Experimental Pain in Participants with Low Back Pain

The second study was identical to the first with the exception of including participants currently experiencing low back pain. These data have not yet been published. Inclusion criteria for this study consisted of currently experiencing low back pain and able to speak and understand English. Exclusion criteria included any systemic medical conditions (e.g. diabetes, hypertension), history of lumbar surgery or fracture, or psychiatric illness, and currently receiving lumbar extension exercise or spinal mobilization for treatment of low back pain. 34 individuals agreed to participate and signed an informed consent form. Baseline characteristics are displayed in table 4-3. Group differences were noted in sex distribution and in fear of pain; however, a significant correlation was not observed between fear of pain and the outcomes measures of post intervention c- fiber mediated pain (r^2= -0.13, p= 0.50), Aδ fiber mediated pain at 47° C (r^2= 0.25, p= 0.18), and at 49° C (r^2= 0.27, p= 0.14). Additionally, sex differences were not observed in c- fiber mediated pain perception ($F_{(1,29)}$= 0.03, p= 0.86, partial η^2< 0.00) or Aδ fiber mediated pain at 47° C ($F_{(1,32)}$= 0.59, p= 0.45, partial η^2= 0.02) or at 49° C ($F_{(1,32)}$< 0.01, p= 0.95, partial η^2< 0.00). Subsequently, the decision was made to use a repeated measure ANOVA model without controlling for fear or sex. A group × time interactions was not observed for Aδ fiber mediated pain in the lower extremity at 47°C ($F_{(2,31)} = 0.54$, p = 0.59, partial $\eta^2 = 0.03$) or at 49°C ($F_{(2,31)} = 0.05$, p = 0.96, partial η^2 <= 0.01). A significant treatment effect in the lower extremity at each temperature was also not observed (Table 4-4). A significant group × time interaction for c- fiber mediated pain was not observed in the lower extremity ($F_{(2,28)} = 2.40$, p =

0.11, partial $\eta^2 = 0.14$). Due to the p-value approaching 0.05 and the moderate effect size, the decision was made to perform an exploratory post- hoc analysis to see if any group difference existed in perception of c- fiber mediated pain. Post-hoc testing revealed that similar to healthy individuals, individuals with low back pain receiving MT reported a significant decrease in c-fiber mediated pain perception (mean difference 7.49 (24.23), p= 0.05) which was not observed in participants riding the stationary bike (mean difference= -3.96 (25.04), p= 0.31) or performing spinal extension exercises (mean difference= 3.81 (30.54), p= 0.40) (Figure 4-2).

Pilot Study 3: The Influence of Expectation on Hypoalgesia Following MT in Healthy Participants

A shortcoming of the design of the prior two studies was that a spinal cord mediating effect (temporal summation) was monitored indirectly via QST; however, the potential interaction with supraspinal mediating effects was not considered. Figure 4-3 depicts the model pathway of the prior two studies. Subsequently, in a follow up study, we attempted to replicate these prior findings while accounting for potential supraspinal influence and these data have been published (Bialosky et al., 2008). Sixty healthy participants signed an informed consent form and agreed to participate. Inclusion and exclusion criteria were identical to study 1. Baseline characteristics of the sample are summarized in table 4-5. Participants underwent baseline quantitative sensory testing to the low back and leg using the same protocols from the prior studies. Due to MT differentiating itself from other interventions in the effect on c- fiber mediated pain in our prior studies we chose to only analyze the effect of MT on c- fiber mediated pain perception in this study. Immediately following the baseline pain perception testing, participants were randomly assigned to receive one of three expectation instructional sets. Participants receiving a positive expectation instructional set were informed they should feel less heat pain following the application of MT. Participants receiving a negative expectation

instructional set were informed they should feel more heat pain following the application of MT. Participants receiving a neutral instructional set were informed it was not known what effect the MT would have on their pain perception. Immediately following the instructional set, all participants received MT and then underwent repeat pain perception testing. A three way interaction was not present between expectation of pain by body area and group assignment (Wilks' Lambda= 0.92, $F_{(2,53)}$= 2.47, p= 0.09, partial η^2= 0.09). A 2 x 3 ANOVA of change in expectation was significant for an interaction in the low back (Wilks' Lambda= 0.85, $F_{(2,53)}$= 4.55, p= 0.02, partial η^2 = 0.15), indicating a differential effect of the instructional set for the low back. Post hoc testing of the low back indicated a significant decrease in expected pain in the positive expectation group (mean difference +7.70, sd= 14.9, p=0.03, Cohen's d effect size= 0.52), a significant increase in expected pain in the negative expectation group (mean difference –6.98, sd= 15.30, p= 0.05, Cohen's d effect size= 0.46), and no change in the neutral expectation group (mean difference +2.18, sd= 14.91, p= 0.53, Cohen's d effect size= 0.15). A 2 x 3 ANOVA of change in expectation was not significant for the lower extremity (Wilks' Lambda= 0.95, $F_{(2,53)}$= 1.42, p= 0.25, partial η^2 = 0.05), indicating a main effect of the instructional set for the lower extremity. Pairwise comparison in the lower extremity indicated a mean increase in expected pain of 12.01 (sd= 12.14, p< 0.01, Cohen's d effect size= 0.99). The results of the instructional set on expected pain perception in the low back are depicted in Figure 4-4. A three way interaction existed suggesting change in pain perception differed by body area and group assignment (Wilks' Lambda= 0.88, F(2,53)= 3.80, p= 0.03, partial η2= 0.13). No interaction between instructional set and pain perception was noted in the lower extremity (Wilks' Lambda= 0.97, F (2,54)= 0.99, p= 0.38, partial η2= 0.04) suggesting the expectation instructional set did not influence MT associated hypoalgesia in the lower extremity. A significant main effect

(Wilks' Lambda= 0.85, F (1,54)= 9.22, p< 0.01, partial η2= 0.15) was found. Paired t- test determined a mean difference of 4.83 (sd= 12.05) between pre and post MT pain ratings with post MT rating being smaller indicating hypoalgesia in the lower extremity after MT. This difference corresponded to a small Cohen's d effect size of 0.21. A significant interaction was present between change in pain perception and group assignment in the low back (Wilks' Lambda= 0.84, F(2,56)= 5.35, p= 0.01, partial η2= 0.16) suggesting a response dependent upon group assignment. Post hoc testing revealed no change in pain perception following MT in participants receiving the positive expectation instructional set (mean difference +1.66, sd= 13.10, p= 0.57, Cohen's d effect size= 0.13) and the neutral expectation instructional set (mean difference +4.17, sd= 13.10, p=0.16, Cohen's d effect size= 0.32). Subjects receiving the negative expectation instructional set exhibited a significant increase in pain perception of moderate magnitude following the MT (mean difference -8.81, sd= 13.42, p< 0.01, Cohen's d effect size= 0.66) (Figure 4-5). The model pathway for this study is shown in Figure 4-6 and clearly demonstrates the spinal effect accounted for by the monitoring of temporal summation and the supraspinal effect, accounted for by expectation.

Summary of Pilot Studies

The mechanisms behind the clinical effectiveness of MT are not established. Limitations of prior mechanistic studies are the study of individual mechanisms without regard for others and a failure to adequately account for non- specific effects. We have proposed a comprehensive model to consolidate the current research and guide future research into the mechanisms of MT and our pilot studies have investigated specific pathways of this model. We observed greater hypoalgesia following MT than other common physical therapy interventions in both healthy participants and those experiencing low back pain. We attributed these findings to a mechanism of action of MT on c- fiber mediated pain at the dorsal horn of the spinal cord due to the

associated observation of decreased temporal summation. A shortcoming of the first two studies was the failure to consider potential supraspinal mechanisms as suggested by the model. We manipulated a potential supraspinal mechanism (expectation) in our third study. Consistent with our first two studies, we observed lessening of temporal summation in the lower extremity of participants independent of group assignment. Conversely, we observed hyperalgesia in the trunk of participants in whom expectation was manipulated to expect greater thermal pain following the MT. This finding suggests a potential role for a supraspinal mechanism and specifically, expectation in the outcomes associated with MT.

Table 4-1. Descriptive statistics of sample (healthy participants) for Pilot Study 1 (George et al., 2006)

Variable	Stationary Bicycle (n = 20)	Lumbar Extension (n = 20)	Spinal Manipulation (n = 20)	p-value
Age (years)	23.90 (3.40)	24.10 (2.60)	24.10 (3.60)	0.98
Sex (# female, %)	12 (60%)	14 (70%)	14 (70%)	0.74
Worst pain experienced (NRS)	68.90 (18.50)	64.00 (21.80)	59.70 (25.90)	0.44
Fear of pain (FPQ)	82.60 (16.70)	75.10 (13.30)	77.50 (22.60)	0.41
Pain catastrophizing (CSQ-R)	7.60 (3.10)	7.20 (3.70)	7.50 (3.80)	0.96
Anxiety (STAI)	45.30 (10.40)	45.50 (11.60)	45.20 (10.70)	0.99
Anxiety sensitivity (ASI)	19.80 (7.60)	16.00 (7.10)	16.00 (7.20)	0.23
Pain threshold (degrees Celsius)	44.70 (2.40)	45.40 (2.20)	44.80 (2.50)	0.59
Pain threshold rating (NRS)	25.00 (21.00)	28.80 (19.00)	21.30 (15.10)	0.44

Key
All data are reported as mean (standard deviation) ratings, unless otherwise indicated.
NRS = Numerical rating scale
FPQ = Fear of Pain Questionnaire
CSQ-R = Coping Strategies Questionnaire-Revised
STAI = State Trait Anxiety Inventory
ASI = Anxiety Sensitivity Index

Table 4-2. Change in Aδ fiber mediated pain in Pilot Study 1 (George et al., 2006)

Variable	Stationary Bicycle (n = 20)	Lumbar Extension (n = 20)	Spinal Manipulation (n = 20)	Partial η^2#	p-value#
NRS change at 47° C	13.20 (17.20)$	12.9 (17.9)$	23.5 (17.3)$	0.08	0.10
NRS change at 49° C	1.2 (20.20)	6.3 (22.4)	12.1 (19.7)$	0.05	0.27

Key
NRS = Numerical rating scale
All data are reported as mean (standard deviation) ratings.
Negative numbers indicate increased pain following treatment.
– Significance and partial eta-square estimate are for the interaction between type of treatment and first pain hypoalgesia
– Significant overall main effect for lower extremity hypoalgesia at 47°C ($F_{(1,57)} = 53.8$, $p < 0.01$) and at 49°C ($F_{(1,57)} = 5.9$, $p = 0.02$)
$ – Significant within group effect for hypoalgesia ($p < 0.05$)

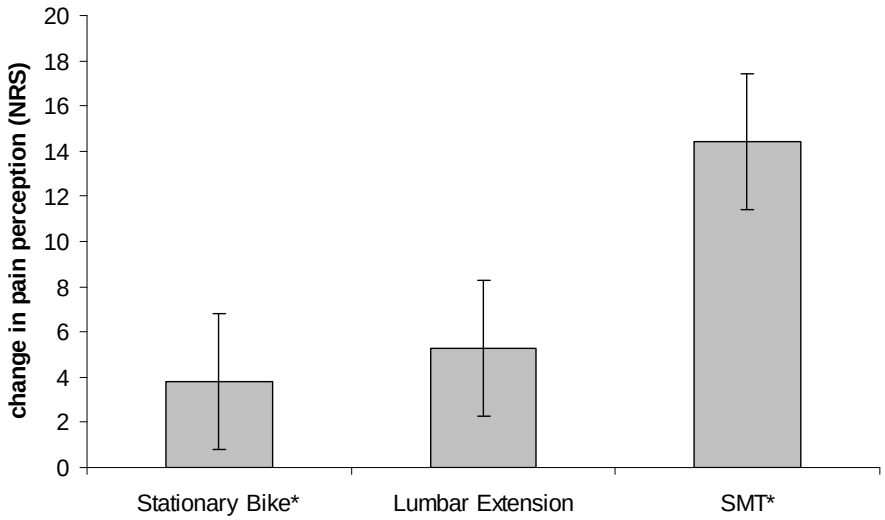


Figure 4-1. The c- fiber mediated hypoalgesia for stationary bicycle, lumbar extension, and spinal manipulation. Positive numbers indicate hypoalgesia. Error bars are 1 standard error. * – indicates statistically significant ($p < 0.05$) difference in intervention for pain sensitivity in lower extremity area. (George et al., 2006)

Table 4-3. Descriptive statistics of sample (participants with low back pain) for Pilot Study 2

Variable	Stationary Bicycle (n = 11)	Lumbar Extension (n = 12)	Spinal Manipulation (n = 11)	p-value
Age (years)	35.55 (13.96)	33.25 (13.27)	30.45 (11.18)	0.65
Sex (# female, %)	6 (55%)	12 (100%)	8 (73%)	0.04
Worst pain experienced (NRS)	79.55 (15.08)	85.42 (8.65)	74.80 (29.65)	0.44
Fear of pain (FPQ)	73.11 (21.85)	93.91 (15.34)	85.55 (16.27)	0.05
Pain catastrophizing (CSQ-R)	11.45 (7.47)	12.08 (5.99)	7.4 (4.72)	0.19
Anxiety (STAI)	93.10 (4.15)	89.36 (8.52)	91.36 (7.94)	0.50
Anxiety sensitivity (ASI)	17.64 (10.43)	20.67 (7.75)	17.90 (8.49)	0.67
Pain threshold (degrees Celsius)	44.66 (4.11)	43.60 (1.61)	44.32 (2.69)	0.69
Pain threshold rating (NRS)	33.39 (24.77)	30.13 (22.28)	14.28 (8.38)	0.11
Duration current LBP (weeks)	197.90 (429.94)	256.60 (358.20)	250.82 (365.32)	0.93
Intensity current LBP (NRS)	41.25 (21.45)	48.09 (29.72)	31.60 (21.17)	0.32

Key
All data are reported as mean (standard deviation) ratings, unless otherwise indicated.
NRS = Numerical rating scale
FPQ = Fear of Pain Questionnaire
CSQ-R = Coping Strategies Questionnaire-Revised
STAI = State Trait Anxiety Inventory
ASI = Anxiety Sensitivity Index

Table 4-4. Change in Aδ fiber mediated pain in Pilot Study 2

Variable	Stationary Bicycle (n = 11)	Lumbar Extension (n = 12)	Spinal Manipulation (n = 11)	Partial η^2#	p-value#
NRS change at 47° C	-0.27 (21.21)	1.71 (34.21)	5.64(14.58)	0.03	0.59
NRS change at 49° C	0.27 (24.47)	-0.54 (32.55)	12.51 (22.7)	<0.01	0.96

Key
NRS = Numerical rating scale
All data are reported as mean (standard deviation) ratings.
Negative numbers indicate increased pain following treatment.
– Significance and partial eta-square estimate are for the interaction between type of treatment and first pain hypoalgesia
– Insignificant overall main effect for lower extremity hypoalgesia at 47°C ($F_{(1,31)} = 1.01$, p= 0.32) and at 49°C ($F_{(1,31)} = 0.02$, p = 0.89)

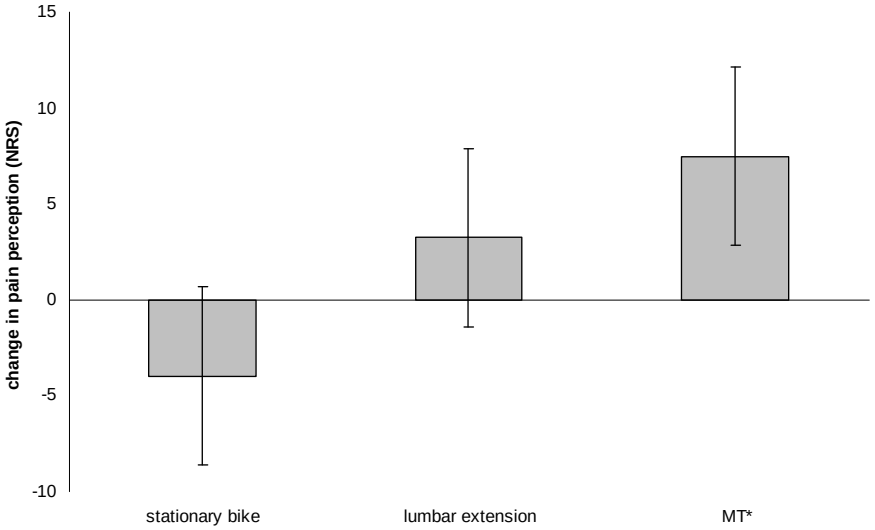


Figure 4-2. The c- fiber mediated hypoalgesia for stationary bicycle, lumbar extension, and spinal manipulation. Positive numbers indicate hypoalgesia. Error bars are 1 standard error. * – indicates statistically significant ($p < 0.05$) difference in intervention for pain sensitivity in lower extremity area.

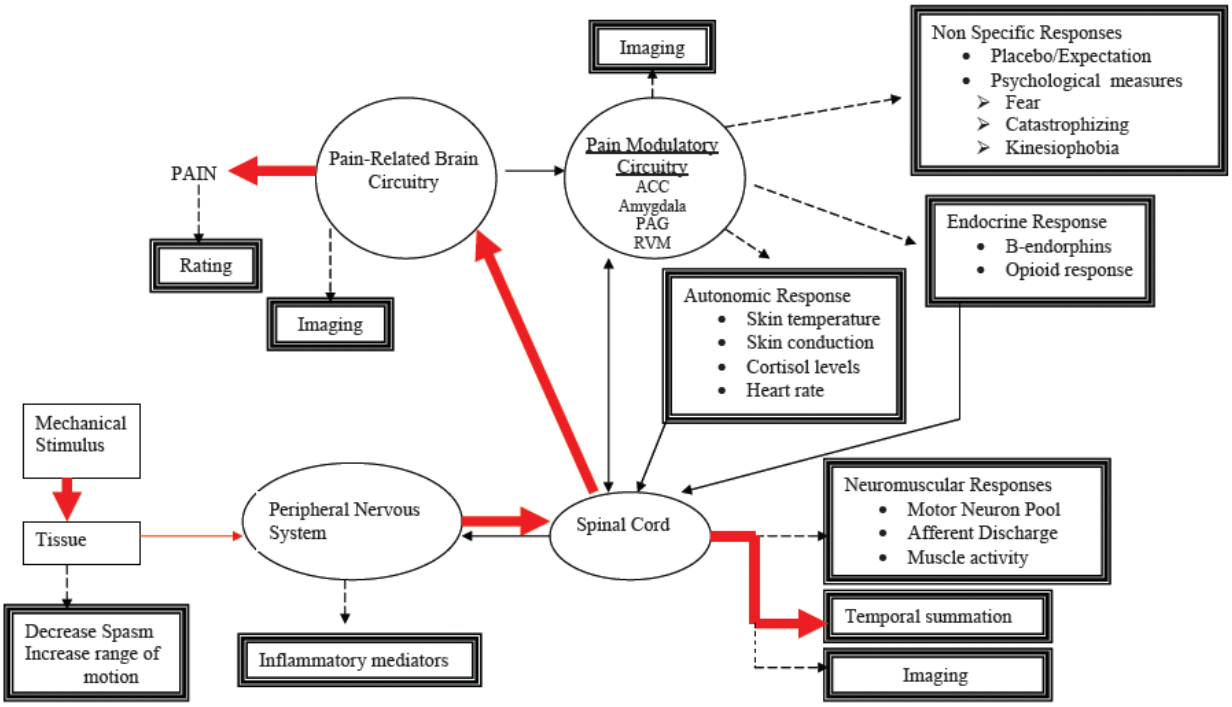


Figure 4-3. Model pathway depicting Pilot Studies 1 and 2. Note a spinal cord mediated effect is inferred by the measurement of an associated response of lessening of temporal summation. Also note, that consideration is not given in the design of these two studies to potential peripheral effect and potential supraspinal effects. ACC = anterior cingular cortex; PAG = periaqueductal gray; RVM = rostral ventromedial medulla

Table 4-5. Descriptive statistics of sample (healthy participants) for Pilot Study 3 (Bialosky et al., 2008)

Variable	Positive (n = 20)	Negative (n = 20)	Neutral (n = 20)	p-value
Age (years)	22.95 (2.06)	23.20 (3.66)	23.08 (3.10)	0.97
Sex (# female, %)	15 (75%)	13 (65%)	16 (80%)	0.55
Worst pain experienced (NRS)	65.00 (21.09)	62.5 (22.62)	75.11 (16.27)	0.13
Fear of pain (FPQ)	72.25 (13.47)	76.65 (14.81)	81.10 (19.43)	0.23
Pain catastrophizing (PCS)	15.15 (9.15)	14.75 (8.43)	17.3 (9.53)	0.63
Anxiety (PASS)	29.25 (15.17)	30.05 (12.26)	36.85 (16.89)	0.22
Pain threshold (degrees Celsius)	42.42 (5.25)	41.97 (3.12)	42.99 (2.89)	0.72
Pain threshold rating (NRS)	13.89 (11.72)	17.40 (18.16)	19.63 (20.33)	0.57

Key
All data are reported as mean (standard deviation) ratings, unless otherwise indicated.
NRS = Numerical rating scale
FPQ = Fear of Pain Questionnaire
PCS = Pain Catastrophizing Scale
PASS = Pain Anxiety Sensitivity Scale

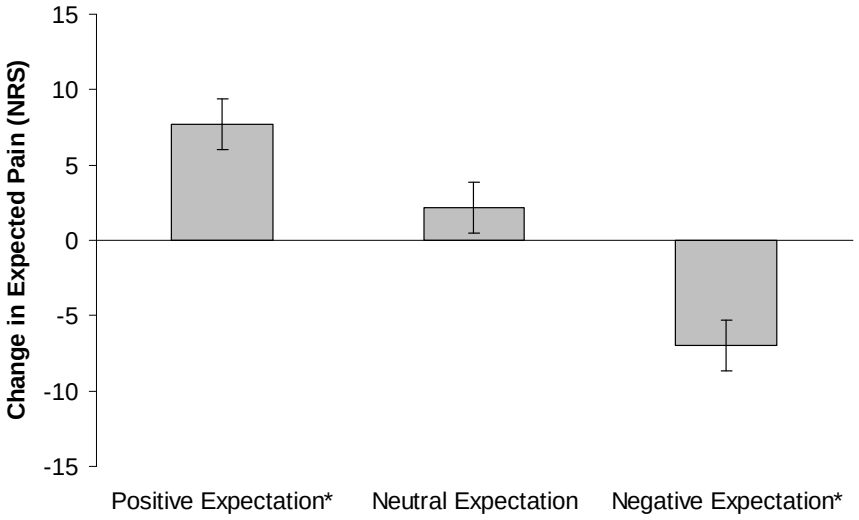


Figure 4-4. Group changes in expectation for pain in the trunk to quantitative sensory testing following MT. Positive numbers indicate an expected decrease in pain perception. Error bars indicate one standard error of the mean. * indicates significant at $p < 0.05$. (Bialosky et al., 2008)

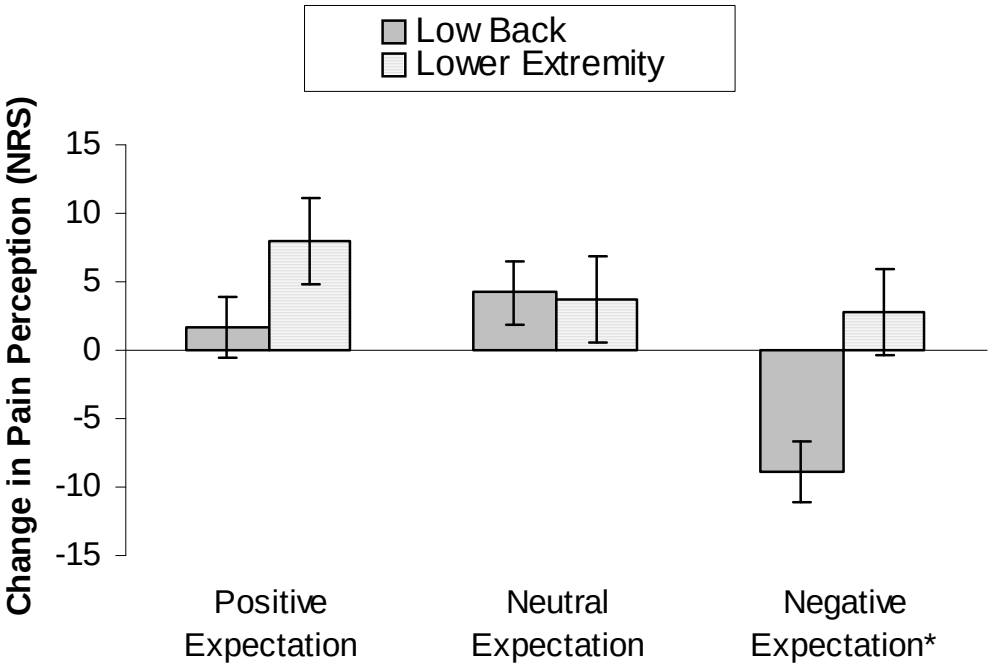


Figure 4-5. The c- fiber mediated hypoalgesia observed in Pilot Study 3. Positive numbers indicate hypoalgesia. Error bars are 1 standard error. * – indicates statistically significant ($p < 0.05$) change in pain perception in low back. (Bialosky et al., 2008)

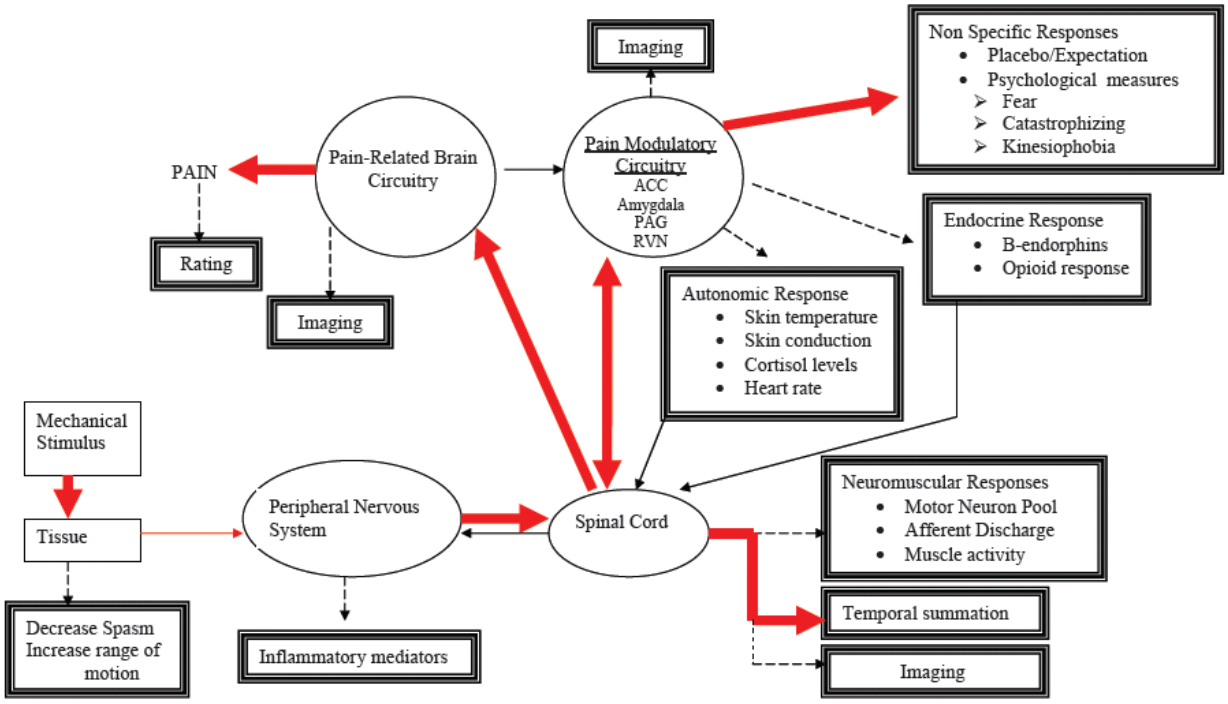


Figure 4-6. Model pathway depicting Pilot Study 3. Note a spinal cord mediated effect is inferred by the measurement of an associated response of lessening of temporal summation. Also note, that a supraspinal mediated effect is inferred by the measurement of an associated response of expectation. Consideration is not given in the design of this study to potential peripheral effects. ACC = anterior cingular cortex; PAG = periaqueductal gray; RVM = rostral ventromedial medulla

CHAPTER 5
METHODS

Specific Aims

1. Determine the believability of a novel placebo for MT in the treatment of carpal tunnel syndrome (CTS) in regards to a) participant's interpretation of which intervention they received and b) their expectation for the effectiveness of the individual interventions.

2. Determine the changes in pain perception to standardized thermal stimuli, self report of pain, and self report of function associated with a specific MT technique and a novel placebo.

3. Determine the relative strength of demographic variables, group assignment, expectation, response to initial quantitative sensory testing, and physical exam variables in predicting three week measures of pain and disability.

Research Hypothesis

1. It was hypothesized that participants receiving the indirect MT would not differ in their interpretation of which intervention they had received or in their expectation of outcome in comparison to participants receiving the direct MT.

2. It was hypothesized that similar to our prior studies, changes in pain perception to standardized thermal stimuli would not differ for protocols specific to Aδ fiber mediated pain. We hypothesized that similar to our prior studies, greater c- fiber mediated hypoalgesia would be observed in participants receiving the direct MT. Furthermore, we hypothesized changes in self report of CTS pain and function would not differ by group assignment.

3. It was hypothesized that expectation would be the strongest predictor of three week measures of pain and disability.

Participants

Participants between the ages of eighteen and seventy were recruited from the clinics of orthopedic surgeons at the University of Florida and the general public through posted flyers, electronic distribution of advertisement, and word of mouth.

Inclusion criteria:

- Participants were required to have a diagnosis of CTS as defined by:
  - hand symptoms in the median nerve distribution and/or
  - clinical examination findings consistent with carpal tunnel syndrome

- CTS symptoms present for greater than twelve weeks
- CTS pain or symptoms rated as at least a 4/10 over the past twenty-four hours

Exclusion criteria:

- Participants not appropriate for conservative intervention for CTS
- non English speaking
- previous surgery for CTS
- prior treatment involving the use of median nerve mobilization
- systemic disease known to cause peripheral neuropathy
- current or history of chronic pain conditions unrelated to CTS
- upper extremity fracture.

Measures

Demographics

A demographic questionnaire was used to gather information related to age, sex, ethnicity, racial group, employment status, marital status, education level, household income, hand dominance, CTS affect side, worse side if bilateral CTS, whether CTS was work related, whether litigation was involved, and duration of CTS.

Expectation

Individual expectation for outcome was assessed using the Patient Centered Outcome Questionnaire (PCOQ) (Robinson et al., 2005). The PCOQ is a five item questionnaire which uses individual 101 point numeric rating scales to quantify the usual, desired, and expected levels of pain, fatigue, emotional distress, and interference with daily activities associated with a pain conditions. Additionally, the PCOQ uses the same numeric rating scale to quantify the rating for each category the subject would consider to be a successful treatment and the self-perceived importance of improvement in each category. We report descriptive results for measures of usual pain, expected pain, and expected interference with daily activities. Additionally, we included the expected measures of pain in our regression analysis of 3 week rating of pain and expected measure of interference with daily activities in our regression analysis for 3 weeks rating of function.

Psychological Questionnaires

Fear of pain questionnaire-III (FPQ-III)

We used a modified version of the The FPQ-III (McNeil & Rainwater, III, 1998) which consists of 9 items, each scored on a 5-point adjectival scale, which measures fear of normally painful situations. Higher scores indicate greater pain related fear. The FPQ has demonstrated sound psychometric properties in both experimental and clinical pain studies (McNeil & Rainwater, III, 1998;Osman et al., 2002;Roelofs et al., 2005).

Pain catastrophizing scale (PCS)

The PCS consists of 13 items specific to individual coping styles with pain which are each quantified with a five point ordinal scale. Higher scores indicate greater levels of catastrophizing. The score may be taken as a whole or as individual factors of rumination, helplessness, and magnification. Prior studies have validated the factor structure and found good internal consistency reliability and validity of the PCS (Osman et al., 1997;Van Damme et al., 2002).

Tampa scale of kinesiophobia (TSK)

The Tampa Scale for Kinesiophobia (TSK) is an 11-item questionnaire, with individual items scored from 1 to 4. The questionnaire was developed to quantify the fear of movement and injury/re-injury for individuals currently experiencing pain. Higher TSK scores indicate greater fear of movement and injury/re-injury due to pain. The TSK has demonstrated acceptable psychometric properties in prior studies (Woby et al., 2005).

Visual analog scale

Separate 10 cm visual analog scales anchored with none at all and worst imaginable were used to quantify fear, anxiety, threat, and challenge in relation to the QST. These measures were obtained only to assure no group differences in the individual variables.

Functional Questionnaires

Disability of the arm, shoulder, and hand questionnaire (DASH)

The DASH is a self report measure of upper extremity disability and contains thirty items, ranging from 1 (no difficulty) to 5 (unable). The DASH contains three modules which are scored independently and includes an 11 question general module, a 4 item work module, and a 4 item sports/performing arts module. The DASH is used in assessment of general upper extremity disorders and has sound psychometric properties (Beaton et al., 2005;Greenslade et al., 2004;Gummesson et al., 2003;Gummesson et al., 2006;Jester et al., 2005). We report only on the 11 question general module of the DASH for descriptive statistics and in analysis.

Boston questionnaire

The Boston Questionnaire is a self report disability measure that is specific to patients with CTS. The Boston Questionnaire is widely used in the assessment of subjects with CTS and has sound psychometric properties (Greenslade et al., 2004;Leite et al., 2006;Sambandam et al., 2007). The Boston Questionnaire contains both an 11 item symptom scale and a 9 item function scale. Each item consists of a 5 point adjectival scale scored from 1 to 5 with lower scores indicating greater function. We report only the 9 item function scale as a measure of function.

Pain Measurement

Mechanical visual analog scale (MVAS)

An MVAS anchored with “No pain” and “The most intense pain sensation imaginable” was used to assess pain. Additionally, an MVAS anchored with “Not at all unpleasant” and “The most unpleasant sensation imaginable” was used to assess symptoms such as tingling and numbness. MVAS are commonly used in the assessment of pain and have demonstrated sound psychometric properties including the characteristics of a ratio scale (Price et al., 1994).

Numeric rating scale (NRS)

An NRS anchored with, "No pain sensation at all" and "The most intense pain sensation imaginable" was used to assess pain. NRS are commonly used in the assessment of pain. While lacking the ratio properties of MVAS (Price et al., 1994), the NRS has demonstrated adequate psychometric properties (Gagliese et al., 2005;Jensen et al., 1986) and is a common measure of both clinical and experimental pain.

Nerve Conduction Study

Participants underwent a nerve conduction study (NCS) which assessed;

- bilateral median motor to abductor pollicis brevis
- median/ ulnar sensory comparison to digit #4 (at 14 cm)
- median/ ulnar sensory comparison – transpalmer (8 cm across wrist)
- median/ radial sensory comparison to digit #1 (at 10 cm)

Physical Examination

The physical examination consisted of measures of wrist range of motion (ROM) using a standard goniometer. Strength was measured using a hand held dynamometer to measure grip strength with the forearm in neutral and the elbow flexed to 90 degrees. Lateral and 3- chuck pinch were assessed using a dynamometer with the elbow flexed to 90 degrees and the forearm pronated. Sensation was assessed using Symmes Weinstein monofilaments to the tip of each digit. Participants closed their eyes and were instructed to indicate when they felt the monofilament. Pressure was applied to just bend the monofilament and each individual stimulus was applied up to three times prior to moving to a thicker monofilament if the subject did not indicate sensation. Additionally, each participant was evaluated for Phalen's test, Tinnel's test over the carpal tunnel, compression test to the median nerve, upper limb tension test with a median nerve bias, and upper limb tension test with an ulnar nerve bias. All special tests were documented as either positive or negative.

Intervention

Participants were randomly assigned to one of two intervention groups. Group 1 received a specific MT technique known as a neurodynamic intervention (NDI) (Figure 5-1A) which consisted of movements known to specifically and forcefully stress the median nerve (Coppieters & Butler, 2007;Coppieters & Alshami, 2007). The NDI consisted of 25 degrees of contralateral cervical sidebending, ipsilateral shoulder depression and abduction to 90 degrees, ER to 90 degrees, 45 degrees of elbow extension, forearm supination, and repetitive wrist and finger flexion and extension through a 90 degree range of motion. Each repetition was controlled to allow for 6 seconds through the entire range and participants received 5 sets of 10 cycles for the first three sessions and 7 sets of 10 cycles for sessions 4 through 6. Group 2 received the indirect NDI (Figure 5-1B) which consisted of movements intended to mimic the direct NDI; however, minimize stress and movement of the median nerve. The indirect NDI consisted of the cervical spine maintained in neutral sidebending, no ipsilateral shoulder depression and abduction to 45 degrees, ER to 45 degrees, 45 degrees of elbow extension, and forearm pronation with the same wrist and finger motion, timing, and repetitions as the direct technique.

Procedures

Refer to figure 5-2 for flow diagram of study procedures. Individuals agreeing to participate signed an informed consent form approved by the University of Florida Institutional Review Board and then completed intake forms consisting of a demographic form, psychological questionnaires, the PCOQ, and functional Questionnaires. Next, participants underwent a nerve conduction study. The NCS was performed by a medical doctor using a TECASynergy N2 ultra-portable 2 channel NCS system (VIASYS Healthcare). Following the NCS, a standardized physical examination was performed by a member of the research team after which the participant was provided with splints for their involved hand(s) along with instructions in use

emphasizing night time wear. Participants then underwent quantitative sensory testing (QST) using thermal stimuli delivered through the Medoc Neurosensory Analyzer (TSA-2001, Ramat Yishai, Israel) with a hand-held, peltier-element-based stimulator. Our QSTprocedure used previously established protocols (Price et al., 2002;Staud et al., 2001) which were consistent with our previously reported pilot studies. Aδ fiber mediated pain was assessed through heat impulses of 47º and 49º C for five seconds each and subjects rated their pain sensation using a 100 mm MVAS. The thermode was applied to the volar forearm for this procedure and thermal stimuli were applied in a random order to avoid order bias. This protocol was performed twice with the thermode repositioned and waiting sixty seconds between each session to avoid accommodation to the stimuli. The average pain rating of the two sessions was used to indicate pain perception associated with each temperature. C- fiber mediated pain was assessed through ten heat pulses at 51º C applied to the thenar surface of the palm of the hand with an inter-stimulus interval of .33 seconds. The average of the first five pulses was used to indicate c- fiber mediated pain perception.

Following the initial testing, subjects were randomly assigned to receive either a direct NDI known to anatomically stress the median nerve (Coppieters & Butler, 2007;Coppieters & Alshami, 2007) or an indirect NDI that lessens the mechanical stress to the median nerve. Participants were positioned for their assigned intervention and received two cycles of wrist flexion and extension in this position. Participants were then asked to again complete the expectation portion of the PCOQ and this served as a measure of expectation following exposure to the intervention. Upon completion of the expectation portion of the PCOQ, participants underwent the first session of their assigned intervention and then immediately underwent follow up QST using the same protocol. Participants were followed over the next three weeks for

application of the randomly assigned intervention. Follow up sessions included measures of pain and symptoms using a MVAS and application of the assigned intervention. Immediately following the assigned intervention, follow up measures of "current" pain and symptoms were obtained using a MVAS. The number of additional sessions was based on the availability of the participant and varied. Approximately three weeks following randomization, participants were seen for a final visit consisting of follow up questionnaires, NCS, physical examination, and pre and post intervention QST.

Statistical Analysis

We analyzed data from one extremity per participant. The involved extremity was used in participants reporting unilateral CTS. The extremity indicated as "more symptomatic" was analyzed in participants with bilateral CTS. In cases of bilateral CTS where the participant reported no difference in pain or symptoms between the hands, the dominant extremity was then chosen for analysis. Individual t-tests and chi square tests were used to assess the direct and indirect NDI groups for post-randomization differences in parametric and non-parametric variables, respectively. Alpha levels were set at 0.05 and all analysis was performed using the SPSS statistical package (version 14.0)

Believability of Placebo

a. A Chi- square analysis was used to compare assessment of group assignment (direct versus indirect treatment). Random assignment was compared to perceived assignment.

b. Repeated measures ANOVA were used to test for an interaction between baseline measure of expectation (after signing the informed consent form) and measure of expectation (after brief exposure to the randomly assigned intervention) and group assignment (direct versus indirect).

Treatment Effects

a. Repeated measure ANOVA were used to test for a group (direct NDI versus indirect NDI) x time (pre to post) interaction for measures of experimental pain sensitivity. Separate models were used to assess immediate differences at baseline, immediate differences at

discharge, and differences between the first measurement at evaluation and the final measurement at discharge.

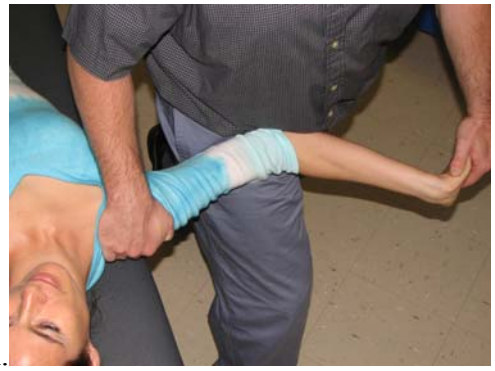
b. Repeated measure ANOVA were used to test for a group (direct NDI versus indirect NDI) x time (baseline to 3 weeks) interaction for NCV measures of distal latency of the median motor to abductor pollicis brevis and the combined sensory index.

c. Separate repeated measure ANOVA were used to test for a group (direct NDI versus. indirect NDI) x time (pre to post) interaction for measures of pain, symptoms, and disability. We used the average of separate MVAS ratings of current, worst in the past 24 hours, and least in the past 24 hours to quantify both pain and symptoms at baseline and at 3 weeks. We were also interested in immediate changes in self report of pain, so separate repeated measure ANOVA models were used with MVAS of current pain prior to and immediately following NDI. The DASH Questionnaire was used as a measure of disability.

Predictors of Outcomes

First, a correlation matrix to investigate associations of predictor variables and dependent variables, as well as to investigate the potential of multicollinearity was created. Separate regression models then assessed the variance explained by the independent variables of age, initial pain or disability, treatment group assignment, immediate hypoalgesic effect, and initial expectation on the dependent variables of 3-week pain and disability scores respectively. Hierarchical models were built using the following order of entry for variables. First, age was entered to account for demographic variables. Second, either baseline pain or function was entered depending upon the model. Third, treatment group was entered to account for direct or indirect neural mobilization received as treatment. Fourth, the immediate hypoalgesic effect was entered to account for neurophysiological modulation occurring during the first session (as had been observed in our previous studies). Finally, initial expectation was entered to account for this variable. R-square changes were tested for each step of the hierarchical model. A final, parsimonious regression model was created by including only those variables that uniquely contribute to the prediction of 3 week pain or disability. Multicollinearity was assessed through observation of the correlation between the independent variables. Frequency distribution was

assessed for outliers. Histograms of the standardized residuals were used to assess for linearity and normal distribution. Homoscedasticity was assessed through analysis of partial residual plots and normal probability plots.

A. 

B. 

Figure 5-1. Examples of randomly assigned interventions. Participant is positioned as noted and force is applied to the tissue through repetitive wrist, finger, and thumb flexion and extension. A) Direct NDI. Note combination cervical, shoulder, elbow, and wrist positioning which imparts movement and stress to the median nerve (Coppieters & Butler, 2007;Coppieters & Alshami, 2007). B) Indirect NDI. Note positioning of cervical spine and upper extremity in way to lessen movement and stress to the median nerve

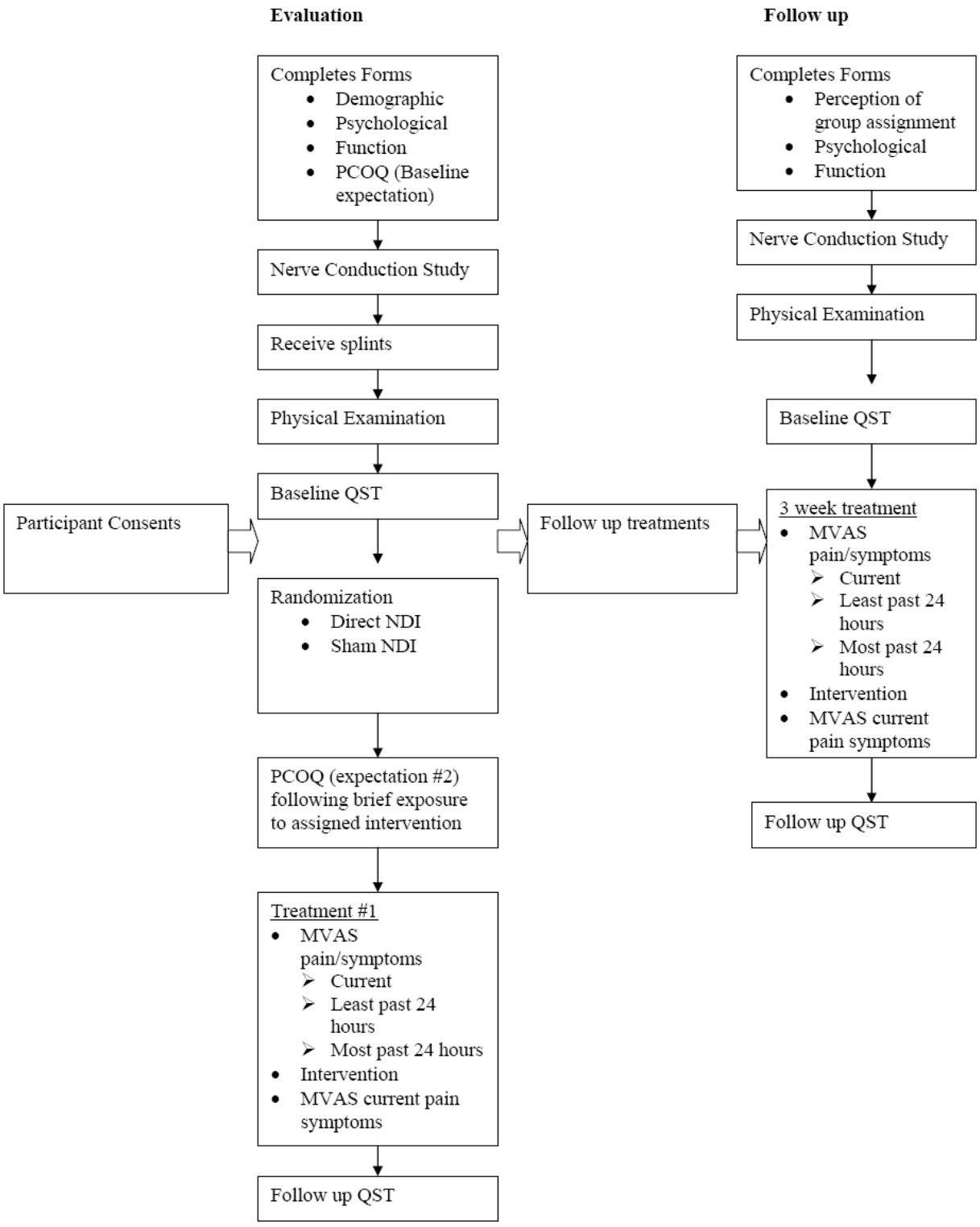


Figure 5-2. Study protocol. PCOQ= Patient Centered Outcome Questionnaire; QST= Quantitative Sensory Testing; MVAS= Mechanical Visual Analog Scale; NDI= Neurodynamic Intervention

CHAPTER 6
RESULTS

Eighty- three individuals were screened for the study and 40 agreed to participate (Figure 6-1). Twenty seven participants reported bilateral CTS. Baseline measures of demographic information, psychological factors, and physical factors did not differ between the groups ($p > 0.05$) (Table 6-1 and 6-2). Range of attended sessions was between 2 and 6 in individuals completing the study and dependent upon individual participant's availability. Mean number of sessions attended was 4.74 (1.37).

Believability of Placebo

Perceived Group Assignment

The frequencies of perceived group assignment did not significantly differ by actual group assignment χ^2 (1, N = 37) = 2.10, p = 0.15). Refer to table 6-3 for perceived compared to actual intervention.

Expectation for Pain at Completion

A group (direct NDI versus indirect NDI) by time (immediately post consent versus following brief exposure to assigned intervention) interaction was not observed for expected pain following the study ($F_{(1,37)}=$ 0.03, p= 0.87, partial $\eta^{2<}$ 0.01) suggesting the groups did not differ in their expectation for pain relief following brief exposure to the assigned intervention. Additionally, a main effect for time was not observed ($F_{(1,37)}=$ 2.38, p= 0.13, partial $\eta^{2=}$ 0.06) suggesting expectation for treatment did not differ at baseline and following brief exposure to the randomly assigned intervention.

Treatment Effects

Associated Experimental Pain Perception

Evaluation pre to post NDI (Table 6-4, Figure 6-2)

Neither a group x time interaction ($F_{(1,38)}$= 0.68, p= 0.41, partial η^2= 0.02) nor a main treatment effect for time ($F_{(1,38)}$= 0.21, p= 0.65, partial η^2= 0.01) was observed for Aδ fiber mediated pain at 47° C

Neither a group x time interaction ($F_{(1,37)}$= 0.53, p= 0.47, partial η^2= 0.01) nor a main treatment effect for time ($F_{(1,37)}$= 0.12, p= 0.73, partial η^2< 0.01) was observed for Aδ fiber mediated pain at 49° C

Neither a group x time interaction ($F_{(1,38)}$= 0.07, p= 0.79, partial η^2< 0.01) nor a main treatment effect for time ($F_{(1,38)}$= 0.04, p= 0.83, partial η^2< 0.01) was observed for c- fiber mediated pain.

Discharge pre to post NDI (table 6-5, Figure 6-3)

Neither a group x time interaction ($F_{(1,35)}$= 0.29, p= 0.59, partial η^2= 0.01) nor a main treatment effect for time($F_{(1,35)}$< 0.01, p= 0.96, partial η^2< 0.01) was observed for Aδ fiber mediated pain at 47° C.

Neither a group x time interaction ($F_{(1,36)}$= 0.20, p= 0.66, partial η^2= 0.01) nor a main treatment effect for time ($F_{(1,36)}$< 0.01, p= 0.99, partial η^2 < 0.01) was observed for Aδ fiber mediated pain at 49° C.

A significant group x time interaction ($F_{(1,37)}$= 6.86, p= 0.01, partial η^2= 0.16) was observed for c- fiber mediated pain.

Baseline evaluation to discharge post NDI (longitudinal) (table 6-6, Figure 6-4)

Neither a group x time interaction ($F_{(1,35)}$= 3.15, p= 0.09, partial η^2= 0.08) nor a main treatment effect for time ($F_{(1,35)}$= 0.66, p= 0.42, partial η^2= 0.02) was observed for Aδ fiber mediated pain at 47° C.

Neither a group x time interaction ($F_{(1,35)}$= 0.69, p= 0.41, partial η^2= 0.02) nor a main treatment effect for time ($F_{(1,35)}$= 1.44, p= 0.24, partial η^2= 0.04) was observed for Aδ fiber mediated pain at 49° C.

A significant group x time interaction ($F_{(1,37)}$= 4.05, p= 0.05, partial η^2= 0.10) was observed for c- fiber mediated pain.

Nerve Conduction Studies

A subgroup of twelve participants received baseline and discharge (3- week) NCS. A group (direct NDI versus indirect NDI) by time (evaluation versus discharge) interaction was not observed for measures of distal latency from median motor to Abductor Pollicis Brevis ($F_{(1,10)}$= 3.44, p= 0.09, partial η^2= 0.26) or the combined sensory index ($F_{(1,10)}$= 1.83, p= 0.21, partial η^2= 0.15). A main treatment effect was not observed for measures of distal latency from median motor to Abductor Pollicis Brevis ($F_{(1,10)}$= .02, p= 0.88, partial η^2< 0.01) or the combined sensory index ($F_{(1,10)}$= 1.06, p= 0.33, partial η^2= 0.10).

Associated Clinical Pain, Symptoms, and Function

Immediate change in clinical pain and symptoms (Figure 6-5)

A group (direct NDI versus indirect NDI) by time (pre NDI to immediately post NDI) interaction was not observed for self report of current pain at either evaluation ($F_{(1,38)}$< .01, p= 0.96, partial η^2< 0.01) or discharge ($F_{(1,37)}$= .59, p= 0.45, partial η^2= 0.02). However, a main treatment effect was observed at both evaluation ($F_{(1,38)}$= 7.92, p= 0.01, partial η^2= 0.17) and discharge ($F_{(1,37)}$= 6.44, p= 0.02, partial η^2= 0.15) suggesting an immediate improvement in pain

which was not dependent upon group assignment. Mean current pain at evaluation baseline was 18.75 (16.31) and at evaluation immediately following NDI was 11.93 (14.02). Mean current pain at discharge baseline was 14.33 (20.14) and immediately following NDI at discharge was 9.85 (16.22). Neither a group (direct NDI versus indirect NDI) by time (pre NDI to immediately post NDI) interaction ($F_{(1,38)}$= 0.04, p= 0.95, partial η^2< 0.01) or main treatment effect ($F_{(1,38)}$= 3.05, p= 0.09, partial η^2= 0.07) was present for self report of current symptoms on evaluation. A group (direct NDI versus indirect NDI) by time (pre NDI to immediately post NDI) interaction ($F_{(1,37)}$= 2.63, p= 0.11, partial η^2= 0.07) was not present for change in self report of symptoms at discharge; however, a main treatment effect for self report of symptoms was observed at discharge ($F_{(1,37)}$= 4.66, p= 0.04, partial η^2= 0.11). Mean current symptoms at discharge were 13.21 (18.93) and immediately following NDI at discharge were 9.46 (15.09).

Change in clinical pain and symptoms over 3 weeks

Neither a group (direct NDI versus indirect NDI) by time (baseline versus discharge) interaction ($F_{(1,37)}$= .16, p= 0.69, partial η^2< 0.01) nor a main treatment effect ($F_{(1,37)}$= 3.34, p= 0.08, partial η^2= 0.08) existed for self report of pain. Neither a group (direct NDI versus indirect NDI) by time (baseline versus discharge) interaction ($F_{(1,37)}$= .04, p= 0.85, partial η^2< 0.01) nor a main treatment effect ($F_{(1,37)}$= 1.48, p= 0.23, partial η^2= 0.04) existed for self report of symptoms. (Table 6-7)

Three week change in function

Neither a group (direct NDI versus indirect NDI) by time (baseline to discharge) interaction ($F_{(1,34)}$= 0.50, p= 0.48, partial η^2= 0.01) nor a main treatment effect ($F_{(1,34)}$= 2.95, p= 0.10, partial η^2= 0.08) was present for the Boston Questionnaire functional scale. A group (direct NDI versus indirect NDI) by time (baseline to discharge) interaction was not present for

the DASH Questionnaire ($F_{(1,34)}$= 0.00, p= 1.00, partial η^2< 0.01); however, a main treatment effect was observed ($F_{(1,34)}$= 8.93, p= 0.01, partial η^2= 0.21). (Table 6-7)

Predictors of Outcomes

Predictors of pain at 3 weeks

We used hierarchical regression to determine the predictors of pain at 3 weeks. 1.) Age, 2.) baseline pain, 3.) group assignment, 4.) first session change in pain immediately following NDI, and 5.) expectation for pain taken at baseline served as predictor variables in the model. A correlation matrix was calculated to note the association between variables and to assess for potential multicollinearity (Table 6-8). The assumption of no multicollinearity did not appear to be violated as all correlations were well below 0.90. Casewise diagnostics indicated 1 participant with standardized residuals of 2.76. No actions were taken as the Cook's distance was < 1 (0.28) and Mahalanobis distance was 4.96. Durbin- Watson for this model was 1.90 suggesting the assumption of independence of errors has been met. A 5 step model was used which provided the following results (Table 6-9 and 6-10). A parsimonious model was then constructed using the significant predictors from the initial model and consisted of baseline pain, change in current clinical pain on evaluation, and expectation for pain (Table 6-11 and 6-12).

Predictors of function at 3 weeks

Next, we used hierarchical regression to determine the predictors of disability at 3 weeks. The DASH score served as the dependent variable. 1.) Age, 2.) baseline DASH, 3.) group assignment, 4.) first session change in clinical pain immediately immediately following NDI, and 5.) baseline expectation for 3 week function served as predictor variables in the model. A correlation matrix was calculated to note the association between variables and to assess for potential multicollinearity (Table 6-13). The assumption of no multicollinearity did not appear to be violated as all correlations were well below 0.90. Casewise diagnostics indicated 1

participant with standardized residuals of -3.06. No actions were taken as the Cook's distance was < 1 (0.31) and Mahalanobis distance was 4.15. Durbin- Watson for this model was 2.85 suggesting the assumption of independence of errors has been met. A 5 step model was used which provided the following results (6-14 and 6-15).

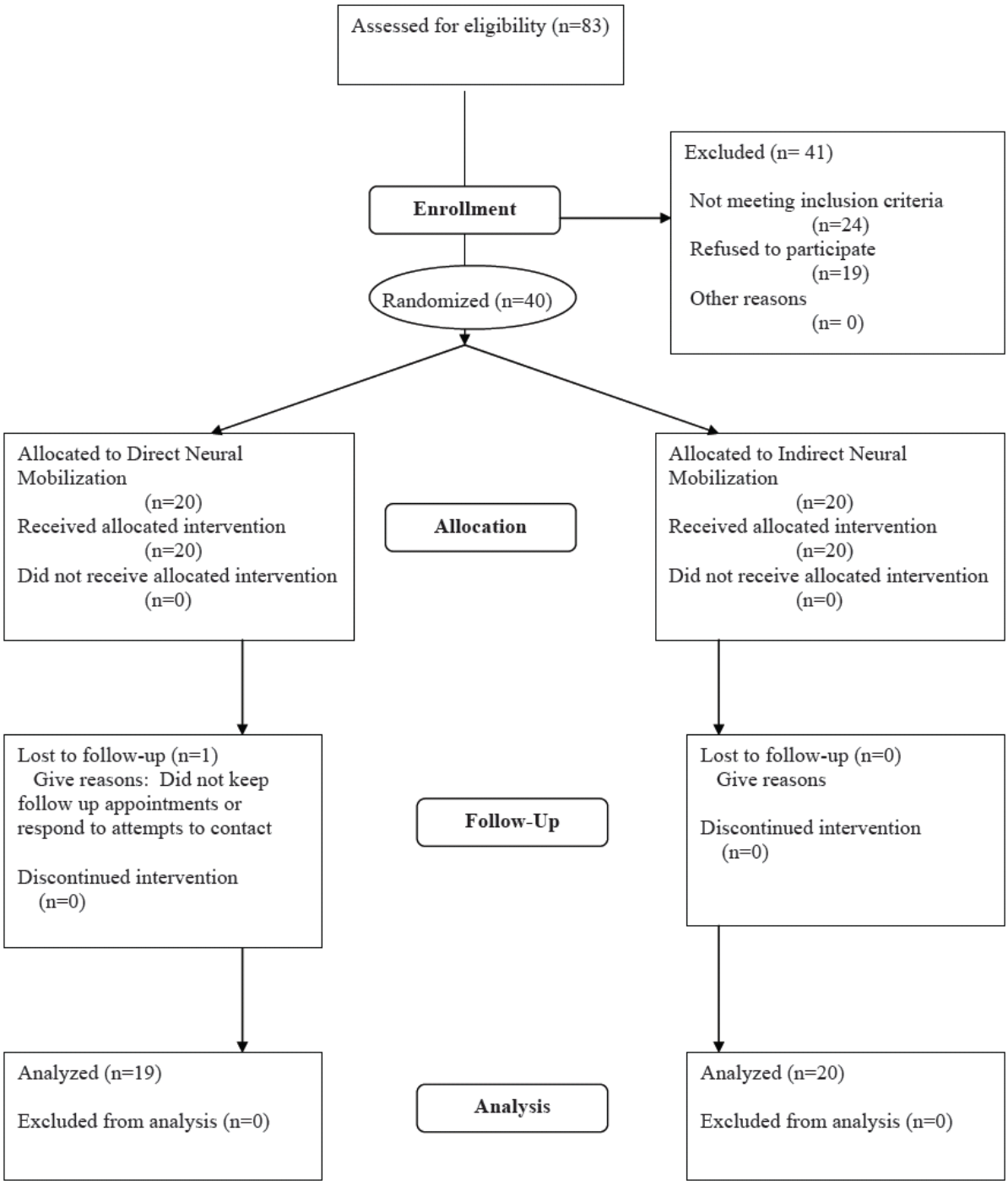


Figure 6-1. Summary of recruitment, enrollment, randomization, allocation, follow up, and analysis for the study.

Table 6-1. Baseline comparison of direct and indirect NDI groups in self report measures

	Direct	Indirect	Total Sample	p- value for difference
Age (years)	44.30 (6.97)	49.50 (12.35)	46.90 (10.25)	0.11
Duration of CTS (weeks)	192.22 (273.21)	362.82 (256.85)	275.09 (275.41)	0.07
PCS	16.85 (11.17)	14.94 (8.79)	15.95 (10.03)	0.57
FPQ	23.05 (6.09)	23.42 (4.88)	23.24 (5.44)	0.84
TSK	23.35 (6.02)	23.35 (6.27)	23.35 (6.05)	0.99
VAS Fear	16.35 (19.33)	20.05 (20.27)	18.20 (19.64)	0.56
VAS Anxiety	14.70 (15.77)	20.15 (21.16)	17.43 (18.63)	0.36
VAS Challenge	17.75 (15.21)	21.10 (25.64)	19.43 (20.88)	0.62
VAS Threat	13.90 (19.62)	13.60 (20.50)	13.75 (19.81)	0.96
Baseline Expectation (Pain)	26.05 (19.51)	27.5 (20.49)	26.78 (19.76)	0.82
Baseline Expectation (Interference)	27.80 (29.58)	20.79 (22.56)	24.38 (26.29)	0.41
Expectation Assessment (Pain) #2	19.25 (20.98)	20.84 (16.72)	20.03 (18.79)	0.80
Usual Pain (PCOQ)	51.25 (28.00)	45.00 (28.52)	48.13 (28.07)	0.49
Boston Questionnaire	17.67 (5.82)	17.83 (6.98)	17.75 (6.34)	0.48
DASH Questionnaire	35.29 (15.35)	40.67 (18.69)	37.98 (17.09)	0.34
Baseline Pain (MVAS)	22.26 (13.70)	18.99 (17.24)	20.63 (15.46)	0.51
Baseline Symptoms (MVAS)	21.88 (1.34)	17.13 (18.01)	19.50 (15.84)	0.35

Key: All data are reported as mean (standard deviation) ratings, unless otherwise indicated. NDI= neurodynamic intervention, PCS = Pain Catastrophizing Scale, FPQ = Fear of Pain Questionnaire, TSK = Tampa Scale of Kinesiophobia, VAS= Visual Analog Scale, PCOQ= Patient Centered Outcome Questionnaire. VAS of fear, anxiety, threat, and challenge are in relation to quantitative sensory testing, Expectation= expectation for pain and interference from PCOQ. Baseline expectation for pain was obtained immediately following informed consent and #2 was obtained following brief exposure to randomly assigned intervention. Boston Questionnaire represents the functional status scale, DASH= Disability of Arm, Shoulder, and Hand Questionnaire, Baseline Pain represents

average of three Mechanical Visual Analog Scale (MVAS) ratings of current pain, worst in past 24 hours, and best in past 24 hours. Baseline Symptoms represents average of three Mechanical Visual Analog Scale (MVAS) ratings of current symptoms, worst in past 24 hours, and best in past 24 hours. Expectation for pain ratings (PCOQ) are not directly comparable to pain ratings (MVAS) so baseline usual pain ratings (PCOQ) are provided to allow direct comparison.

Table 6-2. Baseline comparison of the direct and indirect NDI groups on the physical examination

		Direct	Indirect	Total Sample	p- value for difference
Wrist flexion ROM (in degrees)		67.22 (11.01)	72.16 (7.00)	69.76 (9.38)	0.11
Wrist extension ROM (in degrees)		70.56 (11.62)	66.05 (9.51)	68.24 (10.69)	0.20
Sensation Thumb	Normal	5 (28%)	5 (28%)	10 (28%)	1.00
	Min	10 (56%)	10 (56%)	20 (56%)	
	>Min	3 (17%)	3 (17%)	6 (17%)	
Sensation Index Finger	Normal	6 (33%)	4 (22%)	9 (25%)	0.74
	Min	9 (50%)	11 (61%)	20 (56%)	
	>Min	3 (17%)	3 (17%)	6 (17%)	
Sensation Middle Finger	Normal	4 (24%)	5 (28%)	9 (26%)	0.80
	Min	11 (65%)	12 (67%)	23 (66%)	
	>Min	2 (12%)	1 (6%)	3 (9%)	
Sensation Radial Ring Finger	Normal	4 (22%)	6 (33%)	10 (28%)	0.75
	Min	13 (72%)	11 (61%)	24 (67%)	
	>Min	1 (6%)	1 (6%)	2 (6%)	
Sensation Ulnar Ring Finger	Normal	7 (39%)	5 (28%)	12 (33%)	0.77
	Min	10 (56%)	12 (67%)	22 (61%)	
	>Min	1 (6%)	1 (6%)	2 (6%)	
Sensation Little Finger	Normal	8 (44%)	6 (33%)	14 (39%)	0.42
	Min	9 (50%)	12 (67%)	21 (58%)	
	>Min	1 (6%)	0 (0%)	1 (3%)	
Phalen's Test	+	17 (94%)	15 (79%)	32 (86%)	0.17
	-	1 (6%)	4 (21%)	5 (14%)	
Tinnel's Test	+	14 (78%)	13 (68%)	27 (73%)	0.52
	-	4 (22%)	6 (32%)	10 (27%)	
Compression Test	+	14 (78%)	17 (89%)	31 (84%)	0.34
	-	4 (22%)	2 (11%)	6 (16%)	
ULTT Median bias	+	9 (50%)	8 (44%)	17 (47%)	0.74
	-	9 (50%)	10 (56%)	19 (53%)	
Grip (3 trial average on dynamometer)		21.76 (10.88)	22.25 (7.84)	22.00 (9.35)	0.88
NCS distal latency		4.64 (1.95)	4.61 (1.38)	4.63 (1.64)	0.97

Table 6-2. Continued

	Direct	Indirect	Total Sample	p- value for difference
NCS CSI	1.89 (1.81)	1.92 (1.38)	1.90 (1.53)	0.98
Pain Threshold (°C)	43.26 (2.40)	44.12 (2.99)	43.69 (2.71)	0.32
Rating for pain threshold (MVAS)	18.53 (16.86)	17.00 (13.58)	17.76 (15.13)	0.75
Pain Tolerance (°C)	48.57 (1.34)	47.70 (2.70)	48.13 (2.15)	0.20
Rating for pain tolerance (MVAS)	46.85 (24.41)	39.23 (23.11)	43.04 (23.78)	0.32

Key
All data are reported as mean (standard deviation) ratings, unless otherwise indicated. NDI= neurodynamic intervention, ROM = Range of Motion, Sensation as measured by Symmes Weinstein monofilament: Normal <=2.83, Min= minimal loss of sensation (3.61 to 4.31), > Min= moderate to severe loss of sensation (>=4.56), ULTT = Upper limb tension test. Performed in this study with a median nerve bias (Coppieters & Butler, 2007;Coppieters & Alshami, 2007). NCS= Nerve conduction study, CSI= Combined Sensory Index, MVAS= Mechanical Visual Analog Scale. Pain threshold and tolerance ratings obtained through quantitative sensory testing.

Table 6-3. Comparison of perceived to actual group assignment.

	Indirect NDI	Direct NDI	Total
Perceived Indirect NDI	7 (39%)	12 (63%)	19 (51%)
Perceived Direct NDI	11 (61%)	7 (37%)	18 (49%)

Participants were asked at 3 week follow up session of study to indicate whether they believed they had received direct or indirect neurodynamic intervention (NDI).

Table 6-4. Immediate effects of NDI on pain perception to QST on evaluation

	Pre direct NDI QST rating	Post direct NDI QST rating	Mean difference in pain rating for direct NDI (Pre-Post)	Pre indirect NDI QST rating	Post indirect NDI QST rating	Mean difference in pain rating for indirect NDI (Pre-Post)
Aδ (47° C)	24.05 (21.01)	21.21 (25.44)	2.85	16.65 (16.48)	17.48 (18.04)	-0.83
Aδ (49° C)	38.16 (25.65)	34.40 (26.23)	3.76	33.48 (22.09)	34.80 (27.46)	-1.32
c- fiber	36.92 (22.56)	38.24 (27.95)	-1.32	33.26 (29.88)	33.11 (28.75)	0.15

Pain ratings to quantitative sensory testing on the initial visit comparing baseline ratings with those immediately following neurodynamic intervention. Associated pain quantified with mechanical visual analog scale for Aδ fiber mediated pain and numerical rating scale for c- fiber mediated pain. All data are reported as mean (standard deviation) ratings, unless otherwise indicated. NDI= neurodynamic intervention

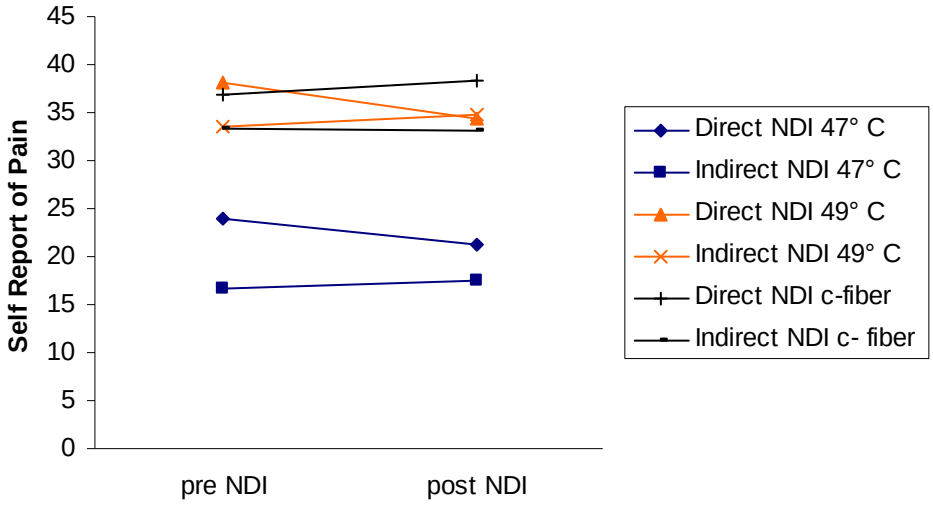


Figure 6-2. Immediate effect of NDI on self report of pain to standardized painful stimuli during evaluation. Pain perception measured with mechanical visual analog scale for 47 and 49° C ratings and using numeric rating scale for c- fiber mediated pain ratings. NDI= neurodynamic intervention.

Table 6-5. Immediate effects of NDI on pain perception to QST at discharge

	Pre direct NDI QST rating	Post direct NDI QST rating	Mean difference in pain rating for direct NDI (Pre-Post)	Pre indirect NDI QST rating	Post indirect NDI QST rating	Mean difference in pain rating for indirect NDI (Pre-Post)
Aδ (47° C)	16.86 (13.56)	15.61 (14.78)	1.25	16.24 (21.42)	19.68 (27.39)	-3.44
Aδ (49° C)	32.66 (22.41)	31.53 (28.68)	1.13	30.15 (29.58)	31.62 (32.49)	-1.47
c- fiber*	43.61 (25.78)	34.86 (24.91)	8.75	43.01 (28.67)	47.16 (32.09)	-4.15

Pain ratings to quantitative sensory testing on the 3 week visit comparing 3 week baseline ratings with those immediately following neurodynamic intervention. Associated pain quantified with mechanical visual analog scale for Aδ fiber mediated pain and numeric rating scale for c- fiber mediated pain. All data are reported as mean (standard deviation) ratings, unless otherwise indicated. NDI= neurodynamic intervention.

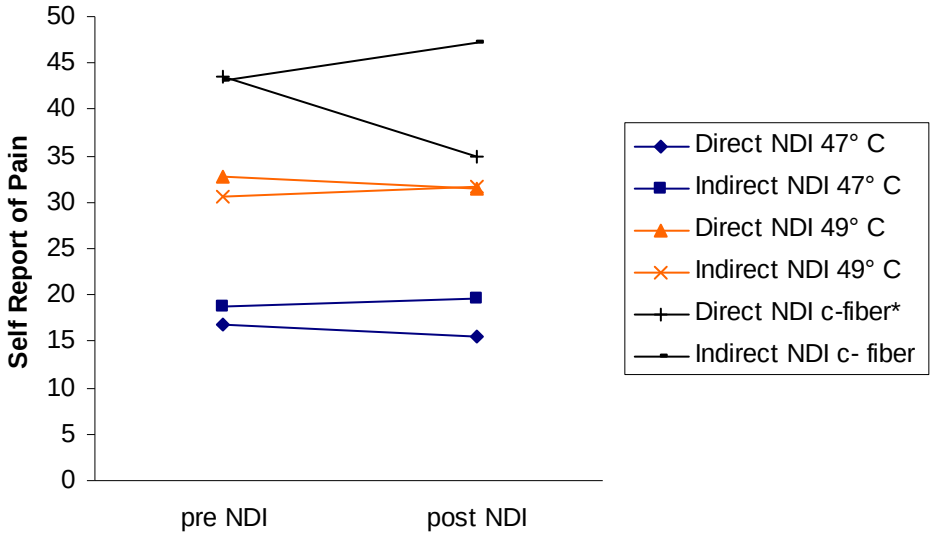


Figure 6-3. Immediate effect of NDI on self report of pain to standardized painful stimuli during discharge. Pain perception measured with mechanical visual analog scale for 47 and 49° C ratings and using numeric rating scale for c- fiber mediated pain ratings. NDI= neurodynamic intervention.

Table 6-6. Longitudinal effect of NDI on pain perception to QST

	Pre direct NDI QST rating	Post direct NDI QST rating	Mean difference in pain rating for direct NDI (Pre-Post)	Pre indirect NDI QST rating	Post indirect NDI QST rating	Mean difference in pain rating for indirect NDI (Pre-Post)
Aδ (47° C)	23.83 (21.12)	15.61 (14.78)	8.22	16.66 (16.93)	19.71 (25.88)	-3.05
Aδ (49° C)	39.53 (25.67)	33.14 (28.61)	6.39	32.92 (22.55)	31.76 (30.70)	1.16
c- fiber	37.18 (23.14)	34.86 (24.91)	2.32	33.26 (29.88)	47.16 (32.09)	-13.90*

Pain ratings to quantitative sensory testing comparing baseline ratings on the initial visit with those immediately following neurodynamic intervention on the 3 week visit. Associated pain quantified with mechanical visual analog scale for Aδ fiber mediated pain and numerical rating scale for c- fiber mediated pain. All data are reported as mean (standard deviation) ratings, unless otherwise indicated. NDI= neurodynamic intervention. *= significant at p≤ 0.05.

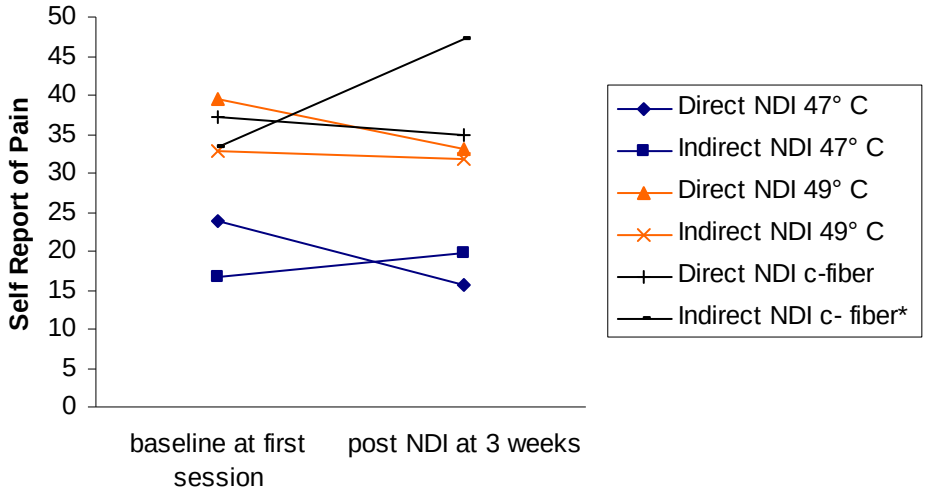


Figure 6-4. Pain perception to standardized thermal stimuli measured longitudinally i.e. baseline at first session to following NDI at 3 weeks. Pain perception measured with mechanical visual analog scale for 47 and 49° C ratings and using numeric rating scale for c- fiber mediated pain ratings. NDI= neurodynamic intervention. * = significant at p≤ 0.05.

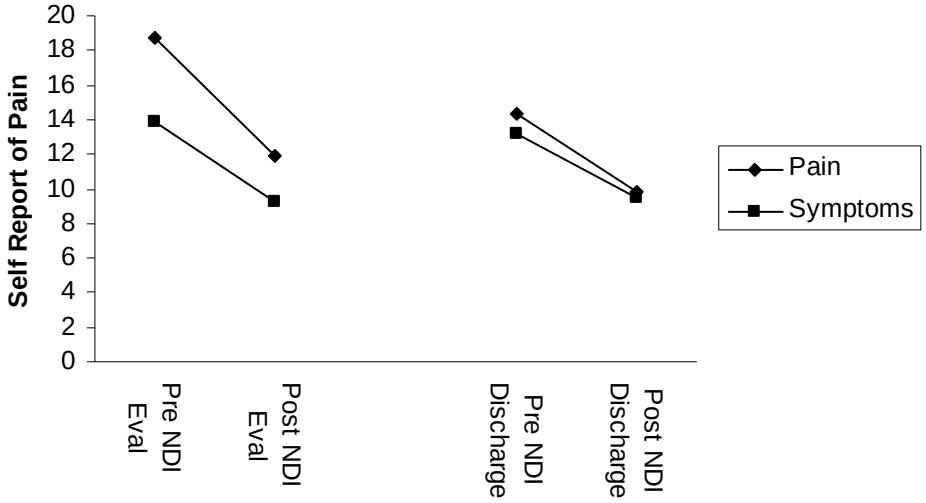


Figure 6-5. Immediate effect of NDI on self report of current carpal tunnel related pain and symptoms. A significant treatment effect ($p<0.05$) independent of group assignment ($p>0.05$) was observed in self reports of pain at evaluation and discharge. A significant treatment effect ($p<0.05$) independent of group assignment ($p>0.05$) was observed for self report of symptoms at discharge; however, significant changes were not observed in symptoms on evaluation ($p>0.05$) Pain and symptom perception were measured with a mechanical visual analog scale. NDI= neurodynamic intervention.

Table 6-7. Baseline to 3 week measures of pain, symptoms, and function for entire sample

	Baseline	3 weeks	p- value for change
Pain	20.46 (15.63)	15.67 (17.00)	0.08
Symptoms	19.31 (16.00)	15.85 (20.51)	0.23
Boston Questionnaire	17.75 (6.34)	16.81(5.8)	0.10
DASH Questionnaire	38.64 (17.31)	33.21 (18.55)	0.01

Key
All data are reported as mean (standard deviation) ratings, unless otherwise indicated.
Pain and symptoms each obtained through mechanical visual analog scale. Ratings of least in past 24 hours, worst in past 24 hours for both pain and symtptoms were obtained and number represents average rating of these 3 values.
Boston questionnaire represents the functional scale
DASH= Disability of arm, shoulder, and hand questionnaire

Table 6-8. Correlation matrix for prediction of rating of pain at 3 weeks

	Pain at discharge	Age	Baseline pain	Change in pain	Baseline expectation
Pain at discharge	1.00				
Age	0.08	1.00			
Baseline pain	0.52*	-0.20	1.00		
Change in pain	-0.20	0.05	0.06	1.00	
Baseline expectation for pain at 3 weeks	0.22	0.21	-0.03	0.19	1.00

Baseline expectation obtained from expectation portion of the PCOQ. *= significant at $p<0.05$

Table 6-9. Regression model for pain at 3 weeks (Full Model)

Model	R	R^2	Adj R^2	F change	p for change
1 Age	0.08	0.01	-0.02	0.24	0.63
2 Age, baseline pain	0.52	0.28	0.24	13.33	<0.01*
3 Model 2 + group assignment	0.54	0.29	0.23	0.83	0.37
4 Model 3 + immediate change in self report of carpal tunnel pain following NDI	0.59	0.35	0.27	3.00	0.09
5 Model 4+ baseline expectation for pain at 3 weeks	0.65	0.42	0.33	4.09	0.05*

Baseline expectation obtained from expectation portion of the PCOQ. *= significant at $p<0.05$

Table 6-10. Regression model for pain at 3 weeks (Individual Variables)

Model	B	Standard error of B	B	p
1				
Age	0.01	0.03	0.08	0.63
2				
Age	0.02	0.02	0.09	0.53
Baseline pain	0.56	0.15	0.52	<0.01*
3				
Age	0.02	0.02	0.12	0.41
Baseline pain	0.55	0.16	0.51	<0.01*
Group assignment	0.45	0.50	0.13	0.37
4				
Age	0.02	0.02	0.14	0.34
Baseline pain	0.57	0.15	0.52	< 0.01*
Group assignment	0.46	0.48	0.14	0.35
Immediate change in self report of carpal tunnel pain following NDI	-0.27	0.15	-0.24	0.09
5				
Age	0.01	0.02	0.08	0.56
Baseline pain	0.57	0.15	0.54	<0.01*
Group assignment	0.48	0.46	0.14	0.31
Immediate change in self report of carpal tunnel pain following NDI	-0.32	0.15	-0.29	0.04*
Baseline expectation for pain at 3 weeks	0.02	0.01	0.28	0.05*

Baseline expectation obtained from expectation portion of the PCOQ. *= significant at p<0.05

Table 6-11. Parsimonious regression model for pain at 3 weeks (Full Model)

Model	R	R^2	Adj R^2	F change	p for change
1 Baseline pain	0.52	0.27	0.25	13.46	< 0.01*
2 Baseline pain + immediate change in self report of CTS pain following NDI	0.57	0.32	0.28	2.88	0.10
3 Model 2 + baseline expectation for pain at 3 weeks	0.63	0.40	0.35	4.60	0.04*

Baseline expectation obtained from expectation portion of the PCOQ. *= significant at p<0.05

Table 6-12. Parsimonious regression model for pain at 3 weeks (Individual Variables)

Model	B	Standard error of B	Beta	p
1				
Baseline pain	0.56	0.15	0.52	<0.01*
2				
Baseline pain	0.58	0.15	0.53	<0.01*
Immediate change in self report of CTS pain following NDI	-0.26	0.15	10.23	0.10
3				
Baseline pain	0.59	0.14	0.54	<0.01*
Immediate change in self report of CTS pain following NDI	-0.32	0.15	-0.29	0.04*
Baseline expectation for pain at 3 weeks	0.03	0.01	0.29	0.04*

Table 6-13. Correlation matrix for prediction of rating of disability at 3 weeks

	Pain at discharge	Age	Baseline DASH	Change in pain	Baseline expectation
DASH at 3 weeks	1.00				
Age	0.41*	1.00			
Baseline DASH	0.82*	0.35*	1.00		
Immediate change in clinical pain following NDI	-0.15	0.06	-0.15	1.00	
Baseline expectation for function at 3 weeks	0.31*	0.03	0.56*	0.18	1.00

* = significant at $p<0.05$

DASH= Disability of Arm, Shoulder, Hand Questionnaire

Immediate change in self report of clinical pain following NDI obtained from mechanical visual analog score of current pain prior to neurodynamic intervention (NDI) and immediately following NDI

Table 6-14. Regression model for disability at 3 weeks (Full Model)

Model	R	R^2	Adj R^2	F change	p for change
1 Age	0.41	0.17	0.15	7.02	0.01*
2 Age, baseline DASH	0.83	0.69	0.68	56.43	<0.01*
3 Model 2 + group assignment	0.83	0.69	0.67	0.00	0.98
4 Model 3 + immediate change in self report of clinical pain following NDI	0.84	0.70	0.66	0.26	0.62
5 Model 4+ baseline expectation for function at 3 weeks	0.85	0.72	0.67	2.36	0.14

DASH= Disability of Arm, Shoulder, and Hand Questionnaire
Immediate change in self report of clinical pain following NDI obtained from mechanical visual analog score of current pain prior to neurodynamic intervention (NDI) and immediately following NDI
Baseline expectation obtained from expectation portion of the PCOQ
*= significant at $p<0.05$

Table 6-15. Regression model for disability at 3 weeks (Individual Variables)

Model	B	Standard error of B	B	p
1				
Age	0.74	0.28	0.41	0.01*
2				
Age	0.25	0.18	0.14	0.18
Baseline DASH	0.83	0.11	0.77	<0.01*
3				
Age	0.25	0.19	0.14	0.18
Baseline pain	0.83	0.11	0.77	<0.01*
Group assignment	0.10	3.66	0.00	0.98
4				
Age	0.27	0.19	0.15	0.18
Baseline pain	0.82	0.12	0.76	<0.01*
Group assignment	0.08	3.71	0.00	0.98
Immediate change in self report of clinical pain following NDI	-0.60	1.19	-0.05	0.62
5				
Age	0.19	0.19	0.11	0.33
Baseline pain	0.96	0.15	0.90	<0.01*
Group assignment	0.92	3.67	0.03	0.80
Immediate change in self report of clinical pain following NDI	0.09	1.25	0.10	0.94
Baseline expectation for function at 3 weeks	-0.17	0.11	-0.20	0.14

DASH= Disability of Arm, Shoulder, and Hand Questionnaire
Immediate change in self report of clinical pain following NDI obtained from mechanical visual analog score of current pain prior to neurodynamic intervention (NDI) and immediately following NDI
Baseline expectation obtained from expectation portion of the PCOQ
*= significant at $p<0.05$

CHAPTER 7
DISCUSSION

Believability of Placebo

We have proposed a model for the mechanistic study of MT. The model allows visualization of the potential mechanisms behind MT (as supported by the current literature) and provides a framework for the design of future studies. The model pathway of the current study is visualized in Figure 7-1. As previously discussed, a weakness of the current mechanistic literature of MT is the failure to adequately account for non- specific effects such at placebo and expectation. A validated placebo does not currently exist for MT. In fact, many prior placebo controlled studies of MT have made use of "placebos" of unknown validity. For example, prior efficacy studies have compared MT to potentially non- similar placebo interventions such as sham laser (Preyde, 2000) or sham ultrasound (Deyle et al., 2000). The use of a non-comparable placebo may be invalid as participants may not be as likely to believe the "placebo" is an actual treatment or may have lower expectations for the placebo than for the studied MT technique. While not studied extensively in MT, the believability and individual expectation of a placebo are important considerations in studies of interventions directed at pain. Similar to MT, acupuncture is an alternative therapy for pain which appears to provide an easier model for a placebo and, in fact, a placebo acupuncture technique has been developed and validated (Pariente et al., 2005). Placebo has been studied more extensively in the acupuncture literature and this body of work may have applicability to MT. Functional imaging studies of acupuncture have noted significant overlap in brain activity between actual acupuncture and placebo acupuncture in which subjects believe they are receiving real acupuncture (Pariente et al., 2005). In contrast, both are dissimilar from placebo acupuncture in which subjects do not believe they are receiving actual treatment. Furthermore, clinical outcomes in acupuncture studies are associated with the

participant's expectations (Kalauokalani et al., 2001;Linde et al., 2007). One study noted no difference between actual and placebo acupuncture in analgesic effect; however, subjects who believed they had received the actual acupuncture treatment experienced significantly less pain than those believing they had received the placebo (Linde et al., 2007). Collectively, these studies suggest the importance of expectation and believability of a given intervention in a placebo controlled study for complimentary and alternative medicine which is likely applicable to MT. The indirect NDI used in our study appears to be a valid placebo in the sense that participants receiving either technique had similar belief's regarding their random assignment of intervention. Subsequently, participants in our study accepted the indirect NDI as an "active" treatment at the same rate as the direct NDI. Interestingly, though not significantly different, a greater percentage of participants receiving the direct NDI reported believing they were receiving the indirect NDI. We did not assess perceived group assignment until the 3 week time point of the study. Future studies may wish to assess perception of group assignment immediately following a brief demonstration of the assigned technique at the initial visit. Quantification of perception at baseline would allow the use of this variable in a regression model as a predictor of future pain or functional outcomes. The design of our study did not allow such an analysis. In addition to the apparent believability of the indirect technique, the expectations for the effectiveness of each intervention were similar. Specifically, individual baseline expectation for pain following participation in the study was similar at baseline and after the participant received a brief demonstration of their assigned intervention. To our knowledge, longitudinal studies of change in expectation have not been performed. While expectation is associated with clinical outcomes, the most informative time point to quantify expectation has not been established. Not only did we observe no between group differences in expectation at

baseline (with presumed lack of specific knowledge of the intervention) and following brief exposure to the intervention, but we also observed a lack of significant main effect between the two time points. Subsequently, a significant change was not observed at baseline or following exposure to the intervention and this suggests that the particular NDI technique used in the current study may not change preconceived expectation. The results of our study indicate that our indirect NDI technique had similar believability and created similar expectations for pain outcomes as the direct NDI in participants presenting with CTS.

Treatment Effects

A second goal of our study was to compare the outcomes in pain and function associated with the direct NDI and the indirect NDI. Prior studies attempting to validate a placebo for MT have emphasized the identification of an inert placebo (Hawk et al., 2002;Hawk et al., 2005;Vernon et al., 2005); however, such criteria may be inappropriate as the placebo literature suggests a robust effect of placebo on pain (Price et al., 2007;Vase et al., 2002;Vase et al., 2003). Clinical studies suggest the same may occur in MT. For example, placebo controlled trials of MT have demonstrated a stronger effect of MT over the placebo group; however, both the intervention and the placebo group have shown significant improvement over non- treatment group (Hawk et al., 2005;Licciardone et al., 2003). The prior studies suggest an appropriate placebo for MT will likely have a significant influence on outcomes and we wished to observe how our indirect NDI compared to the direct NDI.

Response to Experimental Pain

First we observed the perception of experimental pain (QST) and how this differed by intervention. The QST protocols we used in this study includes standard noxious thermal stimuli which have been associated with activity in the dorsal horn of the spinal cord (Craig & Andrew, 2002;Duggan et al., 1990;Jeftinija & Urban, 1994). Subsequently, a benefit of this assessment

over clinical pain assessment is a controlled painful stimulus to which altered pain perception is suggestive of a specific spinal cord mediated effect of MT. In a prior study, we observed hypoalgesia to Aδ fiber mediated pain perception at both 47 and 49° C associated with MT; however, the resultant hypoalgesia did not differ from participants riding a stationary bike or performing lumbar range of motion exercises (George et al., 2006). In the present study, we observed no group dependent or main treatment effects of NDI on pain perception at these temperatures. Similar to our prior studies (George et al., 2006;Bialosky et al., 2008), we observed a c- fiber mediated hypoalgesia in response to MT. Interestingly, the effect was not observed until the three week assessment and was dependent upon group assignment. These findings differ from our prior findings in that our previous studies have included only one session and noted immediate alterations in c- fiber mediated pain perception (Bialosky et al., 2008;George et al., 2006). A potential explanation for the delayed c-fiber mediated hypoalgesia is the difference in biomechanical features of the techniques between our studies. Our pilot studies used a high velocity, low amplitude form of MT. The current study used a slower velocity MT. Several studies have observed greater neurophysiological responses associated with higher velocity and/or more forceful MT (Pickar et al., 2007;McLean et al., 2002;Sung et al., 2005). A plausible explanation is that the biomechanical parameters of the technique used in our first 3 studies produces more immediate neurophysiological responses than the technique in the current study. Additionally, two of our three prior studies included only healthy participants while the current study included individuals with a minimum 12 week history of CTS. Changes in c- fiber mediated pain perception in response to experimental pain are plausibly more difficult to affect in individuals experiencing chronic clinical pain in comparison to the healthy participants in our earlier studies.

In the current study, individual's receiving the direct NDI demonstrated a significant decrease in c- fiber mediated pain perception immediately following the intervention at the 3 week follow up, while those receiving the indirect technique demonstrated a trend toward increased pain perception. A reduction of c- fiber mediated pain associated with MT has been a consistent finding across our studies and represents a potential mechanism for the effectiveness of MT in the treatment of musculoskeletal pain. The c- fibers have been implicated in the progression of acute pain to chronic pain and in the maintenance of chronic pain (Rygh et al., 2005). Subsequently, interventions effective in altering c- fiber mediated pain have potential benefits in halting the progression of acute pain to chronic pain or in the treatment of chronic pain. The collective results of our studies suggest that greater c- fiber mediated hypoalgesia to QST may be observed with MT in comparison to other interventions and these findings are generalized across different types of MT. Specific to the present study, greater c- fiber mediated hypoalgesia was observed in participants with CTS receiving the direct NDI in comparison to those receiving the indirect NDI.

Implications to the Model of the Mechanistic Study of MT

Using the framework of the model, these findings suggest a potential spinal cord mediated effect of MT. Specifically, the associated response of diminished temporal summation suggests a dorsal horn mediated hypoalgesic effect through the c- fibers which differs significantly between the direct and indirect NDI. This finding adds further validity to the proposed placebo in that the direct technique provided greater hypoalgesia than the indirect technique. Subsequently, the indirect technique appears to meet the criteria for an appropriate placebo as it is not distinguishable from the direct technique, does not alter expectation differently than the direct technique, and has a significantly different effect on c- fiber mediated hypoalgesia. These

findings suggest that the indirect NDI used in this study may be an appropriate placebo for further studies of potential supraspinal effects of MT.

Clinical Pain and Symptoms Response

We also studied the effects of NDI on self report of clinical pain and symptoms. We assessed an immediate effect at baseline, an immediate effect at discharge, and the change in self report which occurred over 3 weeks. We found an immediate effect of NDI on self report of CTS pain at both evaluation and 3 week follow up which was not dependent upon group assignment. Additionally, an immediate effect of NDI on self report of symptoms (tingling/numbness) was observed at 3 weeks and this too was independent of group assignment. Interestingly, the participants in our study did not experience a significant reduction in their self report of CTS pain or symptoms over the three week period of the study. Subsequently, both the direct and indirect NDI appear to be effective in producing a transient decrease in pain over multiple sessions and in symptoms over a follow up session which did not correspond to a lasting change in pain or symptoms. These findings suggest that NDI is accompanied by immediate, transient decreases in clinical pain and symptoms which occur regardless of the biomechanical properties of the given intervention; however, are in contrast to responses to experimental pain in which responses were dependent upon the specific technique. Despite the hypoalgesic response to both experimental and clinical pain, longitudinal complaints of pain and symptoms were not altered by participation in this study. These findings are in contrast to others who observed significant decreases in pain and symptoms associated with NDI (Akalin et al., 2002;Rozmaryn et al., 1998;Pinar et al., 2005). One possible explanation for the lack of a lasting change in pain or symptoms in the participants in our study may be the length of our follow up period. Prior studies have observed QST to be predictive of future pain response (Schiff & Eisenberg, 2003;Hartrick et al., 2004;Sterling et al., 2005;Rudin et al., 2008). For example, (Rudin et al.,

2008) observed pre- operative pain sensitivity to QST to be predictive of post operative pain intensity. Group dependent treatment effects were not observed in pain perception to QST in our study until the discharge visit. NDI may require multiple sessions in order to initiate the neuroplastic changes associated with lessening of temporal summation. Longer follow up than the 3 weeks in the current study may be necessary to observe significant changes in self report of CTS pain in individuals receiving NDI. Additionally, our study differed from other studies of the effectiveness of NDI in the treatment of CTS in that other studies were conducted in a clinical setting using participants seeking or referred for treatment (Akalin et al., 2002;Rozmaryn et al., 1998). In contrast, our study occurred in a research setting with participants responding to requests for research participants. Although speculative, the expectations of our participants may have been significantly different than individuals participating in a study as part of their normal clinical care. Furthermore, the participants in our study were informed that they would receive either the direct or indirect intervention while prior studies offered usual care (Akalin et al., 2002;Rozmaryn et al., 1998;Pinar et al., 2005) Prior placebo controlled studies have observed a greater treatment effect when placebo is tested specifically rather than included as a control (Vase et al., 2002). Subsequently, the participant's awareness of the potential to receive an indirect technique may have lessened the magnitude of pain relief in comparison to other studies without the known possibility of receiving a placebo. An interesting observation is that 53% of the participants in our study (including 63% of the participants who received the direct NDI) reported believing they had received the indirect technique. We only assessed perceived group assignment at the end of our study and are therefore, unable to determine if perception of group assignment was causative of clinical pain response or vice versa. Individuals receiving NDI in a clinical setting would likely perceive a direct intervention at a higher rate than we observed. In

summary, we observed transient decreases in pain and symptoms associated with NDI which were not dependent upon group placement. The transient changes combined with the lack of lasting changes in CTS pain and symptoms suggests that future studies may require longer follow up period and perhaps alter the instructional set provided to participants to maximize the magnitude of potential non- specific effects.

Finally, in contrast to what was observed for pain, we observed a main treatment effect for function which was not dependent upon group assignment. Specifically, we observed a significant improvement in self report of function as quantified by the DASH functional questionnaire over three week which did not differ by direct or indirect NDI. Our results are similar to other studies which have observed a significant improvement in function associated with NDI (Pinar et al., 2005;Akalin et al., 2002;Rozmaryn et al., 1998). Interestingly, the biomechanical features of the NDI did not influence the outcome. A general improvement in self report of function was observed whether the participant received the direct or the indirect NDI. These findings are similar to what was observed in immediate effect of NDI on self report of CTS pain in that the use of NDI appeared to be more important than the specific biomechanical mechanism. Furthermore, these findings suggest something other than a biomechanical effect is behind the mechanisms of NDI in the treatment of CTS.

Implications to the Model of the Mechanistic Study of MT

Similar to prior studies (George et al., 2006;Mohammadian et al., 2004;Vernon, 2000;Vicenzino et al., 2001), we observed immediate hypoalgesia of clinical pain associated with MT. The current study adds to this body of literature in that hypoalgesia has been associated with MT (George et al., 2006;Mohammadian et al., 2004;Vernon, 2000;Vicenzino et al., 2001); however, to our knowledge, prior studies have not documented hypoalgesia associated with the particular MT used in the current study (NDI). The model stresses that a biomechanical

force from MT initiates a cascade of neurophysiological effects. The current study suggests that the specific parameters of the biomechanical force are irrelevant in the transient improvements in pain and symptoms associated with NDI in individuals with CTS. Specifically, the participants in our study experienced transient hypoalgesia whether they received a direct or an indirect NDI. The long term (3- week) outcomes in our study were significant only for improvements in function as no significant changes occurred in self reports of pain. Changes in function were not dependent upon group assignment and further suggest a non- specific biomechanical effect of NDI in the mechanism behind the clinical outcomes.

Predictors of Outcomes

Predictors of Pain and Disability

The third goal of our study was to assess individual components of the model as to their ability to predict 3 week outcomes of pain and disability. We observed baseline pain, immediate hypoalgesic response, and baseline expectation for pain at 3 weeks all significantly predictive of clinical pain at 3 weeks. In fact, the final parsimonious model accounted for 40% of the variance in self report of clinical pain at 3 weeks. Our observation of expectation as predictive of 3 week clinical pain ratings is consistent with other studies of musculoskeletal pain in which expectation was predictive of post surgical pain (Pollo et al., 2001), functional outcomes following total joint replacement (Mahomed et al., 2002) and rotator cuff repair (Henn, III et al., 2007), and low back pain treatment outcomes (Goldstein et al., 2002;Heymans et al., 2006;Kapoor et al., 2006;Myers et al., 2008). Specific to MT, a smaller number of studies have observed an association between expectation and outcomes (Kalauokalani et al., 2001;Bialosky et al., 2008). The current study was consistent with prior findings and suggests that expectation predicts a significant amount of the variance in 3 week pain outcomes when controlling for baseline pain and immediate hypoalgesic effect of treatment. Interestingly, expectation was a significant predictor of pain

while group assignment was not. Subsequently, expectation is suggested to play a greater role in the outcomes associated with MT than the actual mechanical properties of the MT. Additionally, we were particularly interested in the predictive value of the immediate clinical pain response to MT. Prior studies of placebo have observed an increased magnitude of the placebo hypoalgesia if the intensity of the stimulus is surreptitiously lessened immediately following the application of the placebo (Price et al., 1999;Colloca & Benedetti, 2006). The participants in our study experienced a main treatment effect of reduced clinical pain immediately following the initial NDI session independent of group assignment. The prognostic value of the immediate clinical pain hypoalgesic response may indicate a direct influence of MT on neuroplastic changes associated with pain (Boal & Gillette, 2004) or a conditioning response related to placebo (Colloca & Benedetti, 2006;Price et al., 1999). The design of our study does not allow more than speculation on the specific mechanism of the prognostic value of immediate clinical pain hypoalgesic effect.

Implications to the Model of the Mechanistic Study of MT

Non- specific effects such as expectation have been implicated in the outcomes of musculoskeletal pain conditions (Myers et al., 2008;Goldstein et al., 2002;Mahomed et al., 2002) and studies have begun to associate expectation with the outcomes following MT (Kalauokalani et al., 2001;Bialosky et al., 2008). The current study provides stronger evidence of a causal relationship between expectation and the outcomes associated with MT in that we observed a longitudinal relationship in individuals experiencing CTS.

Clinical Implications

The current study offers several implications for the clinical use of NDI in the treatment of CTS. First, perception of experimental pain was significantly lessened at the three week follow up session in participants receiving the direct NDI technique. MT has been suggested to exert an

effect upon the neuroplastic changes associated with pain in the central nervous system (Boal & Gillette, 2004). The lessening of temporal summation as observed in the present study is consistent with our prior studies (Bialosky et al., 2008;George et al., 2006) and suggests a potentially similar mechanism. Specifically, central sensitization is characterized by allodynia and hyperalgesia and hypothesized as instrumental in the maintenance of pain conditions (Rygh et al., 2005). Temporal summation serves as a proxy measure of central sensitization and our finding of lessened temporal summation associated with the direct NDI suggests a potential action upon the neuroplastic changes associated with pain. The results of our study suggest the clinical use of NDI may require techniques which provide maximal force and movement to the median nerve in order to affect the neuroplastic changes associated with pain in individuals presenting with CTS. Additionally, neuroplastic changes associated with NDI to the median nerve may not become apparent until several weeks and contrasts to our prior studies of MT to the low back in which reductions in temporal summation were observed immediately following 1 session (George et al., 2006;Bialosky et al., 2008). Subsequently, clinicians using NDI in the treatment of CTS could possibly expect a longer time period to achieve treatment goals than what might be expected with the use of higher force and velocity MT to treat low back pain.

A second clinical implication of the current study is the transient reduction observed in CTS pain and symptoms immediately following the NDI independent of group assignment. Prior studies have observed similar outcomes associated with MT of varying biomechanical features (Hessell et al., 1990;Kent et al., 2005;Ngan et al., 2005). We observed similar findings in that pain and symptoms immediately decreased regardless of whether the NDI was applied in a means to maximally stress and move the median nerve or in a way to reduce the stresses to the nerve. This finding adds to the growing body of literature suggesting outcomes in MT are

dependent upon identifying individuals likely to respond rather than the identification of a specific dysfunction and specific techniques. Concern has been expressed concerning the potential for adverse effects of NDI due to biomechanical stress to the nerves (Shacklock, 2005). Our findings suggest similar transient decreases in clinical pain and symptoms related to CTS may be observed regardless of the biomechanical parameters of the intervention. Subsequently, clinicians concerned for the forces applied with traditional median nerve biased NDI in the treatment of CTS may achieve similar within treatment session results through the use of a technique designed to lessen the mechanical strain.

A third clinical implication of the current study is the 3 week effect on measure of CTS pain and disability. Clinical pain reports did not change significantly from the initial visit to the 3 week follow up. These findings suggest a treatment protocol of splints and NDI for 3 weeks is inadequate to observe a significant lasting change in clinical pain in individuals with chronic CTS. Subsequently, in individuals with a greater than 12 week history of CTS, health care providers may expect no significant changes in clinical pain over the first three weeks with the use of NDI and splints or should consider the additional treatment options if a lasting decrease in pain is a treatment priority for the first three weeks. The non- CTS specific functional questionnaire (DASH Questionnaire) demonstrated a significant improvement over three weeks which was not observed in the CTS specific functional questionnaire (Boston Questionnaire). Despite the significant changes observed in DASH scores, the mean change was 5.43. A clinically meaningful change in DASH score has been suggested as 10 (Gummesson et al., 2003) so our findings are of questionable clinical value. Similar to pain, our findings suggest that 3 weeks is an inadequate time to observe meaningful changes in function in individuals with greater than 12 week history of CTS receiving MT and splints. Clinicians intending to use these

techniques should be aware of this when developing a plan of care for individuals with CTS and should consider alternative treatments if meaningful reductions in disability are desired within a 3 week period.

A final clinical implication is the value of expectation and immediate hypoalgesic effect of clinical pain for predicting pain at 3 weeks. Expectation has been suggested as pertinent in the mechanisms behind the outcomes of MT (Bialosky et al., 2008;Kalauokalani et al., 2001) and the current study re-enforces this notion. Clinicians seeking prognostic indicators may wish to quantify expectation for MT on the initial visit. A patient with higher expectations may strengthen the clinical decision to include MT in the treatment plan. Conversely, in patients with lower expectations for MT, the clinician may wish to consider an alternative form of treatment. Furthermore, our study suggests an immediate hypoalgesic response to NDI in individuals with CTS may serve as a good prognostic indicator. Clinicians may wish to quantify clinical pain immediately prior to and following NDI in individuals with CTS. Based on our observations, NDI may be more effective in individuals experiencing an immediate hypoalgesic effect. Subsequently, future researchers seeking to identify individuals likely to respond favorably to MT may wish to include expectation and an immediate hypoalgesic effect of clinical pain in the tested variables.

Limitations

There are several limitations to the current study. While not intentional, our sample consists only of women. CTS is more common in females (Bongers et al., 2007;Tanaka et al., 1994;McDiarmid et al., 2000), so a higher frequency of women to men was expected; however, with no males represented, the results may not be applicable in men experiencing CTS. A second limitation is the lack of a control group. We are able to compare the findings of the direct to the indirect NDI; however, we are unable to compare either to natural history. Subsequently,

we can not say that our results differ significantly from what would have occurred with no intervention. The lack of a control group also prevents us from commenting on the effect size of the indirect intervention in situations where the groups differ. For example, we observed the direct NDI group to experience significantly less pain perception to c- fiber mediated pain at 3 week follow up than the indirect NDI group; however, we can not ascertain the magnitude of the effect of the indirect NDI in comparison to natural history. A further limitation of this study is our use of the indirect NDI as a placebo. The magnitude of placebo has been observed to be dependent upon a number of factors (Price et al., 1999). In particular, the instructional set given with placebo may influence the magnitude. Specifically, the instruction that a placebo is a "powerful pain killer" has been shown to significantly enhance the effect and particularly in studies where participants are not aware they may be receiving a placebo (Vase et al., 2002;Vase et al., 2003). The participants in our study were aware they had the potential to receive an indirect technique and received no instructional set specific to the pain relieving ability of the NDI. Subsequently, the magnitude of the effect may not have been as high as possible if instructional set was altered. Finally, our indirect technique was based on biomechanical principals to minimize the force and movement through the median nerve in comparison to the direct technique (Coppieters & Butler, 2007;Coppieters & Alshami, 2007). We did not specifically measure the movement or forces associated with either technique and subsequently, are unable to quantify the extent to which they differed.

Future Directions

The present study sets important groundwork for future studies. We have developed a placebo model for NDI which is believable and produces similar expectations as the direct NDI. Future studies are now necessary to clarify the treatment effect. The placebo (indirect NDI) differentiated from the direct NDI in this study in the associated experimental pain perception

observed at 3 weeks. Future studies should provide longer follow up in order to determine if the group differences in experimental pain perception correspond to changes in clinical pain perception.

Future studies should also include a control group to allow comparison to natural history for outcomes in which the direct and indirect NDI do not differ and to allow for determination of the magnitude of placebo effect in outcomes for which they do differ.

Once an adequate placebo model is developed for MT, future studies may also wish to test the placebo alone and include instructional sets suggesting strong analgesic properties as these have been shown to increase the magnitude of the placebo effect (Vase et al., 2002;Vase et al., 2003). Such studies will provide a truer estimate of the effect size of placebo and are likely more representative of the effect observed during clinical care.

Finally, future studies should consider the potential multiple mechanisms of MT. The described model provides a framework for consideration when designing studies of the mechanisms of MT. The mechanisms behind MT are likely multifactorial. Continued attempts should be made to verify individual aspects of the model while continuing to account for others. We believe a priority is to determine the influence and magnitude of non- specific effects on the outcomes associated with MT. Non- specific effects have a potential role in many of the neurophysiological effects associated with MT (Figure 7-2) and have not been adequately accounted for in prior literature. Once the influence of non- specific effects is determined, other pertinent factors may be established.

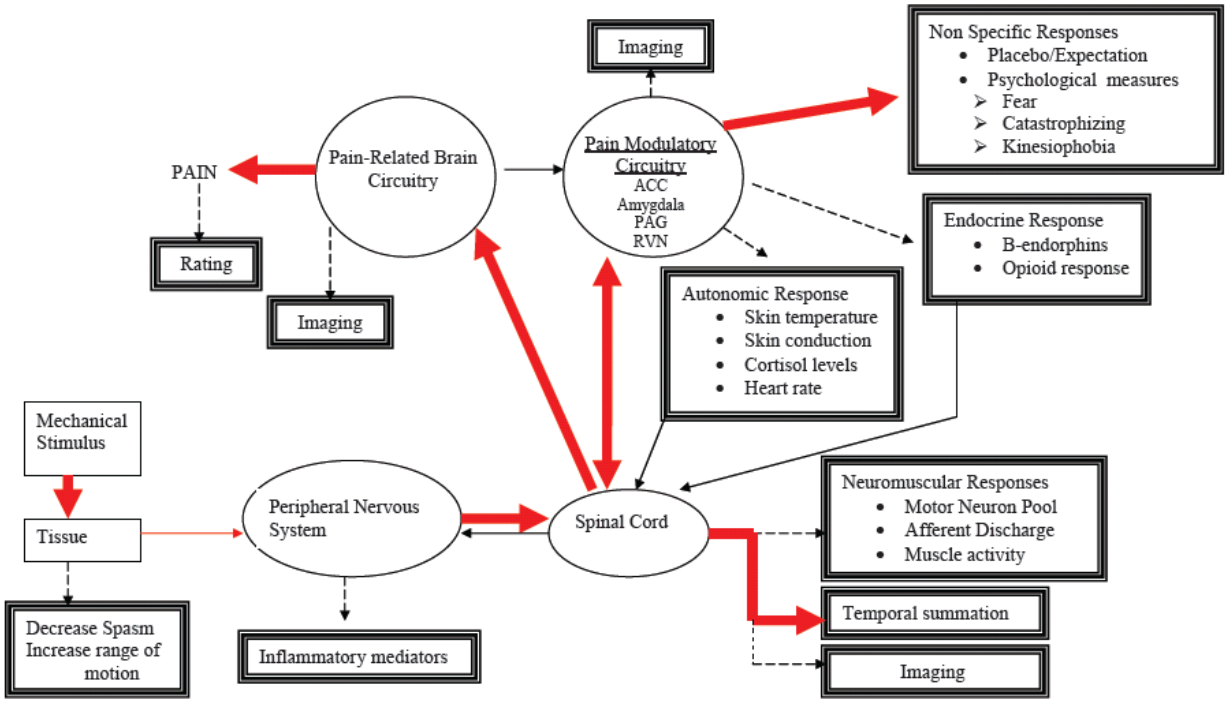


Figure 7-1. Model pathway of dissertation study. Spinal cord mediated effect is inferred by the measurement of an associated response of lessening of temporal summation. Also note, that a supraspinal mediated effect is inferred by the measurement of an associated response of expectation. Note, that consideration is not given in the design of this study to potential peripheral effect. ACC = anterior cingular cortex; PAG = periaqueductal gray; RVM = rostral ventromedial medulla

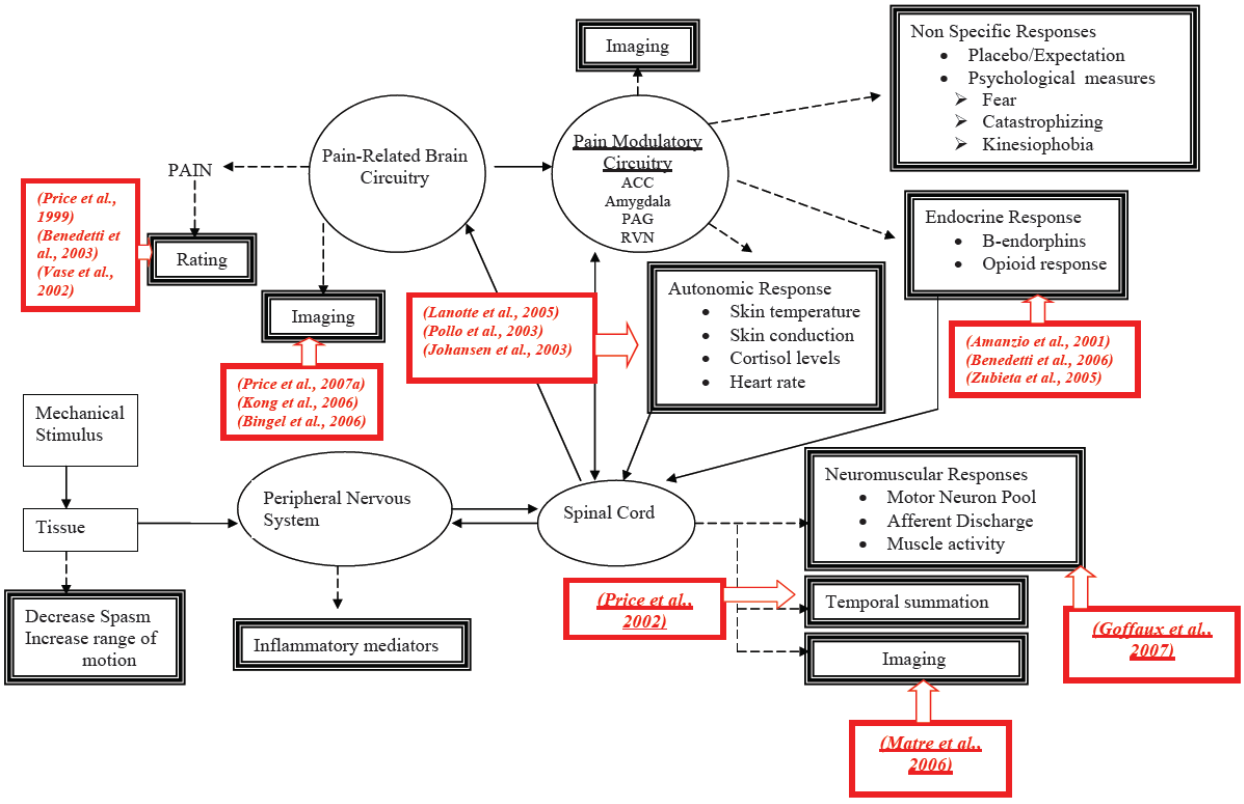


Figure 7-2. Model depicting neurophysiological effects also associated with placebo. Figure emphasizes that many potential mechanisms behind the clinical effectiveness of manual therapy may also be attributed to placebo. An emphasis of future studies should be to determine the magnitude of the placebo effect in the outcomes of manual therapy. ACC = anterior cingular cortex; PAG = periaqueductal gray; RVM = rostral ventromedial medulla

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BIOGRAPHICAL SKETCH

Joel Bialosky graduated from Ithaca college with a bachelor's degree in physical therapy in 1990. He received a master's degree in musculoskeletal physical therapy from the University of Pittsburgh in 1998. He received his PhD in Rehabilitation Science from the University of Florida in 2008.