The Impact of Isometric Exercise on Somatosensory Processing in People with or without Chronic Pain

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THE IMPACT OF ISOMETRIC EXERCISE ON SOMATOSENSORY PROCESSING IN PEOPLE WITH OR WITHOUT CHRONIC PAIN

by

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A Dissertation submitted to the Faculty of the Graduate School,
Marquette University,
in Partial Fulfillment of the Requirements for
the Degree of Doctor of Philosophy

Milwaukee, Wisconsin

December 2019

ABSTRACT

THE IMPACT OF ISOMETRIC EXERCISE ON SOMATOSENSORY PROCESSING IN PEOPLE WITH OR WITHOUT CHRONIC PAIN

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Despite an increase in our understanding of the pathomechanisms of chronic pain and the advancement of new treatments, pharmacological management of chronic pain remains poor. This presents the need for non-pharmacological treatments and understanding their efficacy and mechanisms in managing pain. The purpose of this dissertation was to examine the effects of isometric exercise on the somatosensory system and other biopsychosocial aspects related to pain in individuals with and without fibromyalgia. The first aim was to determine whether isometric exercise improves pain inhibitory mechanisms and vibration sense. The second aim was to determine what biopsychosocial factors influence pain relief following exercise.

In study one, conditioned pain modulation (CPM; a measure of pain inhibitory mechanism) was assessed before and after exercise (submaximal isometric contraction of the knee extensors held for three minutes) and quiet rest in young healthy adults. In study two, CPM and vibration sense were assessed before and after exercise (submaximal isometric contraction of the knee extensors held until exhaustion) and quiet rest in individuals with and without fibromyalgia. In both studies, the influence of biopsychosocial factors (e.g. body composition, physical activity, pain catastrophizing, kinesiophobia, and pain self-efficacy) were assessed.

In study one, local hypoalgesia occurred at the exercising muscle while systemic hypoalgesia was much more variable. CPM decreased at the upper trapezius following exercise in those individuals that reported systemic hypoalgesia and was unchanged in those without systemic hypoalgesia. In study two, local and systemic hypoalgesia occurred with exercise. CPM increased at the deltoid following exercise only in those individuals with impaired baseline CPM irrespective of health status (healthy control or fibromyalgia). Vibration sense increased at a site distal from the exercising muscle (i.e. the index finger). Additionally, pain relief following exercise was not influenced by body composition physical activity, kinesiophobia, and pain self-efficacy.

The results from these studies suggest that CPM and systemic exercise-induced hypoalgesia may have similar mechanisms, and the biopsychosocial factors measured in these studies did not impact the pain relief following exercise. Thus, exercise may be a good modality to restore descending pain inhibition and improve vibratory sense.

ACKNOWLEDGMENTS

Ali Alsouhibani, PT, M.S.

First and Foremost, I would like to thank God, the Almighty, for having made everything possible, giving me strength and courage to complete this work.

Then I would like to thank my advisor, Dr. Marie Hoeger Bement, and express my deepest gratitude and appreciation for her mentorship, encouragement, and guidance throughout my time in the pain laboratory at Marquette University. I would not be who I am today without your continued support during the course of my studies.

I would like to thank, in no particular order, my dissertation committee—Drs. Sandra Hunter, Alexander Ng, Carol Courtney, and Laura Frey Law for their unwavering support and assistance. They provided guidance in all areas that helped me accomplish my research goals and enjoy myself in the process.

In addition, I would like to thank Dr. Henrik Bjarke Vægter, our collaborator in Denmark, who was essential to the first study in this dissertation. His input to the design of the study and suggestions to the manuscript were very valuable.

My colleagues in the pain laboratory and peers in the Clinical and Translational Rehabilitation Health Sciences program, past and present, have been very supportive and encouraging. I learned a lot from our numerous discussions during seminars, lab meetings and other events. Thank you.

A number of individuals involved with data collection, data entry and data checking were extremely helpful to me during this time; I would like to thank them as well. These projects were only possible because of your help and assistance.

Furthermore, I would like to express my sincere appreciation to all the research participants in my studies. They endured the pain and tolerated assessments, all for the sake of science. This work would not be possible without your efforts, time and interest in my studies.

Just as importantly, I would like to thank my wife, Norah Alsuhaibani, and my children, Mohammed and Saleh, who have been an endless source of joy and shared every moment of this process. I could not have done this without you. Thank you for all the sacrifices, patience, support, and love you provided during the past 5 years. I will be forever indebted to you.

Last but not least, I am grateful to my parents, Norah and Mohammed Alsouhibani, and family who supported me throughout my graduate studies, and have been a source of wisdom and inspiration. To them I dedicate this dissertation.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

I. INTRODUCTION AND LITERATURE REVIEW

In the U.S, approximately 1/3 of the population report chronic pain that lasts at least 6 months that cost the U.S economy more than $600 billion annually in lost wages and productivity (Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education, 2011). Chronic pain has been shown to interfere with work, social activities and function reducing overall quality of life (American Pain Foundation, 2006). Despite an increase in our understanding of the pathomechanisms of chronic pain and the advancement of new treatments, pharmacological management of chronic pain remains poor (Turk, Wilson, & Cahana, 2011). Even when pharmacological treatments are effective in reducing pain, they are often presented with numerous side effects and they do not typically enhance physical and emotional functioning and overall health-related quality of life (Turk et al., 2011). One reason for this difficulty in treatment is the complex multidimensional nature of chronic pain. The perception of pain is an interaction between biological, psychological, and sociocultural factors (i.e. biopsychosocial model) (Sluka, 2016). This presents the need for non-pharmacological treatments and understanding their efficacy and mechanisms in managing pain. Exercise is a promising non-pharmacological treatment for patients with chronic pain that has been shown to influence endogenous pain modulation.

Exercise-Induced Hypoalgesia

Exercise is an important treatment modality used in rehabilitation settings for treating patients with chronic pain and is crucial for maintaining physical fitness and overall health. Exercise has been shown to decrease pain induced experimentally in healthy subjects as well as in patients with chronic pain (Naugle et al. 2012). This phenomenon is known as exercise-induced hypoalgesia (EIH) (Koltyn 2000, 2002). The exact mechanism is not completely understood; however, multiple mechanisms have been suggested ranging from peripheral to central mechanisms. Several studies have investigated the role of EIH in healthy individuals and in patients with chronic pain (e.g., osteoarthritis, rheumatoid arthritis and fibromyalgia) and both peripheral and central mechanisms have been considered to be involved in this process (see [Hoeger Bement & Sluka, 2016] for review). However, multiple measurements of pain have been used in the literature to study EIH and results are not always consistent (Naugle et al. 2012).

Different modes of exercise have been shown to reduce pain sensitivity including aerobic, isometric, and dynamic resistance exercise in healthy adults as well as in individuals with chronic pain (Naugle, Fillingim, & Riley, 2012). Previous research has shown that the reduction of pain sensitivity following exercise occurs locally at the exercising muscle (Koltyn, Trine, Stegner, & Tobar, 2001; Kosek & Lundberg, 2003; Umeda, Newcomb, Ellingson, & Koltyn, 2010) and systemically (Hoeger Bement, Dicapo, Rasiarmos, & Hunter, 2008; Koltyn & Umeda, 2007; Kosek & Lundberg, 2003; Lemley, Drewek, Hunter, & Hoeger

Bement, 2014) at remote sites; although greater EIH may occur at the local site compared with distal sites (Vaegter, Handberg, & Graven-Nielsen, 2014b) suggesting both peripheral and central mechanisms may be responsible for EIH. Furthermore, these effects seem to have a dose-response relationship; where a low intensity contraction held for a long duration produces the greatest EIH compared with a low intensity contraction held for a shorter duration (Hoeger Bement et al., 2008; Naugle et al., 2012).

Effects of aerobic exercise in healthy individuals

With aerobic exercise, a single maximal oxygen consumption ($\dot{V}O_2max$) test in young healthy adolescents increased pressure pain thresholds (PPT) (i.e. less pain sensitivity) at the exercising muscle (quadriceps) and at distant sites (deltoid and nail bed) (Stolzman, Danduran, Hunter, & Bement, 2015). However, submaximal aerobic exercise at 50% of $\dot{V}O_2max$ for 20 minutes did not show a significant reduction in PPTs (Vaegter et al., 2014b). This suggests that aerobic exercise needs to be intense enough to show effects. However, Hoffman et al. (2004) have showed a reduction in pressure pain ratings when participants were engaged in longer durations of aerobic exercise at 75% $\dot{V}O_2max$ for 30 minutes, but not when performed for only 10 minutes. In contrast, Ruble et al. (2005) showed no significant change in thermal pain sensitivity for participants performing 75% $\dot{V}O_2max$ for 30 minutes. This discrepancy may be due to methodological differences in testing, as Hoffman et al. used constant pressure on the index finger whereas Ruble et al. used constant heat and cold on the

hand. Of note, Ruble et al. did not find a significant difference between heat and cold, although subjects rated heat as more painful. Using the same measurements as Ruble et al. (2005), another study by Naugle et al. (2014) showed a significant decrease in thermal pain sensitivity when healthy participants performed 25 minutes of aerobic exercise at 50% and 70% Heart Rate Reserve (HRR). Although this disagreement is difficult to explain, some methodological differences did exist. First, the sample used by Naugle and colleagues are younger in age (mean=21.78 years, SD=4.14) as opposed to (mean=32 years, SD=3) in Ruble et al. (2005). Second, the site of measurement was different in the two studies where Naugle et al. (2014) measured thermal sensitivity at the forearm and Ruble et al. measured it at the hand. Also, Naugle et al. (2014) used HRR as the intensity of exercise instead of $\dot{V}O_2max$, which is considered more accurate (Lounana, Campion, Noakes, & Medelli, 2007). Overall, with aerobic exercise, it seems that both intensity and duration are both important to produce hypoalgesia.

Effects of isometric exercise in healthy individuals

Acute isometric exercise has been shown in the literature to reduce pain sensitivity in healthy individuals. Hoeger Bement et al. (2008) have shown a decrease in pain ratings of constant pressure following 3 maximum voluntary contractions (MVC) of the elbow flexors for 2-3 seconds with 1 minute rest between contractions, 80% of MVC held until task failure and 25% of MVC held until task failure but not following 25% of MVC held for 2 minutes. These data

show that both low and high intensity contractions decrease pain, but the low intensity contraction must be held for a longer duration for this to occur. Along those lines, Koltyn et al. (2013) showed a reduction in temporal summation (TS) of repetitive heat stimuli, a measurement thought to represent windup of C fibers in the dorsal horn (Li, Simone, & Larson, 1999; Mendell & Wall, 1965), after isometric contractions of the hand (40% MVC) held until task failure and (25% MVC) for 3 minutes. In addition, performance of isometric contractions of the knee extensors and elbow flexors at 60% MVC twice for 90 seconds (total of 180 seconds) reduced TS of repetitive pressure cuff (i.e., ischemic stimuli) and increased pain tolerance (Vaegter, Handberg, & Graven-Nielsen, 2014a). In the same study, when isometric contractions were performed at 30% MVC held twice for 90 seconds (total of 180 seconds) pain tolerance was increased for both contractions (knee extensors and elbow flexors) but TS of repetitive pressure cuff was only reduced following knee extensors contractions and not following elbow flexors contraction (Vaegter et al., 2014a). This may be due to a larger muscle mass for the knee extensors compared with the elbow flexors. However, when isometric contractions of 25% MVC of the hand were performed for 3 minutes (as opposed to 2 minutes in [Hoeger Bement et al., 2008]) TS of repetitive heat stimuli decreased (Koltyn et al., 2013; Naugle, Naugle, Fillingim, & Riley, 2014). This inconsistency may be due to the different pain induction methods, as discussed earlier with aerobic exercise, since Naugle et al. (2014) and Koltyn et al. (2013) used repetitive heat stimuli to test TS while Vaegter et al. (2014a) and Hoeger Bement et al. (2008) used mechanical stimuli. Also, It’s not clear whether

the results obtained by Vaegter et al. (2014a) were due to the different methods used for testing TS or due to the rest between the two 90 second contractions. Therefore, acute isometric exercise, at a sufficient intensity and duration, has been shown to reduce central pain facilitatory mechanisms (i.e. TS) (Lemley et al., 2014; Vaegter et al., 2014a); however to our knowledge, no study has investigated the effect of acute isometric exercise on central pain inhibitory mechanisms (e.g. Conditioned Pain Modulation [CPM]) (Specific Aim #1).

Effects of dynamic resistance exercise in healthy individuals

Research on the effects of resistance exercise on pain is limited in the literature. Two studies have found that 1 bout of mixed resistance exercises (45 minutes at 75% of 1 repetition maximum [RM]) increases pain threshold and reduces pain ratings of constant pressure (i.e. TS of constant mechanical stimulus) 1 and 5 minutes following the exercise but not 15 minutes following exercise (Focht & Koltyn, 2009; Koltyn & Arbogast, 1998). Only two studies were found to investigate the effect of dynamic resistance exercise on TS of repetitive heat. Bishop et al. (2011) did not observe any reduction in TS when healthy participants performed 3 sets of cervical flexion exercises with 10 repetitions. The reason may be due to low intensity and duration of the exercises performed. As in aerobic and isometric exercises, a high enough intensity and sufficient duration is required to observe changes in TS. However, Alappattu et al. (2011) had tested TS in healthy participants after performing trunk flexion exercises at 80% MVC until fatigue. Interestingly, TS did not change significantly. This could be

attributed to the time of measurement, as TS was measured 48 hours after the performance of exercise. The effect of acute exercise or a single bout of exercise on TS seems to be temporary and does not have long-lasting effects. In the study conducted by Koltyn & Arbogast (1998) reduction in TS was only observed when tested 5 minutes after the exercise and this effect was demolished 15 minutes after exercise. Therefore, from the few studies investigating dynamic resistance exercise, it appears that it may produce hypoalgesia and reduce TS in healthy individuals when performed at a sufficient intensity and duration. Longitudinal studies investigating the effect of resistance exercise programs (e.g., more than 4 weeks) on central pain facilitation and inhibition (e.g. TS and conditioned pain modulation) are required to better understand the long-lasting effect of exercise training.

Effects of exercise in individuals with chronic pain

Studies examining the effects of EIH in populations with chronic pain are limited. Because exact mechanisms of pain modulation and pathophysiology of chronic pain are poorly understood, results of EIH in chronic pain populations are difficult to interpret (Naugle et al., 2012). In a study conducted by Meeus et al. (2014) TS was tested in patients with rheumatoid arthritis and patients with both chronic fatigue syndrome and fibromyalgia before and after performing a single submaximal aerobic test at 75% of age predicted $\dot{V}O_2max$. Interestingly, TS was reduced in patients with rheumatoid arthritis after the exercise but did not change in patients with the both conditions of chronic fatigue syndrome and fibromyalgia,

as well as it did not change in healthy subjects. This indicates that the response to exercise may be different in different chronic pain populations, as the pathophysiology may play a different role in each disease. For example, differences in inflammatory state may explain the difference in their response. In addition, in the case of fibromyalgia, it was found that aerobic exercise to exhaustion (modified Bruce protocol) increased TS of repetitive heat (Vierck et al., 2001), indicating an increase in sensitization.

Initial studies with submaximal isometric exercise in individuals with fibromyalgia reported an increase in pain sensitivity, similar to results following aerobic exercise (Kosek, Ekholm, & Hansson, 1996; Staud, Robinson, & Price, 2005). For example, Staud and colleagues (2005) reported an increase in thermal pain ratings and a decrease in PPTs following a 30% MVC handgrip exercise sustained for 3 minutes in individuals with fibromyalgia compared with healthy controls. Similarly, Kosek and colleagues (1996) reported a decrease in PPTs following a 22% MVC of the knee extensors held until exhaustion or a maximum of 5 minutes in women with fibromyalgia compared with healthy controls. However, a study by Hoeger Bement et al. (2011) found that in women with fibromyalgia there was considerable variability in the pain response following isometric exercise that varied in intensity and duration; with a subgroup of women experiencing an increase in pressure pain threshold and decrease in pain ratings of constant pressure (i.e. reduced pain sensitivity), another subgroup experiencing no change, and another experiencing an increase in pain sensitivity. These results demonstrated that a group of patients with chronic pain

may respond to exercise while others may not respond and the variability in the pain response following exercise may partially be due to the exercising parameters. Determining the parameters of exercise that produce hypoalgesia and understanding the mechanisms of EIH is important in optimizing exercise prescription for patients with chronic pain.

Potential mechanisms of EIH

The mechanisms of EIH are poorly understood, however, opioid and non-opioid mechanisms have been suggested (Hoeger Bement & Sluka, 2016). In animals, administration of naloxone, an opioid antagonist, prevents EIH partially following low intensity aerobic exercise and reverses chronic muscle pain (Bement & Sluka, 2005). In addition, systemic administration of naloxone prevented EIH in mice without tissue injury following wheel running and high intensity swimming (Li, Rhodes, Girard, Gammie, & Garland, 2004; Mazzardo-Martins et al., 2010). These results, therefore, suggest that EIH is mediated, at least in part, by release of endogenous opioids. Furthermore, chronically exercising animals respond less to pharmacological administration of opioids, suggesting cross-tolerance between endogenous and exogenous opioids (Mathes & Kanarek, 2006; Smith & Lyle, 2006). However, results in humans are less consistent; with some studies showing EIH prevention following naloxone administration (Haier, Quaid, & Mills, 1981; Janal, Colt, Clark, & Glusman, 1984) and others showing no change (Droste, Greenlee, Schreck, & Roskamm, 1991; Koltyn, Brellenthin, Cook, Sehgal, & Hillard, 2014). Following exercise training for

4-6 months as an intervention for women with chronic neck pain, beta-endorphins, an opioid peptide, increased along with an increase in PPTs and reduced pain ratings (i.e. hypoalgesia) (Karlsson et al., 2015). The changes in PPTs were not related to the increase in beta-endorphins, suggesting that pain relief following exercise may involve multiple mechanisms.

Serotonergic mechanisms have been implicated in pain relief (Millan, 1999) with serotonin acting as an important neurotransmitter involved in descending inhibitory pathways, including centers in the brainstem such as the periaqueductal gray (PAG) and the rostral ventromedial medulla (RVM) (Basbaum, 1981; Beitz, 1982; Bowker, Westlund, & Coulter, 1982). In animals, the analgesia occurring from muscle simulation is blocked by administering para-chloroamphetamine methyl ester (PCPA), an inhibitor of serotonin synthesis (Hoffmann, Skarphedinsson, & Thoren, 1990). In addition, in healthy non-injured mice, EIH from high intensity swimming was blocked following administration of PCPA (Mazzardo-Martins et al., 2010). Furthermore, in an animal model of neuropathic pain, EIH by treadmill running was blocked by systemic depletion of serotonin (Bobinski et al., 2015). In humans, prolonged gum chewing have been shown to reduce nociceptive withdrawal reflex and pain reports along with an in increase in serotonin levels in the blood stream (Kamiya et al., 2010; Mohri, Fumoto, Sato-Suzuki, Umino, & Arita, 2005). These results suggest the involvement of serotonergic mechanisms of EIH.

Opioidergic and serotonergic mechanisms alone do not fully explain EIH. There is some evidence indicating the interaction of serotonin with the opioid

system to produce hypoalgesia. In animals without tissue injury, induction of muscle pain increases serotonin transporter in the RVM which is prevented by wheel running (Lima, DeSantana, Rasmussen, & Sluka, 2017). In mu-opioid knockout mice and mice administered with naloxone, wheel running did not prevent the increase in serotonin transporter; indicating hypoalgesia is mediated by an interaction between opioid and serotonin. In line with this hypothesis, a recent study investigated the effects of opioid and serotonin transporter genetic polymorphisms on EIH following an isometric contraction of the knee extensors to exhaustion or a maximum of 5 minutes in individuals with and without fibromyalgia (Tour et al., 2017). The authors found that gene-to-gene interactions regulate pain inhibition following exercise, such that greater EIH was associated with individuals having genetically inferred strong opioid signaling combined with weak serotonin signaling.

The role of endocannabinoids in EIH has also been suggested (Dietrich & McDaniel, 2004). In animals without tissue injury, an increase in the expression of cannabinoid receptor CB1 in the brain is found following aerobic and resistance exercise (Galdino, Romero et al., 2014a; Galdino, Romero et al., 2014b) as well as an increase in endocannabinoid plasma levels. In addition, the EIH in these animals was prevented after systemic and central injection of cannabinoid receptors antagonists. In healthy humans, Koltyn et al. (2014) found that following a handgrip isometric contraction for 3 minutes, hypoalgesia occurs along with an increase in circulating endocannabinoids. These studies suggest the involvement of the endocannabinoid system in EIH. However, similar to

serotonergic mechanisms, endocannabinoids do not fully explain EIH which suggest perhaps an interaction with other systems such as opioids. Crombie et al. (2018) explored the possibility of an interaction between opioids and endocannabinoids and found that the increase in endocannabinoid N-arachidonylethanolamine (AEA) following exercise was reduced with administration of naltrexone, an opioid antagonist, compared to placebo.

Another mechanism of EIH that has been proposed is the modulation of the immune system both peripherally and centrally (Sluka, Frey-Law, & Hoeger Bement, 2018). At the muscle, physically active healthy animals have greater macrophages that release anti-inflammatory cytokines (M2) compared to macrophages that release pro-inflammatory cytokines (M1) (Leung, Gregory, Allen, & Sluka, 2016). In addition, local or systemic blockade of IL-10, an anti-inflammatory cytokine, in these animals reversed hypoalgesia by physical activity. These studies suggest that regular exercise can modulate the immune system at the periphery. In healthy humans, regular physical activity reduces pro-inflammatory cytokines (e.g. TNF-α or IL-6) and increases anti-inflammatory cytokines (Jankord & Jemiolo, 2004; Petersen & Pedersen, 2005). In addition, individuals with fibromyalgia following an exercise program improved cytokine profiles (i.e. reduced pro-inflammatory cytokines and increased anti-inflammatory cytokines) (Ortega, Bote, Giraldo, & Garcia, 2012). Therefore, modulation of the immune system peripherally and centrally are possible mechanisms of EIH.

Fibromyalgia Syndrome

Fibromyalgia syndrome (FMS), a chronic pain condition, is characterized by widespread pain in the soft tissue and tender points throughout the body (Neumann & Buskila, 2003). The prevalence of FMS in the general population is 5%, with 80-90% of them being women (Hawkins, 2013). Past research has shown that people with FMS demonstrate central sensitization that is characterized by abnormal endogenous pain modulation such as enhanced pain facilitation (Staud, Vierck, Cannon, Mauderli, & Price, 2001) and reduced pain inhibition (Kosek & Ordeberg, 2000) as well as a reduction in vibratory sense (da Silva, Kazyiama, Teixeira, & de Siqueira, 2013). These changes are related to function, as patients with fibromyalgia are known to have altered functional performance (Costa et al., 2017). Recent studies have suggested that the reduction in vibrotactile sense in patients with chronic pain is caused by abnormal pain processing in the central nervous system (Geber et al., 2008). Therefore, treatments that provide pain relief may also improve vibratory sense. Our laboratory has previously shown that isometric exercise may decrease pain facilitation in healthy individuals (Hoeger Bement et al., 2008; Lemley et al., 2014) and in some individuals with fibromyalgia (Hoeger Bement et al., 2011). Whether exercise improves pain inhibition and/or vibratory sense in patients with FMS remains unclear. It is important to understand the effect of exercise on pain inhibition and vibratory sense in individuals with and without chronic pain to better translate clinically and improve function.

Quantitative Sensory Testing

Quantitative Sensory Testing (QST) is a method that has been used to characterize pain conditions based on mechanisms rather than symptoms (Suokas et al., 2012). The protocol includes the evaluation of responses of the somatosensory system to controlled noxious or non-noxious stimuli such as mechanical, electrical, chemical and/or thermal stimuli (e.g. thresholds, suprathresholds, or tolerance) (Pavlakovic & Petzke, 2010). These responses were categorized previously as static or dynamic measures (Granot, 2009).

Static QST identifies single points along a somatosensory continuum (Uddin & MacDermid, 2016). These measurements may be evaluated locally at the affected site or remotely to assess the peripheral or central nervous system involvement, respectively (Graven-Nielsen & Arendt-Nielsen, 2002). For example, reduced pain thresholds in the upper limb in individuals with knee osteoarthritis indicates sensitization in the central nervous system.

Dynamic QST, on the other hand, disturbs the somatosensory system to evaluate certain mechanism (Arendt-Nielsen & Yarnitsky, 2009). Specifically, these methods have been used to assess the endogenous modulation of pain such as pain facilitation or inhibition. A common method to evaluate pain facilitation and inhibition is TS and CPM, respectively. TS is the excitability of the dorsal horn neurons as a result of repetitive stimulation of the C-fibers (Li, Simone, & Larson, 1999; Mendell & Wall, 1965). Increased TS is indicative of sensitization in the central nervous system (Arendt-Nielsen & Petersen-Felix, 1995; Herrero, Laird, & Lopez-Garcia, 2000; Melzack, Coderre, Katz, &

Vaccarino, 2001) and therefore a decrease of TS is vital in treating patients with chronic pain.

Conditioned pain modulation

Descending inhibitory pathways comprises an important component of endogenous pain modulation. These pathways could be facilitatory or inhibitory (Villanueva, Bouhassira, & Le Bars, 1996). One common pathway is known as the PAG-RVM pathway, which is likely activated by higher centers in the cortex (Neugebauer, Galhardo, Maione, & Mackey, 2009). The PAG, upon activation, sends projections to the spinal cord through the RVM, which results in inhibition of nociception. The stimulation of these centers (i.e. the PAG or RVM) electrically or chemically produces analgesia in animals and humans (Gebhart, Sandkuhler, Thalhammer, & Zimmermann, 1983; Reynolds, 1969). The PAG also sends projections to other nuclei such as the locus coeruleus that, in turn, sends inhibitory projections to the spinal cord (Tsuruoka & Willis, 1996). The exact neurobiological mechanisms of these pathways remain unclear. However, serotonergic, opioidergic, and noradrenergic mechanisms have been implicated (Bannister & Dickenson, 2017).

One method to evaluate central pain inhibition in humans includes CPM, which is described as ‘pain inhibits pain.’ The application of a noxious stimulus at one body location (i.e., conditioning stimulus) attenuates pain reports to another noxious stimulus at a remote location (i.e., test stimulus). This inhibition is the human correlate to diffuse noxious inhibitory control (DNIC) described in the

animal and it's mediated via a spino-bulbo-spinal loop (Le Bars, Dickenson, & Besson, 1979a; Yarnitsky et al., 2010). While the exact anatomical pathway is poorly understood, it is likely different than the PAG-RVM pathway (de Resende, Silva, Sato, Arendt-Nielsen, & Sluka, 2011; Villanueva & Le Bars, 1995). Other nuclei that have been suggested to be involved in DNIC are: subnucleus reticularis dorsalis (SDR), parabrachial nuclei, and locus coeruleus (Bannister & Dickenson, 2017). In animals, lesions in the SDR, but not the PAG or the RVM, results in a diminished DNIC indicating the importance of this structure (Bouhassira, Villanueva, Bing, & le Bars, 1992; Le Bars, Villanueva, Bouhassira, & Willer, 1992). It is not clear whether the SDR then projects directly or indirectly (through other structures) to the spinal cord (Bannister & Dickenson, 2017). In humans, a study using functional magnetic resonance imaging (fMRI) confirmed the importance of the SDR, where the reduction in pain during CPM was associated with a reduction in SDR and parabrachial nuclei signal reductions (Youssef, Macefield, & Henderson, 2016).

The neurotransmitters involved in descending pain inhibition in general and in DNIC/CPM in particular are complex and not fully understood. Opioidergic mechanisms have been implicated in the PAG-RVM pathway (Eippert et al., 2009) as well as early studies investigating DNIC (Le Bars, Chitour, Kraus, Dickenson, & Besson, 1981; Willer, Le Bars, & De Broucker, 1990). Opioids such as morphine can act on the PAG, RVM and spinal cord exerting its analgesic effects (Millan, 2002). In a muscle inflammatory model in rats, injection of naloxone, an opioid antagonist, systemically or in the SDR prevented DNIC

effects but not when injected in the RVM (de Resende et al., 2011). This indicates that DNIC is mediated through opioidergic mechanisms via the SDR and not the RVM. However, in humans results are less consistent with some studies showing a reduction in CPM magnitude following administration of naloxone (Willer et al., 1990) or opioid medications (Arendt-Nielsen et al., 2012) and other studies demonstrating no effect of naloxone (Edwards, Ness, & Fillingim, 2004; Peters, Schmidt, Van den Hout, Koopmans, & Sluijter, 1992) or opioid medication (Suzan et al., 2013) on magnitude of CPM. Therefore, the role if opioids in CPM (in humans) is not clear.

Serotonin and its receptors are available in neurons located in the PAG, RVM and spinal cord and have been implicated in descending inhibition as well as descending facilitation of pain, depending on the specific receptor activated (Beitz, 1982; Bowker et al., 1982). Administration of serotonin to neurons in the spinal cord decreases their activity and results in analgesia (Millan, 1999), suggesting that the PAG-RVM may exert its inhibitory effects through a serotonergic mechanism. However, under certain circumstances and conditions, such as in chronic pain, the serotonergic pathway may switch from being inhibitory to facilitatory (Millan, 1999). Serotonin was also shown to be critical to the DNIC pathway. In a neuropathic pain model in animals, DNIC was restored after application of selective serotonin reuptake inhibitors (SSRIs), indicating the importance of serotonin (Bannister, Lockwood, Goncalves, Patel, & Dickenson, 2017). In humans, lower CPM magnitude was shown to be associated with low

serotonin transporter gene expression (Lindstedt et al., 2011). Thus, serotonergic mechanisms are likely important in the involvement of CPM.

Additionally, the neurotransmitter norepinephrine (i.e. noradrenaline) appears to be crucial in CPM and DNIC pathways. Projections from the locus coeruleus, an essential component of the DNIC circuitry, to the spinal cord are noradrenergic and norepinephrine is primarily found in its nuclei. Stimulation of this region, electrically or chemically, is analgesic and reduces neuronal firing in the spinal cord (Jones & Gebhart, 1987; Li & Zhao, 1993; Tsuruoka & Willis, 1996). However, similar to serotonin, norepinephrine may be inhibitory or facilitatory, dependent on the specific receptor its acting on (Nuseir & Proudfit, 2000). The α_2–adrenergic receptor in the spinal cord is thought to be inhibitory while the α_1–adrenergic receptor is, generally, thought to be facilitatory (Millan, 2002). In animals without tissue injury and a functioning DNIC, administration of α_2–adrenergic receptor antagonists diminished DNIC, indicating a vital role for norepinephrine and the α_2–adrenergic receptor (Bannister, Patel, Goncalves, Townson, & Dickenson, 2015). Therefore, the involvement of noradrenergic mechanisms in CPM are likely.

While the importance of the α_2–adrenergic receptor and norepinephrine was demonstrated in the normal state of DNIC, under pathological conditions restoring DNIC may employ different mechanisms. Namely, interactions with opioidergic and serotonergic systems appear to be important. In an animal neuropathic model, where DNIC is diminished, administration of tapentadol, an opioid agonist and norepinephrine reuptake inhibitor, restored DNIC (Bannister et

al., 2015). Similarly, in patients with neuropathy, tapentadol and duloxetine, a serotonin norepinephrine reuptake inhibitor, were shown to be effective in individuals who had low CPM magnitude, presumably because it restored CPM functionality (Niesters et al., 2014; Yarnitsky, Granot, Nahman-Averbuch, Khamaisi, & Granovsky, 2012). In both studies, the common neurotransmitter was norepinephrine, suggesting that restoring DNIC, and possibly CPM, may require norepinephrine combined with either serotonin or opioid.

Although DNIC has been studied in animals to understand CPM mechanisms in humans, we can only make inferences within the brainstem circuitry (Bannister & Dickenson, 2017). The increased variability of CPM in healthy and patients with chronic pain (Chimenti, Frey-Law, & Sluka, 2018; Potvin & Marchand, 2016) compared to DNIC suggests that there might be differences between animal and human paradigms. In humans, engagement of higher centers in the brain may influence the CPM response and contribute to its variability (Harper et al., 2018). In fact, psychosocial factors have been suggested to contribute to this variability such as expectations (Bjorkedal & Flaten, 2012; Goffaux, de Souza, Potvin, & Marchand, 2009), pain catastrophizing (Edwards et al., 2013; Nahman-Averbuch, Nir, Sprecher, & Yarnitsky, 2016), mood (Edwards, Dolman, Michna et al., 2016), stress level (Geva, Pruessner, & Defrin, 2014), anxiety (Bogdanov et al., 2015; Nahman-Averbuch et al., 2016), and personality traits (Nahman-Averbuch, Yarnitsky, Sprecher, Granovsky, & Granot, 2016). In studies using fMRI, cortical areas such as the anterior cingulate cortex (ACC) (Sprenger, Bingel, & Buchel, 2011) and

the insula (Bogdanov et al., 2015) has been associated with CPM magnitude along with areas in the brainstem region; indicating an influence of other mechanisms in the brain on CPM.

CPM has been used extensively in clinical and experimental research showing its impairment in multiple pain conditions (Lewis, Rice, & McNair, 2012). The increased interest in this measure arises from studies showing its clinical significance in predicting the development of chronic pain (van Wijk & Veldhuijzen, 2010; Yarnitsky et al., 2008) and its potential prognostic value in predicting treatment response (Yarnitsky, 2010). As discussed earlier, Yarnitsky and colleagues have showed that baseline CPM in patients with diabetic neuropathy predicted duloxetine efficacy (Yarnitsky et al., 2012). A similar finding in patients with knee osteoarthritis was reported recently that baseline CPM predicted efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) (Edwards, Dolman, Martel et al., 2016). These predictions are not limited to pharmacological treatments. Recent studies have shown that CPM predicts responses to exercise in healthy adults and adolescents (Lemley, Hunter, & Bement, 2015; Stolzman & Bement, 2016) and patients with chronic pain (Vaegter, Handberg, & Graven-Nielsen, 2016). Specifically, individuals with greater CPM magnitude have greater hypoalgesic responses from exercise. Therefore, increasing the capacity of descending inhibition appears to be vital in the efficacy of chronic pain treatment.

Vibration perception testing

Early QST research have used vibration testing to study mechanisms of touch (Lindblom & Verrillo, 1979), since cutaneous mechanoreceptors (e.g. Merkel cells, Meissner corpuscles, Ruffini endings, and Pacinian corpuscles) also respond to different vibratory frequencies (Gardner & Johnson, 2013b). For example, Merkel cells (innervated by type 1 slow adapting (SA1) axons) respond to vibration frequency between 0-100 Hz. Meissner corpuscles (innervated by type 1 rapid adapting (RA1) axons) respond to vibration frequency between 1-300 Hz. Pacinian corpuscles (innervated by type 2 raped adapting (RA2) axons) respond to vibration frequency between 5-1000 Hz (Gardner & Johnson, 2013b). While these receptors respond to a wide range of vibratory frequencies, there is a certain frequency that they best respond to; it is likely that they overlap in their response to certain frequencies (Bolanowski, Gescheider, Verrillo, & Checkosky, 1988). Vibratory perception testing, hence, examines the somatosensory pathways that are transmitted through large myelinated Aα and Aβ cutaneous sensory fibers (Siao & Cros, 2003). These pathways are mediated through the dorsal column medial lemniscal tract and the dorsal column nuclei in the brainstem. The Aβ fibers (or group II if arising from the muscle), in particular, upon entering the spinal cord divide with some branches ascending ipsilaterally to the medulla and others going into lamina V of the spinal cord. The fibers then cross to the contralateral side at the medulla and terminate in the thalamus then ascend to the primary sensory cortex (Gardner & Johnson, 2013a). Therefore,

the spinal cord, thalamus, and the primary sensory cortex are areas where both noxious and innocuous input are received.

Vibratory perception testing is an integral component of QST, which is a static response using non-noxious stimuli (Lindblom & Verrillo, 1979; Zaslansky & Yarnitsky, 1998). Testing vibration sense is most commonly used in the early detection of neuropathy, specifically diabetic neuropathy (Garrow & Boulton, 2006). As part of the QST battery, vibration testing is recommended in the clinical setting with a graded tuning fork (Rolke et al., 2006). In the research setting, vibration detection is generally measured through electronic instruments such as the biothesiometer (Courtney, Atre, Foucher, & Alsouhibani, 2019; Shakoor, Agrawal, & Block, 2008) or the vibrometer (Dellon, 1983). Despite these recommendations, vibration perception testing is rarely reported in pain research, with the exception of neuropathic pain (Yarnitsky & Granot, 2006).

While centrally mediated changes in patients with chronic pain have been traditionally recognized through evidence of generalized hyperalgesia (Graven-Nielsen & Arendt-Nielsen, 2002; Klede, Handwerker, & Schmelz, 2003), hypoesthesia (i.e. a reduction in sensitivity to sensory stimuli) to innocuous stimuli in this population is also present (da Silva et al., 2013; Leffler, Kosek, & Hansson, 2000; Leffler, Hansson, & Kosek, 2003; Shakoor et al., 2008). The co-existence of systemic hyperalgesia and hypoesthesia may indicate that both of these phenomena are centrally mediated and could potentially be related to each other. Testing hypoesthesia can be done by applying various innocuous stimuli and increasing its intensity until the individual reports sensation (i.e. threshold).

Different sensory modalities have been used in testing hypoesthesia in patients with chronic pain including thermal (heat or cold), mechanical (pressure, vibration, or touch), and movement (propioception) which each provides different information about the somatosensory system.

Clinical and experimental research has suggested that diminished sense of vibration may be due to altered central pain processing rather than peripheral nerve damage (Geber et al., 2008). Experimental induction of noxious heat at the hand has been shown to increase vibration perception threshold (VPT) (meaning it reduces vibration sense) (Apkarian, Stea, & Bolanowski, 1994), a phenomenon that was termed the “touch gate.” This interaction between noxious and innocuous stimuli is not specific to the skin as induction of muscle pain with hypertonic saline inhibits cutaneous touch (Stohler, Kowalski, & Lund, 2001). Also, Geber and colleagues have showed that tactile hypoesthesia caused by various types of experimental pain last longer than the pain itself (Geber et al., 2008); this suggests that the pain-induced changes in vibrotactile sense are due to changes in the central nervous system rather than peripheral sensitivity.

The mechanisms underlying pain-related hypoesthesia are not completely understood, however spinal, supraspinal and cortical mechanisms have been proposed. Apkarian et al. (1994) proposed that since vibrotactile information is mediated primarily through the dorsal column nuclei that receive input directly from dorsal column tracts which bypass spinal cord processing, a supraspinal mechanism is likely. They suggested the thalamus as a location considering that noxious and innocuous sensory information converge. Alternatively, a spinal

mechanism was suggested by Magerle and Treede (2004). They proposed a presynaptic inhibition of primary afferent Aβ-fibers caused by C-fiber input. Specifically, inhibition of sensory information transmitted via Aβ (Group II) fibers may be caused by noxious C (Group IV) fiber input from the periphery, through interneuronal connections, at the spinal level. Perhaps since spinal processing of both Aβ- and C-fibers occur through interneurons in laminas III to V that project to the brain, it is possible that modulation of innocuous stimuli happens there. Cortical mechanisms of pain-related hypoesthesia has also been proposed. Hollins et al. (1996) found that vibrotactile thresholds are elevated (i.e. worse) in individuals with temporomandibular disorder (TMD) compared to healthy control participants and suggested an interaction between clinical pain and innocuous stimuli in the primary somatosensory cortex. Specifically, it was suggested that Brodmann area 3a, which receives input from noxious stimuli, inhibits neurons in area 3b, which receives non-noxious inputs, in the primary somatosensory cortex (Hollins, Sigurdsson, & Morris, 2001). While it is still unclear where this interaction between noxious and non-noxious input is happening, this phenomenon suggests that if pain is reduced then vibration sense should improve.

Finally, the importance of including VPT measurement stems from the fact that it could potentially be related to poor functional outcomes and performance. For example, deficits in vibration detection have been associated with altered joint loading (Shakoor et al., 2012) and perceived instability during functional tasks (Kavchak et al., 2012) in individuals with knee osteoarthritis. In addition, in

individuals with multiple sclerosis, worse vibration thresholds were associated with worse walking and balance outcomes as measured with functional tests such as the 6 minute-walk (6MW), timed up and go, and the berg balance tests (Uszynski, Purtill, & Coote, 2015). Previous research has shown that people with fibromyalgia have decreased vibratory sense (da Silva et al., 2013) in addition to poor walking and balance performance (Costa et al., 2017). It is not known whether exercise improves vibration sense and whether this change, if any, parallels CPM.

Similarities Between EIH and CPM

Although both EIH and CPM evoke pain inhibition, it is unclear if they engage in similar neurobiological mechanisms. Certainly, EIH and CPM have similar manifestations in humans including systemic hypoalgesia in healthy individuals (Lemley et al., 2015; Stolzman & Bement, 2016; Vaegter et al., 2014b), interaction with the opioid systems (Janal et al., 1984; Le Bars et al., 1981; Smith & Yancey, 2003; Willer et al., 1990), and impaired responses in patients with chronic pain (Fingleton, Smart, & Doody, 2016; Vaegter et al., 2016). As discussed above, both CPM and EIH may activate the opioid system. Animal studies have demonstrated that injection of naloxone systemically partially prevents EIH and DNIC (Bement & Sluka, 2005; Le Bars et al., 1981; Mazzardo-Martins et al., 2010). The involvement of opioids in humans are less consistent for both CPM and EIH (Droste et al., 1991; Edwards et al., 2004; Haier et al., 1981; Janal et al., 1984; Koltyn et al., 2014; Peters et al., 1992; Willer et

al., 1990). In addition, serotonergic mechanisms have been implicated in both CPM and EIH. In animals, injecting PCPA, an inhibitor of serotonin synthesis, prevents EIH from muscle stimulation (Hoffmann et al., 1990) and high intensity swimming (Mazzardo-Martins et al., 2010). DNIC is restored in animals of neuropathic pain after application of SSRI (Bannister et al., 2017) and lower CPM is associated with having low serotonin transporter gene (Lindstedt et al., 2011). Thus, opioidergic and serotonergic mechanisms are involved in both CPM and EIH.

Although opioids and serotonin are involved with both CPM and EIH, neither mechanism alone explains the inhibition, indicating an interaction with more than one mechanism. For example, interactions with the opioid system have been suggested with exercise and CPM. With exercise, serotonin and endocannabinoids interact with the opioid system to produce hypoalgesia (Crombie et al., 2018; Tour et al., 2017). With CPM, opioids and serotonin interact with norepinephrine to produce hypoalgesia (Niesters et al., 2014; Yarnitsky et al., 2012). Exercise may also increase levels of norepinephrine, contributing to mechanisms of CPM. It is not known whether these mechanisms are activated together or separately to produce hypoalgsia; nevertheless, some suggest that activation of the specific descending inhibitory mechanism may depend on parameters of CPM stimulation (Nahman-Averbuch et al., 2016) or exercise (Mogil & Belknap, 1997; Naugle et al., 2012).

In addition, similar cardiovascular responses and stimulated cortical areas have been shown with exercise and CPM. The stress response system, including

the hypothalamus-pituitary-adrenal axis and the autonomic nervous system is activated during CPM and exercise (Chrousos & Gold, 1992). This activation results in the release of hormones such as norepinephrine which may, on the level of the spinal cord, result in hypoalgesia. In addition, vasoconstriction could be caused in the non-active muscle during exercise and during CPM (Seals, Taylor, Ng, & Esler, 1994). This, in turn, may increase blood pressure and stimulate baroreceptors that may activate similar brain regions that are involved in pain inhibition such as the ACC, PAG, RVM, and the locus coeruleus (Bruehl & Chung, 2004; Ghione, 1996). Therefore, the similar cardiovascular response of both CPM and EIH may act on the same brain regions and result in descending pain inhibition.

Besides the potential for shared mechanisms (Figure I.1), CPM may contribute to EIH (Lemley et al., 2015; Weissman-Fogel, Sprecher, & Pud, 2008). Specifically, exercise may act as a painful conditioning stimulus, thereby, activating descending inhibitory pathways resulting in systemic hypoalgesia (Weissman-Fogel et al., 2008). This is supported in young healthy adults in which greater hypoalgesia was observed following painful aerobic or isometric exercise compared to non-painful exercise (Ellingson, Koltyn, Kim, & Cook, 2014; Hoeger Bement et al., 2008). Moreover, CPM has been shown to predict EIH in young and old healthy individuals (Lemley et al., 2015) as well as in patients with chronic musculoskeletal pain (Vaegter et al., 2016). In individuals with knee osteoarthritis (OA), those who had normal CPM response experienced EIH

similar to age-matched controls, whereas individuals with abnormal CPM did not experience EIH (Fingleton et al., 2016).

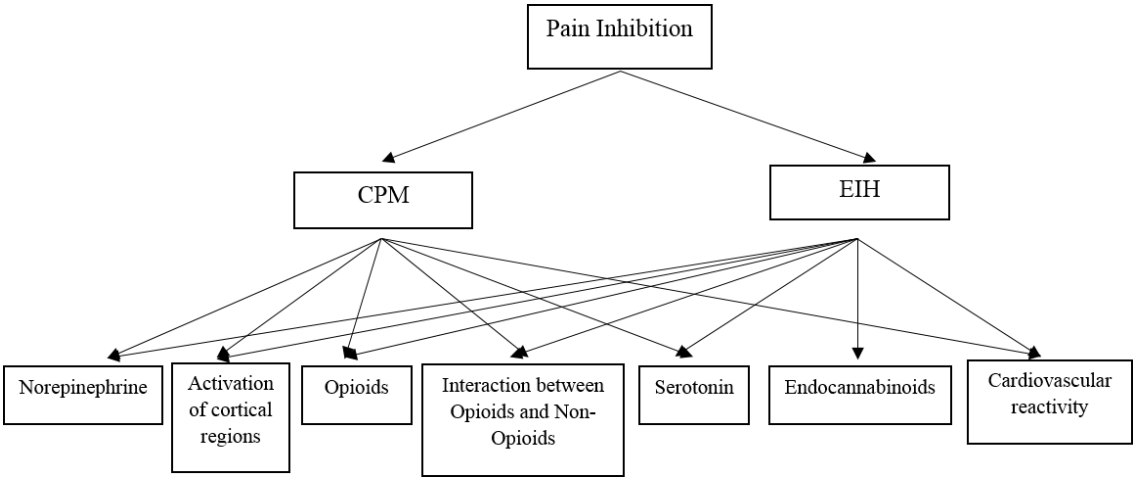


Figure I.1 Potential shared mechanisms between conditioned pain modulation (CPM) and exercise induced hypoalgesia (EIH)

Few studies have examined CPM following an intervention. Dailey et al. (2013) has demonstrated that impaired CPM in individuals with fibromyalgia is restored after the application of transcutaneous electrical nerve stimulation (TENS). Another study has shown enhanced CPM responses in individuals with knee OA after joint mobilization (Courtney, Steffen, Fernandez-de-Las-Penas, Kim, & Chmell, 2016). In addition, enhanced CPM responses were observed in healthy men after transcranial direct current stimulation (tDCS) to the motor cortex (Flood, Waddington, & Cathcart, 2016). Exercise is a modality that is known to activate the motor cortex and may potentially enhance the CPM response in healthy individuals.

Therefore, the main aim of this dissertation was to evaluate CPM following isometric exercise in healthy individuals and individuals with FMS. Given the similar mechanisms between CPM and EIH just discussed, we expect that exercise will contribute to CPM and further enhance its analgesic response immediately following acute isometric exercise. In addition, it is not known if the effects of EIH are specific to pain or extend to the somatosensory system (e.g. vibration sense). Cross-sectional studies have demonstrated better vibration perception acuity in athletes compared to normal healthy controls and vibration perception threshold was correlated with $\dot{V}O_2max$ (Tesarz, Gerhardt, Schommer, Treede, & Eich, 2013). This may indicate that exercise may enhance the perception of vibration leading to better function. To our knowledge, no study has examined the acute effects of isometric exercise on vibration perception (Specific Aim #1).

Factors Contributing to EIH and CPM

Body composition

Evidence on the role of body composition in CPM and/or EIH is scarce. However, recently Stolzman and Hoeger Bement found that CPM was related to lean mass in adolescents across weight status (Stolzman & Hoeger Bement, 2016). In addition, adolescents with higher total body lean mass were found to have greater EIH (Stolzman et al., 2015). One other study has investigated the role of subcutaneous fat on pain sensitivity measures including thermal detection,

pain thresholds, and CPM (Price, Asenjo, Christou, Backman, & Schweinhardt, 2013). When tested on the abdomen, an area with excess subcutaneous fat, the authors found that obese participants were less sensitive to noxious and innocuous stimuli compared to normal weight participants; this sensitivity was correlated to adiposity. However, CPM was not different between the groups in areas with little subcutaneous fat (the forehead). This suggests that body composition might play a role in CPM and EIH in individuals across weight status. The effect of body composition on CPM or EIH is not known in individuals with FMS. Part of this dissertation investigated the role of body composition in CPM and EIH (Specific Aim #2).

Physical activity

Physical activity is an important factor that impacts pain perceptions and overall health. Healthy individuals who self-report higher physical activity show a greater CPM response compared to their less active counterparts (Lemley et al., 2015; Naugle & Riley, 2014; Stolzman & Bement, 2016). In addition, using accelerometery, vigorous intensity physical activity was shown to be related to the magnitude of CPM in healthy men and women (Umeda, Lee, Marino, & Hilliard, 2016). In regards to EIH, adolescents with greater sedentary bouts show less EIH (Stolzman et al., 2015). Besides its effect on CPM or EIH, physical activity was demonstrated to be inversely related to muscle pain during exercise in women with and without fibromyalgia (Umeda, Corbin, & Maluf, 2015). This may have a great impact on exercise adherence in people with chronic pain, as it

is thought that they are deconditioned and less physically active. Therefore, it is important to understand the role of physical activity in CPM and EIH to better translate this to rehabilitation settings. This dissertation measured self-reported and objective physical activity and investigated its role in EIH (Specific Aim #2).

Pain catastrophizing

In individuals with and without chronic pain, psychosocial factors are widely acknowledged to contribute to the experience of pain (Sluka, 2016). Pain catastrophizing is an exaggerated negative mental state during an actual or anticipated pain experience (Sullivan, Bishop, & Pivik, 1995). Pain catastrophizing has been shown to reduce CPM in healthy adults (Goodin et al., 2009). In people with chronic pain, catastrophizing has been found to predict poor outcomes following an exercise-based rehabilitation program (Cecchi et al., 2011) and were related to less favorable treatment effects (Edwards, Bingham, Bathon, & Haythornthwaite, 2006). Specific to EIH, pain catastrophizing has not been investigated in people with fibromyalgia. Unlike trait or dispositional pain catastrophizing, which characterizes catastrophizing in general, the situational or state-like catastrophizing is related to a specific pain experience and may contribute uniquely to pain in laboratory settings (Edwards et al., 2006). In healthy men and women, situational pain catastrophizing was shown to predict change in TS after exercise (Brellenthin, Crombie, Cook, Sehgal, & Koltyn, 2017). In this dissertation we used both to identify the influence of dispositional

pain catastrophizing as well as situational that is specific to the pain experience before and after exercise.

Fear of movement

Fear of movement is frequently reported by individuals with fibromyalgia (Burwinkle, Robinson, & Turk, 2005) and fear avoidance behaviors are known to exist in patients with chronic pain such as low back pain. Fear avoidance behaviors result in increased disability and present an obstacle for recovery from acute and chronic low back pain (Rainville et al., 2011). Clinically, using a fear avoidance behavior-based intervention such as graded exposure to treat patients with chronic pain shows promise in pain management (George & Zeppieri, 2009). It has been shown also that fear avoidance behaviors are highly prevalent in patients with FMS and it is related to the severity of symptoms, self-reported quality of life and disability (Nijs et al., 2013). Moreover, in people with chronic musculoskeletal disorders, fear of movement was related to reports of pain during physical activity (Damsgard, Thrane, Anke, Fors, & Roe, 2010). Minimizing movement may decrease pain reported during exercise as well as following exercise.

Pain self-efficacy

Pain self-efficacy refers to the ability of the individual to have coping mechanisms with regards to pain. This construct was first derived from the social

learning theory, where self-efficacy is described as the level of confidence an individual has in regards to achieve a specific outcome (Bandura, 1977). Self-efficacy has been linked to pain as well as physical activity, and it has been shown that having higher self-efficacy predicts better functional outcomes. Bandura et al. showed that the perceived confidence in tolerating pain predicted actual tolerance of pain irrespective of controlling the pain pharmacologically or cognitively (Bandura, O'Leary, Taylor, Gauthier, & Gossard, 1987). In patients with chronic knee osteoarthritis who had higher self-efficacy in controlling their pain, had higher pain thresholds and tolerance compared to patients with lower self-efficacy (Keefe, Lefebvre, Maixner, Salley, & Caldwell, 1997). In addition, in patients with chronic low back pain, higher self-efficacy in carrying out a specific activity was correlated with their ability in the actual performance of that activity (Council, Ahern, Follick, & Kline, 1988). The influence of pain self-efficacy on EIH has not been investigated. Therefore, this dissertation examined the effects of pain self-efficacy on EIH in people with and without FMS (Specific Aim #2). The potential benefits of investigating these constructs and clinical implications would include the focus on strategies that promotes self-efficacy at the beginning of the intervention and potentially engagement of it throughout the treatment plan.

Significance and Purpose

Restoring CPM has been shown to be critical in the management of chronic pain (Dailey et al., 2013; Yarnitsky et al., 2012); therefore, understanding the effects of exercise on CPM allows for a more personalized use of exercise in

rehabilitation settings. Because the effects of isometric exercise on CPM in healthy individuals has not been previously investigated, this dissertation tested the effects first in young healthy individuals (study one) following a 30% MVC of the knee extensors sustained for 3 minutes. The second study in this dissertation (chapter 3) investigated the effects of isometric exercise on CPM in individuals with and without FMS. CPM was measured following 30% MVC of the knee extensors until task failure.

Another part of this dissertation was to investigate the effects of isometric exercise on vibration sense. Reduced vibration sense in individuals with chronic pain (da Silva et al., 2013; Shakoor et al., 2008) has been associated with poor functional outcomes (Kavchak et al., 2012; Shakoor et al., 2012); and individuals with FMS have been shown reduced vibration sense (da Silva et al., 2013) in addition to reduced functional performance (Costa et al., 2017). It has been suggested that the changes in innocuous perception in individuals with chronic pain are centrally mediated (Geber et al., 2008), similar to the changes in pain processing. Considering that innocuous perception, such as vibration sense, are influenced by pain (i.e. existing pain reduces innocuous perception) (Apkarian et al., 1994) and exercise may reduce pain; we propose that following exercise, as hypoalgesia occurs (pain reduces), vibration sense will improve. The effects of isometric exercise on vibration sense was investigated in study two (chapter 3). Studying the effects of isometric exercise on vibration sense and the mechanisms underlying these effects has the potential to facilitate our

understanding in how rehabilitation may influence sensory perception and possibly function.

Finally, numerous factors have been suggested to modulate or effect EIH in individuals with and without FMS. These factors include body composition, physical activity, and psychosocial factors. In the first study in this dissertation (chapter 2), the effects of body composition, self-reported physical activity, and pain catastrophizing on EIH in young healthy adults were studied. In study two (chapter 3), the effects of the aforementioned factors along with accelerometery measured physical activity, fear of movement, and pain self-efficacy on EIH in individuals with and without FMS were studied. Knowing what factors influence the pain relief following exercise has the potential to be used in clinical practice. This in turn help us understand whether incorporating strategies such as reducing pain catastrophizing and fear of movement and increasing pain self-efficacy is of particular importance.

Based on this past research and to fill the significant gaps in the nonpharmacological management of pain, the following aims are being proposed:

Specific Aims and Hypotheses

Aim 1: Examine the effect of isometric exercise on vibratory sense and CPM in healthy individuals and in patients with FMS.

Hypothesis: Isometric exercise will enhance CPM and improve vibratory sense.

Sub aim 1: Examine the effect of a 30% MVC of the quadriceps muscle held for 3 minutes on CPM in young healthy individuals.

Sub aim 2: Examine the effect of a 30% MVC of the quadriceps muscle held to exhaustion on CPM and vibratory sense in patients with FMS and age matched controls.

Aim 2: Determine factors that impact the pain response following isometric exercise in healthy individuals and in patients with FMS.

Hypothesis: Lower fat mass, greater lean mass, higher physical activity levels, higher pain self-efficacy, and lower pain catastrophizing and fear of movement will be related to greater EIH.

Sub aim 1: Determine factors that impact the pain response following a 30% MVC of the quadriceps muscle held for 3 minutes in young healthy individuals.

Sub aim 2: Determine factors that impact the pain response following a 30% MVC of the quadriceps muscle held to exhaustion in patients with FMS and age matched controls.

II. SYSTEMIC EXERCISE-INDUCED HYPOALGESIA FOLLOWING ISOMETRIC EXERCISE REDUCES CONDITIONED PAIN MODULATION

This is a pre-copyedited, author-produced version of an article accepted for publication in *Pain Medicine* following peer review. The version of record [Ali Alsouhibani, Henrik Bjarke Vaegter, Marie Hoeger Bement, Systemic Exercise-Induced Hypoalgesia Following Isometric Exercise Reduces Conditioned Pain Modulation, Pain Medicine, Volume 20, Issue 1, January 2019, Pages 180–190] is available online at: https://doi.org/10.1093/pm/pny057.

Introduction

Conditioned pain modulation (CPM) and exercise-induced hypoalgesia (EIH) have similar manifestations in humans including systemic hypoalgesia in pain-free individuals (Lemley et al., 2015; Stolzman & Bement, 2016; Vaegter et al., 2014b), interaction with the opioid systems (Janal et al., 1984; Le Bars et al., 1981; Smith & Yancey, 2003; Willer et al., 1990), and impaired responses in patients with chronic pain (Fingleton et al., 2016; Vaegter et al., 2016). Furthermore, CPM, which is often described as ‘pain inhibits pain,’ may contribute to EIH (Lemley et al., 2015). Specifically, exercise may act as a painful conditioning stimulus, thereby, activating descending inhibitory pathways resulting in systemic hypoalgesia (Kosek & Lundberg, 2003; Lemley et al., 2014). This is supported in young healthy adults in whom greater hypoalgesia was observed following painful aerobic or isometric exercise compared with non-

painful exercise (Ellingson et al., 2014; Hoeger Bement et al., 2008). Moreover, CPM has been shown to predict EIH in young and old healthy individuals (Lemley et al., 2015) and in patients with chronic musculoskeletal pain (Vaegter et al., 2016). In individuals with knee osteoarthritis (OA), those with normal CPM responses experienced EIH, whereas individuals with abnormal CPM did not experience EIH (Fingleton et al., 2016).

Physical activity level and body composition may contribute to both EIH and CPM. For instance, physically active individuals show a greater CPM response compared with their less active counterparts (Lemley et al., 2015; Naugle & Riley, 2014; Stolzman & Hoeger Bement, 2016), and EIH is less in adolescents with greater sedentary bouts (Stolzman et al., 2015). In relation to body composition, CPM efficiency was related to lean mass in adolescents (Stolzman & Hoeger Bement, 2016), and adolescents with higher total body lean mass experience greater EIH (Stolzman et al., 2015). Thus, similar contributing factors, such as physical activity and body composition, influence how people respond to a potentially noxious stimulus (i.e., exercise or a conditioning stimulus).

Acute isometric exercise has been shown to reduce central pain facilitatory mechanisms (i.e. temporal summation of pain) (Vaegter et al., 2014a); however to our knowledge, no study has investigated the effect of acute isometric exercise on central pain inhibitory mechanisms (i.e. CPM). Previous research has shown that stimulation of the motor cortex, via transcranial direct current stimulation, enhances CPM in healthy men (Flood et al., 2016).

Accordingly, activation of the motor cortex occurs with exercise and may enhance the CPM response.

Initially, CPM was used to quantify efficiency of descending pain inhibition in healthy and clinical populations (Lewis et al., 2012). This technique has progressed to predict non-pharmacological treatment responses (Lemley et al., 2015; Stolzman & Bement, 2016; Vaegter et al., 2016) and identify how treatments impact endogenous pain modulation. Therefore, repetitive CPM testing is frequently done within and between sessions. The reliability of CPM depends on the parameters of stimulation, study methodology, and study population (Kennedy, Kemp, Ridout, Yarnitsky, & Rice, 2016). Research is ongoing to identify if CPM reliability is consistent across these parameters.

The primary aim of this study was to investigate both the local (quadriceps) and systemic (upper trapezius) effects of lower extremity isometric exercise on the CPM response in young healthy individuals. Moreover, the experimental design allowed for investigation of the between- and within-session reliability of CPM. Because physical activity and anthropometrics may influence CPM and EIH, these measures were also included. It was hypothesized that 1) isometric exercise would enhance the CPM response in young healthy individuals and 2) CPM would have fair to good between- and within-session reliability.

Methods

Subjects

Thirty young healthy and pain-free men and women (mean age, 19.3 ±1.5 years; 15 females) completed the study. Individuals were excluded from the study if they presented with the following: 1) acute or chronic pain, 2) mental health disorder, 3) history of traumatic injury or neurological disorder, 4) inability to tolerate ice water (e.g. Reynaud's disease or cold urticaria), 5) or contraindication to exercise. Screening done via the phone eliminated two potential participants. On the days of testing, participants were asked to refrain from exercise. The protocol was approved by the Institutional Review Board at Marquette University.

Experimental design

Participants completed one familiarization session and two randomized and counterbalanced experimental sessions (isometric exercise or quiet rest) that were separated by one week. During the familiarization session, subjects signed a written informed consent, completed body composition testing (dual-energy X-ray absorptiometry [DXA] scan), and were familiarized to the experimental procedures and the pressure pain device. Because the performance of maximal voluntary isometric contractions (MVIC) may influence pain perception in young adults (Hoeger Bement et al., 2008; Koltyn et al., 2001), MVIC force was

determined at the end of the familiarization session. Specifically, three MVICs were performed with the right knee extensor muscles with 1 minute rest between contractions. Participants were given verbal encouragement to achieve maximal force. The highest value was used to calculate the submaximal (30% MVIC) target force in the exercise session.

During the experimental sessions (Figure II.1), CPM was assessed before and after isometric exercise or quiet rest. In both sessions, 20 minutes of quiet rest separated the first CPM assessment and initiation of exercise or quiet rest as previous studies have shown that the conditioning effects of pain return to baseline within 15 minutes (Lewis et al., 2012). Participants also completed the pain catastrophizing scale (PCS) (Sullivan et al., 1995) and international physical activity questionnaire (IPAQ) (Craig et al., 2003), during the quiet rest in the first and second experimental sessions, respectively. These measures were collected to assess their potential influence on CPM and EIH.

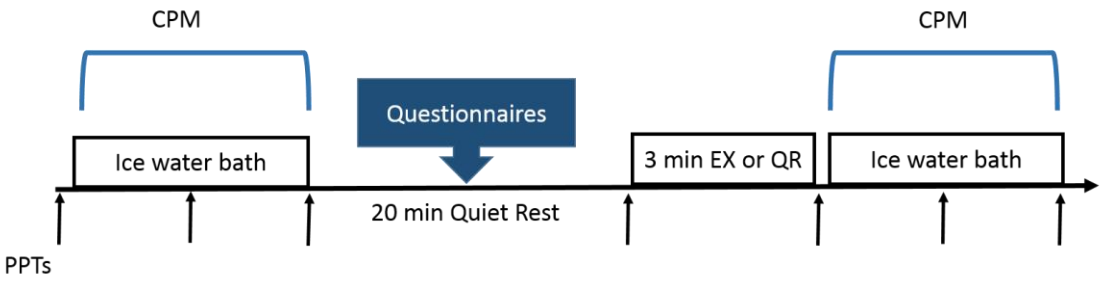


Figure II.1 Study design of the experimental sessions.
"↑"= PPTs at the quadriceps and upper trapezius muscle. Abbreviations: PPT, pressure pain threshold; CPM, conditioned pain modulation; EX, exercise; QR, quiet rest.

Conditioned pain modulation

Pressure pain thresholds (PPTs) were measured at the right upper trapezius and right quadriceps muscles (test stimuli) before, during (after 20 seconds), and after submersion of the left foot in a noxious ice water (0°C ± 1°C) bath (conditioning stimulus). Participants were instructed to keep their foot in the ice water bath until the PPTs were completed at which point they removed their foot from the ice water bath. During foot submersion, foot pain intensity was measured at 20 seconds using a 0-10 numerical rating scale (NRS) with the following anchors: 0= "no pain" and 10= "worst pain" (McCaffery & Pasero, 1999) followed by PPT measurements. Immediately after foot removal from the ice water bath, peak pain intensity was measured.

Exercise

Participants performed a submaximal (30% MVIC) isometric contraction of the right knee extensor muscles that was held for three minutes while seated upright on the edge of a plinth table. The hips and knees were positioned at 90° while the right foot was unsupported and aligned with the plinth table's metal leg. A hand held dynamometer (Commander Echo Muscle Testing Dynamometer, JTech Medical, USA) was stabilized using Velcro® straps to the leg of the plinth and around the participant's leg (above the malleolus). Two stabilizing straps were placed over the thighs, one distal to the hip joint and the other proximal to the knee joint. Subjects were instructed to fold their arms across their chest and to extend their knee while pushing against the Velcro® strap attached to the dynamometer. During the performance of the submaximal isometric contraction, participants were instructed to match the target force as displayed on the wireless portable monitor (Commander Echo Console, JTech Medical, USA) while receiving verbal encouragement to maintain the force. All participants maintained the force for the entire three minutes. Participants were asked to rate their perceived exertion using a 0-10 scale with the following anchors: 0= "nothing at all" and 10= "very very strong" and pain intensity in the leg in relation to the muscle contraction using the NRS at the beginning of the contraction, midway (1.5 minutes), and at the end of the contraction (3 minutes).

Pressure pain thresholds

During each experimental session, PPTs were measured a total of seven times at the quadriceps and upper trapezius muscles with a handheld algometer (Algomed, Medoc Ltd); three times with each of the two CPM protocols (before, during, and after ice), and one immediately before quiet rest or exercise (20 minutes after the first CPM protocol) (Figure 1). For the PPTs, a 1-cm^2 rubber tip was used with a ramp protocol at a rate of 50 kPa/sec. Subjects were instructed to press a timing device when the pressure first changed to pain, which was electronically recorded in kilopascals. To minimize exposure time to ice water, two PPT trials were recorded at each site with a 10-second interstimulus interval and the two trials were averaged at each measurement site for further analysis. At the beginning of each experimental session, the order for the sites (upper trapezius and quadriceps) was randomized and counterbalanced and kept consistent throughout the session. PPTs were recorded with the participant seated upright in a chair with their knees and hips at 90°. The sites were located and marked as follows: the quadriceps muscle site was located midway between the anterior superior iliac spine and the patella, while the upper trapezius muscle site was located midway between the C7 spinous process and the lateral tip of the acromion (Ekstrom, Donatelli, & Soderberg, 2003).

Body composition

Body composition was measured using a total body scanner (Lunar iDXA, GE Healthcare, Madison, WI). Scan analyses were performed using enCore™ software (version 14.10, GE Healthcare) to obtain the following outcome measures: body mass index (BMI), total body fat (%), android fat (%), gynoid fat (%), android/gynoid (A/G) ratio, leg fat (%), leg lean (lbs), and visceral fat mass (lbs).

Statistical analysis

Data were analyzed using the IBM Statistical Package for Social Sciences (SPSS version 23, Armonk, NY, USA) and reported as mean ± SD in the text and tables and mean ± SEM in the figures. Normality was checked using the Kolmogorov-Smirnov test. Outliers were tested with the Grubbs test and removed when significant.

Conditioned Pain Modulation at Baseline

A repeated-measures analysis of variance (ANOVA; session [exercise and quiet rest] x site [quadriceps and upper trapezius] x time [before, during and after ice]) was performed to determine if PPTs increased at the upper trapezius and quadriceps muscle during and/or after the baseline ice water bath performed in the two experimental sessions. In addition, a repeated measures ANOVA was done comparing the relative change in CPM at baseline between sessions (quiet

rest and exercise) at each site (upper trapezius and quadriceps). Relative change was calculated while the foot was submerged in ice water: $CPM_{during\ ice}$= ([PPT during ice – PPT pre ice]/ PPT pre ice) and immediately following removal of the foot from ice water: $CPM_{after\ ice}$= ([PPT after ice – PPT pre ice]/ PPT pre ice). This analysis was repeated with sex as a between-subject factor to examine sex differences in CPM at baseline. To identify potential differences in peak pain intensity of the ice water bath and the total time of foot submersion in the ice during CPM protocols, paired t-tests or the Wilcoxon signed rank test for non-normally distributed data were done as appropriate.

Exercise-Induced Hypoalgesia

To identify potential changes in PPT following quiet rest and exercise (i.e., EIH), a repeated-measures ANOVA was performed (session [exercise and quiet rest] x site [quadriceps and upper trapezius] x time [PPTs pre- and immediately post-rest and exercise]). This analysis was repeated with sex as a between-subject factor to identify potential sex differences.

Conditioned Pain Modulation after exercise and quiet rest

To investigate the effect of exercise on the CPM response, relative change in CPM following quiet rest and exercise was analyzed using a repeated-measures ANOVA (session [exercise and quiet rest] x site [quadriceps and upper trapezius] x time [CPM performed pre- and post-exercise or quiet rest]). Because there was considerable variability in systemic but not local EIH, EIH responders and non-responders at the upper trapezius muscle were categorized based on the PPT minimum detectable change (42.7 kPa) in a healthy pain-free population

with a non-pharmacological intervention (Walton et al., 2011). Subjects who had an increase in PPT greater than 42.7 kPa at the upper trapezius muscle after exercise compared with pre-exercise were placed in the EIH responders group (n= 9). Changes in CPM at the upper trapezius following quiet rest and exercise were analyzed using repeated measures ANOVA with EIH response (responders and non-responders) as a between-subject factor (time x session x EIH response). When a significant effect was found, *post hoc* analyses were done using paired t tests. Independent t tests or the Mann-Whitney U tests for non-normally distributed data were performed between the groups (EIH responders or non-responders) to identify potential differences in characteristics.

Within and between session reliability of CPM

To examine the reliability of CPM between sessions, repeated-measures ANOVA were done comparing the relative change in CPM at baseline at each site. Within the quiet rest session, relative change in CPM was compared using a repeated measures ANOVA (time [pre- and post-rest] x site [quadriceps and upper trapezius]). Intraclass correlations (ICCs) on the bases of absolute agreement were computed for relative change in $CPM_{during\ ice}$ between sessions (pre- session 1 and session 2) and within the quiet rest session for each site with 95% confidence interval (CI).

Correlations

To determine potential factors that influenced CPM and or EIH, Pearson correlations or Spearman correlations for non-normally distributed data were calculated to determine associations between the relative changes in CPM and

EIH, body composition measures, pain catastrophizing (PCS), and self-reported physical activity (IPAQ). In addition, Spearman correlations were performed between the relative changes in CPM or EIH and the pain intensity induced by the ice or exercise, respectively. Because the absolute change in CPM was not normally distributed, all the analyses were performed using the relative change in CPM. For statistical significance, a *P* value ≤ 0.05 was used initially (i.e. for RM ANOVA); however a more rigorous alpha level was selected ($p \leq 0.01$) to minimize type I and II errors with multiple group comparisons (i.e. *post hoc* analyses) and multiple correlations (Avin & Law, 2011; Garamszegi, 2006).

Results

Participant characteristics

A summary of the subject characteristics is found in Table II.1. According to body mass index (BMI) classification, 8 participants (26%) were overweight and 22 participants (73%) were normal weight. The individuals' self-reported physical activity levels were categorized as either moderate or vigorous; no participants reported low physical activity level. The majority of pain catastrophizing scores were considered normal as well; four participants had a score greater than 30. The following variables were non-normally distributed and therefore nonparametric tests were used: PCS scores, physical activity scores, pain intensity scores during ice water submersion, duration of ice water bath

submersion, A/G ratio, and visceral fat mass (lbs). One outlier was identified and removed from the variable $CPM_{after\ ice}$ at the quadriceps muscle.

Table II.1 Participant characteristics

	All Participants n= 30	Systemic EIH Responders n= 9 (30%)	Systemic EIH non-responders n= 21 (70%)	P-value
Age (yr)	19.3 ± 1.5	19.7 ± 1.3	19.8 ± 1.6	0.803
Females (%)	n= 15 (50%)	n= 4 (44%)	n= 11 (52%)	0.695
Exercise				
MVC	368.5 ± 107.9	399.2 ± 143.1	355.4 ± 90	0.414
Peak pain	3.8 ± 2.5	3.4 ± 2.1	4.0 ± 2.6	0.571
Peak RPE	5.5 ± 2.1	4.7 ± 2.3	5.8 ± 1.9	0.242
Weight status and body composition				
BMI	23.0 ± 3.1	22.2 ± 3.2	23.3 ± 3.0	0.230
Total body fat (%)	24.3 ± 6.8	23.1 ± 7.2	24.8 ± 6.8	0.554
Android fat (%)	22.8 ± 8.4	22.0 ± 7.9	23.2 ± 8.7	0.733
Gynoid fat (%)	26.5 ± 8.6	25.0 ± 9.6	27.2 ± 8.4	0.533
Android/gynoid (A/G) ratio	0.86 ± 0.2	0.89 ± 0.13	0.85 ± 0.22	0.213

Leg fat (%)	25.6 ± 8.2	24.2 ± 8.7	26.1 ± 8.1	0.573
Leg lean (lbs)	19.2 ± 4.5	19.3 ± 4.8	19.1 ± 4.5	0.906
Visceral fat mass (lbs)	0.35 ± 0.38	0.30 ± 0.25	0.37 ± 0.42	0.982
Physical Activity				
IPAQ total walking MET-(minutes/week)	1495.1 ± 1011.0	1827.8 ± 853.9	1352.5 ± 1057.9	0.245
IPAQ total moderate MET-(minutes/week)	674.6 ± 1506.7	550.0 ± 867.5	728.0 ± 1726.5	0.772
IPAQ total vigorous MET-(minutes/week)	1900.0 ± 1665.0	1680.0 ± 1570.3	1994.2 ± 1732.7	0.617
IPAQ MET-(minutes/week)	4069.7 ± 2963.8	4057.8 ± 3033.4	4074.9 ± 3009.4	0.989
IPAQ total sitting	2991.0 ± 1124.1	2503.3 ± 959.8	3200.0 ± 1144.9	0.122
Pain catastrophizing				
PCS-Total	18.1 ± 10.1	21.0 ± 12.8	16.8 ± 8.8	0.699
PCS-Helplessness	6.6 ± 5.0	6.2 ± 2.8	6.7 ± 5.7	0.792
PCS-Magnification	4.1 ± 2.7	3.4 ± 2.1	4.4 ± 2.9	0.345

PCS-Rumination	7.3 ± 4.1	6.4 ± 2.9	7.7 ± 4.5	0.554

BMI, body mass index; IPAQ, International Physical Activity Questionnaire; PCS, Pain Catastrophizing Scale; yr, year; RPE, rate of perceived exertion. There were no significant differences between systemic EIH responders and non-responders.

Conditioned pain modulation at baseline

Subjects completed all the CPM protocols except two subjects who removed their foot from ice water before completing the test. These subjects, however, kept their foot in the ice water for at least 20 seconds and completed all PPT assessments. The analyses of CPM were done with and without these subjects, which did not affect the results. Subjects reported moderate to severe peak pain intensity (NRS= 6.6 ± 1.8) during submersion of foot in the ice water bath. Peak pain intensity during foot submersion in ice decreased significantly between sessions (session 1: 7.0 ± 1.0; session 2: 6.4 ± 1.7; $p = 0.01$) but was similar within sessions ($p > 0.05$). The average duration for submersion of the foot in ice water was 99.7 ± 24.5 seconds. This was dependent on PPT duration for each subject and was similar across all CPM protocols ($p > 0.05$).

Results of the analysis for baseline CPM demonstrated a site x time interaction ($F(2,28) = 3.526$, $p < 0.05$, $\eta_p^2 = 0.201$). *Post hoc* analysis showed that while the foot was submerged in the ice water bath ($CPM_{during\ ice}$), there was an increase in PPTs at the quadriceps muscle and upper trapezius ($p < 0.001$), which signifies CPM (Figure II.2). The majority of subjects reported $CPM_{during\ ice}$ (28/30). Immediately following removal of the foot from the ice water bath

($CPM_{after\ ice}$), PPTs were not significantly different from baseline at the quadriceps and upper trapezius muscles ($p > 0.05$). In addition, PPTs were higher at the quadriceps muscle compared with the upper trapezius muscle ($p < 0.001$) (Figure II.2); however, $CPM_{during\ ice}$ had similar relative change between the two sites ($p > 0.05$) (Figure II.3). No other interactions were found ($p > 0.05$). When analyses were repeated with sex as a between-subject factor, no main effects of sex or interactions were found ($p > 0.05$). Pain intensity at 20 seconds, peak pain intensity during ice water bath, and duration of ice water bath submersion were not related to the relative change in CPM in all protocols at both sites ($p > 0.05$).

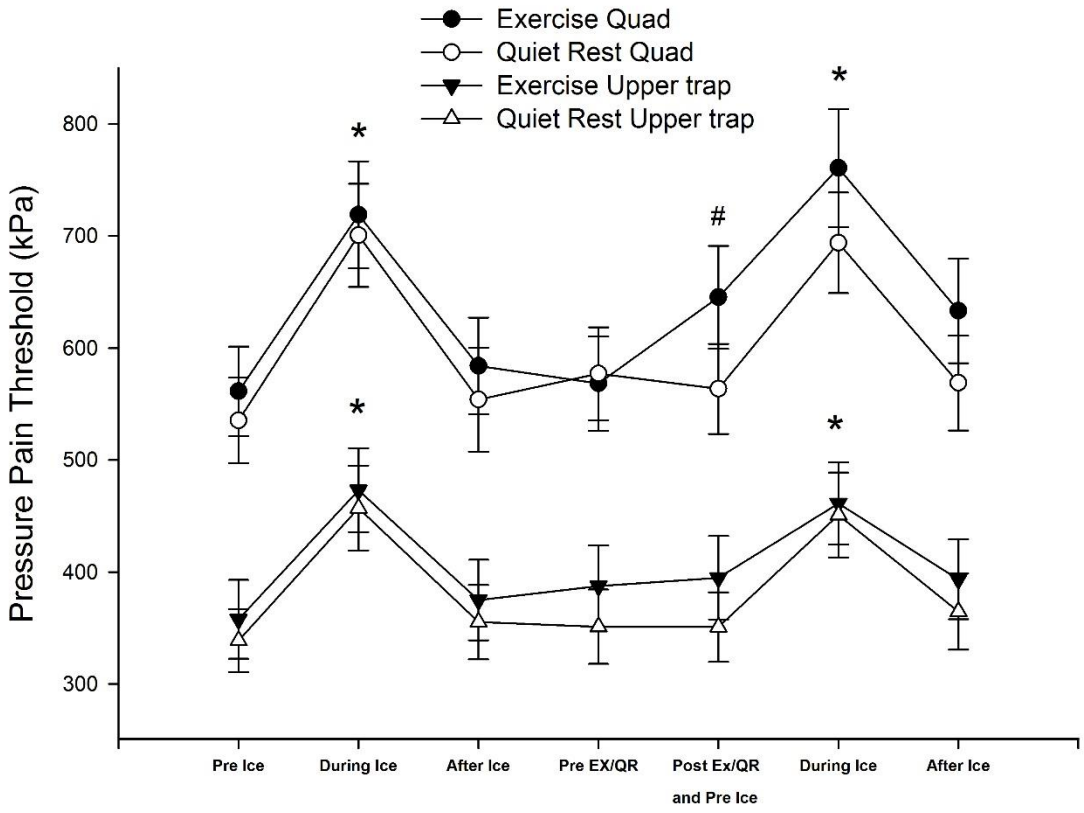


Figure II.2 Pressure pain thresholds (kPa) at the quadriceps muscle and the upper trapezius muscle during the exercise session and the quiet rest session.

Significantly different compared to pre ice (*) and significantly different compared to pre exercise ($^{\#}$). Data are presented as mean ± SEM. Abbreviations: EX, exercise; QR, quiet rest.

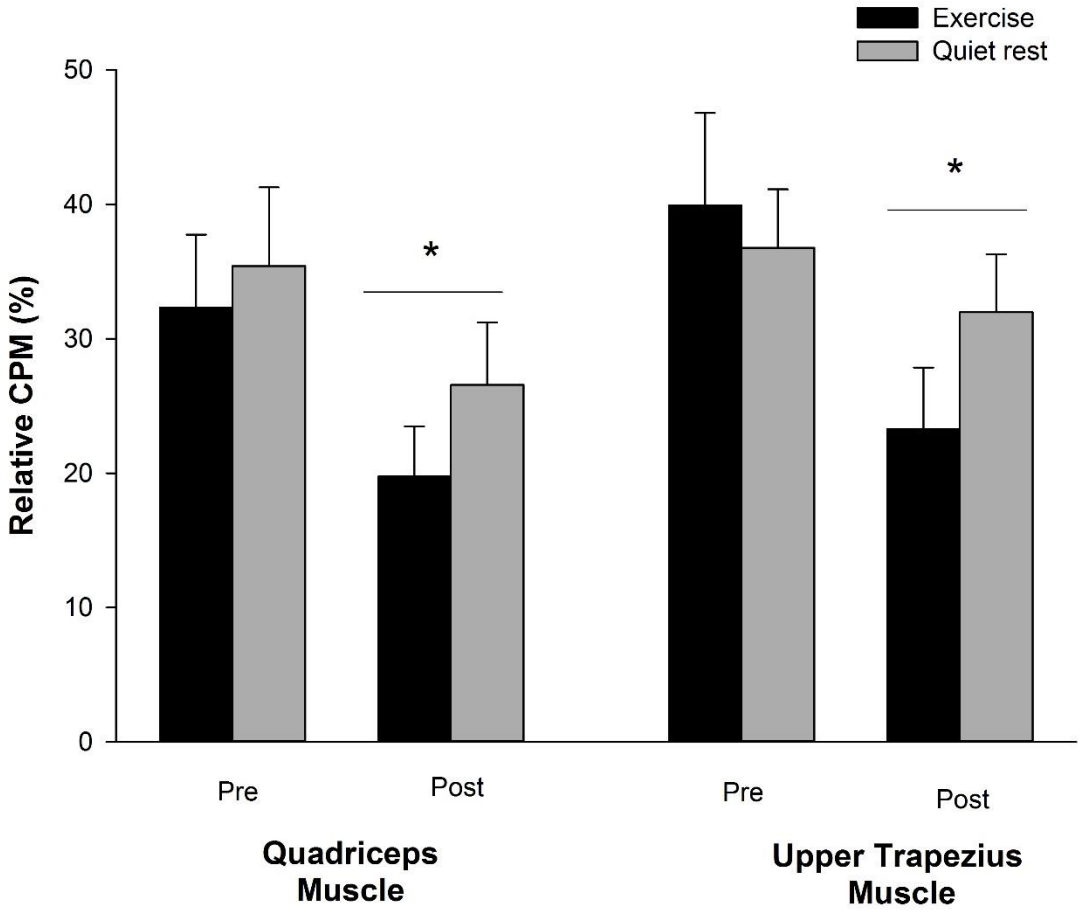


Figure II.3 Relative change in CPM at the quadriceps muscle and the upper trapezius muscle before and after exercise or quiet rest. Significantly different compared to pre exercise or quiet rest (*). Data are presented as mean ± SEM. Abbreviations: CPM, conditioned pain modulation.

Exercise-induced hypoalgesia

During exercise, subjects reported no pain (NRS= 0.0 ± 0.3) at the beginning of the isometric contraction, minimal pain (NRS= 2.2 ± 1.9) at the midpoint, and moderate pain (NRS= 3.8 ± 2.5) at the end. Likewise, subjects

reported ‘very weak’ exertion (RPE= 1.6 ± 1.5) at the beginning of the isometric contraction, ‘somewhat strong’ exertion (RPE= 4.1 ± 1.5) at the midpoint, and ‘strong’ exertion (RPE= 5.5 ± 2.1) at the end.

For PPTs, there was a session x site x time interaction ($F(1,29) = 13.203$, $p = 0.001$, $\eta_p^2 = 0.313$). *Post hoc* analyses showed PPTs increased following exercise at the quadriceps muscle (mean = 15 ± 19% change; $p < 0.001$) and were unchanged following quiet rest ($p > 0.05$) (Figure II.2). At the upper trapezius muscle, no significant differences in PPTs were found (mean = 2 ± 14 % change; $p > 0.05$) following exercise or quiet rest. Due to differences in the EIH response at the upper trapezius muscle, participants were divided into systemic EIH responders (n=9) and non-responders (n=21). The average change in PPTs at the upper trapezius muscle following exercise for EIH responders was 20 ± 9 % compared with -5 ± 8 % in the non-responders. When analyses were repeated with sex as a between-subject factor, no main effects of sex or interactions were found ($p > 0.05$). Neither RPE nor pain intensity at all time points during the exercise were related to EIH at either site ($p > 0.05$).

Conditioned pain modulation after exercise and quiet rest

Following quiet rest and exercise, $CPM_{during\ ice}$ decreased at the quadriceps and upper trapezius muscles ($F(1,29) = 13.069$, $p = 0.001$, $\eta_p^2 = 0.311$); this decrease was similar for the quiet rest and exercise sessions (time x session: $p > 0.05$, $\eta_p^2 = 0.052$) and between sites (session x site x time: $p > 0.05$, $\eta_p^2 = 0.037$) (Figure II.3). At the quadriceps muscle, $CPM_{during\ ice}$ decreased

following exercise (32% to 19%) and quiet rest (35% to 26%). Similarly, $CPM_{during\ ice}$ decreased at the upper trapezius following exercise (40% to 23%) and quiet rest (37% to 32%).

The CPM response was different following exercise compared with quiet rest in systemic EIH responders and non-responders (time x session x EIH response; $p = 0.03$, $\eta_p^2 = 0.154$). *Post hoc* analyses showed that the EIH responders had a significant decrease in the CPM response following exercise (52% to 8%; $p = 0.01$) without any change following quiet rest (27% to 22%; $p > 0.05$) (Figure II.4). The EIH non-responders did not have a significant change in their CPM response following exercise (34% to 29%) or quiet rest (40% to 36%; $p > 0.05$).

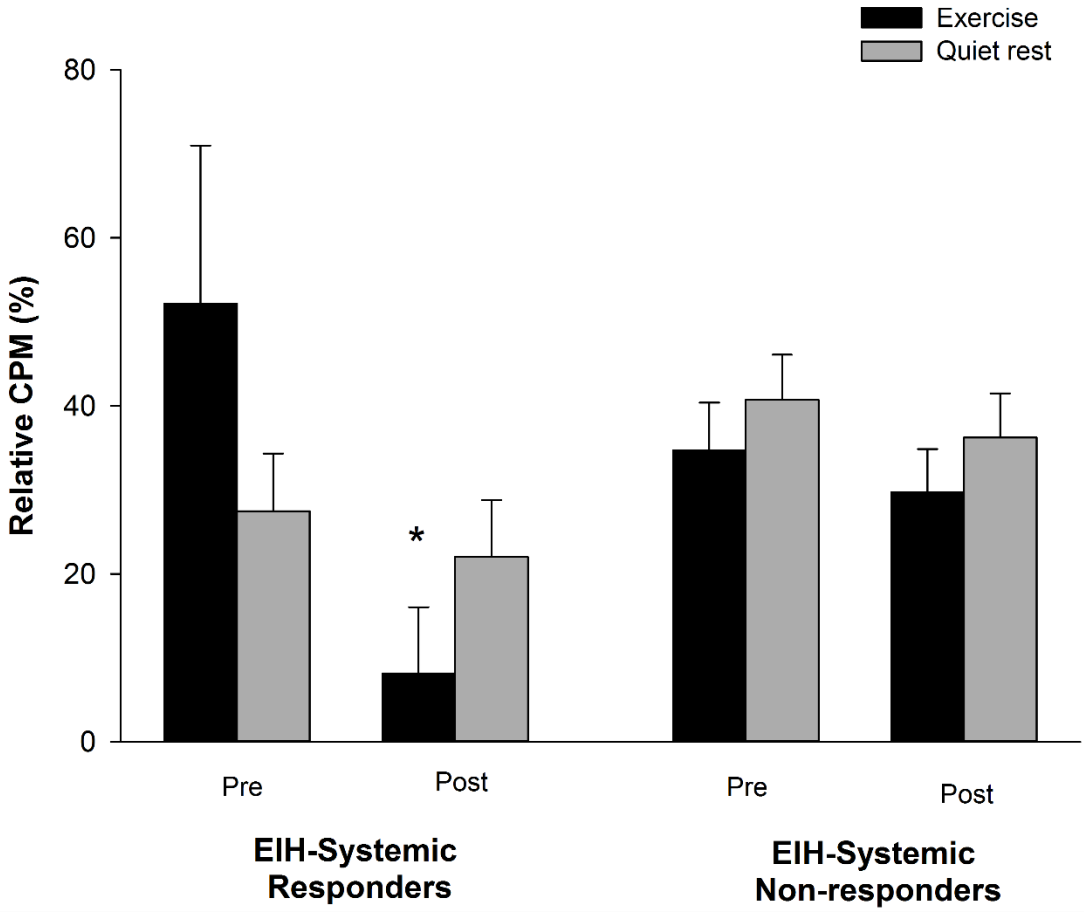


Figure II.4 Relative change in CPM at the upper trapezius muscle before and after exercise or quiet rest for EIH systemic responders and non-responders.

Significantly different compared to pre exercise (*). Data are presented as mean ± SEM. Abbreviations: CPM, conditioned pain modulation.

Within- and between-session reliability of CPM

Results from the ANOVA showed no significant main effects or interactions within or between sessions; the relative change in baseline CPM was similar between the first and second sessions, and the CPM responses were

similar within the quiet rest session ($p > 0.05$). ICC results are shown in Table II.2. There was a fair to good within-session reliability for CPM during the quiet rest and poor reliability when comparing relative change in CPM at baseline between the two sessions.

Table II.2 Reliability values (ICCs) and percent change for CPM within and between sessions

		Percent change	ICCs (95% CI)
Within quiet rest session	CPM Quad trial 1	35.4%	0.707 (0.395 to 0.859)
	CPM Quad trial 2	26.5%	
	CPM Upper trap trial 1	36.7%	0.433 (-0.190 to 0.730)
	CPM upper trap trial 2	31.9%	
Between sessions	CPM Quad session 1	33.4%	0.208 (-0.715 to 0.628)
	CPM Quad session 2	34.2%	
	CPM Upper trap session 1	38.6%	0.350 (-0.401 to 0.694)
	CPM upper trap session 2	38.1%	

ICC, intraclass correlation coefficient; CPM, conditioned pain modulation; CI, confidence interval

Correlations

Self-reported physical activity (IPAQ MET-min/week and IPAQ total walking MET-min/week) was moderately correlated with EIH at the quadriceps muscle; however, this relationship did not reach statistical significance when correcting for multiple correlations ($r = 0.43$, $p = 0.02$ and $r = 0.38$, $p = 0.04$, respectively). Similarly, $CPM_{during\ ice}$ at the quadriceps after exercise was moderately related to A/G ratio ($r = 0.432$, $p = 0.02$) but failed to reach statistical significance after adjusting for multiple correlations. No other relations were found for pain catastrophizing, physical activity, or body composition with CPM or EIH ($p > 0.05$).

Discussion

The novel finding of the study was that individuals who reported systemic EIH had a significant decrease in CPM following exercise only, whereas those individuals that had no systemic EIH had no change in CPM following exercise or quiet rest. Thus, activation of descending inhibitory pathways was less following sustained isometric contractions for those individuals with systemic EIH indicating the possibility of shared mechanisms with CPM. Moreover, this study demonstrated that the decrease in CPM response after exercise and quiet rest was comparable and the within-session reliability of the CPM protocol used was fair to good. The reliability of CPM between sessions was poor.

Conditioned pain modulation

In the current study CPM occurred only when the testing and conditioning stimuli were performed at the same time, which is in agreement with previous studies (Kosek & Ordeberg, 2000; Leffler, Hansson, & Kosek, 2002; Oono, Wang, Svensson, & Arendt-Nielsen, 2011; Vaegter et al., 2014b; Vaegter et al., 2016), but not in line with other studies (Lewis et al., 2012; Pud, Sprecher, & Yarnitsky, 2005) or recent recommendations for CPM testing that favor measuring the test stimulus sequential to the conditioning stimulus (Yarnitsky et al., 2015). The discrepancy in these results could possibly be explained by the location of the conditioning stimulus, as the location in the previous studies (Lewis, Heales, Rice, Rome, & McNair, 2012; Pud et al., 2005) was the hand while the present study used the foot. The representation of the hand in the brain is larger than the foot, which may have yielded more central activation and a longer-lasting effect compared with the current study (Le Bars et al., 1979a). The results of Vaegter et al. (2014b) support this hypothesis where a higher CPM magnitude was observed during cold pressor test on the hand compared with the foot.

To our knowledge, this is the first study to report reliability of CPM with foot submersion in a conditioning ice water bath. Despite acceptable within-session reliability (fair to good), CPM decreased following quiet rest. This decrease reflects the mean change in CPM magnitude as a group, whereas ICCs represent the differentiability of the measure between subjects. Thus following

quiet rest, CPM decreased but the rank of subjects between others was relatively the same yielding an acceptable ICC value.

One approach to attenuate potential changes in CPM magnitude following quiet rest is to increase the duration of the washout period. Valencia et al. (Valencia et al., 2014) found that a repeated assessment of CPM with a washout period of two minutes was not adequate, as CPM magnitude decreased significantly in the second CPM trial even with good to excellent reliability. Previous studies have been equivocal in relation to the washout period with ranges from two to 60 minutes (Kennedy et al., 2016). The reliability in these studies was between fair and excellent (Cathcart, Winefield, Rolan, & Lushington, 2009; Lewis et al., 2012; Valencia et al., 2014) but not all studies examined the difference in CPM magnitude following the washout period. Therefore, future studies with repeated CPM assessments should consider a longer washout period.

In the current study the between-session reliability was poor despite similar magnitude between the two sessions. A recent study by Imai et al. (Imai, Petersen, Morch, & Arendt Nielsen, 2016) tested the reliability of CPM using different test and conditioning stimuli and concluded that the best between-session reliability was achieved measuring PPTs during hand submersion in ice water (0-4°C) (ICC = 0.49). One potential reason for the poor between-session reliability in the current study could be the low temperature (i.e. high intensity) of the conditioning stimulus. Olesen et al. (Olesen, van Goor, Bouwense, Wilder-Smith, & Drewes, 2012) observed poor reliability (ICC = 0.10) when using a

conditioning cold water immersion of the hand at 2°C for 3 minutes in patients with chronic pain. The authors reported that not all patients tolerated the conditioning stimulus, which may have impacted the reliability and was similar to our study, in which two people did not tolerate the ice water bath. Furthermore, a systematic review of the CPM reliability suggested temperatures between 8°C and 12°C of the cold conditioning water for improving repeatability (Kennedy et al., 2016). Thus, these results demonstrate that reliability may be lower when applying a stronger conditioning stimulus (ice water) to a larger surface area (foot vs. hand).

The comparable decrease in CPM following exercise and quiet rest suggests that the modulatory effects of pain are not restored following the first CPM exposure, despite PPTs returning to baseline following the washout period. Thus, using a static pain assessment (PPTs) as a restorative marker for a dynamic process (CPM) may not be appropriate. Alternatively, the influence of expectations of a painful response has been shown to affect the CPM magnitude (Lariviere, Goffaux, Marchand, & Julien, 2007) where a higher expectation of the noxious conditioning stimulus results in a lower CPM magnitude. While not measured in this study, it is possible that participants in the current study had a higher expectation for the conditioning stimulus in the second CPM testing that resulted in a lower CPM magnitude.

Exercise-induced hypoalgesia

In the current study, EIH occurred locally at the exercising muscle (quadriceps muscle) and not systemically (upper trapezius muscle). The local effects are in line with previous research showing greater EIH effects at the exercising muscle compared with contralateral or distal sites (Kosek & Lundberg, 2003; Vaegter et al., 2014b). However, several studies have demonstrated systemic hypoalgesia after isometric exercise (Vaegter et al., 2014a; Vaegter et al., 2014b). One explanation for the lack of systemic hypoalgesia is that baseline CPM testing negatively impacted systemic EIH, potentially due to their shared manifestations. It is possible that CPM is a contributing mechanism to systemic EIH. As CPM was initiated earlier in the session and not enough washout period was provided to restore CPM, systemic EIH was not observed. Not all our data support this explanation as there were no correlations observed between CPM and EIH. Previous research has demonstrated an association between CPM and EIH across the lifespan (Lemley et al., 2015; Stolzman & Bement, 2016; Vaegter, Handberg, Jorgensen, Kinly, & Graven-Nielsen, 2015). This relation is more consistent when EIH is measured systemically and following exhaustive exercise. However, similar to the current study, Vaegter et al. (Vaegter et al., 2014b) showed no correlation between CPM and EIH after low-intensity isometric exercise held for three minutes. The relation between CPM and EIH is likely dependent on both the exercise dose and testing site for EIH.

To our knowledge, this is the first study to investigate the effect of isometric exercise on CPM. Because stimulation to the motor cortex enhances CPM, we expected that CPM would be enhanced following exercise. Contrary to our hypothesis, CPM decreased following exercise only in those individuals who had systemic EIH. This is potentially related to 1) a ceiling effect for PPTs and the exercise-induced increase in PPT attenuated the subsequent testing stimulus (Granot et al., 2008) or 2) systemic hypoalgesia that occurs following exercise is due to CPM. Arendt-Nielsen et al. (Arendt-Nielsen, Sluka, & Nie, 2008) found that two concurrent painful conditioning stimuli (muscle pain and cold presser pain) had a decreased effect than either stimulus alone. Because the exercise protocol in this study was painful, the increase in PPTs at the upper trapezius muscle following exercise may actually be a CPM protocol, with exercise acting as the conditioning stimulus and PPT the testing stimulus. EIH responders experienced a 20% increase in PPTs following exercise and an additional 8% increase following the ice conditioning stimulus, which is comparable to what they have experienced with the conditioning stimulus alone in the quiet rest session (27%). The non-responders had only local hypoalgesia (i.e., quadriceps muscle) following exercise; the lack of hypoalgesia systemically (i.e. upper trapezius muscle) suggests that local exercise effects do not influence CPM due to different mechanisms. Previous reports have shown that CPM magnitude is influenced by the intensity of conditioning stimulus but not by the pain reported during the conditioning stimulus (Nir, Granovsky, Yarnitsky, Sprecher, & Granot, 2011). Likewise, in this study, pain reported during exercise or ice water bath did

not influence EIH nor CPM. If exercise produces hypoalgesia via activation of the CPM response, then increasing the exercise intensity (i.e. the conditioning stimulus) should produce greater hypoalgesia.

Emerging evidence has shown that body composition and physical activity may influence EIH and CPM (Lemley et al., 2015; Naugle & Riley, 2014; Stolzman et al., 2015; Stolzman & Hoeger Bement, 2016). This is contrary to the current study in that body composition and self-reported physical activity were not correlated with EIH or CPM. This is similar to a recent study by Black et al. (Black et al., 2017) that showed no relation between EIH and physical activity assessed via accelerometer. These results may be due to the homogenous sample in the current study as most individuals reported moderate to vigorous physical activity levels and normal to slightly overweight BMI levels. Likewise, the weakly correlated pain catastrophizing scores with neither CPM nor EIH may be due to relatively normal catastrophizing scores (e.g. only four individuals above 30) observed in this sample.

Several potential limitations should be taken into consideration. First, a small number of individuals had a systemic EIH response (n=9) possibly due to the low intensity and short duration of the isometric exercise thereby limiting the generalizability of the results. Future studies should verify these results following an exercise duration that is known to produce systemic effects (e.g. isometric exercise until task failure or aerobic exercise). In addition, the between-session reliability of CPM was poor. However, this should have minimal effects with our results since we are comparing changes in CPM within session. Finally, the

results in the present study are generalizable to young healthy adults only. It is unclear whether individuals with chronic pain would yield similar results.

Despite these limitations, several clinical implications can be drawn from this study. Our results suggest that the systemic effects of exercise activate descending inhibitory pathways, making exercise a good clinical modality in the management of pain. Thus, in individuals with impaired CPM, the systemic effects of exercise maybe more variable in producing pain-relieving effects. The local effects, however, do not appear to be mediated by CPM and could be an alternative clinical tool in those conditions with impaired CPM. Finally, our results show the potential benefits in assessing CPM to help guide clinical decision-making. With repeated assessments, an appropriate length of time (e.g. greater than 23 minutes) is necessary for the restoration of CPM. Additional research that includes individuals with chronic pain is essential, including whether this relation between systemic EIH and CPM occurs with exercise training. Understanding these effects in patients will allow for a more targeted use of exercise in the management of pain.

Conclusion

Individuals that experienced EIH systemically had an attenuated CPM response compared with those individuals that only experienced local EIH. The results raise the possibility that there are shared mechanisms between CPM and systemic EIH. In addition, CPM decreased following exercise and quiet rest,

which may be due to an insufficient washout period, while the within-session reliability was fair to good and the between-session reliability was poor.

III. ISOMETRIC EXERCISE RESTORES CONDITIONED PAIN MODULATION AND ENHANCES VIBRATION SENSE IN PEOPLE WITH AND WITHOUT FIBROMYALGIA

Introduction

Fibromyalgia syndrome (FMS) is a chronic pain condition that is characterized by widespread pain in the soft tissue and tender points throughout the body (Neumann & Buskila, 2003). The prevalence of FMS in the general population is 5%, which primarily affects women (Hawkins, 2013). Past research has shown that people with FMS demonstrate abnormal endogenous pain modulation such as enhanced pain facilitation (Staud et al., 2001) and reduced pain inhibition (Kosek & Hansson, 1997) as well as a reduction in vibratory sense (da Silva et al., 2013). Unlike pain modulation, vibration perception is not typically used to assess chronic musculoskeletal pain. Clinically, testing vibration sense is most commonly used in the early detection of neuropathy, specifically diabetic neuropathy (Garrow & Boulton, 2006). Clinical and experimental research, however, has suggested that diminished sense of vibration in populations with chronic pain may be due to altered central pain processing rather than peripheral nerve damage (Apkarian et al., 1994; Geber et al., 2008; Hollins et al., 1996; Magerl & Treede, 2004). Whether transient reductions in pain improves vibratory sense in this population is not known.

Exercise-induced hypoalgesia (EIH) is a phenomenon where a decrease in pain occurs with exercise (Hoeger Bement & Sluka, 2016) locally at the

exercising muscle (Koltyn et al., 2001; Kosek & Lundberg, 2003; Umeda et al., 2010) and systemically (Hoeger Bement et al., 2008; Koltyn & Umeda, 2007; Kosek & Lundberg, 2003; Lemley et al., 2014) at remote sites. Different modes of exercise have been shown to reduce pain sensitivity including aerobic, isometric, and dynamic resistance exercise in healthy adults as well as in individuals with chronic pain (Naugle et al., 2012). In patient populations, such as FMS, variability in the pain response after exercise has been reported in that some people experience pain relief while others experience pain exacerbation following acute isometric exercise (Hoeger Bement et al., 2011). This variability may be due to differences in baseline (pre-exercise) conditioned pain modulation such that CPM predicts EIH in young and older healthy adults (Lemley et al., 2015; Stolzman & Bement, 2016). Additionally, we have shown that individuals who exhibit systemic EIH following an acute bout of isometric exercise have a significantly reduced CPM response, suggesting that systemic EIH may potentially work through similar mechanisms as CPM (Alsouhibani, Vaegter, & Hoeger Bement, 2018). It is not known, however, how isometric exercise effects CPM in individuals with FMS who are known to have an impaired CPM response.

Therefore, the primary aim of this study was to examine the effect of isometric exercise held to exhaustion on pain inhibition (conditioned pain modulation) and vibratory sense locally at the exercising muscle and systemically in patients with FMS and age matched controls. A secondary aim was to determine factors that may impact the pain response following isometric exercise including body composition, physical activity levels, and psychosocial factors

(Sluka, 2016). We hypothesized that individuals with FMS will have reduced CPM and vibratory sense compared to controls and that exercise will restore CPM and enhance vibration perception both locally and systemically. Additionally, body composition, physical activity levels and psychosocial factors will be related to the EIH response in both individuals with and without FMS; those with higher physical activity levels and better body composition and psychosocial outcomes will report greater EIH.

Methods

Participants

Twenty one individuals with FMS (18 women and 3 men, mean age ± SD, 50.5 ± 3.26) and 22 age-matched controls (20 women and 2 men, mean age ± SD, 49.2 ± 2.83) were recruited from a large Midwestern metropolitan area (Milwaukee, WI) through advertisements. Data were collected between July 2018 and August 2019. Participants were screened and excluded if they had the following: 1) cardiovascular disease, 2) neurological disorder, 3) cancer, 4) contraindications to exercise, 5) diabetes, 6) contraindications for the DEXA scan (e.g. pregnancy and claustrophobia), 7) arthritis, 8) osteoporosis, 9) Reynaud's disease, 10) neuropathy, 11) surgery in the past year, 12) inability to comply with study protocols, or 13) unstable medical or psychiatric condition (e.g. uncontrolled hypertension, anxiety or depression). Medication use in participants with FMS was allowed as long as they were stable for at least 2 weeks. The

Institutional Review Board at Marquette University approved the protocol of this study and a written informed consent was obtained from all participants at the start of the study. The study is registered at ClinicalTrials.gov (NCT03778476).

Experimental design

Participants participated in one familiarization session and two randomized experimental sessions (isometric exercise or quiet rest) with approximately one week separating sessions. At the beginning of the familiarization session, participants were given the written informed consent and completed a medical history form and physical activity readiness questionnaire (PARQ). The PARQ is a screening tool for physical activity readiness recommended by the American College of Sports Medicine (ACSM). If any medical concerns were noted, the participant was not allowed to exercise. Additional questionnaires during the familiarization included the following for all participants: Short form McGill questionnaire (SF-MPQ), dispositional-Pain Catastrophizing Scale (PCS) and for participants with FMS: Revised Fibromyalgia Impact Questionnaire (FIQR), and 2010 American College of Rheumatology Preliminary diagnostic criteria for Fibromyalgia (ACR) (Wolfe et al., 2010). Next participants were instructed on the experimental procedures followed by measurements in the following order: vibration perception thresholds (VPTs), familiarization to the pressure pain device, body composition, and familiarization to CPM and the exercise protocol by performing maximal voluntary contractions (MVCs).

During the experimental sessions (exercise or quiet rest), participants started each session by completing the SF-MPQ (for all participants) and the FIQR (for participants with FMS only). VPTs and CPM were measured twice, before and after exercise or quiet rest. After each CPM trial, situational-PCS was given in reference to the ice water bath experience (conditioning stimulus). In both sessions, and immediately following the first CPM trial, MVCs of the right knee extensor muscles were performed. Specifically, 3 MVCs were completed with one minute of rest between trials and the highest value was used to calculate the exercise intensity (i.e. 30% MVC). Participants were verbally encouraged to achieve maximal force. Following completion of the MVCs, forty-five minutes of rest occurred before the start of exercise or quiet rest. During this time, participants completed the Pain Self-Efficacy Questionnaire (PSEQ) and Tampa Scale for Kinesophobia (TSK). Participants were given instructions on the Actigraph physical activity monitor in the first experimental session and completed the Physical Activity Assessment Tool (PAAT) and the International Physical Activity Questionnaire (IPAQ) in the second experimental session.

Vibration perception thresholds (VPT)

VPTs in the familiarization session were tested at 4 sites using the Biothesiometer (Bio-Thesiometer, USA) with a vibratory tip (1.3 cm cylinder) that oscillated at a frequency of 120hz / 60 cycle. The device is considered reliable and has been used in previous studies (Courtney, Steffen, Fernandez-de-Las-Penas, Kim, & Chmell, 2016; Courtney, Atre, Foucher, & Alsouhibani, 2019;

Shakoor et al., 2008). The sites were located and marked as follows: right quadriceps muscle (halfway between the anterior superior iliac spine and the base of the patella), right deltoid muscle (one third from the acromion to the lateral epicondyle), right index finger (halfway between the distal and proximal interphalangeal joints), and the right abdomen (2 cm lateral to the umbilicus). These sites were chosen to determine if differences between groups, if any, are wide spread throughout the body or site specific. During the experimental sessions, however VPTs were measured only at 2 sites (the right quadriceps muscle and index finger) to test the effects locally at the exercising muscle and systemically. Participants were instructed to sit upright in a standard chair with their knees and hips at 90°. At the testing sites, one examiner held the probe and rested the tip against the skin of the participant while the other examiner increased the intensity slowly (1 volt per second). Participants were asked to close their eyes during testing and report when they first feel sense of vibration. Three testing trials were performed while the device was in place and the average of trials were recorded and used for analyses. Prior to testing, participants were given a demonstration on the effect of the biothesiometer by placing the device on their palm and increasing the amplitude from zero to moderate then to higher levels. Because changes in skin temperature may effect VPT measurements (Green, 1977), before each VPT measurement, temperature of the skin was measured using an infrared surface scanner DermaTemp 1001 LN (Exergen Corporation, Watertown, MA).

Conditioned pain modulation

Pressure pain thresholds (PPT), described in further detail below, were used as the test stimuli measured at the right deltoid and quadriceps muscles before, during (after 20 seconds), and after submersion of the left foot in a noxious circulating ice water (6°C ± 1°C) bath (the conditioning stimulus) for 2 minutes. Participants were instructed to keep their foot in the ice water bath for the entire 2 minutes until the PPTs were completed. If a participant didn't tolerate the test and chose to remove the foot before the end of 2 minutes, PPTs were still measured and included in the analyses. Foot pain intensity during foot submersion was measured at 20 seconds using the NRS followed by PPT measurements and at the end of 2 minutes just before foot removal. Immediately after foot removal from the ice water bath, peak pain intensity was measured followed by PPTs after ice. After the test, the situational pain catastrophizing scale (S-PCS) (Campbell et al., 2010) was given in reference to the ice water bath.

Exercise

The exercise task consisted of a submaximal isometric contraction (30% MVC) of the right knee extensor muscles held to exhaustion. The positioning of participants and exercise set up was the same as previously described (Alsouhibani et al., 2018). Briefly, participants were seated upright on an edge of

a plinth table with their hips and knees positioned at 90° stabilized with 2 straps over their thighs (distal to the hip and proximal to the knee). The right foot was aligned with the plinth table's leg unsupported. A hand held dynamometer (Commander Echo Muscle Testing Dynamometer, JTech Medical, USA) was attached to the leg of the plinth and stabilized using Velcro® straps around the leg of participants just above the malleolus. While performing MVCs, participants were instructed to extend their knee pushing against the Velcro® strap attached to the dynamometer as hard as they can while folding their arms across their chest. While performing the exercise task, participants were told to leave their arms resting over their thighs to reduce potential contractions of the upper limb. Participants were instructed to match a target force displayed on a wireless portable monitor (Commander Echo Console, JTech Medical, USA) during the performance of the submaximal isometric contraction. Participants received verbal encouragement to maintain the force. Exhaustion was determined when participants were unable to maintain the force within 10% of the target force for 3 out 5 consecutive seconds (Hoeger Bement et al., 2008; Lemley et al., 2014; Lemley et al., 2015). Participants were asked to rate their perceived exertion (RPE) using a 0-10 scale with the following anchors: 0= "nothing at all" and 10= "very very strong" and pain intensity using the NRS before the start of exercise and every minute until the end of exercise. After the end of exercise and the measurement of PPTs, a final pain intensity at the leg was measured just before the measurement of VPT.

Pressure pain thresholds

During each experimental session, PPTs were measured a total of 8 times at the right quadriceps and deltoid muscles with a handheld algometer (1-cm^2 rubber tip, delivery rate 50 kPa/sec) (Somedic, Sweden); three times with each of the two CPM protocols (before, during, and after ice), and two immediately before and after quiet rest or exercise (45 minutes after the 1st CPM protocol) (Figure III.1). The 2 sites were similar to the VPTs assessments (i.e. the quadriceps muscle halfway between the anterior superior iliac spine and the base of the patella and the deltoid muscle one third from the acromion to the lateral epicondyle). Participants were instructed to press a trigger when the pressure first changed to pain that was recorded in kilopascals. To minimize participants' exposure to multiple PPTs, only 2 PPT trials per location were measured with a 10 second inter-stimulus interval. In addition, the location of PPTs was shifted 1 cm up or down after the 4^{th} PPT measurement (i.e. before exercise or quiet rest) to minimize peripheral tenderness. The two PPT trials recorded at each site were averaged for further analysis. The order for the sites (deltoid and quadriceps) were randomized at the beginning of each experimental session and kept consistent throughout the session and were measured in alternation (e.g. deltoid – quadriceps – deltoid – quadriceps). Participants were seated upright in a chair with their knees and hips at 90° during all PPT measurements.

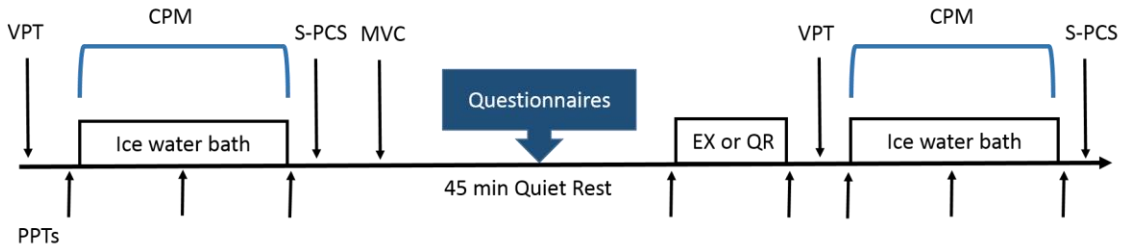


Figure III.1 Study design of the experimental sessions.
"↑"= PPTs at the quadriceps and deltoid muscle. Abbreviations: PPT, pressure pain threshold; CPM, conditioned pain modulation; VPT, vibration perception threshold; S-PCS, situational pain catastrophizing scale; MVC, maximum voluntary contraction; EX, exercise; QR, quiet rest.

Body composition

A total body scanner (Lunar iDXA, GE Healthcare, Madison, WI, USA) was used to quantify body composition. Participants were instructed to refrain from food and drink 1 - 2 hours before the session and to remove all metal items prior to the body scan. Standard height and weight was measured prior to the scan. If participants did not fit under the scanner a half scan of the right side was done and the left side was estimated from the right (n=2). The following outcome measures were obtained from the scan: body mass index (BMI), total fat (%), total lean mass (lbs), total bone mineral content (BMC) (lbs), android fat (%), gynoid fat (%), android/gynoid ratio (A/G ratio), right arm fat (%), right arm fat mass (lbs), right arm lean mass (lbs), right arm BMC (lbs), right leg fat (%), right leg fat mass (lbs), right leg lean mass (lbs), right leg BMC (lbs), and visceral

adipose tissue mass (lbs). Scans were analyzed using the Encore Software (version 14.10, GE Healthcare, Madison, WI).

Physical activity

During the first experimental session, participants were given an activity monitor (Actigraph, wGT3X-BT, Pensacola, FL) to wear on the non-dominant wrist for 7 days. Participants were encouraged to keep the activity monitors on their wrists for the full 7 days and were provided daily logs to complete regarding sleep time, physical activity, and removal time if any. Activity monitors along with the logs were collected during the second experimental session. Actilife software (Actilife 6.13.1, Pensacola, FL) was used to download and analyze Actigraph Data with “worn on wrist” correction applied. Troiano algorithm and the daily logs were used to identify and remove the non-wear time from physical activity calculation. The data of four valid days (2 weekdays and 2 weekends) were used for all participants, which have been shown to be a representative for the data of 1 week (Migueles et al., 2017). Activities were divided into either sedentary/light activities or moderate to vigorous physical activities (MVPA) based on Freedson criteria (Freedson, Melanson, & Sirard, 1998).

Questionnaires

Pain Catastrophizing Scale: This is a 13-item scale that evaluates the tendency of participants to magnify the threat value of pain and has 3 different

dimensions: helplessness, rumination, and magnification (Sullivan et al., 1995). For each item participants score using a 5-point Likert scale. Greater scores indicate higher pain catastrophizing levels with a score of 30 being the cutoff for clinically relevant pain catastrophizing. While this scale measures catastrophizing in relation to a general past pain experience (termed: dispositional pain catastrophizing), another version of this scale was developed to measure in relation to a recent painful experience (termed: situational pain catastrophizing) (Campbell et al., 2010). This is a short version of the dispositional pain catastrophizing scale (6-items) and is asked in reference to a recent painful experience. The dispositional scale was given once to participants at the beginning of the familiarization session while the situational scale was given 5 times throughout the study after every CPM trial in reference to the ice water bath experience.

Short Form McGill Pain Questionnaire (SF-MPQ): This questionnaire measures the multiple aspects of pain (affective, sensory, and cognitive) related to current pain (Melzack, 1987). Higher scores represent higher pain. This was given to all participants at the beginning of each session.

Revised Fibromyalgia Impact Questionnaire (FIQR): This questionnaire evaluates mood and symptoms related to fibromyalgia and other components of health status that are believed to be affected by fibromyalgia. The questionnaire evaluates the 3 domains: overall impact, symptoms, and function during the past week. This was given to individuals with FMS only at the beginning of each session. Higher scores represent more severe symptoms (Bennett et al., 2009).

Pain Self Efficacy Questionnaire (PSEQ): This is a 10-item questionnaire that measures the confidence individuals have in performing activities while in pain. Each item is scored on a 7-point Likert scale from 0 “not confident at all” to 6 “completely confident.” The total score ranges from 0 to 60 with higher scores indicating stronger self-efficacy beliefs (Nicholas, 2007). This was given to all participants during the quiet rest of the second session.

Tampa Scale of Kinesiophobia (TSK): This questionnaire evaluates movement-related fear of pain and fear avoidance behaviors. It is an 11-item scale with each item scored from 1 “strongly disagree” to 4 “strongly agree”. The scores range from 11 to 44 with higher scores indicating greater fear of pain and movement (Woby, Roach, Urmston, & Watson, 2005). This was given to all participants during the quiet rest of the second session.

Physical Activity Assessment Tool (PAAT): This questionnaire is a self-reported measure of physical activity that asks participants to report on physical activity in the past week. It measures the type, frequency and duration of moderate and vigorous activities. The outcome is total moderate or vigorous minutes per week (Meriwether, McMahon, Islam, & Steinmann, 2006). This was given to all participants in the quiet rest of the third session.

International Physical Activity Questionnaire (IPAQ): This questionnaire is another self-reported measure of physical activity that asks participants to report on physical activity in the past week. This questionnaire has 4 domains: occupation, transportation, household, and leisure; all of which report the total time in minutes. In addition, the total time spent sitting per week is also

reported (Craig et al., 2003). This was given to all participants after the PAAT in the quiet rest of the third session.

Data analysis

Data were analyzed using the IBM Statistical Package for Social Sciences (SPSS version 26, Armonk, NY) and reported as mean ± standard deviation (SD) in the text and tables and mean ± standard error (SE) in the figures. Normality was checked using the Kolmogorov-Smirnov test and visual inspection of Q-Q plots. Extreme outliers were tested with the Grubbs test and when significant were winsorized to one unit greater than the next outlying score (Dixon, 1980). Independent t tests or the Mann-Whitney U tests for non-normally distributed data were performed between the groups (healthy controls or FMS) to identify potential differences in characteristics. Friedman's test was used to compare if changes occurred to SF-MPQ or FIQR across sessions.

Baseline Conditioned Pain Modulation: To determine if PPTs increased for the 2 groups at the deltoid and quadriceps muscles during and/or after the ice water bath compared to baseline (i.e., CPM) in the two experimental sessions a repeated measures Analysis of Variance (RM ANOVA) (session [exercise and quiet rest] x time [PPTs before, during and after ice] x site [deltoid and quadriceps]) was performed with group (healthy controls and FMS) as between subject factor. In addition, a RM ANOVA was done comparing the absolute and relative change in CPM at baseline between sessions (quiet rest and exercise) at each site (deltoid and quadriceps) with a between subject factor group. Absolute

change was calculated for each site as the difference between PPTs during ($CPM_{during\ ice}$) or after ($CPM_{after\ ice}$) ice water bath submersion and baseline PPTs. In addition, the relative change was calculated at each site while the foot was submerged in ice water: ($RelCPM_{during\ ice}$) = ([(PPT during ice – PPT pre ice)/ PPT pre ice] x 100) and immediately after ice water: ($RelCPM_{after\ ice}$) = ([(PPT after ice – PPT pre ice)/ PPT pre ice] x 100). In addition, pain perceived during the ice water bath and S-PCS at baseline CPM trials were examined with session as within subject factor and group as a between subject factor.

To determine whether PPTs returned to baseline after the 45 minutes of quiet rest a RM ANOVA was performed (session [exercise and quiet rest] x time [baseline PPTs and PPTs before exercise quiet rest] x site [deltoid and quadriceps]) with group as a between subject factor. These analyses were followed by post hoc testing using paired and independent t tests.

CPM Responders and Non-Responders: Participants for both groups were categorized as CPM responders based on the change in the standard error of measurement (SEM) of PPTs (Vaegter, Petersen, Morch, Imai, & Arendt-Nielsen, 2018). First SEMs for each site were calculated by performing a RM ANOVA for baseline PPTs of all 3 sessions and then taking the square root of its mean square error for both groups (Vaegter et al., 2018; Weir, 2005). Participants who had an increase in PPTs during or after the ice water bath compared to baseline PPTs larger than the calculated SEM for each site were classified as CPM responders. This classification was done for the absolute change in CPM with each calculation method (i.e. $CPM_{during\ ice}$ and $CPM_{after\ ice}$). In

addition, classification of CPM responders and non-responders was made for the relative change in CPM (Locke et al., 2014). This was done by calculating the percent change of SEM from the average baseline PPTs for each group at each site (e.g. % SEM change = (SEM-Average PPT)/Average PPT). Participants were then classified as CPM responders if the relative CPM change was larger than the % SEM change. This was also done for each calculation method (i.e. $RelCPM_{during\ ice}$ and $RelCPM_{after\ ice}$).

Preliminary analyses showed variability of CPM responders and non-responders across the two experimental sessions. Therefore, classification was done based on the first CPM trial of each respective session (exercise and quiet rest). To identify agreement of responders between the two sites at each baseline CPM protocol and between sessions of baseline CPM protocols Cohen's Kappa was used. Kappa statistics of 0.81-1 were considered almost perfect agreement, 0.61-0.8 substantial agreement, 0.41-0.6 moderate agreement, 0.21-0.4 fair agreement, 0-0.2 slight agreement, and <0 as poor agreement (Landis & Koch, 1977). In addition, a chi-square test was performed to determine if the proportion of responders and non-responders in each group were different for all CPM trials in the experimental sessions.

Conditioned Pain Modulation after Exercise and Quiet Rest: To investigate the effect of exercise on the CPM response, CPM following exercise and quiet rest were analyzed using a RM ANOVA (session [exercise and quiet rest] x CPM trial [CPM pre and post exercise or quiet rest] x site [deltoid and quadriceps]) with a between subject factor group. To examine whether the

effects of exercise on CPM are similar in responders and non-responders a RM ANOVA (CPM trial [CPM pre and post exercise or quiet rest]) for each session and site separately with 2 between subject factors (group [healthy and FMS] and CPM response [responders and non-responders]. This was done for each site with all CPM calculation methods (i.e. $CPM_{during\ ice}$, $CPM_{after\ ice}$, $RelCPM_{during\ ice}$, and $RelCPM_{after\ ice}$) each with their respective classification method. When significant effects were found, post hoc analyses were done using paired t-tests. To identify potential differences in perceived pain intensity during ice water bath immersion or S-PCS following CPM for protocols in experimental sessions, RM ANOVA (session [exercise and quiet rest] x CPM trial [pain or S-PCS pre and post exercise or quiet rest]) was done with between subject factor group (healthy controls and FMS). Post hoc testing with paired t-tests or the Wilcoxon signed rank test for non-normally distributed data were done as appropriate.

Pressure Pain Thresholds after Exercise and Quiet Rest: To examine if PPTs increased locally at the exercising muscle and/or systemically for each group a RM ANOVA was performed (session [exercise and quiet rest] x time [PPTs pre and immediately post exercise and rest] x site [deltoid and quadriceps]) with between subject factor group. In addition, the absolute and relative change in PPTs at each site was compared between sessions using a RM ANOVA (session [exercise and quiet rest] x site [deltoid and quadriceps]) with between subject factor group. The analyses were followed by post hoc testing using paired t-tests.

Vibration Perception Threshold: To investigate the effect of exercise on VPTs, VPTs following exercise and quiet rest were analyzed using a RM ANOVA (session [exercise and quiet rest] x time [VPTs pre and immediately post exercise or quiet rest] x site [deltoid and quadriceps]) with a between subject factor group. In addition, the absolute and relative change in VPTs at each site was compared between sessions using a RM ANOVA (session [exercise and quiet rest] x site [deltoid and quadriceps]) with between subject factor group. The analyses were followed by post hoc testing using paired t-tests.

Correlations: To investigate factors that influenced EIH or the CPM response following EIH, Pearson or Spearman correlations were performed with VPTs, questionnaire data, body composition, and physical activity. In addition, these correlations were performed to determine if pain during exercise, or ice water bath were related to EIH, or CPM, respectively. The relation of skin temperature to VPTs were investigated using Pearson correlations as well as whether the change in VPT values were related to the change in temperature following exercise or quiet rest. These analyses were done for all participants combined unless there were differences at baseline with measurements, then they were done separately for each group. To reduce type 1 and type 2 errors due to multiple correlations, a more rigorous p-value was selected ($p= 0.01$) to denote significance (Avin & Law, 2011; Garamszegi, 2006).

Results

Participants characteristics

Table III.1 summarizes participants' characteristics. Pain medications for individuals with FMS were as follows: Acetaminophen (n=5), NSAIDs (n=4), Amitriptyline (n=2), Tramadol (n=3), Hydrocodone (n=1), Gabapentin (n=3), Duloxetine (n=2), Milnacipran (n=1), Lamotrigine (n=2), Cyclobenzaprine (n=4), Clonazepam (n=1), Escitalopram (n=1), Tizanidine (n=1), Eletriptan (n=1), Trazadone (n=1), Diazepam (n=1), and Dicyclomine (n=1). Four individuals (19%) reported not taking any pain medications. All participants completed all sessions except for one control participant who did not show up for the third session which was an exercise session; data of the first and second session was kept and analyzed. One individual with FMS refused to perform the body scan for personal reasons. Five participants were excluded from accelerometery data for the following reasons: 1) refused to wear actigraph (n=2); 2) did not meet wear time criteria (i.e. at least 4 days of wear time) (n=2); and 3) lost actigraph (n=1).

Table III.1 Participant characteristics

	Healthy Controls	n	Fibromyalgia	n	P-value
Age (yr)	49.1 ± 13.3	22	50.5 ± 14.9	21	0.763

Males	n= 2		n= 3		
SF-MPQ					
Sensory	0.68 ± 1.1	22	6.6 ± 5.6	21	**< 0.001**
Affective	0.15 ± 0.5	22	1.6 ± 1.9	21	**< 0.001**
VAS	0.42 ± 0.7	22	2.8 ± 2.1	21	**< 0.001**
PPI	0.36 ± 0.6	22	1.4 ± 0.9	21	**< 0.001**
Total	0.82 ± 1.4	22	8.0 ± 6.5	21	**< 0.001**
FIQR					
FIQR functional			26.7 ± 19.7	21	
FIQR overall impact			7.1 ± 5.2	21	
FIQR symptom			45.0 ± 20.3	21	
FIQR total			38.6 ± 19.7	21	
Pain					
Catastrophizing					
Scale					
PCS- Magnification	1.5 ± 2.1	22	5.1 ± 3.7	21	**< 0.001**
PCS- Rumination	1.9 ± 2.5	22	8.5 ± 4.4	21	**< 0.001**
PCS- Helplessness	2.0 ± 3.8	22	10.2 ± 4.4	21	**< 0.001**
PCS- Total	5.4 ± 8.0	22	23.9 ± 10.9	21	**< 0.001**
Vibration Threshold					
VPT index	5.6 ± 2.1	22	5.3 ± 2.0	21	0.820
VPT deltoid	11.1 ± 4.0	22	16.2 ± 8.9	21	**0.026**
VPT quadriceps	18.0 ± 6.5	22	17.9 ± 8.9	21	0.989

VPT abdomen	17.9 ± 7.4	22	21.1 ± 9.3	21	0.219
Exercise					
MVC (lbs.)	293.3 ± 102.0	21	289.1 ± 98.8	21	0.892
Target force (30% MVC)	88.1 ± 30.5	21	86.7 ± 29.6	21	0.878
Time to exhaustion (min)	7.0 ± 4.1	21	5.3 ± 2.3	21	0.103
Pain at the end (0-10)	7.4 ± 2.3	21	8.5 ± 2.1	21	0.142
RPE at the end (0-10)	8.7 ± 1.5	21	9.0 ± 1.5	21	0.593
Body composition					
BMI	27.9 ± 5.7	22	31.5 ± 8.5	20	0.105
Total body fat (%)	37.3 ± 8.2	22	41.5 ± 9.0	20	0.125
Total lean mass (lbs)	100.1 ± 17.9	22	105.1 ± 17.8	20	0.376
Total body BMC (lbs)	5.6 ± 0.9	22	5.5 ± 1.1	20	0.694
Android fat (%)	39.8 ± 12.5	22	46.4 ± 12.2	20	0.094
Gynoid fat (%)	40.7 ± 8.0	22	43.6 ± 9.0	20	0.271
Android/gynoid (A/G) ratio	0.9 ± 0.2	22	1.0 ± 0.2	20	0.204
Right arm fat (%)	37.3 ± 9.1	22	38.2 ± 10.0	20	0.784
Right arm fat (lbs)	3.7 ± 1.4	22	3.9 ± 1.6	20	0.577
Right arm lean (lbs)	5.6 ± 1.4	22	5.8 ± 1.4	20	0.655

Right arm BMC (lbs)	0.3 ± 0.1	22	0.3 ± 0.1	20	0.244
Right leg fat (%)	35.6 ± 7.8	22	38.2 ± 8.4	20	0.309
Right leg fat (lbs)	11.0 ± 4.6	22	12.7 ± 4.4	20	0.220
Right leg lean (lbs)	18.0 ± 3.4	22	18.9 ± 4.3	20	0.434
Right leg BMC (lbs)	1.0 ± 0.2	22	0.9 ± 0.2	20	0.721
Visceral fat mass (lbs)	1.6 ± 1.2	22	2.8 ± 2.0	20	**0.027**
Physical Activity					
Accelerometery					
Sedentary (%)	52.8 ± 8.3	19	53.3 ± 7.3	19	0.850
Light (%)	34.0 ± 7.1	19	33.7 ± 5.9	19	0.895
Moderate/vigorous (%)	13.1 ± 5.9	19	12.9 ± 5.8	19	0.916
Average MVPA per day (min)	189.0 ± 85.4	19	186.0 ± 83.5	19	0.916
Vector magnitude counts per minute	1673.3 ± 485.3	19	1602.6 ± 411.5	19	0.631
Self-report					
IPAQ total walking MET-(minutes/week)	1598.7 ± 1871.6	21	2354.8 ± 2708.7	21	0.489
IPAQ total moderate MET-(minutes/week)	1550.5 ± 1645.2	21	2384.2 ± 3226.1	21	0.724

IPAQ total vigorous MET-(minutes/week)	607.6 ± 1078.4	21	2796.2 ± 5087.2	21	0.226
IPAQ MET-(minutes/week)	3858.4 ± 3090.5	21	7603.4 ± 9736.0	21	0.521
IPAQ total sitting	1894.8 ± 1152.8	21	2452.1 ± 1464.9	21	0.365
PAAT total moderate per week	294.3 ± 356.1	21	503.7 ± 605.0	21	0.248
PAAT total vigorous per week	53.3 ± 69.7	21	157.5 ± 249.7	21	0.261
PAAT total moderate/vigorous per week	339.8 ± 381.3	21	1559.3 ± 4357.1	21	0.190
Other questionnaires					
TSK	16.8 ± 4.1	22	26.1 ± 7.2	21	**< 0.001**
PSEQ	53.2 ± 10.3	22	35.2 ± 9.8	21	**< 0.001**

SF-MPQ, Short form McGill Pain Questionnaire; VAS, visual analog scale; PPI, present pain intensity; FIQR, Revised Fibromyalgia Impact Questionnaire; VPT, vibration perception threshold; MVC, maximal voluntary contraction; BMI, body mass index; IPAQ, International Physical Activity Questionnaire; PAAT, Physical Activity Assessment Tool; MVPA, moderate to vigorous physical activity; PCS, Pain Catastrophizing Scale; yr, year; RPE, rate of perceived exertion; TSK, Tampa Scale of Kinesiophobia; PSEQ, Pain Self-Efficacy Questionnaire.

One outlier was detected and adjusted from each of the following variables: $CPM_{after\ ice}$ at the quadriceps post exercise, $RelCPM_{during\ ice}$ and $RelCPM_{after\ ice}$ at the quadriceps pre quiet rest, relative EIH at the quadriceps, PCS total, PCS helplessness subscale, VPT at the index in the first session, right arm lean mass, IPAQ total MET, and PAAT total vigorous activity. Two outliers were detected and adjusted from the following variables: the absolute and relative change in PPT at the quadriceps following quiet rest, IPAQ total moderate MET, IPAQ total vigorous MET, PAAT total moderate activity and PAAT total moderate to vigorous activity. Analyses were performed with and without outlier adjustments with no differences in the results.

SF-MPQ and FIQR did not differ across sessions ($p > 0.05$) for both groups. Compared to healthy controls, individuals with FMS had significantly higher SF-MPQ and PCS scores and lower TSK and PSEQ scores ($p < 0.001$). Only one healthy participant had a PCS score above 30 and a low PSEQ (value of 12) score. Body composition and physical activity were not significantly different between groups ($p > 0.05$) with the exception of visceral adipose tissue ($p < 0.05$). VPT measures were higher in individuals with FMS only at the deltoid site ($p < 0.05$).

Baseline conditioned pain modulation

Participants completed all the CPM protocols except two participants (one from each group) who removed their foot from ice water before completion of the two minutes. These participants kept their foot, however in the ice water for at

least 20 seconds and completed all PPT assessments and their data were used in the analyses.

Results of the analysis for baseline CPM demonstrated a main effect of site ($F(1,40) = 76.187$, $p < 0.001$, $\eta_p^2 = 0.656$), time ($F(1,40) = 38.819$, $p < 0.001$, $\eta_p^2 = 0.493$), and group ($F(1,40) = 6.879$, $p = 0.012$, $\eta_p^2 = 0.147$). Post hoc analyses showed there was an increase in PPTs at the deltoid and quadriceps muscles while the foot was submerged in the ice water bath ($CPM_{during\ ice}$) and immediately following removal of the foot from the ice water bath ($CPM_{after\ ice}$), which signifies CPM ($p < 0.005$; Figure III.2). This effect was significant for both groups; however, individuals with FMS had significantly lower PPTs than healthy controls at all time points ($p < 0.01$; Figure III.2 B). In addition, PPTs were higher at the quadriceps muscle compared with the deltoid muscle ($p < 0.01$; Figure III.2). No other interactions were found ($p > 0.05$).

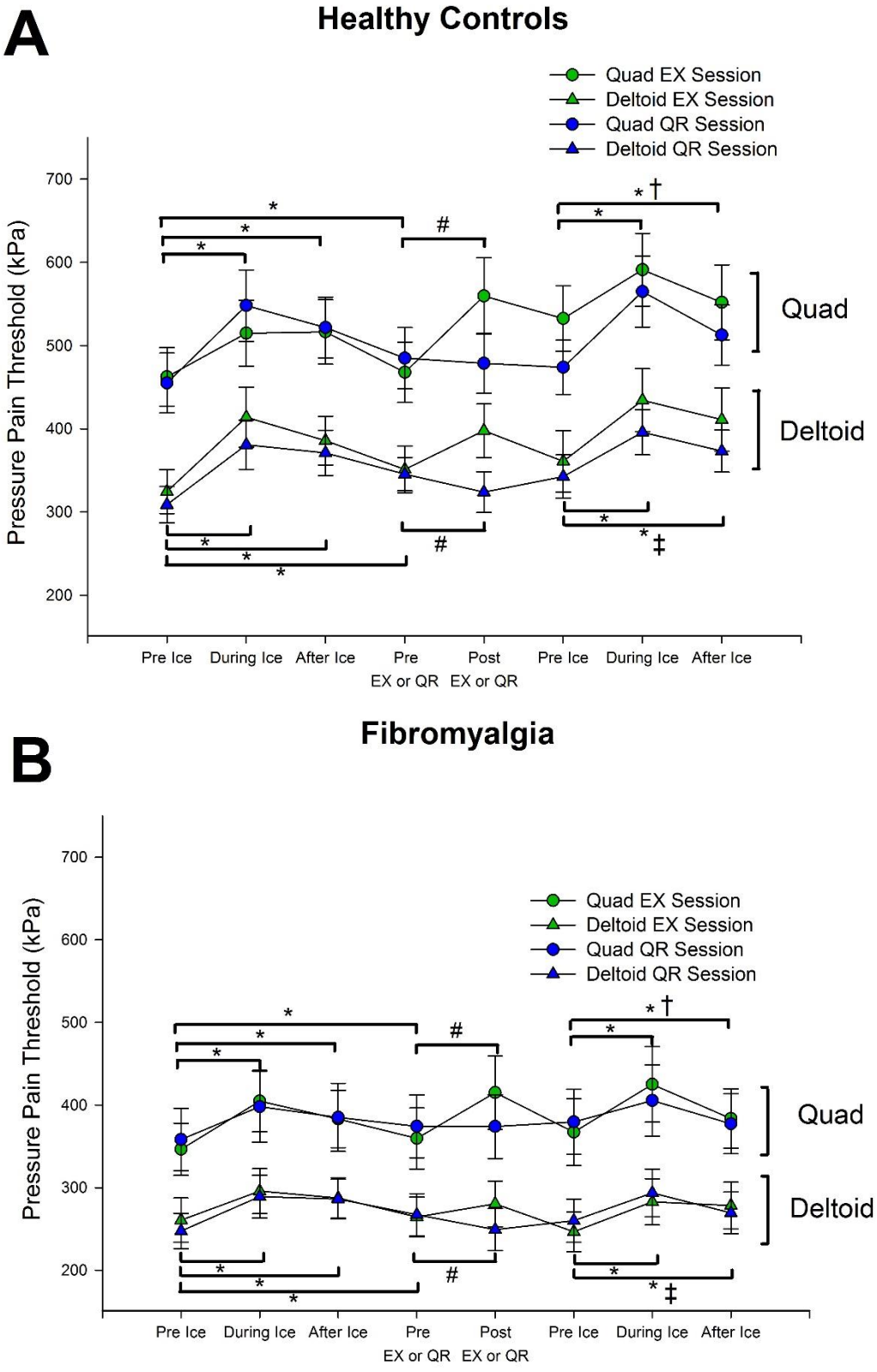

A
Healthy Controls
Quad EX Session
Deltoid EX Session
Quad QR Session
Deltoid QR Session
Pressure Pain Threshold (kPa)
700
600
500
400
300
200
Quad
Deltoid
Pre Ice
During Ice
After Ice
Pre
EX or QR
Post
EX or QR
Pre Ice
During Ice
After Ice
B
Fibromyalgia
Quad EX Session
Deltoid EX Session
Quad QR Session
Deltoid QR Session
Pressure Pain Threshold (kPa)
700
600
500
400
300
200
Quad
Deltoid
Pre Ice
During Ice
After Ice
Pre
EX or QR
Post
EX or QR
Pre Ice
During Ice
After Ice

Figure III.2 Pressure pain thresholds (kPa) at the quadriceps muscle and the deltoid muscle during the experimental sessions (exercise or quiet rest) for healthy controls (A) and fibromyalgia (B) participants.

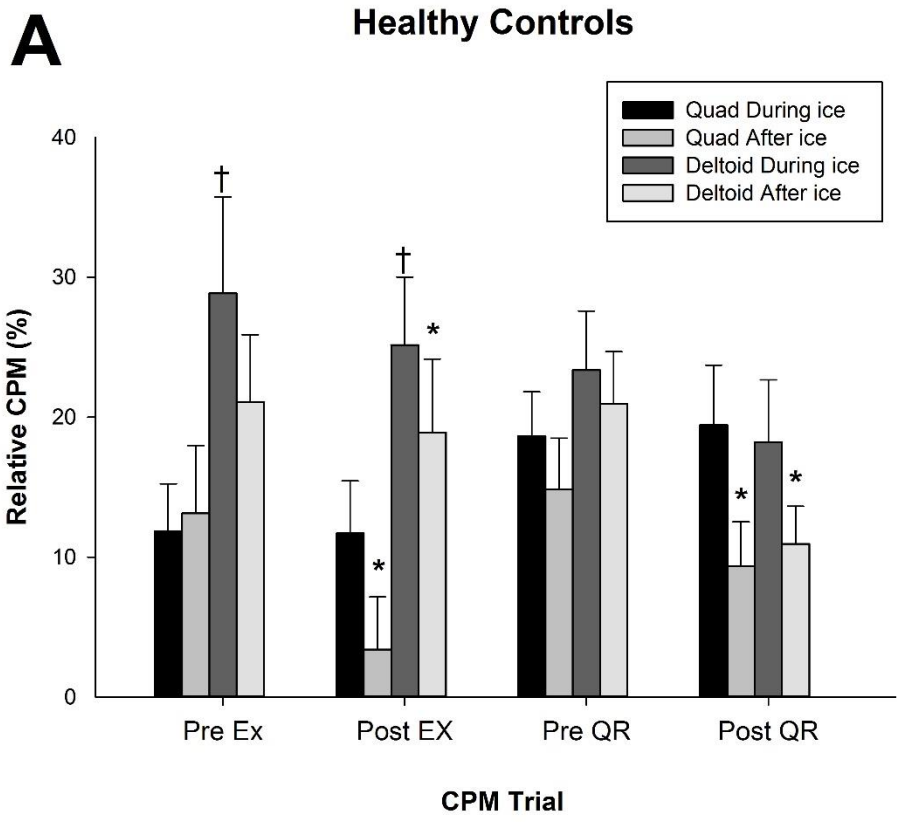
CPM occurred before and after exercise and quiet rest as demonstrated by the increased PPTs during and after ice water bath submersion. The increase in PPTs following exercise at the quadriceps and deltoid muscles represent local and systemic EIH, respectively. Absolute $CPM_{after\ ice}$ (PPT after ice – PPT pre ice) reduced for the quadriceps following exercise and quiet rest (†) and reduced for the deltoid following quiet rest only (‡). Significantly different compared to pre ice at both sessions (*) and significantly different compared to pre exercise ($^{\#}$) for the exercise session. Data are presented as mean ± SE. Abbreviations: EX, exercise; QR, quiet rest.

When comparing the two sites, however using the absolute or relative change there was a session x site x group interaction for $RelCPM_{during\ ice}$ ($F(1,40) = 4.349$, $p < 0.05$, $\eta_p^2 = 0.098$; Figure 3) and $CPM_{during\ ice}$ ($F(1,40) = 4.833$, $p < 0.05$, $\eta_p^2 = 0.108$). Post hoc analyses for $RelCPM_{during\ ice}$ showed a difference only among healthy controls between the two sites in the exercise session (deltoid = 28 ± 31% vs quadriceps = 11 ± 15%; $p < 0.05$; Figure III.3 A) and for $CPM_{during\ ice}$ between the groups for the deltoid in the exercise session (healthy controls = 89 ± 97 kPa vs FMS = 35 ± 71 kPa; $p < 0.05$) and the quad in the quiet rest session (healthy controls = 93 ± 79 kPa vs FMS = 39 ± 65 kPa; $p < 0.05$). There were no differences, however in baseline CPM calculated after ice ($RelCPM_{after\ ice}$ and $CPM_{after\ ice}$) between sessions, sites, or groups ($p > 0.05$).

Individuals with FMS perceived greater pain during the ice water bath and scored the S-PCS higher than healthy controls ($p < 0.05$) but were similar across baseline CPM trials (session and session x group; $p > 0.05$).

When we examined whether PPTs returned to baseline after the 45 min quiet rest, results demonstrated a main effect of time ($F(1,40) = 6.243$, $p = 0.017$,

η_p^2= 0.135), site (F(1,40) = 75.053, p < 0.001, η_p^2= 0.652), and group (F(1,40) = 5.905, p = 0.020, η_p^2= 0.129). No other main effects or interactions were found (p > 0.05). Post hoc showed that PPTs did not completely return to baseline before exercise or quiet rest (p = 0.017). In addition, as shown before, healthy controls and the quadriceps muscle had higher thresholds (p < 0.05).


A
Healthy Controls
Quad During ice
Quad After ice
Deltoid During ice
Deltoid After ice
Relative CPM (%)
40
30
20
10
0
†
†
*
*
*
*
Pre Ex
Post EX
Pre QR
Post QR
CPM Trial

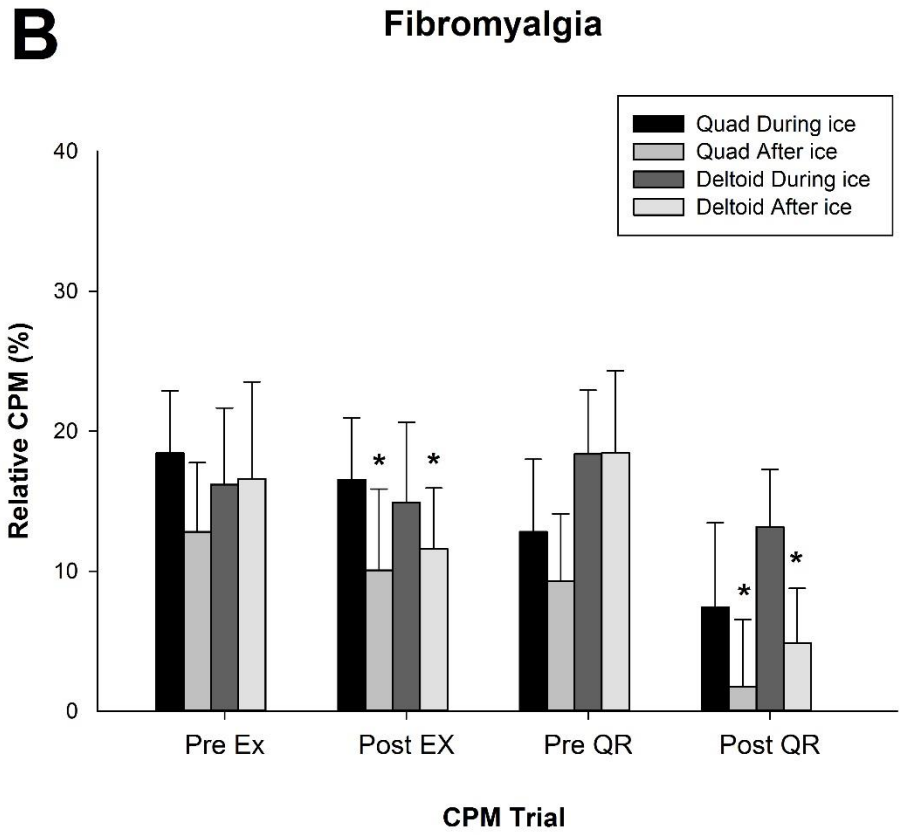

B
Fibromyalgia
Quad During ice
Quad After ice
Deltoid During ice
Deltoid After ice
Relative CPM (%)
40
30
20
10
0
*
*
*
*
Pre Ex
Post EX
Pre QR
Post QR
CPM Trial

Figure III.3 Relative change in CPM at the quadriceps muscle and the deltoid muscle before and after exercise or quiet rest for healthy control (A) and fibromyalgia (B) participants.

Significantly different than pre (*) and significantly different than quadriceps (†). Data are presented as mean ± SE. Abbreviations: CPM, conditioned pain modulation; EX, exercise; QR, quiet rest; During ice, ($RelCPM_{during\ ice}$) = ([(PPT during ice – PPT pre ice)/ PPT pre ice] x 100); After ice, ($RelCPM_{after\ ice}$) = ([(PPT after ice – PPT pre ice)/ PPT pre ice] x 100).

CPM responders and non-responders

The SEM at the deltoid was 41.41 kPa for healthy control participants and 55.06 kPa for individuals with FMS. This corresponds to %13.37 change in healthy controls and %21.59 change in individuals with FMS, respectively. The SEM at the quadriceps was 79.29 kPa for healthy control participants and 59.6 kPa for individuals with FMS. This corresponds to %17.55 change in healthy controls and %16.55 change in individuals with FMS, respectively. The number of CPM responders and non-responders for each CPM trial using all calculation methods are shown in Figure III.4. There were no differences in proportion of CPM responders between healthy controls and FMS ($p > 0.05$) except for baseline $CPM_{during\ ice}$ at the deltoid in the exercise session ($\chi^2(1) = 4.709$, $p = 0.03$) and quiet rest session ($\chi^2(1) = 5.225$, $p = 0.022$).

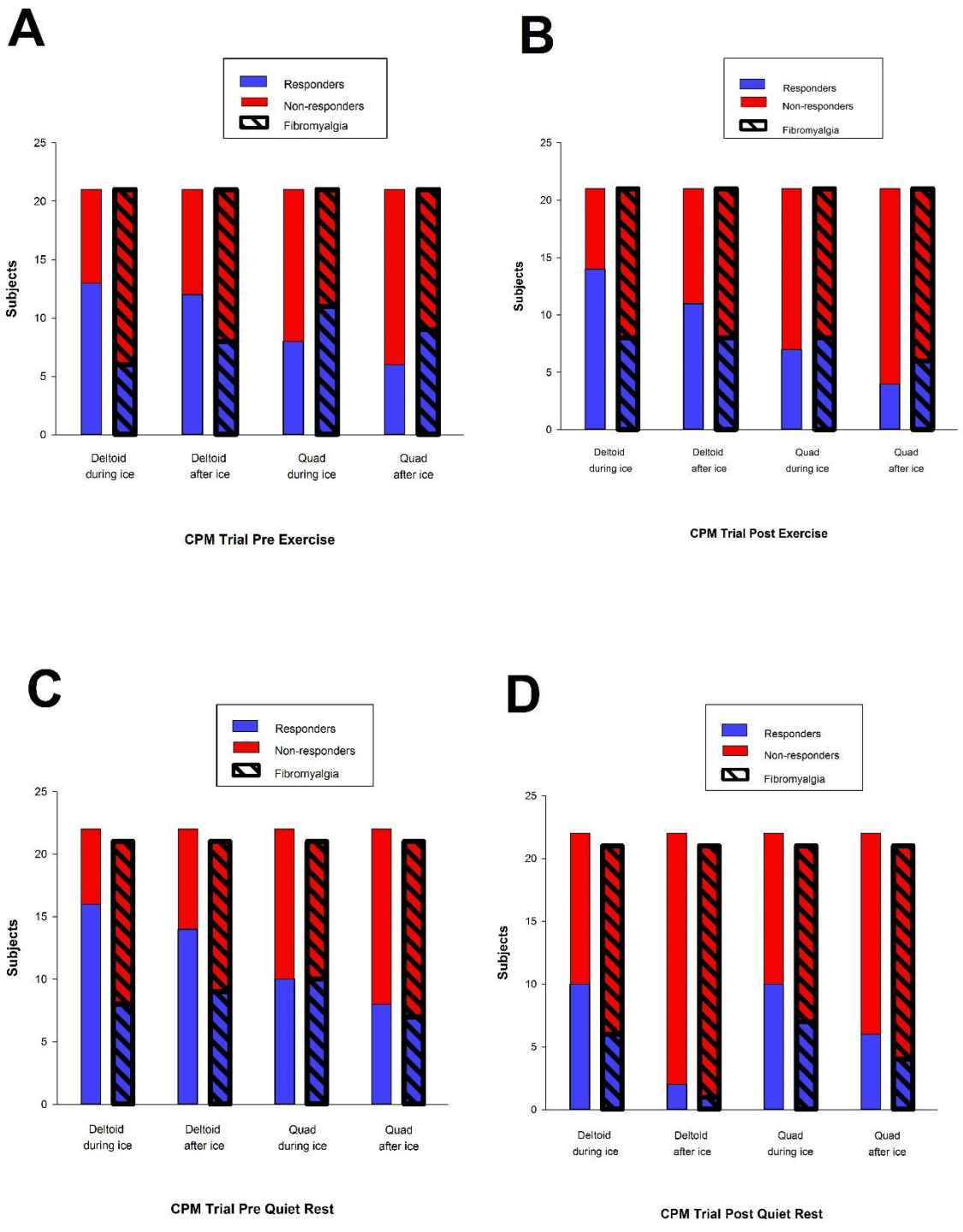


Figure III.4 Number of CPM responders (blue) and non-responders (red) for healthy controls (solid bars) and fibromyalgia (hashed bars).

CPM trial pre exercise (A), post exercise (B), pre quiet rest (C) and post quiet rest (D).

The CPM responders and non-responders agreement between sites was variable across CPM trials and dependent on calculation method. In the baseline CPM trial of the exercise session, agreement between sites was only significant with $CPM_{during\ ice}$ ($\kappa = 0.549$, $p = 0.005$) and $RelCPM_{after\ ice}$ ($\kappa = 0.447$, $p = 0.027$) for healthy controls. In the CPM trial following exercise, agreement between sites was only significant with $RelCPM_{during\ ice}$ ($\kappa = 0.625$, $p = 0.002$) and $RelCPM_{after\ ice}$ ($\kappa = 0.444$, $p = 0.049$) for individuals with FMS. In baseline CPM trial of the quiet rest session, agreement between sites was significant for individuals with FMS only with $CPM_{during\ ice}$ ($\kappa = 0.615$, $p = 0.004$) and $RelCPM_{during\ ice}$ ($\kappa = 0.422$, $p = 0.049$). Following quiet rest, however, agreement between sites for both groups were significant with $CPM_{during\ ice}$ (healthy controls: $\kappa = 0.450$, $p = 0.035$; FMS: $\kappa = 0.444$, $p = 0.040$) and $RelCPM_{during\ ice}$ (healthy controls: $\kappa = 0.450$, $p = 0.035$; FMS: $\kappa = 0.538$, $p = 0.011$). Agreement of CPM responders and non-responders within each site between baseline CPM protocols of experimental sessions were not significant except for individuals with FMS for $RelCPM_{after\ ice}$ (deltoid: $\kappa = 0.507$, $p = 0.020$; quadriceps: $\kappa = 0.690$, $p = 0.001$) and $RelCPM_{during\ ice}$ (quadriceps only :$\kappa = 0.432$, $p = 0.044$). Thus, agreement of responders and non-responders between sites within the same CPM protocol was moderate. In addition, consistency of responder or non-responder within the same site between sessions was also moderate. Given this moderate consistency only with certain calculation methods, it was necessary to evaluate CPM following exercise and quiet rest in responders and non-responders at each site separately.

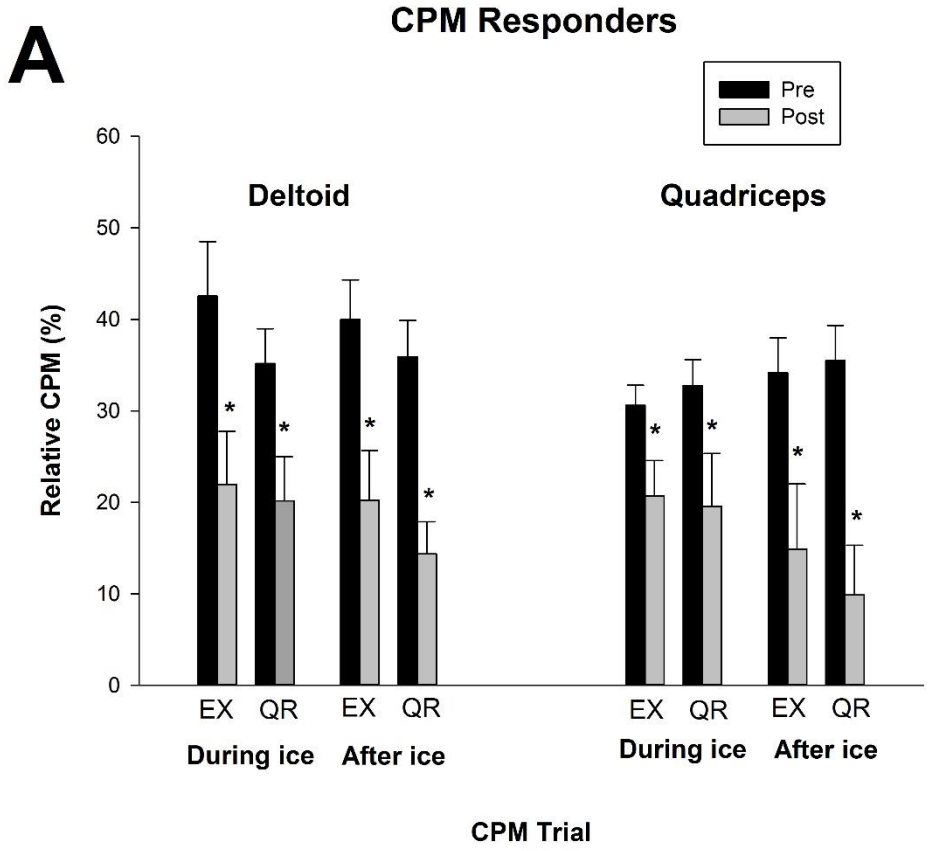
Conditioned pain modulation following exercise and quiet rest

Results of the analyses of $CPM_{during\ ice}$ and $RelCPM_{during\ ice}$ showed a significant session x site x group ($F(1,40) = 13.191$, $p = 0.001$, $\eta_p^2 = 0.248$; $F(1,40) = 9.359$, $p = 0.004$, $\eta_p^2 = 0.190$; respectively). No main effects of CPM trial or interactions were found ($p > 0.05$). $CPM_{after\ ice}$ showed a significant session x CPM trial x site ($F(1,40) = 10.146$, $p = 0.003$, $\eta_p^2 = 0.202$). No interactions with group were found; however, a main effect of group was significant ($F(1,40) = 4.090$, $p = 0.050$, $\eta_p^2 = 0.093$). Post hoc analyses showed that $CPM_{after\ ice}$ reduced for the quadriceps following exercise ($p = 0.043$) and quiet rest ($p = 0.043$) and reduced for the deltoid following quiet rest only ($p < 0.001$; Figure III.2). When analyzing $RelCPM_{after\ ice}$, however there was only a main effect of trial ($F(1,40) = 11.039$, $p = 0.002$, $\eta_p^2 = 0.216$) and a main effect of site ($F(1,40) = 6.732$, $p = 0.013$, $\eta_p^2 = 0.144$) with no other interactions or main effects (Figure III.3). Post hoc analyses show that CPM decreased after exercise and quiet rest ($p = 0.002$), and the decrease was higher for the deltoid compared with the quad ($p = 0.013$).

When analyzing each trial separately with group and CPM response as a between subject factor a significant CPM trial x CPM response interaction was found for all calculation methods at the deltoid ($CPM_{during\ ice}$: $F(1,38) = 25.497$, $p < 0.001$, $\eta_p^2 = 0.402$; $RelCPM_{during\ ice}$: $F(1,38) = 15.900$, $p < 0.001$, $\eta_p^2 = 0.295$; $CPM_{after\ ice}$: $F(1,38) = 19.759$, $p < 0.001$, $\eta_p^2 = 0.342$; $RelCPM_{after\ ice}$: $F(1,38) = 12.546$, $p = 0.001$, $\eta_p^2 = 0.248$) and the quadriceps ($CPM_{during\ ice}$: $F(1,38) = 7.851$,

$p = 0.008$, $\eta_p^2 = 0.171$; $RelCPM_{during\ ice}$: $F(1,38) = 8.874$, $p = 0.005$, $\eta_p^2 = 0.189$; $CPM_{after\ ice}$: $F(1,38) = 9.846$, $p = 0.003$, $\eta_p^2 = 0.206$; $RelCPM_{after\ ice}$: $F(1,38) = 7.552$, $p = 0.009$, $\eta_p^2 = 0.166$) in the exercise session. Post hoc analyses showed that for CPM responders CPM was reduced following exercise for both muscles ($p < 0.05$) but for non-responders CPM increased for the deltoid muscle only ($p \leq 0.01$; Figure III.5).

In the quiet rest session, there was also a significant CPM trial x CPM response interaction for all calculation methods at the deltoid ($CPM_{during\ ice}$: $F(1,39) = 7.905$, $p = 0.008$, $\eta_p^2 = 0.169$; $RelCPM_{during\ ice}$: $F(1,39) = 10.759$, $p = 0.002$, $\eta_p^2 = 0.216$; $CPM_{after\ ice}$: $F(1,39) = 21.155$, $p < 0.001$, $\eta_p^2 = 0.352$; $RelCPM_{after\ ice}$: $F(1,39) = 9.609$, $p = 0.004$, $\eta_p^2 = 0.198$) and the quadriceps ($CPM_{during\ ice}$: $F(1,39) = 6.872$, $p = 0.012$, $\eta_p^2 = 0.150$; $RelCPM_{during\ ice}$: $F(1,39) = 6.401$, $p = 0.016$, $\eta_p^2 = 0.141$; $CPM_{after\ ice}$: $F(1,39) = 5.626$, $p = 0.023$, $\eta_p^2 = 0.126$; $RelCPM_{after\ ice}$: $F(1,39) = 16.912$, $p < 0.001$, $\eta_p^2 = 0.302$). Post hoc testing showed that for CPM responders CPM was reduced following quiet rest for both muscles ($p < 0.05$) with no significant change for non-responders except for $CPM_{after\ ice}$ at the deltoid where CPM was further reduced ($p < 0.01$; Figure III.5).


A
CPM Responders
Pre
Post
Deltoid
Quadriceps
Relative CPM (%)
60
50
40
30
20
10
0
EX QR EX QR
During ice After ice
EX QR EX QR
During ice After ice
CPM Trial

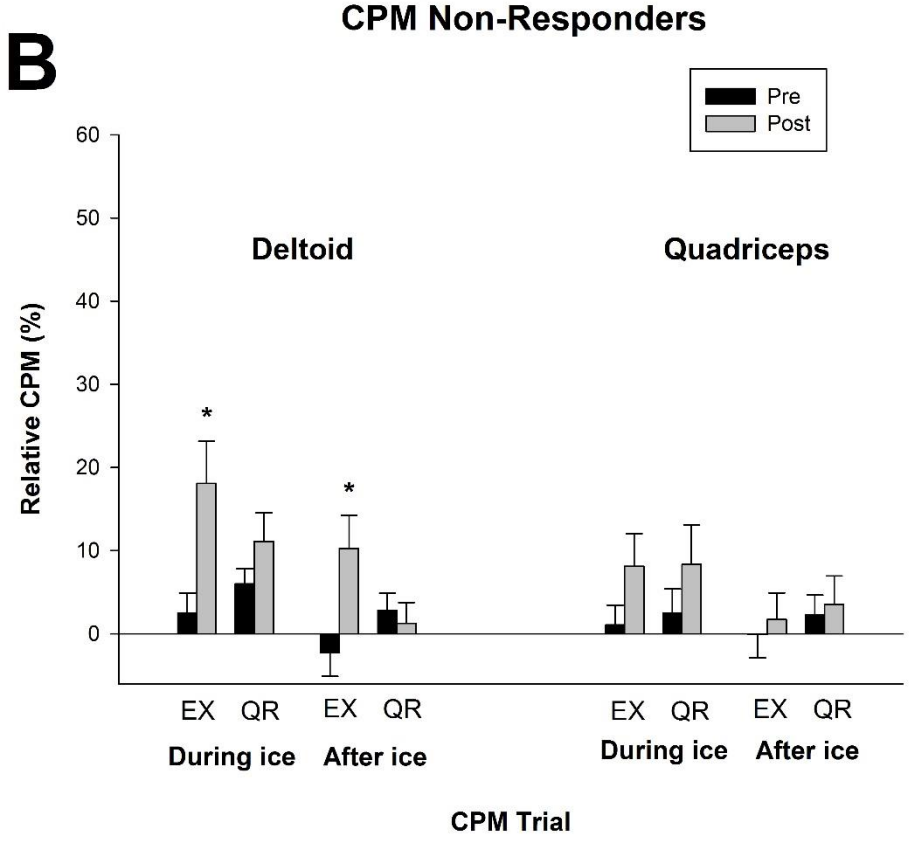

B
CPM Non-Responders
Pre
Post
Deltoid
Quadriceps
Relative CPM (%)
60
50
40
30
20
10
0
EX QR EX QR
During ice After ice
EX QR EX QR
During ice After ice
CPM Trial

Figure III.5 Relative change in CPM at the quadriceps and deltoid muscles before and after exercise or quiet rest for CPM responders (A) and non-responders (B).

Significantly different compared to pre exercise or quiet rest (*). Data are presented as mean ± SE. Abbreviations: CPM, conditioned pain modulation; EX, exercise; QR, quiet rest; During ice, ($RelCPM_{during\ ice}$) = ([(PPT during ice – PPT pre ice)/ PPT pre ice] x 100); After ice, ($RelCPM_{after\ ice}$) = ([(PPT after ice – PPT pre ice)/ PPT pre ice] x 100).

Analyses of perceived pain perception during the ice water bath and S-PCS showed there was a session x CPM trial interaction (pain at 20 sec: $F(1,40) = 5.382$, $p = 0.026$, $\eta_p^2 = 0.119$; pain at the end: $F(1,39) = 4.810$, $p = 0.034$, $\eta_p^2 = 0.110$; peak pain: $F(1,40) = 5.341$, $p = 0.026$, $\eta_p^2 = 0.118$; S-PCS: $F(1,40) = 8.482$, $p = 0.006$, $\eta_p^2 = 0.175$). No interactions with group were found; however, a main effect of group for all these variables were found. Post hoc analyses showed S-PCS was reduced after exercise ($p < 0.05$) with no change following quiet rest ($p > 0.05$) and peak pain increased following quiet rest ($p < 0.01$). Post hoc analyses of other variables were not significant following exercise or quiet rest ($p > 0.05$). Pain intensity and S-PCS were overall higher in individuals with FMS than healthy controls.

Pressure pain thresholds after exercise and quiet rest:

Before the start of exercise, all participants reported an exertion of 'nothing at all' (RPE = 0/10). Healthy controls reported no pain before the start of exercise except for 2 participants who reported pain of 1/10 NRS; individuals with FMS reported an average 1.04 ± 0.32. At the end of exercise, all participants

reported severe pain (healthy controls: NRS= 7.4 ± 2.3; FMS: NRS= 8.5 ± 2.09) and close to ‘very very strong’ exertion (healthy controls: RPE= 8.7 ± 1.5; FMS: RPE= 9.04 ± 1.5). Duration of exercise for healthy participants was 7.03 ± 4.11 minutes and 5.3 ± 2.34 for individuals with FMS. There were no significant differences between groups in all these variables ($p > 0.05$); although two healthy control participants exercised for approximately 17 minutes.

For PPTs, there was a session x time ($F(1,40) = 20.845$, $p < 0.001$, $\eta_p^2 = 0.343$) and a time x site ($F(1,40) = 5.044$, $p = 0.03$, $\eta_p^2 = 0.112$) interaction. No interactions for group were found; however, a main effect of group was significant ($F(1,40) = 6.327$, $p = 0.016$, $\eta_p^2 = 0.137$). Post hoc analyses showed that PPTs increased at both sites in the exercise session ($p < 0.01$; Figure III.2) and decreased following quiet rest for the deltoid site only ($p = 0.043$). PPTs were higher for healthy controls compared with FMS ($p = 0.016$).

When comparing the absolute and relative change in PPTs between the sessions there was a main effect of session (absolute: $F(1,40) = 22.583$, $p < 0.001$, $\eta_p^2 = 0.361$; relative: $F(1,40) = 20.909$, $p < 0.001$, $\eta_p^2 = 0.343$) and a main effect of site (absolute: $F(1,40) = 6.708$, $p = 0.013$, $\eta_p^2 = 0.114$; relative: $F(1,40) = 4.773$, $p = 0.035$, $\eta_p^2 = 0.107$). No main effect of group or interactions were found ($p > 0.05$). Post hoc analyses showed that the absolute and relative change in the exercise session for both sites were significantly greater than the change in the quiet rest session ($p < 0.005$), indicating local and systemic EIH.

Vibration perception threshold

VPT analyses showed there was a session x time x site interaction ($F(1,40) = 8.084$, $p = 0.007$, $\eta_p^2 = 0.168$). No main effects or interactions for group were found. Post hoc analyses showed that VPT at the index decreased following exercise ($p < 0.001$) with no change following quiet rest ($p > 0.05$). VPT at the quadriceps did not change following exercise ($p > 0.05$) but decreased following quiet rest ($p = 0.024$; Figure III.6).

When comparing the absolute and relative change in VPTs between the sessions there was a session x site interaction (absolute: $F(1,40) = 8.082$, $p = 0.007$, $\eta_p^2 = 0.168$; relative: $F(1,40) = 17.731$, $p < 0.001$, $\eta_p^2 = 0.307$). No main effect of group or interactions were found ($p > 0.05$). Post hoc analyses showed that the absolute and relative change in the exercise session for the index finger were significantly lower than in the quiet rest session (i.e. following exercise systemic vibration improved) ($p < 0.05$; Figure III.6)

The change for the quadriceps, however, was lower in the quiet rest session (i.e. better sensitivity) but higher in the exercise session (i.e. worse sensitivity).

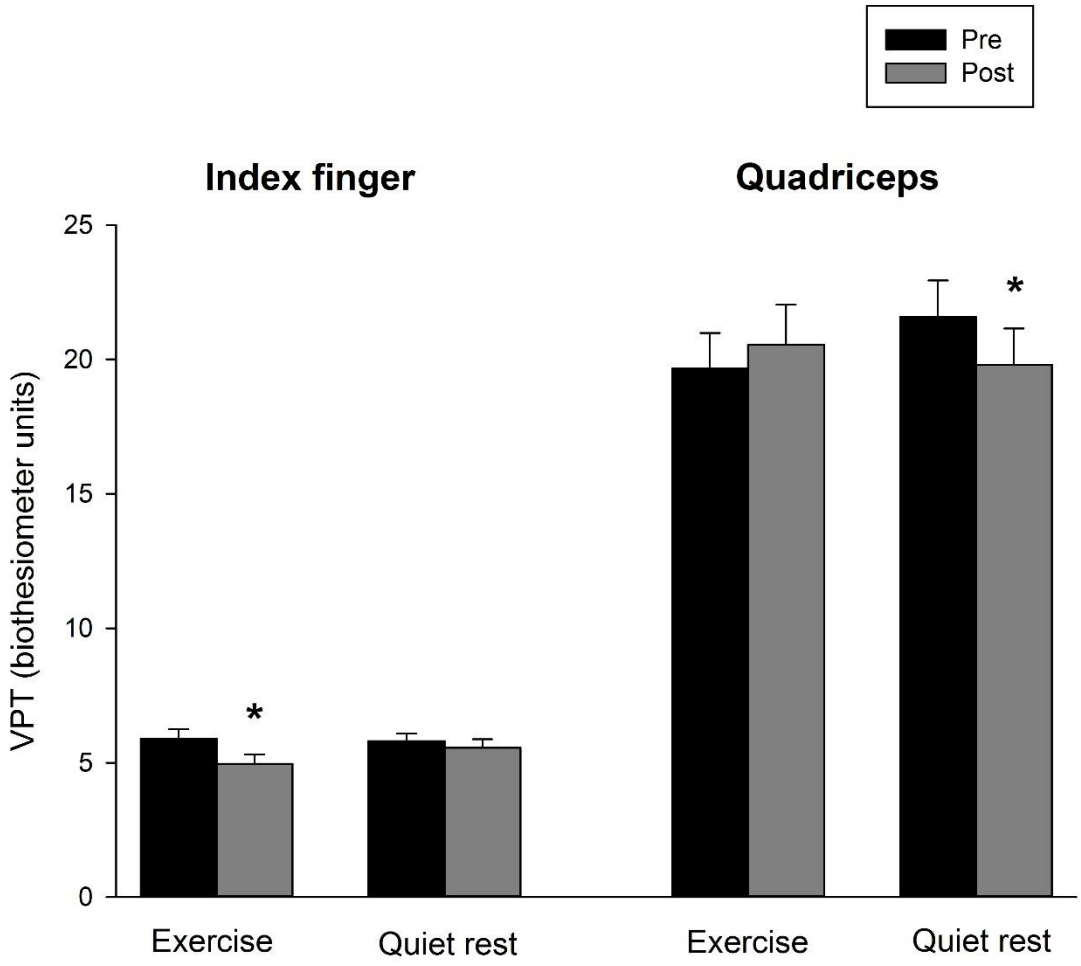


Figure III.6 Vibration perception thresholds (biothesiometer units) at the index finger and the quadriceps muscle before and after exercise and quiet rest.

Significantly different compared to pre exercise or quiet rest (*). Data are presented as mean ± SE. Abbreviations: VPT, vibration perception threshold.

Correlations

VPTs were not related to skin temperature ($p > 0.05$) except for the abdomen site measured in the first session ($r = -0.0413$, $p = 0.006$). The change in vibration at both sites following exercise and quiet rest were not related to the change in skin temperature ($p > 0.05$). Pain during exercise, the six minute walk test, and ice water bath were not significantly related to EIH, distance covered, or CPM for all trials ($p > 0.05$), respectively. EIH was not related to any other measures except for absolute EIH at the quadriceps muscle and PSEQ in healthy control participants ($r = 0.614$, $p = 0.003$). Following exercise $CPM_{during\ ice}$ at the quadriceps was related to percent light activity measured through accelerometery ($r = -0.420$, $p = 0.009$). This relation was not consistent with other calculation methods and was not related to other activity measures ($p > 0.05$). In individuals with FMS, the FIQR functional subscale was related to $CPM_{after\ ice}$ and $RelCPM_{after\ ice}$ at the quadriceps following exercise ($r = 0.574$ and $r = 0.556$, $p < 0.01$; respectively). The functional subscale was also related to $RelCPM_{after\ ice}$ at the quadriceps ($r = 0.576$, $p = 0.006$). S-PCS was not related to CPM measurements ($p > 0.05$) except for $RelCPM_{after\ ice}$ in individuals with FMS following exercise at the quadriceps ($r = 0.568$, $p = 0.007$). However, S-PCS was related to pain intensity during the ice water bath for all CPM measurements in healthy controls only ($r \geq 0.591$, $p \leq 0.005$). All other relations with CPM following exercise were non-significant ($p > 0.05$).

Discussion

The novel finding of the study was that individuals who had a reduced CPM response prior to exercise, had a significant increase in CPM systemically (i.e. at the deltoid) following exercise only, whereas those individuals that had a 'normal' functioning CPM prior to exercise had a decrease in CPM following exercise and quiet rest. This was true for both groups and using all calculation methods of CPM. Thus, a sustained isometric contraction may have activated descending inhibitory pathways in individuals with reduced CPM irrespective of their change in PPTs or their health status (healthy or FMS). This study also demonstrated that VPTs in both groups decreased systemically (i.e. vibratory sense improved at the index finger) following exercise with no significant change following quiet rest. Moreover, situational catastrophic thoughts (i.e. S-PCS) for the ice water bath were significantly reduced following exercise for both groups with no significant change in the pain intensity associated with the noxious stimulus.

Conditioned pain modulation

In the present study, CPM was similar between individuals with FMS and healthy controls. This finding is in contrast to multiple studies showing impaired CPM in individuals with FMS (Lewis et al., 2012). Previous studies, however have shown increased variability in the CPM response compared with healthy controls with some individuals having functional CPM (Chimenti et al., 2018).

Thus one explanation is that individuals with FMS who participated in this study were higher functioning compared with participants in previous studies, as shown by the lower FIQR scores compared with previous studies (Merriwether et al., 2018; Wang et al., 2018)(mean total FIQR in the current study = 38.6 vs. 52.4 to 60.4 in past studies). This is also shown by the lack of difference in body composition and physical activity measures between healthy controls and individuals with FMS. Higher levels of physical activity was previously linked to better CPM in young and older adults (Naugle, Ohlman, Naugle, Riley, & Keith, 2017; Naugle & Riley, 2014). Considering this study was advertised as the 'exercise and pain study'; it's conceivable that individuals with FMS who contacted us were interested in exercise as an intervention and had higher levels of physical activity.

In addition, CPM occurred both during and following ice water bath immersion. This is in agreement with previous studies (Lewis et al., 2012; Pud et al., 2005) but not in line with others (Kosek & Ordeberg, 2000; Leffler et al., 2002; Vaegter et al., 2014b; Vaegter et al., 2016). We recently performed a CPM protocol similar to the one used in this study on young healthy adults and found that CPM occurred during, but not following, the ice water immersion (Alsouhibani et al., 2018). Furthermore, in that study, CPM was not restored following 23 minutes of quiet rest, suggesting carry over effects from the first CPM trial. The protocol used in this study was recently piloted in young healthy adults with a longer washout period (45 minutes), and CPM was restored. Paradoxically, the 50 minute washout period in this study (45 min quiet rest + 5

min additional rest in the quiet rest session) did not seem to be sufficient, as CPM magnitude was significantly reduced following quiet rest. Reasons for these differences between young healthy adults and healthy middle aged women could be related to reduced hepatic and renal metabolism as people age (Klotz, 2009). The specific molecular role of CPM is still debatable; however, opioidergic, serotonergic and noradrenergic mechanisms have been implicated (Le Bars & Villanueva, 1988; Le Bars et al., 1992; Le Bars et al., 1981; Roerig, Fujimoto, & Tseng, 1988; Yaksh, 1985). As such, clearance of the specific neurotransmitters released by CPM could be reduced with age (Karrer, McLaughlin, Guaglianone, & Samanez-Larkin, 2019; Seals & Esler, 2000), making the CPM effect last longer. While age could be one reason for the difference between the two protocols, other differences are also possible. For example, expectations of a painful response has been shown to influence CPM magnitude (France et al., 2016) where anticipating a lower noxious conditioning stimulus results in greater CPM magnitude. It is possible that participants in the current study since they were familiarized to CPM in the first session, unlike in the previous study (Alsouhibani et al., 2018), had a higher expectation for the conditioning stimulus in the following sessions resulting in a lower CPM magnitude with longer lasting effects. The range of CPM magnitude in our previous study of young healthy adults was 32-40% (Alsouhibani et al., 2018) compared with 11-28% in the current study.

CPM responders and non-responders

Our results showed that 1) differences between sites (deltoid and quadriceps) within the same CPM protocol, and 2) differences between sessions within the same site. To our knowledge, this is the first study to report differences in CPM responders and non-responders at different sites of measurement within the same CPM protocol. For example, the same person could be a CPM responder at the deltoid muscle but not quadriceps muscle. Previously, studies have shown disagreement in the number of CPM responders and non-responders between different CPM protocols suggesting that CPM may have different inhibitory effects using different modalities (Vaegter et al., 2018). In the current study, however, we show that the inhibitory effects of CPM might not be the same for different muscles using the same modality. Although CPM is considered a systemic response, it may exert differential inhibitory effects on different muscles. In a recent study, the effects of CPM on the nociceptive withdrawal reflex differed based on the muscle tested (Jure, Arguissain, Biurrun Manresa, & Andersen, 2019) with inhibitory effects on some muscles but not others. This suggests that within the same individual the inhibitory effects of CPM may be site specific. The reasons for this deferential effect, however, is not known and warrants further study. We could speculate that differences in body composition between the two sites may explain this difference. Previously, lean mass was shown to be related to CPM in adolescents (Stolzman & Hoeger

Bement, 2016). In the current study, however, body composition did not explain this difference as body composition was not related to CPM.

Similar to the moderate consistency between sites (within the same CPM trial), a moderate consistency between sessions (within the same site) was observed in this study only in individuals with FMS. The absence of a significant agreement among CPM responders and non-responders in healthy participants between sessions could possibly be attributed to the inherit nature of CPM being a dynamic process. Multiple biopsychosocial factors have been shown to effect CPM (Hermans et al., 2016), which are known to fluctuate between sessions. For example, attentional factors have been shown to effect CPM such that if participants are given instructions to focus on the test stimulus compared to no instructions, greater CPM magnitude is observed (Defrin, Tsedek, Lugasi, Moriles, & Urca, 2010). While instructions to all participants were the same in the current study (i.e. to focus on the test stimulus), perhaps some participants were not consistent in their focus to the test stimuli during both sessions (e.g. the instruction to focus on the test stimulus was ignored in one session). In addition, expectations were shown to effect CPM magnitude where expecting lower pain (hypoalgesia) during CPM, results in greater CPM magnitude compared to expecting no change or greater pain (hyperalgesia) (France et al., 2016). While not measured in this study, it is possible that expectations of participants regarding CPM varied across sessions effecting its consistency. These hypotheses, however, requires further investigation.

Exercise-induced hypoalgesia

In the current study, EIH (i.e., increase in PPTs) occurred locally and to a lesser extent systemically in both groups. Previous research have shown that individuals with FMS have either worse or more variable pain responses to exercise compared to healthy controls. The significant hypoalgesic response in individuals with FMS found in this study, in contrast to previous studies (Kadetoff & Kosek, 2007; Staud et al., 2005), could either be explained by the permission of medications use in this study and/or the higher functioning group recruited in this study. In previous studies participants with FMS were usually asked to eliminate medication use at least 2 weeks prior to the study (e.g. [Staud et al., 2005]), unlike the current study where medication use was allowed. However, numerous studies have reported the poor adherence of individuals with FMS to exercise, mainly due to pain exacerbation following exercise. It is not known whether continued use of medications will enhance pain relief following exercise and thereby adherence would improve. In addition, whether the effects of exercise interacts with the use of medications is currently unknown.

The most interesting result of this study, however, is the distinctive effects of exercise on CPM responders and non-responders. Individuals who were classified as CPM non-responders prior to exercise experienced an enhanced CPM following exercise only systemically at the non-exercising muscle (i.e. the deltoid), regardless of EIH response, suggesting activation of descending inhibitory pathways. While individuals who were classified as CPM responders

prior to exercise experienced a reduction in CPM following exercise, regardless of EIH response. These responses occurred in both healthy controls and individuals with FMS. Interestingly, CPM was reduced following exercise in young healthy adults who report systemic EIH (Alsouhibani et al., 2018). Alternatively, when performing exercise immediately following CPM, hypoalgesia does not occur (Gajsar, Nahrwold, Titze, Hasenbring, & Vaegter, 2018). Thus, our results along with these studies suggest that CPM and systemic EIH may have similar mechanisms.

Following exercise, there was no change in CPM at the exercising muscle in CPM non-responders which could be explained by the fact that the inhibitory effects of CPM omits the spinal segment of the corresponding conditioning stimulus (Le Bars, Dickenson, & Besson, 1979b). Participants reported severe pain with our exercise protocol, thus the exercise may have acted as a conditioning stimulus. If the exercise in this study was considered a conditioning stimulus activating the inhibitory system, then the systemic inhibition may have omitted the quadriceps region; accordingly, no change was observed in CPM at the quadriceps region. An alternative explanation could be that the mechanism by which local hypoalgesia occurs following exercise is different than systemic. These findings, nevertheless could have important clinical implications; because CPM may be activated at sites distal from the exercising muscle in individuals with low CPM, therapists may advise patients to exercise the entire body for maximal benefits of exercise.

There is some evidence showing that certain treatments are only effective in individuals with low CPM. For example, Yarnitsky et al. (Yarnitsky et al., 2012) have shown that in patients with neuropathic pain duloxetine may enhance the CPM response only in individuals who have low CPM. Other treatments such as joint mobilization, and transcutaneous electrical nerve stimulation have also been shown to activate CPM (Courtney Steffen, Fernandez-de-Las-Penas, Kim, & Chmell, 2016; Dailey et al., 2013). Relevant to exercise, transcranial direct current stimulation to the motor cortex have been shown to enhance the CPM response (Flood et al., 2016). Similarly, exercise is known to activate the motor cortex, which may have potentially enhanced the CPM response in individuals with inefficient CPM in the current study.

Along with the increase in PPTs and the CPM changes following exercise, was a reduction in S-PCS in both groups. This reduction occurred despite unchanged pain reports of the ice water. This change was noticeable by participants as one participant stated after she completed the S-PCS that "although the pain [of the ice water bath] was similar to the previous test, I wasn't worried as much after the exercise." In longer clinical trials, changes in situational pain catastrophizing has been shown to precede changes in pain in individuals with FMS (Campbell et al., 2012). In addition, these changes in catastrophizing were shown to predict changes in pain but not vice versa. One potential mechanism in which exercise training reduces pain is by inducing changes in pain catastrophizing. Another possibility, as suggested by Campbell et al., is that the acute reduction in pain catastrophizing may enhance adherence to exercise

rehabilitation programs that will consecutively reduce clinical pain. However, future studies are needed to test this hypothesis.

Vibration perception threshold

Baseline vibration perception in this study was reduced in people with FMS compared with healthy controls only at the deltoid site. Research have shown that deficits in vibration in individuals with musculoskeletal pain could be caused by abnormal central processing rather than peripheral sensitivity (Geber et al., 2008). Experimentally induced pain increased vibration thresholds in healthy individuals (i.e. worse sensitivity) (Apkarian et al., 1994), a phenomenon termed the “touch gate.” These vibration thresholds were shown to be elevated in patients with chronic pain (Hollins et al., 1996; Shakoor et al., 2008) including FMS (da Silva et al., 2013). In the current study, vibration threshold was only reduced at the deltoid which could be related to pain itself. A common tender point in patients with FMS is between the shoulder joint and neck. Although the VPT measurement at the deltoid was not exactly at these tender points, previous research have shown that touch gating (i.e. the influence of pain on vibrotactile sensation) could possibly be related to dermatomal or somatotopical organization (Bolanowski, Maxfield, Gescheider, & Apkarian, 2000). Meaning that touch gating only occurs when the location of noxious and innocuous stimuli are localized within the dermatomal or somatotopical region. While pain was not measured at the time of measurement, possibly pain in the shoulder region in individuals with FMS may have altered the VPT at the deltoid site.

Results of this study showed a reduction in VPT following exercise only systemically at the index finger. This result parallels the enhancement of CPM systemically. The lack of a change in the quadriceps site could be potentially explained by the pain at that site at the time of measurement in some individuals. There was certainly more variability in the pain at time of VPT measurement as well as the change in VPT response at the quadriceps. This explanation, however, is not fully supported by our results as there was no correlation between pain at time of measurement and VPT measurement at the quadriceps. Changes in VPT after non-pharmacological treatments have been rarely investigated. One study, however have demonstrated a reduction in VPT following joint mobilization in individuals with knee osteoarthritis (Courtney Steffen, Fernandez-de-Las-Penas, Kim, & Chmell, 2016). Further studies are needed to determine whether changes in vibration sense follow changes in pain, potentially making it a clinical tool for pain sensitivity.

Correlations

We found that higher temperature of the skin was only related to vibration at the abdomen site (i.e. better perception). The effect of temperature changes on vibration thresholds were mixed in the literature with some studies showing as temperature increases threshold decreases (i.e. better vibration sensitivity) (Green, 1977; Harazin & Harazin-Lechowska, 2007) and others showing no effect (Bolanowski et al., 2000; Wiles, Pearce, Rice, & Mitchell, 1991). The results in this study suggest that the relation between temperature and vibration

is likely site dependent. Perhaps this relation is more likely to occur with glabrous skin.

In the present study, pain intensity during ice water bath immersion and during exercise was not correlated to neither CPM nor EIH. This finding is in line with our previous finding in healthy young adults (Alsouhibani et al., 2018) as well as the finding of others (Granot et al., 2008; Lemley et al., 2015; Vaegter et al.; Weissman-Fogel et al., 2008). It has been suggested previously that the intensity of the conditioning stimulus but not the pain perceived from it is related to the magnitude of CPM (Nir et al., 2011). Similarly, if exercise works through activating the CPM response it would be logical that the intensity of exercise would be related to the magnitude of EIH. This was not supported by the present study as there were no correlation between exercise time and EIH. It is possible, however, that the exercise intensity, being percent MVC instead of time to exercise failure, would be related to EIH. This has not been tested in the current study as all participants exercised at a similar intensity.

Finally, S-PCS was only related to CPM in individuals with FMS at the quadriceps following exercise. This relation was positive indicating higher negative thoughts and feelings about the ice water bath after the CPM protocol resulted in higher CPM. This relation, however was only true for one calculation method and was not consistent with other methods of calculation. Additionally, S-PCS was related to pain intensity only in healthy control participants and not in individuals with FMS. The negative thoughts and feelings individuals with FMS experience during the ice water bath may possibly be a complex one not purely

related to pain. Unlike healthy controls where their negative feelings are only associated with the simple pain experience during ice water.

Conclusion

In summary, this study demonstrated that in both healthy controls and individuals with FMS a single isometric fatiguing exercise increases PPTs (i.e. EIH) locally at the exercising muscle and systemically at a distant muscle. In persons with low CPM, regardless of their EIH response, isometric exercise enhances CPM systemically. These changes were coupled with lower sensitivity to vibration sense systemically and an overall decrease in situational catastrophizing toward the noxious ice water bath. We propose the use of a personalized approach towards pain management with exercise where varying the exercised limbs in individuals who have impaired CPM may produce the greatest results. Further studies are needed investigating the effects of these results while using specific pain medications.

IV. DISCUSSION AND CONCLUSION

This dissertation was the first to examine the effects of isometric exercise on CPM and vibration perception in healthy individuals and individuals with FMS. While pain thresholds and temporal summation following isometric exercise has received attention in the literature, there is a scarcity of information regarding CPM and vibration sense in individuals with and without FMS, an important part of the pain processing system. In addition, there is limited evidence on the psychosocial factors that impact EIH and CPM following isometric exercise in individuals with and without FMS. The aims of this dissertation were to 1) examine the effect of isometric exercise on vibratory sense and pain inhibition in individuals with and without FMS, and 2) determine factors that impact the pain response following isometric exercise in individuals with and without FMS. In study one, we examined the effects of a 30% MVC static contraction of the knee extensors for 3 minutes in young healthy adults on CPM. We also examined the effects of body composition, self-reported physical activity, and pain catastrophizing on the EIH and CPM response following the isometric contraction. In study two, we examined the effects of a 30% MVC static contraction of the knee extensors until exhaustion on CPM and vibration sense in individuals with and without FMS. Biopsychosocial factors including, body composition, physical activity, pain catastrophizing, fear of movement, and pain self-efficacy were also investigated in relation to CPM and EIH following the isometric contraction.

In study one we tested the first aim (sub aim 1) and found that following an isometric contraction of the knee extensors for 3 minutes in young healthy adults, EIH occurred locally at the exercising muscle (i.e. increase in PPTs at the quadriceps muscle). Considerable variability, however, regarding the systemic response (i.e. PPTs at the upper trapezius muscle) was observed, indicating that the exercise might not have been long enough to elicit a systemic EIH response in all participants. Nevertheless, some individuals (n=9) did experience EIH systemically (i.e. at the upper trapezius), and the CPM response following the exercise in those individuals was significantly reduced compared with individuals who didn't experience EIH systemically. This suggests that different mechanisms may be activated for local and systemic EIH, where systemic EIH might employ a mechanism similar to CPM. In addition, CPM was attenuated following exercise and quiet rest, which may be attributed to an insufficient washout period. In this chapter we also tested the second aim (sub aim 1) and found that the biopsychosocial factors (i.e. body composition, self-reported physical activity, and pain catastrophizing) were not shown to be related to either EIH or CPM following exercise. This lack of relations was possibly due to the homogeneity of the sample that was recruited as most of the participants were lean, active and had low scores of catastrophizing.

In study two we tested the first aim (sub aim 2) by having individuals with and without FMS perform an isometric contraction of the knee extensors (30% MVC) until task failure. We found that EIH occurred locally at the exercising muscle (i.e. the quadriceps) and systemically (i.e. the deltoid) for both groups. In

addition, we found that the CPM response following isometric exercise was dependent on whether individuals were CPM responders or non-responders at baseline (pre-exercise). Individuals who were CPM non-responders (i.e. they had impaired CPM) reported an increase in CPM following exercise at the deltoid muscle only (i.e. systemically) with no significant change at the exercising muscle (i.e. locally). In individuals who had a normal functioning CPM response, CPM was reduced after exercise and quiet rest at both sites (deltoid and quadriceps). Furthermore, vibration sense was better perceived in both groups following exercise systemically (i.e. at the index finger) with no significant change at the exercising muscle (i.e. the quadriceps muscle). This enhancement in vibration sense paralleled the enhancement of CPM systemically (at the deltoid muscle). However, no correlation was observed between CPM magnitude and change in VPT following exercise. Therefore, whether the systemic enhancement in vibratory sense was a direct result of CPM enhancement renders further investigation.

In this chapter we also tested the second aim (sub aim 2) and found that the psychosocial factors (i.e. body composition, physical activity (self-report and accelerometer-measured), pain self-efficacy, fear of movement, and pain catastrophizing) were not shown to be related to either EIH or CPM following exercise except for pain self-efficacy in healthy individuals and situational pain catastrophizing. Pain self-efficacy in healthy controls was moderately correlated to absolute EIH at the quadriceps and situational pain catastrophizing was significantly reduced following exercise for both groups compared with quiet rest.

Exercise Induced Hypoalgesia

In this dissertation EIH was tested following an isometric contraction (30% MVC) of the knee extensors held for 3 minutes in young adults and until exhaustion in middle aged adults and individuals with FMS. EIH occurred only locally, at the exercising muscle, following the 3 minute contraction in young adults while both local and systemic EIH occurred following the contraction until exhaustion in middle aged adults and individuals with FMS. Previous studies have suggested that a stronger and long lasting EIH occurs following low contractions held until exhaustion compared with low contractions held for shorter periods (Hoeger Bement et al., 2008). Similar results were demonstrated in this dissertation in that systemic EIH occurred only with the isometric contraction held to exhaustion.

An important finding is that systemic EIH occurred in healthy middle-aged women and women with fibromyalgia. Previous literature has shown variability in the pain response following the performance of isometric contractions in women with fibromyalgia (Hoeger Bement et al., 2011). Interestingly, young adults did not report systemic EIH following a submaximal isometric contraction held for three minutes, which may have been too low of a dose. Thus, these results add to the current literature showing the benefits of exercise in the management of chronic pain in that exercise may produce widespread pain relief that is not localized to the exercising muscle. Furthermore, the results suggest that localized exercise to exhaustion may be beneficial.

Conditioned Pain Modulation

In study one, CPM occurred only during ice water bath immersion of the foot and for most individuals (28/30). This is in contrast to what we found in study two in that CPM (increase in PPTs) occurred during and after the ice water bath immersion, which is similar to what others have reported (Lewis et al., 2012; Pud et al., 2005). Recommendations of CPM measurement (Yarnitsky et al., 2015) state that CPM should be measured following the conditioning stimulus. This discrepancy between studies one and two may be explained by sex differences because the group is predominantly women in study two. One study using a protocol similar to the one used in this dissertation demonstrated that in men CPM occurred only during submersion of the hand in ice water bath while in women CPM occurred during and after ice water submersion (Vaegter et al., 2015). However, in study one, when analyses of CPM were repeated with sex as a between subject factor, the results did not change (meaning CPM occurred only during ice).

Slight differences in CPM protocol could also explain these differences. The temperature of ice water used was higher in the CPM protocol (i.e. the intensity of conditioning stimulus was less) in study two (6°) compared with study one (0°), and the duration of foot submersion was fixed to 2 minutes in study two and averaged 99.7 seconds in study one (i.e. individuals remove the foot as soon as PPTs were complete). Perhaps the reduced intensity of the conditioning stimulus and the longer foot submersion in ice water bath in study two yielded longer lasting effects; thus, CPM occurred during and after ice water submersion.

These results, nevertheless, may have future research and potentially clinical implications, as the choice of measuring the test stimulus during or after the conditioning stimulus may influence the results and interpretation.

In this dissertation we found that CPM following quiet rest was reduced in both studies, despite longer washout period in study two. While PPTs in study one returned to baseline before the next CPM measurement, in study two PPTs were still elevated before exercise or quiet rest. This suggests that a static QST measure (e.g., PPTs) may not be suitable as a restorative indicator of a dynamic QST (e.g., CPM). With repeated CPM measurements, previous studies have included washout periods that ranged from 2-60 minutes (Kennedy et al., 2016) with some studies suggesting PPTs returning to baseline after 15 minutes (Lewis et al., 2012). Surprisingly, the CPM protocol in study two was piloted in young healthy adults and found that a washout period of 45 minutes was sufficient to restore CPM. This suggests that a washout period may potentially depend on age or sex of the sample tested. Perhaps a sample that is either older or predominantly women need longer washout periods to fully restore CPM. This reasoning, however, needs further investigation.

Somatosensory Changes Following Exercise

In this dissertation, the somatosensory assessments following isometric exercise included CPM and vibration sense. In both studies one and two, the reduction in CPM at the exercising muscle (i.e. the quadriceps) following exercise was comparable to the reduction following quiet rest, despite a strong local

hypoalgesic response (i.e. increase in PPTs following exercise). Therefore, exercise does not appear to affect CPM when measured at the exercising muscle. In contrast to the CPM results at the exercising muscle, the change in CPM following exercise at a muscle distal from the exercising muscle (i.e. the upper trapezius or the deltoid) was dependent on the baseline CPM response (i.e. CPM responders or non-responders; study two) and whether participants reported systemic EIH (i.e. systemic EIH responders and non-responders; study one). These findings along with previous findings that EIH was reduced following CPM (Gajsar et al., 2018) suggest that both systemic EIH and CPM have similar manifestations and may share mechanisms.

Although the studies in this dissertation were not designed for conclusions regarding neurobiological mechanisms, some inferences can be made from previous studies. Both CPM and exercise have been shown to have similar cardiovascular reactivity responses that activates baroreceptors (Cui, Wilson, Shibasaki, Hodges, & Crandall, 2001; Seals et al., 1994). This activation have been shown to stimulate areas in the brainstem that are involved in descending pain inhibition such as the locus coeruleus, nucleus tractus solitarius, and PAG (Bruehl & Chung, 2004; Ghione, 1996), which triggers the opioidergic, serotonergic, or noradrenergic mechanisms, or their interaction, to produce hypoalgesia systemically. Therefore, it is possible that once the specific mechanism is activated, and the neurotransmitter involved has been utilized, reactivation immediately with CPM or exercise results in a reduced release of this neurotransmitter. This is supported by the reduced CPM response following the

insufficient quit rest washout period in study one. Hypoalgesia following exercise locally, however, may employ different mechanisms as CPM was unaffected. Considering that during exercise there is vasodilation at the exercising muscle (Seals et al., 1994), in contrast to vasoconstriction with CPM and with exercise at non-exercising muscles, a peripheral mechanism is possible such as modulation of the immune system (e.g. increasing anti-inflammatory cytokines and reducing pro-inflammatory cytokines at the exercising muscle) (Sluka et al., 2018).

In study one all participants except 2 were CPM responders but there were variations in the systemic EIH response, whereas in study two there were variations in the baseline CPM response but less variation in the systemic EIH response. Additionally, the finding in study two that CPM was restored following exercise only at a site distal from the exercising muscle (i.e. the deltoid) suggests that exercise may preferentially restore CPM systemically (i.e. at sites other than the exercising muscle) only in individuals with impaired CPM. Previous studies, in individuals with neuropathic pain, duloxetine, a serotonin norepinephrine reuptake inhibitor, and tapentadol, an opioid agonist and norepinephrine reuptake inhibitor, were effective in individuals with low CPM (Niesters et al., 2014; Yarnitsky et al., 2012). The common neurotransmitter in both studies was norepinephrine, which is known to be activated with exercise (Cui et al., 2001; Seals et al., 1994). Thus, perhaps CPM was restored by the release of norepinephrine which interacted with opioid or serotonin to produce hypoalgesia systemically.

While these results are valuable in determining the mechanisms following a single bout of exercise, the mechanisms following exercise training remains elusive and worth investigating in future research as exercise training constitutes the foundation of rehabilitation programs. Clinically, these results can be incorporated in different ways. For example, a clinician may advise exercising the whole body for pain relief for activation of descending inhibitory mechanisms.

Changes in the somatosensory system following exercise also included changes in vibratory sense. In study two, vibration sense improved following exercise at a site distal from the exercising muscle (i.e. the index finger). This systemic improvement paralleled the systemic improvement in CPM. However, there was no significant correlation between the change in vibration sense and CPM, suggesting it may not be directly related. The fact that vibration sense did not change locally at the exercising muscle (i.e. the quadriceps) could either be because of the pain at the time of measurement or the lack of change in CPM locally; although there was no significant correlation between pain perceived at the time of measurement and VPTs or the change in VPTs. Because reduced vibration sense has been linked to function (Kavchak et al., 2012; Shakoor et al., 2012; Uszynski et al., 2015) and it has been shown that individuals with FMS have reduced vibratory sense and functional performance (Costa et al., 2017; da Silva et al., 2013), it is worthwhile for future research to investigate whether an enhancement in VPT long term would lead to better functional performance.

Biopsychosocial Factors

The second aim of this dissertation was to test whether biopsychosocial factors would be related to the EIH response. The factors that were tested included, body composition, physical activity, pain catastrophizing, fear of movement, and pain self-efficacy. In the first study none of the factors were significantly correlated with the EIH response in young healthy adults. This was potentially due to the homogeneity of the sample as most individuals who participated were classified as lean, active and had low pain catastrophizing scores. In study two, none of the factors were related to the EIH response except for pain self-efficacy in healthy controls. Although this relation was not robust (e.g. it was only related to absolute measurement of EIH at the quadriceps), pain self-efficacy has recently been shown to be an important factor in pain management (Costa Lda, Maher, McAuley, Hancock, & Smeets, 2011). In fact, previous literature shows that individuals who have higher pain self-efficacy scores are more likely to benefit from exercise rehabilitation programs and therefore adhere to them (Frost, Klaber Moffett, Moser, & Fairbank, 1995; Tonkin, 2008). A common issue in individuals with FMS is adherence to exercise programs (Russell et al., 2018; van Santen et al., 2002); thus, we hypothesized that individuals who have greater pain relief following isometric exercise would be more confident in carrying out activities despite the pain (i.e. higher pain self-efficacy scores). This relation, however, was not observed in individuals with FMS, possibly because pain relief following exercise in this population is multifactorial and not dependent on one factor. Pain processing in individuals

with FMS is complex and perhaps other factors influenced pain relief following exercise irrespective of pain self-efficacy.

Recent studies have suggested that body composition and physical activity may play a role in EIH and CPM (Lemley et al., 2015; Naugle & Riley, 2014; Stolzman et al., 2015; Stolzman & Hoeger Bement, 2016).This relation is contrary to the findings in this dissertation. In studies one and two, body composition and both self-reported and accelerometer-measured physical activity were not related to either EIH or CPM. In study one, the lack of associations could be due to the homogeneity of the sample as most individuals were active and lean. The participants' physical activity level were either classified as moderate or vigorous on the IPAQ and had an average BMI of 23 which is considered normal. However, this explanation is not supported by the findings in the second study as the sample was more heterogeneous and there were still no relations. The discrepancies throughout the literature could be related to the differences in EIH and CPM measurement or differences in body composition and physical activity measurements. The findings in this dissertation, however, are similar to a recent study showing no correlation between physical activity assessed via accelerometer and EIH in healthy young adults (Black et al., 2017). In addition, another study showed no correlation of both self-reported and accelerometer-measured physical activity with pain sensitivity measures, including CPM, in individuals with FMS even when controlled for BMI and age (Merriwether et al., 2018). It is possible that the effects of body composition and physical activity on EIH or CPM are only observed at a certain threshold or

simply non-linear in nature. Conversely, because physical activity was only measured during one week of participation in the study, it is not known whether physical activity levels were routine or recently changed, which may change the relation with pain. Some studies have suggested that initial engagement in physical activity may increase pain in individuals with FMS (Kop et al., 2005) but would reduce pain when engaged routinely.

In this dissertation, pain catastrophizing levels (dispositional) were not related to EIH or CPM. However, in the second study we found that situational catastrophizing towards the ice water bath (the conditioning stimulus during CPM) was reduced following exercise in both groups, despite no change in pain intensity. This finding suggests that a single bout of exercise effects how people view pain despite no change in the pain intensity. In longer interventional clinical trials, situational catastrophizing about pain has been shown to change before pain intensity (Campbell et al., 2012). In addition, changes in situational pain catastrophizing predicted changes in pain but not vice versa, suggesting that perhaps after repeated bouts of exercise changes in pain will follow. Therefore, changes in psychosocial variables directly related to pain may be important in inducing changes in pain intensity. Whether this will change will lead to better adherence is not known and worth investigating.

Fear of movement has been shown to be an important factor related to symptoms of FMS (Nijs et al., 2013). To reduce fear of movement clinically, using a fear avoidance behavior-based intervention such as graded exposure has shown promise in pain management (George & Zeppieri, 2009). However, in this

dissertation, despite individuals with FMS reporting higher TSK values (i.e. greater kinesiophobia) it did not influence the hypoalgesia experienced after the isometric contraction. The average TSK values in this dissertation in individuals with FMS were comparable to a previous study (Roelofs et al., 2007) of more than 300 individuals with FMS (24.5 vs. 26.1, respectively). It is possible that because there is no movement with isometric exercise there was no relation between fear of movement and EIH. Thus, potentially, using isometric exercise in individuals with high levels of kinesiophobia in the clinic may be useful.

Summary

This dissertation demonstrated that a single bout of isometric exercise produces hypoalgesia in healthy young and middle aged adults as well as individuals with FMS. Local hypoalgesia occurred following submaximal isometric contractions held for three minutes and until exhaustion, whereas systemic hypoalgesia occurred only after the contraction held until exhaustion. In study one, CPM was shown to be reduced following an isometric contraction held for three minutes in areas where systemic hypoalgesia occurred (i.e. upper trapezius muscle); local hypoalgesia (EIH at the exercising muscle) did not affect CPM. In study two, a single bout of isometric contraction held until fatigue activated CPM systemically (i.e. the deltoid muscle) in individuals with impaired CPM irrespective of increase in PPTs following the contraction (i.e. EIH) and health status (healthy control or FMS). Taken together, these results suggest that CPM and EIH may have similar manifestations and modulatory effects such as similar

cardiovascular responses and stimulation of specific brain regions activating opioidergic, serotonergic, or noradrenergic mechanisms. Additionally, these changes were coupled with an increase in vibration perception sensitivity systemically (i.e. the index finger) and a reduction in situational pain catastrophizing. This suggests that deficits in vibration sense which is thought to be centrally mediated by pain may improve with isometric exercise. Which has the potential, pending further research, to enhance functional performance. Future studies investigating the long term effects of exercise on CPM, VPT, and S-PCS are important to help clinicians in the targeted use of exercise.

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