The Influence of Autonomic Function on Pain Modulation Before and After Exercise and Cognitive Task in Fibromyalgia

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THE INFLUENCE OF AUTONOMIC FUNCTION ON PAIN MODULATION BEFORE AND AFTER EXERCISE AND COGNITIVE TASK IN FIBROMYALGIA

by

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ABSTRACT
THE INFLUENCE OF AUTONOMIC FUNCTION ON PAIN MODULATION BEFORE AND AFTER EXERCISE AND COGNITIVE TASK IN FIBROMYALGIA

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Fibromyalgia (FM) is a chronic pain condition characterized by widespread pain. People with FM have alterations in autonomic function compared to healthy individuals. Exercise can decrease pain in people with FM, however some people with FM experience pain exacerbation when initiating exercise. Whether variability in pain at rest and following exercise is related to altered autonomic function, including the potential implications with other stressful events such as mental math, is not known. This dissertation aimed at investigating: 1) the relation between cardiovascular autonomic function and central pain facilitation and inhibition, measured by temporal summation of pain (TS) and conditioned pain modulation (CPM) and 2) the relation between cardiovascular autonomic function and pain modulation following submaximal isometric exercise and mental math in people with and without FM.

For aim 1, sympathetic and parasympathetic function, measured by Valsalva maneuver and deep breathing test, were measured along with CPM (assessed at the forearm and quadriceps) and TS (assessed at the forearm). Only control participants had CPM at the quadriceps while both groups had similar CPM at the forearm. Sympathetic function was associated with CPM at the forearm in people with FM only. Both groups had similar TS which was not associated with baseline autonomic function. Parasympathetic function was not related to CPM or TS.

For aim 2, autonomic function was assessed at baseline and during exercise and mental math. Pressure pain thresholds were assessed before and after exercise and mental math to assess the change of pain. Following exercise, only control participants reported pain relief while people with FM had variable pain responses, whereas both groups had variable pain responses following mental math. People that reported greater pain relief following exercise also reported greater pain relief following mental math and had greater baseline sympathetic function.

Our results show that sympathetic function is related to central pain inhibition but not central pain facilitation. Additionally, sympathetic function may help explain the variability in pain following exercise and mental math. Thus, future studies should investigate whether interventions that improve sympathetic function can improve central pain inhibition and pain sensitivity to physical and cognitive stress.

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ANS	Autonomic Nervous System
BMI	Body Mass Index
COMPASS 31	Composite Autonomic Symptom Score
CPM	conditioned Pain Modulation
DASS-21	Depression, Anxiety, and Stress Scale
DNIC	Diffuse Noxious Inhibitory Control
DXA	Dual-Energy X-Ray Absorptiometry
ECG	Electrocardiogram
EIH	Exercise-Induced Hypoalgesia
FIQR	Revised Fibromyalgia Impact Questionnaire
FM	Fibromyalgia
fMRI	Functional Magnetic Resonance Imaging
HPA	Hypothalamus-Pituitary-Adrenal
HRV	Heart Rate Variability
IPAQ	International Physical Activity Questionnaire
MVIC	Maximum Voluntary Isometric Contraction
MVPA	Moderate to Vigorous Activities
NMDA	N-methyl-D-aspartate
NTS	Nucleus of the Solitary Tract
PAG	Periaqueductal Gray
PASS-20	Pain Anxiety Symptoms Scale
PCS	Dispositional Pain Catastrophizing Scale
PNS	Parasympathetic Nervous System
PPT	Pressure Pain Thresholds

QST	Quantitative Sensory Testing
RM ANCOVA	Repeated Measures Analysis Of Covariance
RM ANOVA	Repeated Measures Analysis of Variance
RMSSD	Root Mean Square of Successive Differences in R-R Intervals
RPE	Ratings of Perceived Exertion
RVM	Rostral Ventromedial Medulla
SD	Standard Deviation
SEM	Standard Error of the Mean
SF-MPQ	Short-Form McGill Pain Questionnaire
SIH	Stress-Induced Hypoalgesia
SNS	Sympathetic Nervous System
TS	Temporal Summation
Vo2 max	Maximal Oxygen Uptake

LIST OF TABLES

LIST OF FIGURES

CHAPTER ONE
INTRODUCTION AND LITERATURE REVIEW

Introduction

Chronic pain affects approximately 20% of the people in the united stated (Dahlhamer et al., 2018) and costs the United States around $560 billion annually (Institute of Medicine Committee on Advancing Pain Research & Education, 2011). One of the common chronic pain conditions is fibromyalgia (FM), which occurs in 2-8% of the people worldwide (Queiroz, 2013). FM is associated with symptoms such as widespread pain, fatigue, insomnia, depression, anxiety and others (Clauw, 2014; McBeth & Mulvey, 2012; Schaefer et al., 2011). These symptoms can impact daily activities and decrease work productivity in around 50% of patients despite treatment (Schaefer et al., 2011). Furthermore, pharmacological interventions for chronic pain have been shown to cause serious side effects such as hyperalgesia and addiction that may be life-threatening (Dowell et al., 2016; Wersocki et al., 2017). For example, opioid-related deaths are about 49,000 annually (National Institute on Drug Abuse, 2018). Therefore, alternative interventions that are safe and cost-effective are needed.

The widespread pain in people with FM is likely due to changes in central endogenous pain modulation, manifested by enhanced pain facilitation and/or reduced pain inhibition, measured by temporal summation of pain (TS) and conditioned pain modulation (CPM), respectively (Cagnie et al., 2014; O'Brien et al., 2018; Sluka & Clauw, 2016). These changes in TS and CPM among people with FM are variable (Potvin & Marchand, 2016; Potvin et al., 2012). The factors that explain this heterogeneity are not fully known, however, some researchers have suggested that autonomic function may be related to CPM and TS (Chalaye et al., 2014; Chung et al., 2008; Nahman-Averbuch, Dayan, et al., 2016). To address this gap, aim one will

investigate the relation between cardiovascular autonomic function and central pain facilitation and inhibition.

Exercise is one of the interventions that is recommended to people with FM (Ablin et al., 2013; Hauser et al., 2010; Macfarlane et al., 2017). However, some people with FM may experience an increase in pain while others experience pain relief following a single exercise session (Daenen et al., 2015; Hoeger Bement et al., 2011). Similar to exercise, only some people with FM have an increase in pain in response to cognitive stress (Coppieters et al., 2016; Crettaz et al., 2013). The factors that are related to this pain variability with exercise or cognitive stress are not completely known. Some researchers have suggested that the pain response following exercise may be related to the alterations in autonomic function and the abnormality in the stress response system (Daenen et al., 2015; Nijs et al., 2012; Oosterwijck et al., 2017). Aim two will examine the relation between cardiovascular autonomic function and endogenous pain modulation following physical and cognitive tasks (submaximal isometric exercise and mental math, respectively). Understanding the factors that are related to the pain response following exercise may lead to better exercise prescription.

The first chapter of this dissertation will provide background information on CPM, TS, and the pain responses with exercise and cognitive task in people with and without FM. The review of literature also includes the potential role of the autonomic nervous system (ANS) in central pain modulation (CPM and TS) at rest and following exercise or a cognitive task.

Fibromyalgia

FM is one of the common pain conditions (Queiroz, 2013), and it affects women more than men (Arout et al., 2018). The symptoms of FM involve widespread pain, fatigue, insomnia, depression, anxiety and others (Clauw, 2014; McBeth & Mulvey, 2012; Schaefer et al., 2011). In addition, FM is associated with changes in central endogenous pain modulation manifested by enhanced pain facilitation and reduced pain inhibition (Cagnie et al., 2014; O'Brien et al., 2018; Sluka & Clauw, 2016). People with FM may also experience hypersensitivity to non-noxious stimuli such as auditory, visual or tactile stimuli (Geisser et al., 2008; Hollins et al., 2009; Lopez-Sola et al., 2014).

The diagnosis of FM evolved over the years as the research of FM has advanced. For instance, the American college of rheumatology diagnostic criteria that was published in 1990 focused only on pain. The criteria of FM included having at least 11 out of 18 specified tender points that involved the application of pressure to these sites by an examiner (Wolfe et al., 1990). In 2010, the diagnostic criteria was updated and included self-report assessment of widespread pain and the severity of the other associated symptoms such as depression, insomnia, constipation, dizziness, and abdominal pain (McBeth & Mulvey, 2012; Wolfe et al., 2016). The symptoms of FM suggest alterations in central pain processing, hypothalamus-pituitary-adrenal axis (HPA axis), and the ANS (Sluka & Clauw, 2016). Therefore, FM is a chronic pain and multi-symptom disorder (Arnold et al., 2019).

While the treatment of FM is challenging, there are a number of prescription guidelines available to help clinicians (Ablin et al., 2013; Burckhardt et al., 2005; Hauser et al., 2010; Macfarlane et al., 2017). These guidelines recommendations include non-pharmacological interventions as the first line of treatment and to

individualize treatment based on patient symptoms. A recent guideline by the original European League Against Rheumatism has recommended both pharmacological and non-pharmacological treatment for FM (Macfarlane et al., 2017). Pharmacological treatment included a recommendation for the use of duloxetine (serotonin and norepinephrine reuptake inhibitor), tramadol (weak opioids), pregabalin (anticonvulsant), and cyclobenzaprine (muscle relaxant). The guideline recommended against the use of strong opioids and antipsychotics. Non-pharmacological interventions that were recommended included exercise, cognitive behavioral therapy, acupuncture, and mindfulness-based therapies. Aerobic and resistance exercises were the only interventions that were strongly recommended in this guideline although some patients may experience an exacerbation of their symptoms initially (Macfarlane et al., 2017). The guideline by the original European League Against Rheumatism encouraged more research to better understand the factors that could explain the variability in pain responses when initiating specific treatment (Macfarlane et al., 2017).

Quantitative Sensory Testing

Quantitative sensory testing (QST) can be used to characterize endogenous pain modulation in the peripheral and central nervous system in conditions such as FM and involves the application of different noxious or non-noxious stimuli to assess and quantify sensory function in healthy and patient populations (Arendt-Nielsen & Yarnitsky, 2009; Fillingim et al., 2016; Hubscher et al., 2013). QST techniques include measuring pain threshold and allodynia. Pain threshold is the minimum intensity of a stimulus that results in pain whereas allodynia is pain in response to non-noxious stimulus (Arendt-Nielsen & Yarnitsky, 2009; Fillingim et al., 2016). People with FM have allodynia and lower thermal and mechanical pain thresholds

when compared to pain-free individuals (Nielsen & Henriksson, 2007; Woolf, 2011). Other QST techniques include TS and CPM, which are used to assess central pain facilitation and inhibition, respectively.

Conditioned Pain Modulation

CPM is a measure of the integrity of descending inhibitory pain mechanisms and incorporates the concept of 'pain inhibits pain' (Lewis et al., 2012; O'Brien et al., 2018; Yarnitsky et al., 2010). The assessment of CPM is done by applying two noxious stimuli (test and conditioning stimulus). The noxious test stimulus is administered first and then again during or right after the noxious conditioning stimulus. Less pain reported from the test stimulus with the application of the conditioning stimulus indicates intact or efficient CPM. For example, the increase in pressure pain threshold during cold water bath relative to baseline pressure pain threshold indicates efficient CPM. CPM has been shown to predict the development of chronic post-surgical pain (Yarnitsky et al., 2008) and the response to both pharmacological (Grosen et al., 2013; Yarnitsky et al., 2012) and non-pharmacological interventions such as exercise (Lemley et al., 2015; Stolzman & Bement, 2016).

CPM involves activation of the spino-bulbo-spinal pathway. Early animal studies showed that lesion to subnucleus reticularis dorsalis significantly reduced diffuse noxious inhibitory control (DNIC), which is the term used for CPM in animal research (Bouhassira et al., 1992) whereas lesion to other areas of descending inhibition such periaqueductal gray (PAG) (Bouhassira et al., 1990) and rostral ventromedial medulla (RVM) does not affect DNIC (Bouhassira et al., 1993). Other animal studies showed the involvement of opioidergic system (de Resende et al.,

2011), serotonergic system (Bannister et al., 2017; Bannister et al., 2015), and noradrenergic system (Bannister et al., 2015).

In humans, using functional magnetic resonance imaging (fMRI), CPM was associated with the activation of PAG and higher cortical areas such as amygdala, anterior cingulate cortex, and somatosensory (Piche et al., 2009; Sprenger et al., 2011). Moreover, human research also supported the role of subnucleus reticularis dorsalis (Youssef et al., 2016) and the role of opioidergic (King et al., 2013), serotonergic (Treister et al., 2011), and noradrenergic pain mechanism in CPM (Baba et al., 2012; Parent et al., 2015). For instance, Baba et al., 2012 showed that the administration of dexmedetomidine, which inhibits the release of norepinephrine from locus coeruleus, significantly reduced CPM in a dose-dependent manner (Baba et al., 2012).

Differences in protocol have been shown to influence the CPM response including the type of conditioning stimulus (Oono et al., 2011; Vaegter et al., 2018), duration and intensity of conditioning stimulus (Granot et al., 2008; Razavi et al., 2014; Smith & Pedler, 2018), type of test stimulus (Nahman-Averbuch et al., 2013; Vaegter et al., 2018), and test stimulus site (Gajsar et al., 2018; Oono et al., 2011). A systematic review on CPM protocols recommended the use of pressure pain threshold as a test stimulus and cold water as a conditioning stimulus with a temperature below 12˚C that can be tolerated by people with and without chronic pain for approximately 2 minutes (Kennedy et al., 2016).

Besides protocol factors, age and sex can influence the magnitude of the CPM response. There are studies that suggest that CPM is lower in women (Da Silva et al., 2018; Fillingim et al., 2009) and older individuals (Lemley et al., 2015; Riley et al.,

2014). In addition, greater physical activity (Naugle & Riley, 2014; Umeda et al., 2016) and greater lean mass (Stolzman & Hoeger Bement, 2016) are associated with greater CPM. Lastly, some psychological outcomes can influence CPM. Higher levels of pain catastrophizing, which is an exaggerated negative mental set towards pain (Sullivan et al., 1995), has been shown to correlate with reduced CPM (Traxler et al., 2019; Weissman-Fogel et al., 2008). Other psychological outcomes that are associated with CPM include stress (Geva & Defrin, 2018), anxiety, and depression (Nahman-Averbuch, Nir, et al., 2016).

Conditioned Pain Modulation in People With FM

People with FM have lower or less efficient CPM compared to controls (O'Brien et al., 2018). This difference in CPM exists even when using different types of modalities for the test and conditioning stimuli including thermal or mechanical stimuli (Harper et al., 2018; O'Brien et al., 2018). People with FM also have lower CPM compared to other chronic pain conditions including chronic low back (Gerhardt et al., 2017) and irritable bowel syndrome (Chalaye et al., 2012). Moreover, among people with FM, there is variability in CPM responses with some individuals having intact CPM whereas others have impaired CPM (O'Brien et al., 2018; Potvin & Marchand, 2016). Further research is needed to better understand the factors that contribute to CPM variability in people with FM.

Temporal Summation of Pain

TS is a measure of central pain facilitation. The assessment of TS may include the application of ten heat or pressure stimuli of the same intensity (repetitive TS) or the application of constant pressure or heat stimulus for 30 seconds or longer (tonic TS) (Granot et al., 2006). TS has been shown to predict the development of chronic

postoperative pain following total knee replacement (Petersen et al., 2015) and the responsiveness to pharmacological treatment such as opioids (Eisenberg et al., 2010).

TS reflects the wind-up of C-fibers in the dorsal horn of the spinal cord in response to constant or repetitive noxious stimulus (Granot et al., 2006). Spinally, blocking the N-methyl-D-aspartate (NMDA) receptors results in inhibition of TS (Herrero et al., 2000; Zhou et al., 2011). Animal and human studies also revealed the role of opioids (Dickenson & Sullivan, 1986; Enggaard et al., 2001) and $\alpha 2$ adrenergic receptors in inhibiting TS (Herrero et al., 2000; Sullivan et al., 1992). Supraspinally, individuals who have greater functional connectivity between anterior cingulate cortex and RVM had lower TS (Cheng et al., 2015). This finding suggests that descending pain inhibitory mechanisms could be involved in TS.

The parameter or the protocol of TS may influence the magnitude of TS. For repetitive TS, the recommendation for the frequency is to deliver noxious stimuli every 3 seconds or less (Price et al., 1977). Another factor that can influence the magnitude of TS is the size of the stimulation area; greater stimulation area is associated with greater TS (Nie et al., 2009). Additionally, the location of the stimulation can influence the magnitude of TS. Graven-Nielsen et al., 2015 showed greater TS in the leg compared to the arm (Graven-Nielsen et al., 2015). Other factors that may influence the TS include the modality of the stimulus (O'Brien et al., 2018), the intensity of the painful stimulus (Staud et al., 2014), and the method of stimulus delivery including tonic or repetitive stimuli (Granot et al., 2006).

The magnitude of TS tends to be lower in men (Fillingim et al., 2009; Sarlani et al., 2004), younger individuals (Naugle, Cruz-Almeida, et al., 2016), physically active people (Naugle & Riley, 2014), and those who have greater lean mass (Awali

et al., 2018). Also, psychological factors may influence TS (Robinson et al., 2004). For example, greater pain catastrophizing is associated with greater TS (Edwards et al., 2006; George et al., 2007; Wideman et al., 2014). Thus, these factors should be taken into consideration when using TS.

Temporal Summation of Pain in People With FM

The magnitude of TS is greater in people with FM compared to pain-free individuals indicating greater pain facilitation (O'Brien et al., 2018; Staud et al., 2003). People with FM have greater TS than people with low back pain (Goubert et al., 2017). Mechanistically, using NMDA receptors antagonist results in significant reduction in TS in people with and without FM (Staud, Vierck, et al., 2005). During TS, a study showed that people with FM had greater activation in the dorsal horn of the spinal cord and less activation in areas of descending pain inhibition such as RVM, nucleus of the solitary tract (NTS), and locus coeruleus compared to pain-free individuals (Bosma et al., 2016).

The parameters of the TS may affect the difference between people with and without FM. For instance, Staud et al., 2014 studied the effect of the intensity of the stimulus on the magnitude of TS in people with FM. The study showed that the difference between people with FM and controls increased as the temperature increased indicating that the temperature used in the TS protocol is an important factor to consider when studying the difference in TS between people with and without FM (Staud et al., 2014). Another factor that has been shown to predict TS in people with FM is pain catastrophizing. Greater pain catastrophizing is associated with greater TS (Schreiber et al., 2017). More research is needed to understand the factors that associate with greater TS in people with FM.

Exercise-Induced Hypoalgesia

Exercise-induced hypoalgesia (EIH) is the reduction of pain sensitivity caused by acute exercise (Naugle et al., 2012). A single bout of exercise can result in EIH not only in the exercising region (local EIH) but also in non-exercising body parts (systemic EIH) in people with and without chronic pain. The effect of exercise on pain have been studied in animal models and humans. In animals, different types of exercise such as treadmill running, wheel running and swimming decrease mechanical and thermal pain sensitivity in healthy animals and different models of pain including inflammatory pain and neuropathic pain models (Lima et al., 2017).

There are many factors that influence the magnitude of EIH in humans. The type and the dose of the exercise can influence EIH. For example, isometric exercise produces greater EIH than aerobic or dynamic resistance exercises (Naugle et al., 2012). In addition, the intensity and the duration of exercise can affect EIH. Hoffman et al., 2004 showed that an intensity greater than 50% of maximal oxygen uptake (Vo_2 max) and duration greater than 10 minutes are needed to elicit EIH with aerobic exercise (Hoffman et al., 2004). On the other hand, a lower intensity and a longer duration isometric exercise produces the greatest EIH in younger adults (Hoeger Bement et al., 2008) whereas EIH is not dependent on intensity and duration in older adults (Lemley et al., 2014). Moreover, EIH can be greater at the exercising muscle compared to distant muscles. Kosek et al., 2003 found that isometric exercise of either quadriceps or shoulder led to greater EIH at exercising muscles compared to non-exercising body regions (Kosek & Lundberg, 2003). Vaegter et al., 2013 showed similar findings after cycling where greater EIH was experienced at the exercising region (quadriceps) compared to distant regions (biceps and trapezius) (Vaegter et al.,

2014). Therefore, exercising muscle, the type and dose of the exercise can affect the magnitude of EIH.

There are other factors that may affect EIH magnitude including age, sex, physical activity, body composition, and psychological outcomes. Naugle showed that younger adults experience greater EIH following isometric exercise compared to older adults (Naugle, Naugle, et al., 2016) whereas Lemley et al., 2015 found no difference in EIH between younger and older adults (Lemley et al., 2015). In regards to sex, women usually have greater EIH than men (Koltyn et al., 2001; Lemley et al., 2014). Moreover, individuals who spent more time in moderate to vigorous activities (MVPA) experience greater EIH (Ohlman et al., 2018). In regard to body composition, greater lean mass is associated with greater EIH (Stolzman et al., 2015). Furthermore, there are a number of psychological factors that have been shown to associate with EIH. For example, Brellenthin et al., 2017 found situational catastrophizing and negative mood measured by the profile of mood states questionnaire were associated with lower EIH (Brellenthin et al., 2017). In addition, enhancing expectation through education about EIH results in greater EIH compared to general education about exercise (Jones et al., 2017).

The EIH response is variable among people with chronic pain where some individuals experience pain relief while others experience pain increase. The variability of EIH may depend on exercising regions in some chronic pain populations such as those with regional pain, i.e., people with regional pain may report greater EIH when exercising non-painful body regions compared to painful regions. Burrows et al., 2013 demonstrated that people with knee osteoarthritis experienced EIH at the painful knee when they exercised the upper limb and experienced no EIH following lower limb exercise (Burrows et al., 2014). Similar findings were reported in people

with shoulder myalgia where exercising the quadriceps led to greater EIH at the painful shoulder compared to exercising the painful shoulder (Lannersten & Kosek, 2010). However, people with widespread pain such as participants with FM may have lower local and systemic EIH regardless of the exercising muscle (Lannersten & Kosek, 2010). Understanding the factors and the mechanisms that influence EIH in people with FM can lead to better exercise prescription.

A number of mechanisms can explain the pain relief associated with exercise including the increase of opioids (Bement & Sluka, 2005; Stagg et al., 2011), increase of serotonin (Bobinski et al., 2015; Mazzardo-Martins et al., 2010), increase of gamma-aminobutyric acid (GABA) levels in the spinal cord (Kami et al., 2016), noradrenergic mechanism through the locus coeruleus (Lopez-Alvarez et al., 2018), reductions in pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin-1β (Bobinski et al., 2015; Chen et al., 2012), increase anti-inflammatory cytokines such as interleukin-10 (Leung et al., 2016), and the involvement of dopaminergic pathway (Wakaizumi et al., 2016). In addition, pain exacerbation following exercise is associated with the increase in central pain excitability caused by the increase of phosphorylation of NMDA receptors in the medullary raphe nuclei (Sluka et al., 2012). The dose of exercise may influence pain relief in animals. Stagg et a., 2011 found that treadmill running on high speed was associated with greater hypoalgesia compared to low speed (Stagg et al., 2011). Following isometric exercise, EIH has been shown to associate with the increase in endocannabinoids (Koltyn et al., 2014) and the interaction between opioids and endocannabinoids systems (Crombie et al., 2018).

One of the mechanisms of EIH that has been suggested is the activation of CPM system. A number of studies showed a significant positive association between EIH and CPM (Fingleton et al., 2017; Lemley et al., 2015; Stolzman & Bement, 2016); individuals with greater CPM report greater pain relief with exercise. Exercise can result in localized pain in the exercising muscles which may activate CPM leading to greater pain inhibition. Ellingson et al., 2014 studied if greater pain during exercise can elicit greater EIH in young healthy participants. They found that occluding the leg while cycling led to greater pain during exercise and greater EIH following the exercise compared to exercising without occlusion (Ellingson et al., 2014).

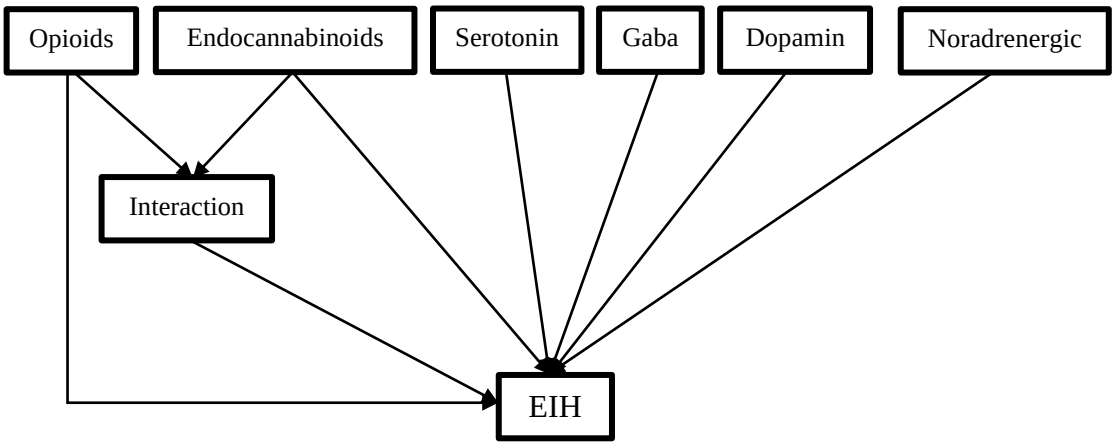

Figure 1.1: Summary of the mechanisms of exercise-induced hypoalgesia (EIH)

Exercise-Induced Hypoalgesia in People With FM

Exercise training has been shown to be effective for people with FM. Cochrane reviews show that both aerobic and resistance exercises improve symptoms such as pain, fatigue, sleep, physical function, and overall quality of life (Bidonde et al., 2017; Busch et al., 2013). In contrast, acute exercise may exacerbate pain in people with FM. Staud et al., 2005 demonstrated that following a handgrip exercise performed at an intensity of 30% maximum voluntary isometric contraction (MVIC)

for 90 seconds, people with FM experienced mechanical and thermal hyperalgesia at the ipsilateral and contralateral forearm whereas pain-free individuals experienced EIH at both sites using mechanical and thermal stimuli (Staud, Robinson, et al., 2005). Lannersten et al., 2010 studied the difference between people with FM and people with shoulder myalgia following exercising the quadriceps and infraspinatus (the painful shoulder for people with shoulder myalgia). The results showed that people with shoulder myalgia experienced EIH only following exercising the quadriceps whereas people with FM did not experience EIH following either exercise (Lannersten & Kosek, 2010). Hoeger Bement et al., 2011 found that a group of people with FM experienced EIH while the other two groups experienced hyperalgesia or no change although all three groups had similar increase in pain and exertion at the end of the exercise (Hoeger Bement et al., 2011). These findings have led to more interest in studying the factors that explain the variability in pain response following exercise in people with FM. Tour et al., 2017 investigated the relation between EIH and some genetic variants in people with and without FM. The study did not find an association between EIH and a single genetic polymorphism but the interaction between some opioid and serotonin genes was associated with greater EIH in the entire sample (Tour et al., 2017). Furthermore, studying pain exacerbations after a single session of exercise may improve adherence to exercise training. Thus, identifying the factors that influence EIH is needed to better prescribe exercise to people with chronic pain.

Stress-Induced Hypoalgesia

Stress-induced hypoalgesia (SIH) is the reduction of experimental pain sensitivity caused by a stressful stimulus (Butler & Finn, 2009). There are two main types of SIH which are unconditioned and conditioned SIH. Unconditioned SIH involves the change of pain sensitivity following the exposure to stressful stimulus

such as mental math or electrical shock. Conditioned SIH is the reduction in pain sensitivity following the exposure to a cue that was paired previously to a stressful stimulus such as exposing a participant to a light or a noise that was paired previously with electrical shock (Butler & Finn, 2009; Ford & Finn, 2008). The mechanisms of SIH include opioids and non-opioids mechanisms. Naloxone, which is opioids antagonist, attenuates SIH following cognitive task in young healthy participants (Fechir et al., 2012). Other SIH mechanisms include serotonergic, noradrenergic, and cannabinoidergic mechanisms (Butler & Finn, 2009). Watkins et al., 1984 showed that blocking either adrenergic or serotonergic receptors in the spinal cord can attenuate SIH in mice (Watkins et al., 1984).

Among healthy individuals, cognitive task can increase, decrease or have no effect on experimental pain sensitivity. Bement et al., 2010 showed that healthy individuals who had SIH had greater anxiety and stress at baseline (Hoeger Bement et al., 2010). Timmers et al., 2016 showed that the increase of cortisol during cognitive task and fear of pain predicted the increase of heat pain threshold following cognitive task (Timmers et al., 2018). Geva et al., 2018 divided participants into high- or low-stress based on their perceived stress reactivity during cognitive task. The results showed that the low-stress group had greater reduction in heat pain ratings (Geva & Defrin, 2018). People with chronic pain may experience hyperalgesia following cognitive task. Cathcart et al., 2008 demonstrated that people with tension headache experienced hyperalgesia following mental math task, and the hyperalgesia response was associated with the increase in perceived stress (Cathcart et al., 2008). In addition, kids with recurrent abdominal pain also experience hyperalgesia following a cognitive task (Dufton et al., 2008). Therefore, stress may cause hyperalgesia in people with chronic pain and cause hypoalgesia or no change in healthy individuals.

Stress-Induced Hypoalgesia in People With FM

Stress can exacerbate pain in people with FM. Fischer et al., 2016 tracked momentary and daily pain and stress for 14 days in people with FM. The main finding of this study was that stress levels at a certain point can predict pain levels at the next assessment point which suggests that the increase in stress can worsen pain in people with FM (Fischer et al., 2016). Crettaz et al., 2013 showed that people with FM had reduction in heat and pressure pain threshold indicating worsening of pain after performing cognitive stress task (Crettaz et al., 2013). Coppieters, et al., 2016 demonstrated that cognitive stress led to an increase in TS and a reduction in CPM in people with FM (Coppieters et al., 2016). Other studies did not utilize QST to assess SIH but utilized perceived pain assessment and showed pain exacerbation or variable pain responses following cognitive task in people with FM (Nilsen et al., 2007; Thieme et al., 2015). Thus, investigating the factors that explain pain exacerbation in response to cognitive stress in people with FM is needed to better manage FM symptoms including pain and stress.

Comparison Between Exercise and Cognitive Task

The reduction of pain following exercise (i.e., EIH) may be a form of SIH. Animals research studies on the mechanisms of SIH have utilized stressful exercise protocols including forced swimming or swimming in cold water. Additionally, less stressful protocols such as spontaneous running have also been studied. Shye et al., 1982 trained rats on spontaneous running and found that acute spontaneous running increased pain threshold indicating that non-stressful exercise can inhibit pain (Shyu et al., 1982). In people with FM, performing aerobic exercise at the intensity that they prefer can result in a hypoalgesic response (Newcomb et al., 2011). Therefore, different forms of exercise may incorporate different levels of SIH.

There are some similarities between the change of pain following exercise and cognitive task that is designed to induce stress. First, both tasks can evoke a decrease in pain sensitivity in healthy individuals but may increase pain sensitivity in people with chronic pain (Coppieters et al., 2016; Crettaz et al., 2013; Hoeger Bement et al., 2010; Nilsen et al., 2007; Timmers et al., 2018). Second, both tasks evoke a strong cardiovascular reactivity and some studies showed significant association between the cardiovascular response and EIH and SIH (al'Absi & Petersen, 2003; Black et al., 2016). However, the cardiovascular response might be lower following cognitive task compared to exercise. Wasmund et al., 2002 found that performing a handgrip exercise for five minutes resulted in greater increase in muscle sympathetic nerve activity, blood pressure and heart rate compared to five minutes of mental math task (Wasmund et al., 2002). This finding of lower cardiovascular response following cognitive task may explain why young healthy individuals have variable SIH (Hoeger Bement et al., 2010). Lastly, similar to exercise, cognitive task may activate opioid and non-opioid mechanisms (Butler & Finn, 2009; Fechir et al., 2012; Hohmann et al., 2005). Therefore, these similarities between the change of pain following exercise and cognitive task suggest some shared mechanisms.

Since people with FM are reported to have abnormal response to physical and cognitive tasks, a study that compares the similarities and differences between the pain responses following both tasks is needed. For example, it is known that a sub-group of people with FM may experience hyperalgesia following isometric exercise (Hoeger Bement et al., 2011), however, it is not clear whether the same group would have a similar experience following a mental math task. Aim 2 will investigate the relation between the change of pain following physical and cognitive tasks

(submaximal isometric exercise and mental math, respectively) in people with FM and age- and sex-matched controls.

Autonomic Nervous System

The ANS consists of two major systems which are the sympathetic (SNS) and parasympathetic nervous system (PNS). Both systems innervate most organs in the body, and they are tonically active. The PNS is more dominant at the "rest and digest" state while the SNS activity increases during the "fight and flight" response (Johnson et al., 2013; Saper, 2002; Ulrich-Lai & Herman, 2009). The ANS regulates many critical functions such as heart rate, blood pressure, respiration, thermoregulation, and gastrointestinal function. The hypothalamus is the main region that controls homeostasis and modulates ANS in case of stress, fear, or any change in the body that perturbs homeostasis such as inflammation. Therefore, the hypothalamus receives inputs from areas such as amygdala, hippocampus, or any sensory inputs (Johnson et al., 2013; Saper, 2002). Besides the hypothalamus, there are centers in the brain stem that modulate the preganglionic neurons of SNS and PNS such as the rostral ventrolateral medulla and the nucleus of the solitary tract (Kenney & Ganta, 2014; Saper, 2002; Ulrich-Lai & Herman, 2009). These centers receive inputs from afferent ANS signals and from the hypothalamus. Moreover, the activation of HPA axis is one of the ways of modulating the ANS. The HPA axis activation leads to the release of cortisol, epinephrine and norepinephrine from the adrenal gland. The release of epinephrine and norepinephrine cause further increase in sympathetic activation (Kenney & Ganta, 2014; Ulrich-Lai & Herman, 2009).

The output information from the brain stem that is related to the SNS goes to the preganglionic efferent neurons at the thoracolumbar region of the spinal cord which then synapses with the postganglionic neurons that innervate the organs. Most

postganglionic neurons are adrenergic (they release norepinephrine) except the neurons that innervate the sweat glands are cholinergic (they release acetylcholine). On the other hand, the preganglionic efferent fibers of the PNS originate in either the brain stem and travel in some cranial nerves or originate in sacral spinal cord segments. The preganglionic neurons of PNS synapse with the postganglionic cholinergic neurons near or within the target organs. The vagus nerve gives around 75% of the PNS innervation including organs such as the heart and lungs. The postganglionic neurons of PNS are cholinergic (Johnson et al., 2013; McCorry, 2007; Saper, 2002).

Certain tests are performed to evaluate the ANS function. Some of these evaluation methods are self-report questionnaires such as the composite autonomic symptom score (COMPASS 31). The COMPASS 31 evaluates autonomic symptoms by asking about different functions that are regulated by the ANS such as orthostatic tolerance, skin color, sweating, gastrointestinal and bladder function (Sletten, 2012). The cardiovascular ANS that regulates heart rate and blood pressure can be assessed via deep breathing test and Valsalva maneuver (Low, 2004; Low et al., 2013). Deep breathing assesses the cardiovascular PNS while the Valsalva maneuver can assess cardiovascular SNS. The importance of deep breathing test and Valsalva maneuver lies in their capabilities of detecting cardiovascular ANS dysfunction, quantifying its severity, and determining its distribution (sympathetic, parasympathetic or both) (Low, 2004; Low et al., 2013).

Deep breathing evaluates the cardiovascular PNS through the coupling between respiration and heart rate that is mediated by their shared efferent neuron (vagus nerve) (Low, 2004; Low et al., 2013). During breathing, heart rate increases during inhalation and decreases during exhalation. This change in heart rate is

mediated by the PNS. The deep breathing test is done by performing six breathing cycles with each cycle consisting of a five-second inhalation and five-second exhalation (10-second cycle) while continuous heart rate data is collected. The magnitude of the change in heart rate is calculated by averaging the difference of heart rate of each respiratory cycle (heart rate at end of expiration – heart rate at end of inspiration).

The Valsalva maneuver can evaluate the cardiovascular sympathetic function via the change of blood pressure during the maneuver (Jones & Gibbons, 2015; Low et al., 2013; Vogel et al., 2005). The Valsalva maneuver is performed by forceful expiration against resistance at a certain pressure for 15 seconds and it consists of four phases. In the first phase, there is an increase in blood pressure caused by the increase in intra-thoracic and intra-abdominal pressure. The second phase starts with a reduction in blood pressure caused by reduction in venous return and cardiac output (early phase 2) that leads to activation of baroreceptors which results in the activation of SNS that causes an increase in blood pressure (late phase 2). In Phase 3, which is the end of Valsalva maneuver and lasts around one to two seconds, there is a drop of blood pressure caused by the decrease of intra-thoracic pressure and the termination of the maneuver. In phase 4, heart rate returns to baseline level but the arteriolar system remains vasoconstricted which results in an overshoot in blood pressure. In addition, the increase of blood pressure in phase 4 is mediated by the SNS. The cardiovascular SNS function can be quantified by the time it takes for the systolic blood pressure to return to baseline at the end of the maneuver (Low, 2004; Low et al., 2013; Vogel et al., 2005).

The cardiac ANS function can also be evaluated by heart rate variability (HRV) through continuous electrocardiogram (ECG) data collected over a period of

time. The advantage of HRV over other tests such as deep breathing or Valsalva maneuver is that it can evaluate the modulation of cardiac ANS during exercise or other tasks (Perini & Veicsteinas, 2003). The limitation of HRV is that it does not quantify the severity of ANS dysfunction or determine its distribution. HRV is the most commonly used method, and it assesses the variation of heart rate that is caused by cardiorespiratory coupling (Jones & Gibbons, 2015; Perini & Veicsteinas, 2003). Reduced HRV is associated with hypertension, physical inactivity, obesity, smoking, and diabetes (Sgoifo et al., 2015; Thayer & Lane, 2007). Analysis of HRV can be done by using time domain and/or frequency domain. The most common outcome measure of HRV is root mean square of successive differences in R-R intervals (RMSSD) which represents the beat to beat variation in heart rate ("Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology," 1996).

Isometric exercise can be used as a test of cardiovascular ANS function. When isometric exercise is performed at 25% - 35% of MVIC, heart rate and blood pressure progressively increase (Macefield & Henderson, 2015; Seals et al., 1988). The increase in the cardiovascular response is initially mediated by parasympathetic withdrawal, and as the exercise continues, SNS causes further increase in cardiovascular activity (Martin et al., 1974). Peripheral factors such as types III and IV muscle afferents contribute to the autonomic cardiovascular activation through NTS that excites the rostral ventrolateral medulla (Fisher & White, 2004; Macefield & Henderson, 2015). Afferents from arterial baroreceptors to the NTS also contribute to the increase in blood pressure during exercise (Fisher & White, 2004). Therefore,

heart rate, blood pressure and HRV can provide important information about the modulation of ANS help during exercise.

Autonomic Function in People With Fibromyalgia and Pain-Free Individuals

People with FM have altered autonomic function including reduced parasympathetic function (Reyes Del Paso et al., 2010). Others have shown that people with FM also have reduction in sympathetic function manifested by reduced stroke volume measured with impedance cardiography (Reyes del Paso et al., 2011; Reyes Del Paso et al., 2010). During deep breathing test, people with FM have lower HRV indicating reduced PNS function, and during tilt test, they experience hypotension which indicates a reduced SNS function (Bou-Holaigah et al., 1997; Furlan et al., 2005; Zamuner et al., 2016). Moreover, the impairment of autonomic system is related to the severity of the symptoms measured with the revised FM impact questionnaire (FIQR) (Lerma et al., 2011; Vincent et al., 2014; Zamuner et al., 2016). Thus, these autonomic findings suggest alterations in the parasympathetic and sympathetic function in people with FM. More research is needed to study the relation between pain modulation and ANS function in people with FM.

Cardiovascular autonomic function in people with FM has been evaluated in response to different types of stressors such as exercise, mental task, or cold presser test (Giske et al., 2008; Kadetoff & Kosek, 2010; Nilsen et al., 2007; Reyes Del Paso et al., 2010). In response to cognitive task, people with FM have less increase in blood pressure compared to pain-free controls (Nilsen et al., 2007; Reyes Del Paso et al., 2010). Reyes Del Paso and colleagues also studied the cardiovascular autonomic function in people with FM before and after cold pressor test. People with FM had lower HRV and baroreceptor sensitivity at baseline, and only controls had an increase

in HRV following the ice-water bath while people with FM had no significant change (Reyes del Paso et al., 2011). Kadetoff et al., 2010 found that people with FM had lower plasma epinephrine before and after isometric quadriceps exercise performed until task failure compared to controls (Kadetoff & Kosek, 2010). Giske et al., 2008 studied people with FM and controls that were matched in sex, age, physical activity, and body mass index (BMI), and found that people with FM had lower plasma epinephrine following intermittent isometric exercise (Giske et al., 2008). These studies indicate that people with FM have reduced cardiovascular response to physical and cognitive tasks.

Relation Between Autonomic Function and Quantitative Sensory Testing

There are some shared mechanisms between QST and cardiovascular autonomic modulation. Multiple brain cites such as PAG, NTS and the locus coeruleus are involved in pain and cardiovascular modulation (Saper, 2002). Electrical stimulation to the PAG in people with chronic pain resulted in pain reduction which was significantly related to the reduction of blood pressure (Green et al., 2006), whereas stimulation of the NTS can result in increase in blood pressure and hypoalgesia (Aicher & Randich, 1990). In animal models, studies have revealed a reduction in cardiovascular parasympathetic function as a result of induction of widespread pain (Oliveira et al., 2012; Sabharwal et al., 2016). In healthy participants, morphine causes an increase in pressure and heat pain thresholds along with an increase in blood pressure and heart rate (Fillingim et al., 2005). Lastly, some non-pharmacological interventions such as joint mobilizations and manipulations result in hypoalgesia and increased blood pressure and heart rate, which researchers hypothesized that the activation of PAG is a mediator for such a response (Bialosky et

al., 2018; Paungmali et al., 2003). Collectively, these findings provide evidence for the presence of shared mechanisms between pain and autonomic modulation.

Conditioned Pain Modulation and Autonomic Function

Despite the shared mechanisms between the cardiovascular autonomic function and pain modulation, the relation between CPM and autonomic function is not fully clear. Chalaye et al., 2013 reported a positive association between the increase in blood pressure during the conditioning stimulus (cold water bath) and CPM response in pain-free participants (Chalaye et al., 2013). The same research group conducted a similar study in people with FM and pain-free controls, and they found that people with FM had lower CPM response and lower increase in systolic blood pressure although they experienced greater pain intensity from the cold water. Another finding of this study was a significant positive correlation between the increase in systolic blood pressure during the cold water bath and CPM magnitude in people with FM and controls (Chalaye et al., 2014). The CPM response in these two studies was assessed after the removal of the conditioning stimulus while the blood pressure was taken during the conditioning stimulus. In contrast, Nilsen et al., 2014 studied the relation between CPM that was assessed during the conditioning stimulus and blood pressure response in healthy men. The authors reported no relation between the change in blood pressure and CPM (Nilsen et al., 2014). Therefore, the relation between blood pressure and CPM is not consistent in the literature.

The mechanism that could explain the relation between blood pressure and CPM in people with and without FM may involve activation of areas of descending pain inhibition that are also known to be involved in autonomic modulation such as PAG and locus coeruleus. People with FM have lower activation of these areas during CPM. In addition, noradrenergic mechanisms are known to contribute to sympathetic

modulation and pain inhibition. For instance, the increase of norepinephrine levels is associated with greater CPM (Parent et al., 2015), and blocking α2 adrenergic receptors at the spinal cord can significantly reduce CPM (Bannister et al., 2015).

HRV has also been shown to correlate with CPM. Greater HRV at baseline is associated with greater CPM in children (Tsao et al., 2013) and young healthy men (Nahman-Averbuch, Dayan, et al., 2016). However, using propranolol increases HRV but it does not cause a further increase in CPM in healthy individuals (Petersen et al., 2018). One explanation for the relation between baseline HRV and CPM is the activation of NTS via vagus afferents from the heart can lead to greater pain inhibition (Aicher & Randich, 1990). The NTS also sends projections to other areas of descending inhibition such as locus coeruleus and PAG (Bruehl & Chung, 2004). However, the reduction in HRV at baseline could be driven by low parasympathetic tone and/or elevated sympathetic tone. The use of other baseline autonomic assessment such as deep breathing test may help in explaining if the relation between CPM and HRV is mediated by altered baseline parasympathetic function. Therefore, more research is needed to better understand the relation between CPM and baseline autonomic function in people with FM.

Similar to CPM, there is variability in sympathetic and cardiovascular responses to the cold pressor task that may be at least partially due to age and sex. Younger women have lower increase in mean arterial pressure during cold pressor compared to men (Stone et al., 2019). This attenuated response could be caused by vasodilation that younger women have during cold pressor while men and older women have vasoconstriction (Miller et al., 2019). Additionally, there could be other factors besides age and sex contributing to sympathetic and cardiovascular reactivity during the cold pressor task. Haung et al., 2019 divided subjects into responders and

non-responders based on the muscle sympathetic nerve activity changes during the first 30 seconds of the cold pressor task. At baseline, both groups had similar age, sex, BMI, blood pressure, and muscle sympathetic nerve activity. However, responders had greater peak muscle sympathetic nerve activity, greater increase in mean arterial pressure and greater peak pain during the two minutes of the cold pressor (Huang et al., 2019). In addition to inter-individual variability, the sympathetic responses may differ by body region. For example, Jacob et al., 2000 showed an increase in vascular resistance in the contralateral arm and a decrease in vascular resistance in the leg during cold pressor stimulus applied to the hand (Jacob et al., 2000). Thus, similar to CPM, the sympathetic and cardiovascular responses during cold pressor are complex and can be influenced by many factors.

Temporal Summation of Pain and Autonomic Function

There is limited evidence about the effect of autonomic function on TS in people with and without FM. In people with FM, Kim et al., 2015 studied TS of mechanical pain and its relation to HRV in people with and without FM. They found people with FM had greater TS, and greater TS magnitude in people with FM was associated with greater reduction in the high frequency component of HRV during TS task. However, resting HRV and TS were not correlated (Kim et al., 2015). In addition, HRV is not associated with TS in healthy individuals (Nahman-Averbuch, Dayan, et al., 2016). Peterson et al., 2018 studied the effect of propranolol, which is a β blocker, on TS. They found that propranolol resulted an increase in HRV and reduction in heart rate but did not affect TS (Petersen et al., 2018). The relation between PNS and TS has been investigated through the use of vagal nerve stimulation. Napadow et al., 2012 used transcutaneous vagus nerve stimulation in people with pelvic pain. The study showed that the stimulation significantly reduced

anxiety levels and demonstrated a trend towards a reduction in TS (Napadow et al., 2012). Thus, the relation between parasympathetic function and TS is not clear.

Blood pressure has also been shown to correlate with TS. Chung et al., investigated the relation between resting blood pressure and TS of heat in pain-free people and people with low back pain. They found that greater resting systolic blood pressure was associated with lower TS in pain-free people, and associated with greater TS in people with low back pain (Chung et al., 2008). The positive relation between blood pressure and TS in people with chronic pain may change to a negative relation after recovery. Copa et al., 2018 reported lower TS of heat in adolescents with resolved functional abdominal pain was associated with greater resting systolic blood pressure. The relation did not exist in those who have ongoing symptoms (de la Coba et al., 2018). The mechanism that explains this relation between resting blood pressure and TS is not fully understood but it is not an opioidergic mechanism. Bruehl et al., 2002 found that opioids blockade does not affect the significant association between higher resting blood pressure and lower TS of pressure pain in pain-free individuals (Bruehl et al., 2002).

The first aim of the study will investigate the relation of baseline cardiovascular autonomic function and central pain facilitation and inhibition, measured by TS and CPM, in people with and without FM.

Relation Between Autonomic Function and Exercise-Induced Hypoalgesia

Several researchers have proposed that EIH is related to cardiovascular autonomic function in pain-free individuals and people with FM (Coppieters et al., 2016; Daenen et al., 2015; Nijs et al., 2012). First, a meta-analytic review showed that isometric exercise produces a greater EIH response than aerobic or dynamic resistive exercises which could be due to a stronger exercise pressor response that results in

greater cardiovascular response and greater EIH (Naugle et al., 2012). Isometric exercise performed for as short as two minutes at 40% to 50% of MVIC can produce a systemic hypoalgesic response (Koltyn & Umeda, 2007). These findings led to more research investigating the relation between EIH and the cardiovascular response. Black et al. found that EIH following isometric quadriceps exercise was associated with the increase in mean arterial blood pressure during the exercise (Black et al., 2016). On the other hand, Umeda et al., 2010 found that the blood pressure increased in a dose-response manner when comparing isometric tasks of different duration (1 minute, 3 minutes, and 5 minutes) but EIH was not dependent on the dose (Umeda et al., 2010). Thus, the relation between EIH and autonomic function in healthy individuals is equivocal.

In people with FM, the alteration in cardiovascular autonomic function has been proposed as one of the factors that lead to exercise intolerance and post-exercise symptoms exacerbations (Daenen et al., 2015; Nijs et al., 2012). During exercise, the SNS causes an increase in cardiac output and vasoconstriction in non-exercising body regions to redistribute the blood to the exercising muscles. In addition, the sympathetic activation is associated with a localized vasodilation within the exercising muscles (Fisher & White, 2004). People with FM have reduced blood flow during and following static and dynamic exercise (Elvin et al., 2006). Therefore, the reduction of the autonomic response during low to moderate isometric exercise may result in less vasodilation and consequently greater ischemia, pain and fatigue.

Another explanation for the relation between the ANS and EIH is the activation of HPA axis. Exercise activates the HPA axis leading to the release of cortisol from adrenal medulla along with catecholamines such as epinephrine and norepinephrine (Stranahan et al., 2008). The catecholamines cause a further increase

in cardiovascular ANS. In addition, cortisol and catecholamines are involved in suppressing pro-inflammatory cytokines (Gleeson et al., 2011). However, people with FM have reduced cortisol and catecholamine levels during exercise, although they report greater pain and exertion compared with controls (Giske et al., 2008; Kadetoff & Kosek, 2010). These findings may help explain why people with FM have greater levels of pro-inflammatory cytokines after an acute bout of exercise (Torgrimson-Ojerio et al., 2014).

Lastly, there are areas in the brain involved in both autonomic modulation and EIH. One of these areas is PAG. Williams et al., 1990 showed that lesion to the PAG did not affect baseline blood pressure but attenuated the increase of blood pressure during isometric contraction generated by electrical stimulation in cats (Williams et al., 1990). In an animal model of neuropathic pain, forced exercise increases opioid expression in the PAG and RVM along with an increase in anti-nociception effect, and systemic block of opioids by naloxone (opioid antagonist) prevents the anti-nociceptive effect of exercise (Stagg et al., 2011). The same study showed greater release of opioid and anti-nociception with high intensity exercise compared to low intensity (Stagg et al., 2011). In addition, PAG receives projections from other areas that modulate the ANS such as the hypothalamus and amygdala, and it sends projections to areas such as locus coeruleus (Bruehl & Chung, 2004; Linnman et al., 2012). Locus coeruleus has a role in modulating sympathetic function and can also modulate pain during exercise (Bruehl & Chung, 2004; Lopez-Alvarez et al., 2018). Therefore, the dysfunction in the areas that modulate pain and autonomic function may result in reduced EIH and altered cardiovascular response during exercise. Aim 2 will investigate the relation of the cardiovascular autonomic function and pain

modulation following submaximal isometric exercise in people with FM and age- and sex-matched controls.

Relation Between Autonomic Function and Stress-Induced Hypoalgesia

Previous research has shown relations between SIH and autonomic function. Al'Absi et al., 2003 showed that the increase in systolic blood pressure during the cognitive task was associated with greater SIH. The study also showed that the increase of stroke volume and cardiac output were associated with greater SIH (al'Absi & Petersen, 2003) Fechir et al., 2011 demonstrated that naloxone attenuated SIH and prevented the increase in systolic blood pressure during cognitive task compared to placebo (Fechir et al., 2012). These findings suggest the cardiovascular response during the cognitive task is associated with SIH in healthy individuals.

The cardiovascular autonomic response during cognitive task is variable among young healthy individuals. Carter et al., 2009 divided young healthy participants into sympathetic responders and non-responders based on the increase in muscle sympathetic nerve activity levels during the mental math task. The study showed that perceived stress was not different between sympathetic responders and non-responders (Carter & Ray, 2009). Lautenschlager et al., 2015 found that greater SIH following a cognitive task was associated with the increase in muscle sympathetic nerve activity during cognitive task in young healthy participants (Lautenschläger et al., 2015).

People with FM have lower cardiovascular autonomic response during a cognitive task. Nilsen et al., 2007 studied the difference in the cardiovascular autonomic response to cognitive stress in people with and without FM. People with FM had less increase in heart rate and diastolic blood pressure compared to controls. In addition, the increase in heart rate was associated with lower increase in pain

among people with FM (Nilsen et al., 2007). Thieme et al., 2015 performed a cluster analysis to study the variability among FM participants following a cognitive task. The results demonstrated four clusters but the majority of the participants fell into two main clusters that varied in pain, stress, and cardiovascular response at baseline and during cognitive task. The first cluster had higher blood pressure, higher pain, higher stress at baseline and greater increase in blood pressure during the cognitive task compared to the second cluster of participants (Thieme et al., 2015). Therefore, studying the variability in SIH and its relation to the cardiovascular autonomic function in people with FM may help in better understanding how stress interacts with pain in people with FM.

Significance and Purpose

This dissertation will examine several aspects relating to pain perception at rest (baseline) and following cognitive and physical tasks in healthy and chronic pain population. First, the relation between cardiovascular autonomic function and baseline pain perception will be examined including central pain facilitation and inhibition. Understanding the relation between pain modulation and autonomic function may lead to better pain management for FM. For example, finding a negative relation between TS and sympathetic function suggests that pain interventions that improve sympathetic function, such as duloxetine, may be beneficial for people with enhanced TS. In addition, the pain response following physical and cognitive tasks (exercise and mental math, respectively) will be compared and the potential mediating factors will be explored. Cardiovascular autonomic function will be assessed at baseline and during exercise and mental math. Discerning the role of autonomic functioning in the pain response following exercise will provide the necessary evidence to elucidate potential mechanisms in promoting EIH resulting in optimal exercise prescription.

Furthermore, comparing the pain responses between exercise and mental math is a unique approach to advance understanding of the relation between pain and stress, as well as insight into changes that occur with chronic pain (Figure 1.2).

Specific Aims

Aim 1: To study the relation between cardiovascular autonomic function and central pain facilitation and inhibition, measured by TS and CPM, in people with FM and age- and sex-matched controls.

Hypothesis 1: *People with FM will have altered cardiovascular autonomic function compared with controls.*

Hypothesis 2: *There will be an association between cardiovascular autonomic function and endogenous pain modulation (TS and CPM); people with altered cardiovascular autonomic function will report greater TS and lower CPM.*

Aim 2: To investigate the relation between cardiovascular autonomic function and endogenous pain modulation following physical and cognitive tasks (submaximal isometric exercise and mental math, respectively) in people with FM and age- and sex-matched controls.

Hypothesis 1: *Perceived stress and cardiovascular autonomic response will increase during both submaximal isometric exercise and mental math for all participants.*

Hypothesis 2: *People with FM will have reduced cardiovascular autonomic function at baseline and during submaximal isometric exercise and mental math task compared to controls.*

Hypothesis 3: *The cardiovascular autonomic function at baseline and during exercise and mental math will be negatively associated with the pain response following these tasks; people with altered cardiovascular autonomic function will*

report an increase of pain following both exercise and mental math, which will be comparable between the two tasks.

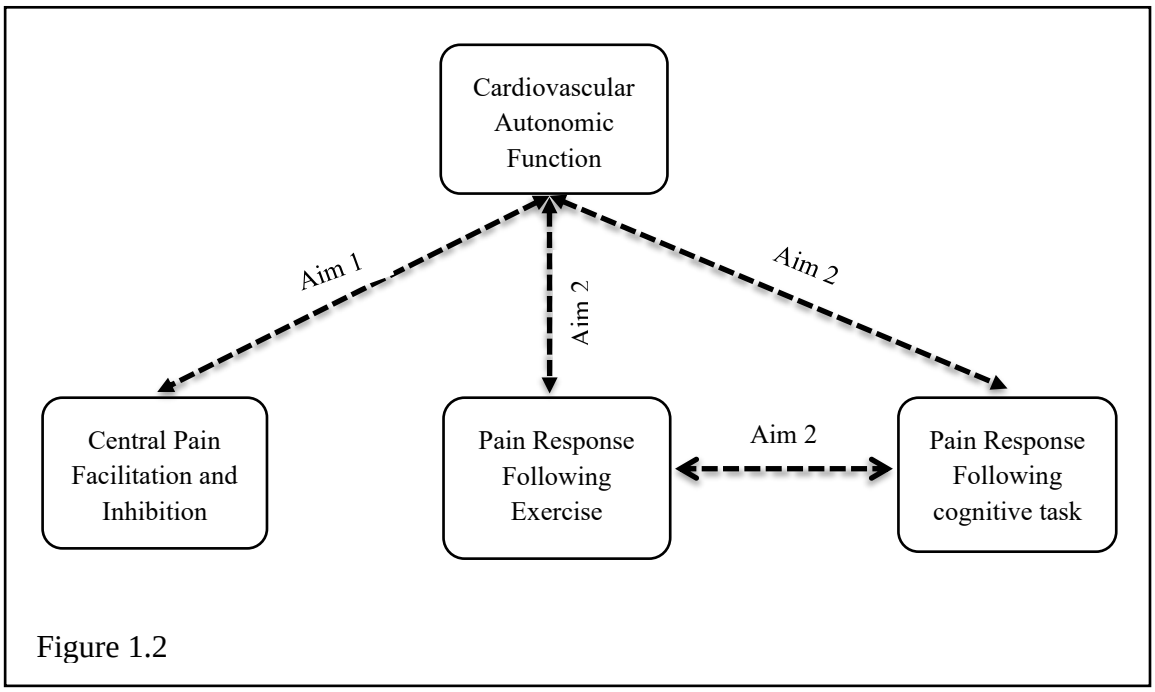

Figure 1.2: The aims of the study.

CHAPTER TWO

The RELATION BETWEEN AUTONOMIC FUNCTION AND ENDOGENOUS PAIN MODULATION IN PEOPLE WITH AND WITHOUT FIBROMYALGIA

Introduction

Fibromyalgia (FM) is a chronic pain condition that is manifested by widespread pain and other symptoms such as fatigue, depression, insomnia, and morning stiffness (McBeth & Mulvey, 2012; Wolfe et al., 2010). The number of symptoms vary among people with FM, however, the diagnosis of FM involves evaluating the number of pain sites, and the severity of the symptoms (Wolfe et al., 2010). The widespread pain that people with FM have is due to abnormal central pain processing that leads to increased pain facilitation and/or reduced pain inhibition (Cagnie et al., 2014; O'Brien et al., 2018; Sluka & Clauw, 2016). These changes in central pain processing may be manifested by enhanced temporal summation of pain (TS) and/or attenuated conditioned pain modulation (CPM) (O'Brien et al., 2018), which are variable among people with FM (Potvin & Marchand, 2016; Potvin et al., 2012). The reasons for this heterogeneity are not completely known, however, autonomic nervous system dysfunction has been suggested to contribute to the symptoms of fibromyalgia (Di Franco et al., 2009; Light et al., 2009; Martinez-Martinez et al., 2014; Meeus et al., 2013; Riva et al., 2012; Vincent et al., 2014).

Previous research supports the relation between autonomic function and endogenous pain modulation. For example, CPM in humans involves the activation of areas of descending inhibition like the periaqueductal gray (PAG) and locus coeruleus (Baba et al., 2012; Harper et al., 2018; Knudsen et al., 2018; Piche et al., 2009). TS involves windup of C-fibers in the dorsal horn of the spinal cord (Herrero et al., 2000)and may involve activation of supraspinal areas like the PAG, and nucleus

tractus solitarius (NTS) (Bosma et al., 2016; Cheng et al., 2015). These brain areas are also known to modulate autonomic function (Aicher & Randich, 1990; Green et al., 2006; Green et al., 2005; Samuels & Szabadi, 2008). Furthermore, studies have shown associations between the change of cardiovascular autonomic function and CPM and TS. For example, the increase of systolic blood pressure during CPM was positively related to the magnitude of the CPM response in healthy participants and people with FM (Chalaye et al., 2013; Chalaye et al., 2014). In regards to TS, higher baseline systolic blood pressure was associated with higher TS in people with chronic low back pain (Chung et al., 2008). Thus, the cardiovascular autonomic nervous system may be related to endogenous pain modulation and may provide insight into the heterogeneity in chronic pain populations including FM. A more comprehensive study that investigates different aspects of autonomic function including sympathetic and parasympathetic function and their relations to CPM and TS is needed since understanding the involvement of autonomic functioning with pain modulation may help in the treatment of people with FM.

The aim of the study was to investigate the relation between cardiovascular autonomic function and central pain facilitation and inhibition, measured by TS and CPM, in people with FM and control participants that were matched for age and sex. The potential factors that are known to correlate with pain and autonomic function were also investigated including body composition and physical activity (Awali et al., 2018; Eyre et al., 2014; Sandercock et al., 2005; Stolzman & Hoeger Bement, 2016). We hypothesized that people with FM would have altered cardiovascular autonomic function at baseline compared to control participants, and baseline cardiovascular autonomic function would be associated with CPM and TS.

Methods

Participants

Twenty people with FM (2 men) and 18 age- and sex-matched control participants (2 men) participated in this study. All participants were screened via the phone and excluded if they had cardiovascular disease, autoimmune disease, neurological disorder, cancer, pulmonary disease except controlled asthma, recent orthopedic surgery, diabetes, psychiatric conditions such as bipolar or schizophrenia, or taking medications known to influence autonomic function. The protocol of the study was approved by the institutional review board at Marquette University.

Research Design

Participants partook in three sessions in the following order: 1) cardiovascular autonomic assessment; 2) CPM; and 3) TS (Figure 2.1). At the beginning of session 1 (cardiovascular autonomic assessment session), all participants read and signed the informed consent, reviewed the health data form from the phone screening, and completed the short-form McGill pain questionnaire (SF-MPQ) and composite autonomic symptoms score 31 (COMPASS 31). People with FM completed the revised fibromyalgia impact questionnaire (FIQR). Next, electrocardiogram (ECG) and beat-to-beat blood pressure were recorded for 10 minutes for HRV analysis and as a baseline measure (i.e., systolic blood pressure, diastolic blood pressure, and heart rate). Participants then performed the deep breathing test and Valsalva maneuver, completed dispositional pain catastrophizing scale (PCS), and were familiarized to the TS and CPM protocols. The familiarization involved conducting full TS (including individualization task) and CPM protocols. Lastly, participants were issued an activity monitor (Actigraph) (wGT3X-BT Pensacola, FL) to wear for 7 days.

At the beginning of the second session (CPM), participants completed the international physical activity questionnaire (IPAQ) followed by assessment of CPM. ECG and beat-to-beat blood pressure were collected for 5 minutes before CPM and during the entire CPM protocol. Situational PCS was completed after CPM in reference to the cold water bath. Participants underwent dual-energy x-ray absorptiometry (DXA) scan at the end of session 2. The third session was similar to the second except participants performed the individualization task followed by TS protocol instead of CPM.

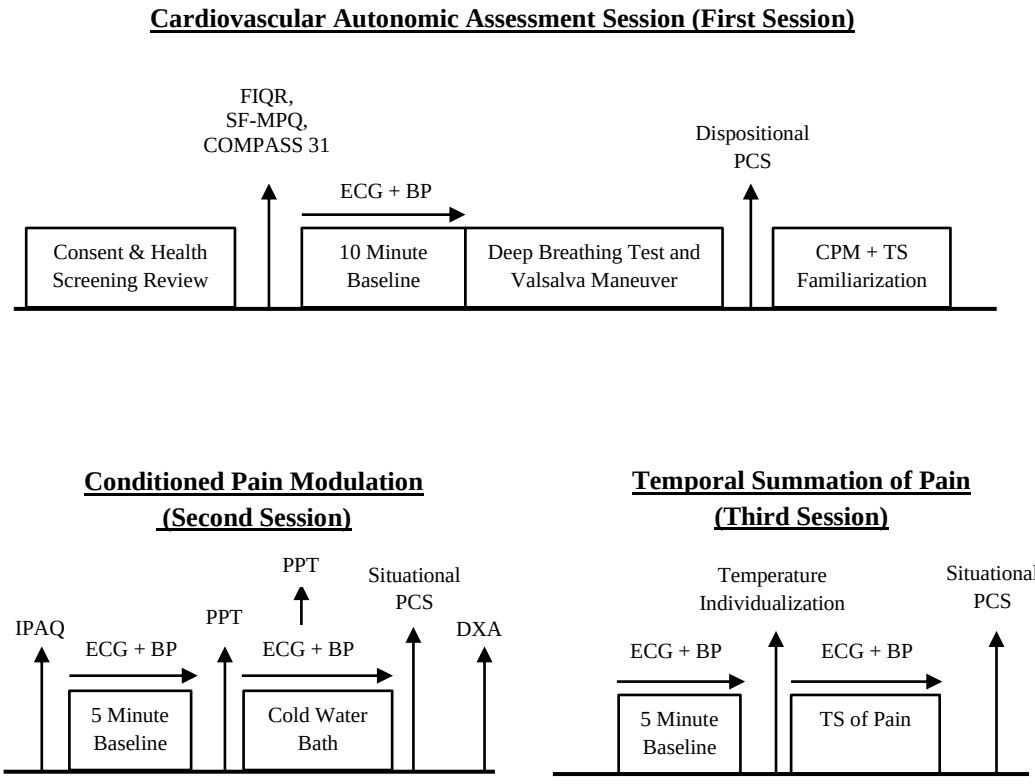

Figure 2.1: Protocol of study.
FIQR= revised fibromyalgia impact questionnaires, *SF-MPQ*= short-form McGill pain questionnaire, *COMPASS 31*= Composite autonomic symptom score 31, Dispositional *PCS*= pain catastrophizing scale, *CPM* conditioned pain modulation, *TS*= temporal summation of pain; *IPAQ*= international physical activity questionnaire, *PPT*= pressure pain threshold; *ECG*= electrocardiogram, *BP*= blood pressure; Situational PCS= situational pain catastrophizing scale; *DXA*= dual-energy x-ray absorptiometry. Participants completed three non-randomized sessions. In the first session, participants underwent baseline autonomic function assessment and CPM and TS familiarization. The second and third sessions involved autonomic function in conjunction with CPM and TS assessments, respectively.

Conditioned Pain Modulation

For the CPM protocol, pressure pain threshold (PPT) was the test stimulus and a cold water bath was the conditioning stimulus. PPTs at a rate of 50 kPa/second were assessed twice at the right quadriceps (midpoint between the anterior superior iliac spine and the patella) and right volar forearm (proximal one-fourth the distance between the elbow and the wrist) in a randomized order before and during left foot immersion in cold water bath (6˚C ± 1˚C) for two minutes. After 20 seconds of immersing the foot in the cold water and at the end of the two minutes, participants were asked to rate the pain in the foot from 0 (no pain) to 10 (worst pain). The magnitude of CPM was calculated as [During-CPM PPT – Pre-CPM PPT].

Temporal Summation of Heat Pain

TS was assessed using heat pulses (Medoc Neurosensory Analyzer, TSA-2, Ramat Yishai, Israel) that were individualized for each participant. The individualization task involved the application of twelve heat pulses to the volar aspect of the right forearm. The temperature of the pulses ranged from 39˚C – 50˚C and the participants were asked to rate each pulse from 0 (no pain) to 10 (worst pain). The temperature that resulted in pain60 (pain rating of 6 out of 10) was used as the noxious stimulus during TS test (Granot et al., 2006). In case a participant provided pain ratings lower than pain60 in the individualization task, the highest temperature of 50˚C was used. During the TS test, participants received ten heat pulses with ramp and return rate of 8˚C/second to the baseline temperature. The peak stimulus interval was 0.6 second and the inter-stimulus interval was 0.3 second. The baseline temperature was 8˚C below the individualized temperature for all participants. Therefore, peak to peak interval was 2.9 seconds. Participants were asked to rate the

first, third, fifth, eighth and tenth stimuli. The TS magnitude was calculated as the difference of pain ratings between the first and tenth stimuli.

Revised Fibromyalgia Impact Questionnaire

This questionnaire evaluates the severity of FM symptoms over the past 7 days. There are three domains: symptoms, overall impact, and function. Higher scores indicate greater symptom severity (Bennett et al., 2009; Burckhardt et al., 1991).

Short-Form McGill Pain Questionnaire

The SF-MPQ evaluates different aspects of pain such as affective, sensory, and overall pain intensity (Melzack, 1987).

Cardiovascular Autonomic Function Tests

The autonomic nervous system regulates different cardiovascular functions (e.g., heart rate and blood pressure), which can be assessed by performing distinct tests including HRV, deep breathing test, and the Valsalva maneuver. HRV evaluates both the sympathetic and parasympathetic innervation to the heart. Deep breathing test evaluates the cardiovascular parasympathetic function through the coupling between respiration and heart rate. The Valsalva maneuver can evaluate the cardiovascular sympathetic adrenergic function via the change of blood pressure during the maneuver (Jones & Gibbons, 2015; Low, 2004; Low et al., 2013).

Heart Rate and Blood Pressure

Heart rate and blood pressure were assessed during all three sessions, including before and during CPM and TS. Heart rate data were obtained through ECG through surface electrodes that measure electrical activity of the heart. Three electrode leads were placed at right clavicle (negative electrode), left lower rib (positive electrode), and left clavicle (ground electrode) and ECG amplifier (Biopac ECG 100C) was used. The amplifier parameters involved a gain of 2000, low pass

filter of 35 Hz, and high pass filter of 1 Hz. Participants were instructed to avoid movement to limit artifacts. Beat-to-beat blood pressure data was collected through finger cuff sensors placed on the left hand using non-invasive blood pressure system (NIBP100D, CNSystems, Austria) and Biopac amplifier (Biopac DA100C). The amplifier setup included a gain of 1000, low pass filter of 300 Hz and high pass filter of direct current. After placing the blood pressure cuff, the arm was rested on a table, and participants were instructed to avoid moving the left arm to avoid creating artifacts. The blood pressure was calibrated for every participant using standard arm cuff. The data acquisition system used for all cardiovascular autonomic assessment was Biopac MP150 (Biopac, Goleta, California). The quality of the ECG and blood pressure signals were visually inspected before data collection. The sampling rate for ECG and blood pressure data were set at 2000 Hz.

Heart Rate Variability

HRV was calculated from ECG data that was collected in all three sessions using the same ECG setup as heart rate. In the first session, ECG data was collected for ten minutes while the participant was in supine. In the second and third sessions, ECG data was collected before CPM and TS for five minutes, and during CPM and TS while the participant was in a seated position with both arms supported. In all baseline ECG assessments, participants were instructed to relax. HRV analysis was conducted using Kubios software. After importing raw ECG data in Kubios software, a validated automatic correction algorithm was utilized to detect and correct missing or ectopic beats (Lipponen & Tarvainen, 2019). The main outcome was the root mean square of successive differences of R-R intervals (RMSSD); this is the most common outcome of HRV and represents the beat to beat variation of heart rate ("Heart rate variability. Standards of measurement, physiological interpretation, and clinical use.

Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology," 1996).

Deep Breathing

Deep breathing test was performed after baseline HRV assessment in the first session while the participant was supine. For the deep breathing test, participants were asked to perform six breathing cycles with each cycle consists of a five seconds inhalation and 5 seconds exhalation (10-second cycle). Participants performed practice trials until they performed respiratory cycles without sudden inhalation or exhalation or holding the breath. Continuous heart rate and respiratory rate data were recorded. The magnitude of the change in heart rate was calculated by averaging the difference of heart rate of each respiratory cycle (heart rate at end of expiration – heart rate at end of inspiration) (Jones & Gibbons, 2015; Low, 2004; Low et al., 2013). Respiratory chest expansion data was used to indicate peak inspiration and expiration and was collected by Biopac respiratory transducer (TSD 201) and respiration amplifier (RSP 100) (Biopac, Goleta, California).

Valsalva Maneuver

Valsalva maneuver was performed after the deep breathing test while the participant was in supine position. Participants were instructed to perform a forceful expiration at a pressure of 40 mm Hg for 15 seconds. This was done by blowing into a syringe that was connected to a pressure gauge, which was placed in front of the participants for visual feedback. The syringe had a leak to maintain an open glottis, and feedback of the time was provided. Beat-to-beat blood pressure data were collected during the maneuver. Participants performed two practice trials with one minute of rest between the trials. Then, participants performed at least two maneuvers with three minutes of rest between the maneuvers. The maneuver was rejected if

expiration time was shorter than 10 seconds or the expiration pressure was less than 30 mm Hg. The cardiovascular sympathetic adrenergic function was quantified as the time it took for the systolic blood pressure to recover to baseline level following the end of the maneuver (Jones & Gibbons, 2015; Low, 2004; Low et al., 2013; Vogel et al., 2005).

Composite Autonomic Symptom Score 31

This 31-item questionnaire evaluates 6 domains of autonomic nervous system which are secretomotor, orthostatic intolerance, vasomotor, bladder function, gastrointestinal, and pupillomotor function. Higher scores indicate greater autonomic symptoms (Sletten, 2012; Solano et al., 2009; Vincent et al., 2014).

Dispositional Pain Catastrophizing Scale

This 13-item scale evaluates the negative mental set towards pain (Sullivan et al., 1995). There are three sub-scales: magnification, rumination, and helplessness. Greater scores indicate greater pain catastrophizing.

Situational Pain Catastrophizing Scale

The situational PCS is a 6-item questionnaire that explores the negative mental set or catastrophizing thinking specific to a particular experimental pain experience (Campbell et al., 2010; Edwards et al., 2006). Situational PCS was completed immediately after CPM in reference to the cold water bath and immediately after the TS in reference to the heat pulses.

Body Composition

Anthropometrics were assessed with DXA (Lunar iDXA, GE Healthcare, Madison, Wisconsin). The DXA data were analyzed by encore software (GE Healthcare, Madison, Wisconsin). The following outcomes were used in this study: visceral fat (kg), right arm fat and lean masses (kg), and right leg fat and lean masses

(kg). Additionally, BMI was calculated as weight divided by the square of height (kg/m^2).

Physical Activity

To quantify physical activity, participants wore an Actigraph (wGT3X-BT Pensacola, FL) on the waist for seven days. Participants were asked to complete a log about certain daily activities such as sleep time, exercise time, and when the Actigraph was removed. The data of four valid days (wear time of at least ten waking hours), which is a valid representative for the data of a week (Migueles et al., 2017), were analyzed with Actilife software (Actilife 6.13.1, Pensacola, FL) (Migueles et al., 2017). The Freedson criteria was used to identify the time spent on moderate to vigorous physical activities (MPVA) and the number of steps (Freedson & John, 2013; Freedson et al., 1998; Sasaki et al., 2011).

Statistical Analysis

Data were statistically analyzed by the Statistical Package for the Social Sciences (Version 25, IBM, Armonk, NY). Data are presented in text and tables as mean ± standard deviation (SD), and in figures as mean ± standard error of the mean (SEM). After normality assessment, Independent *t*-tests or Mann-Whitney *U* tests were used for baseline group comparisons.

To evaluate CPM, repeated measures analysis of variance (RM ANOVA) was conducted with a trial (Pre-CPM and During-CPM) by site (forearm and quadriceps) as with within-group variables, and condition (FM and controls) as between-group variable. To evaluate TS between the FM group and controls, RM analysis of covariance (RM ANCOVA) was done in order to control for the effect of the individualized temperature (the target temperature which was the temperature that resulted in pain60). Previous studies showed that the individualized temperature is

positively associated with the magnitude of TS (Awali et al., 2018; Granot et al., 2006; Potvin et al., 2012). The between-group variable for the RM ANCOVA was condition (FM and controls), and the within-group variable was heat pulse number (time: first, third, fifth, eighth, and tenth heat pulse). Post hoc t-tests were conducted for group comparison if there was a significant interaction for CPM or TS. Because the post hoc analysis was planned, the p-value was set at 0.05 (Field, 2013). Independent *t*-tests or Mann-Whitney *U* tests were used for group comparisons in pre-CPM PPT, pain at 20 seconds and at the end of the cold water bath, the individualized temperature of TS, and situational pain catastrophizing after the CPM and TS.

Cardiovascular outcomes (heart rate, HRV, systolic and diastolic blood pressure) during the cold water bath were analyzed at 30-second windows (30, 60, 90, 120 seconds) and a 30-second pre-CPM window was used as baseline. For the TS, since the length of task was 30 seconds, one 30-second window (during-TS) was analyzed in addition to 30-second pre-TS window. For each cardiovascular outcome assessed during CPM and TS, RM ANOVA was used with condition as between-group variable (FM and controls) and time as within-group variable. Independent *t*-tests were conducted for group comparisons following RM ANOVA if needed. For follow-up comparisons on cardiovascular outcomes, Bonferroni correction was used since no specific hypothesis was pre-determined (Field, 2013).

Pearson or Spearman correlation was done to determine the association between CPM and cardiovascular or autonomic outcomes. Partial correlation was conducted for TS and cardiovascular and autonomic outcomes to control for the effect of the individualized temperature. The p-value was set at $p \leq 0.05$ for correlations specific to the main aim or hypothesis. For other correlations, the p-value was set at $p < 0.01$ in order to correct for multiple comparisons (Field, 2013).

Sample Size Analysis

The power analysis was conducted using G*power 3.1. The effect size was taken from correlation coefficients from studies that showed an association between baseline autonomic function or the change of autonomic function and CPM or TS (Kim et al., 2015; Nahman-Averbuch, Dayan, et al., 2016). The number of participants that was determined was 15 participants per group for 80% statistical power at $\alpha = 0.05$.

Results

Participants Characteristics

One participant with FM dropped out after the first session, and the data of this participant was excluded from the analysis since the participant did not perform the main measures of the study (i.e., CPM or TS). Another participant with FM did not perform CPM because of fear of pain from the cold water bath; all other assessments were completed and included in the analysis. For the physical activity monitor data, 8 participants with FM and one control participant did not meet the minimum wear time criteria of at least four valid days.

People with and without FM were middle-aged individuals (two men in each group) (Table 1). Average BMI was similar between the groups and in the overweight category; although 6 participants with FM and 8 control participants were normal or underweight. People with FM had similar lean and fat mass in the arm and the leg, measured via DXA, but higher visceral fat than people without FM. Both groups were classified as physically active, and exceeded the minimum requirement of at least 150 minutes of moderate physical activity (Piercy et al., 2018). Thus, people with and without FM were of similar age, sex, body composition, and physical activity. Specific to pain, people with FM reported higher levels of baseline pain measured by

SF-MPQ and higher levels of dispositional PCS. Only two participants with FM had scores above 30 which is the clinical relevance level of dispositional PCS (Sullivan et al., 1995).

Specific to resting cardiovascular measures assessed in the first session, people with FM had higher baseline heart rate but similar systolic and diastolic blood pressure. Heart rate and blood pressure were within normal ranges for both groups (Mason et al., 2007; Whelton et al., 2018). The deep breathing test scores were similar between groups, indicating similar baseline cardiovascular parasympathetic function. The HRV was also similar between the groups, indicating similar cardiac autonomic balance. People with FM had longer Valsalva recovery time (i.e., lower sympathetic function). In addition, people with FM reported greater autonomic symptoms (COMPASS 31), including reduction in non-cardiovascular functions such as secretomotor, pupillomotor, bladder, and gastrointestinal functions.

Table 2.1: Baseline Differences Between People With and Without Fibromyalgia

		With FM (n= 19) Mean ± SI	Without FM (n= 18) Mean ± SD	p Value
Sex (Men)		2	2	
Age (years)		49.8 ± 11.4	49.4 ± 11.9	.92
SF-MQP		**11.8 ± 9.8****	.11 ± .5	< .01
FIQR		45.8 ± 22.5	-	
Dispositional PCS				
	Rumination Subscale	4.6 ± 4.1	3.3 ± 3.2	.52
	Helplessness Subscale	**7.7 ± 6.3****	2.2 ± 2.4	< .01
	Magnification Subscale	3.4 ± 3.6	1.8 ± 1.9	.22
	Total PCS Score	**15.6 ± 12.5***	7.3 ± 6.6	.049
Baseline Cardiovascular Assessment				
	Heart Rate (Beats)	**74.3 ± 11.3***	65.8 ± 8.3	.01
	Systolic Blood Pressure (mmHg)	119.9 ± 15.2	115.7 ± 11.2	.36
	Diastolic Blood Pressure (mmHg)	74.1 ± 9.4	70.1 ± 5.6	.13
Cardiovascular Autonomic Function				
	Deep Breathing Test (beats)	13.1 ±5.6	10.5 ±5	.13

	Valsalva Recovery Time (Sec)	**2.8 ± 2.4****	1.3 ±1.2	< .01
	RMSSD of HRV (ms)	23.2 ± 13.2	26.5 ± 15.3	.69
Self-report Autonomic Function (COMPASS 31)				
	Orthostatic Intolerance	**12.2 ± 10.4****	0.9 ± 3.8	< .01
	Vasomotor	**1.1 ± 1.4***	0.0 ± .0	.03
	Secretomotor	**5.8 ± 3.4****	0.7 ± 1.3	< .01
	Gastrointestinal	**8.5 ± 5.7****	2.8 ± 2.1	< .01
	Bladder	**1.8 ± 2.1***	0.2 ± .4	.02
	Pupillomotor	**2.2 ± 1.2****	0.9 ± 0.7	< .01
	Total	**31.6 ± 15.2****	5.5 ± 5.2	< .01
Body Composition				
	BMI	29.0 ± 8	26.5 ± 5	.41
	Visceral Fat Mass (kg)	**1.0 ± .6***	.5 ± .4	.03
	Right Arm Lean Mass (kg)	2.4 ± .8	2.5 ± .9	.36
	Right Arm Fat Mass (kg)	1.6 ± .9	1.4 ± .5	.56
	Right Leg Lean Mass (kg)	7.8 ± 1.7	8.0 ± 1.7	.52
	Right Leg Fat Mass (kg)	5.6 ± 2.6	4.4 ± 1.5	.15
Physical Activity				
	Average Daily Time in MVPA (min)	45.2 ± 32.2	65.9 ± 35.1	.13
	Average Daily steps	7586.6 ± 2274.6	9184.9 ± 3067.3	.15

SF-MPQ= short-form McGill pain questionnaire; *FIQR*= revised fibromyalgia impact questionnaire; Dispositional *PCS*= dispositional pain catastrophizing scale; *Sec*= second; *RMSSD*= root mean square of successive RR interval differences; *HRV*= heart rate variability*; ms*= millisecond; *COMPASS 31*= composite autonomic symptoms score; *BMI*= body mass index; *kg*= kilogram, *MVPA*= moderate to vigorous physical activity. Data are presented as mean ± SD. * $p < 0.05$, ** $p < 0.01$.

Conditioned Pain Modulation

Eighteen participants in both groups underwent the CPM protocol. One participant with FM removed her foot from the cold water after 30 seconds because of inability to tolerate the pain but completed all PPTs assessment needed for the CPM. The statistical analysis of CPM was conducted with and without this participant and the results were not different. We included all the data in the analysis because CPM effect can be assessed after removing the conditioning stimulus (Alsouhibani et al., 2018; Kennedy et al., 2016). People with FM had lower pre-CPM PPT at the forearm (FM: 219.5 ±114.4; controls: 335.4 ±107; p< .01) but not the quadriceps (FM: 344.4

±164.2; controls: 407.9 ±158; p= .25) (Figure 2.2). After placing the foot in the cold water bath, both groups reported moderate pain at 20 seconds (FM: 5.1 ±2.9; controls: 3.5 ±2.3; p= .07), however, people with FM reported higher pain at the end of the two minutes (FM: 7.3 ±2.4; controls: 5 ±2.3; p< .01). In regard to the CPM magnitude, there was group differences in the overall magnitude of CPM [group x trial interaction: (F (1, 34) = 6.3, P= .02, η_p^2 = .16)]. In addition, the results also revealed that the group difference in CPM was site-specific [group x trial x site interaction, (F (1, 34) = 30.3, p< .01, η_p^2 = .47)] (Figure 2.2). Post hoc showed that both groups had similar CPM magnitude at the forearm (FM: 35.9 ±46.1; controls: 33.4 ±56; p= .89) but only controls had CPM at the quadriceps (FM: 5.3 ±50; controls: 90.4 ±65; p< .01). In addition, people with FM had higher situational PCS immediately after the CPM protocol (FM: 11.5 ±6.8; controls: 4.1 ±5.2; p< .01).

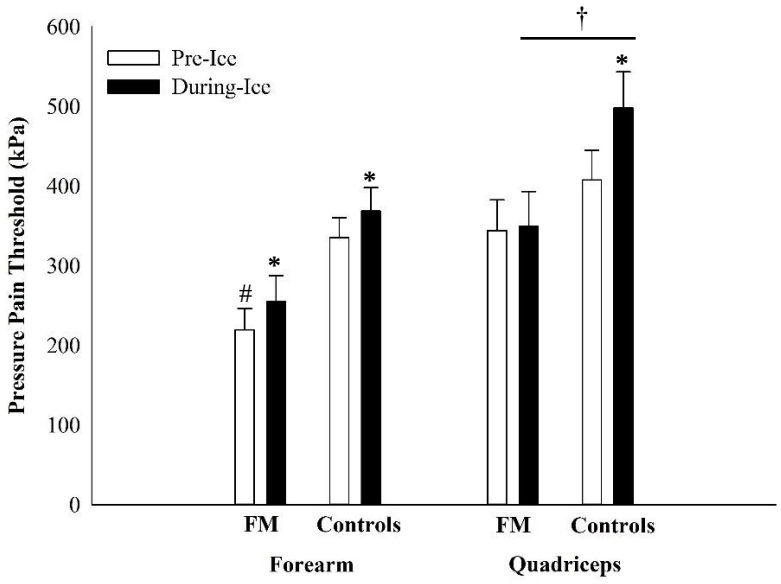

Figure 2.2: Pressure pain thresholds at the forearm and the quadriceps at rest (pre) and during cold water.
(#) indicates baseline differences in PPTs (main effect of group). (*) indicates significant increase in PPTs during cold water relative to baseline PPTs. (†) indicates significant group differences in CPM magnitude. Data are presented as mean ±SEM. People with FM had lower baseline PPT at the forearm but similar PPT at the quadriceps compared to control

participants. Both groups experienced CPM at the forearm but only control participants experienced CPM at the quadriceps [group x trial x site interaction (F (1, 34) = 30.3, p< .01, $\eta_o 2$= .47)].

Cardiovascular Assessment at Rest and During Conditioned Pain Modulation

The blood pressure data of one participant with FM was excluded from the analysis because of excessive left arm movement and lost blood pressure signal during CPM. During the cold water bath, people with FM had higher HR [main effect of group, (F(1,32)= 23.7, p< 0.01, η_p^2 = .43)] (Figure 2.3). There was a significant difference in the heart rate during the cold water bath [group x time interaction, (F (2.5, 79) = 4.4, p= .01, η_p^2 = .12)]. Post hoc analysis showed that only people with FM had an increase in the heart rate in the first 30 seconds of placing the foot in the cold water bath (FM: 4.7 ±2.6, controls: -.2 ±2.5; p< .01) compared to baseline, and only controls experienced reduction in heart rate by the end of the cold water bath relative to baseline (FM: - .6 ±2.9, controls: - 3.9 ±4.4; p< 0.01). In addition, there was a significant increase in diastolic blood pressure during cold water bath [main effect of time, (F (2.4, 75.3) = 7.2, p< .01, η_p^2 = .18)]. Post hoc revealed a significant increase in diastolic blood pressure at 90 seconds of the cold water bath relative to baseline (p< 0.01). Systolic blood pressure and HRV did not change during the cold bath.

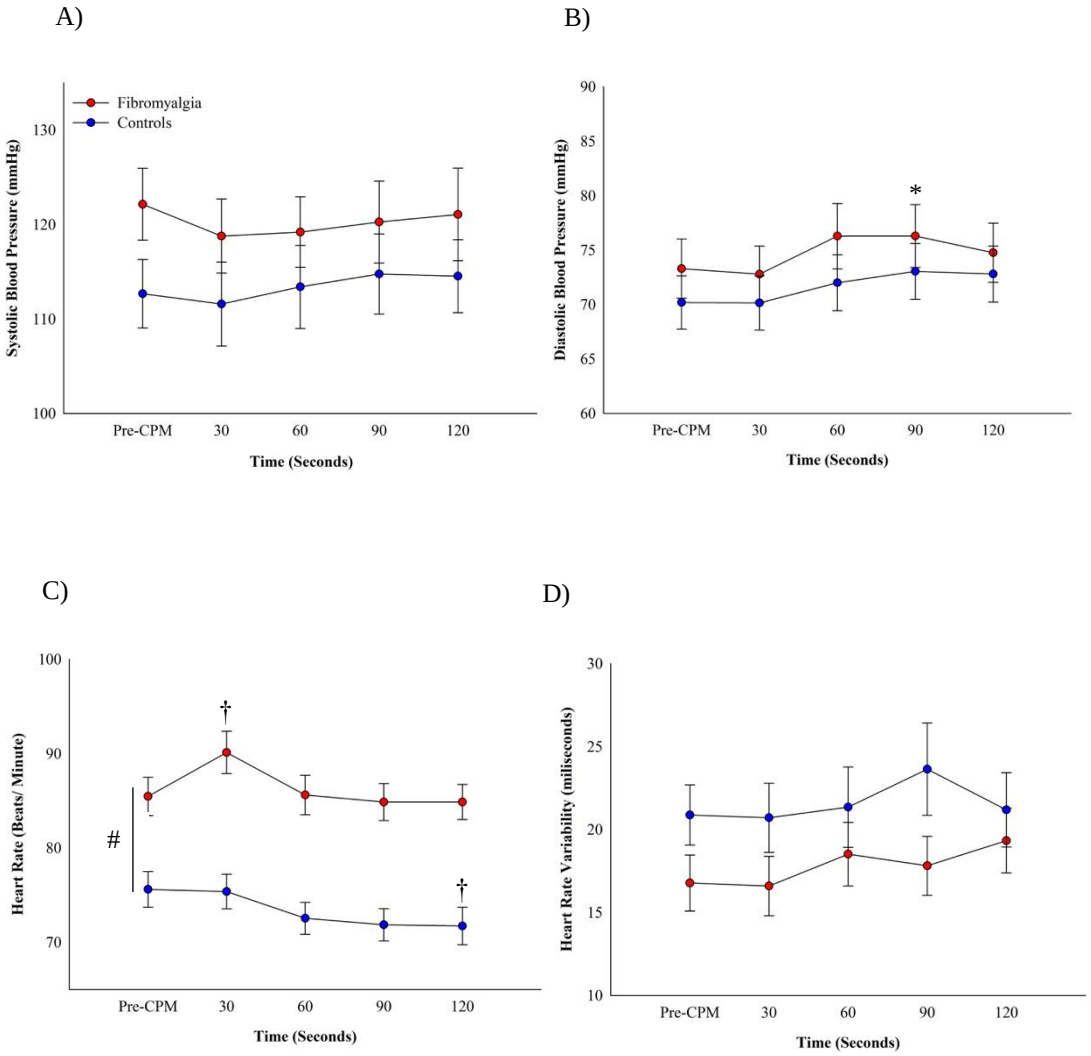

Figure 2.3: Cardiovascular response at rest (pre-CPM) and during CPM.
(#) indicates significant group differences at baseline (main effect of group). (*) indicates a significant change relative to baseline (main effect of time). (†) indicates significant differences between groups in the change relative to baseline (group x time). Diastolic blood pressure significantly increased at 90 seconds relative to baseline. In addition, only people with FM had an increase in heart rate in the first 30 seconds of foot immersion in the cold water bath, and only controls had a reduction in heart rate at the end. Data are presented as mean ±SEM.

Temporal Summation of Pain

Nineteen participants with FM and 18 pain-free individuals underwent TS protocol. The individualized temperature was not significantly different between the groups (FM: 47.1 ±3.8; controls: 49.1 ± 1.9; p= .11). Seven participants with FM and 11 controls reported pain lower than pain60 during the individualization protocol; the

highest temperature (50 °C) was utilized with those participants for the TS protocol. The individualized temperature was positively correlated with the magnitude of TS (r_s= .45, p<0.01), indicating that those who were less sensitive to heat (higher temperature at pain60) experienced greater TS. Pain increased during the TS protocol [main effect of time, (F (1.6, 54.2) = 4.3, P= .03, η_p^2 = .11), with no group differences (F (1.6, 54. 2) = .2, P= .75, η_p^2 = .01) after controlling for individualized temperature (Figure 2.4). Situational PCS completed after the TS protocol was not different between groups (FM: 5.1 ±5.4; controls: 3.1 ±4.6; p= .09).

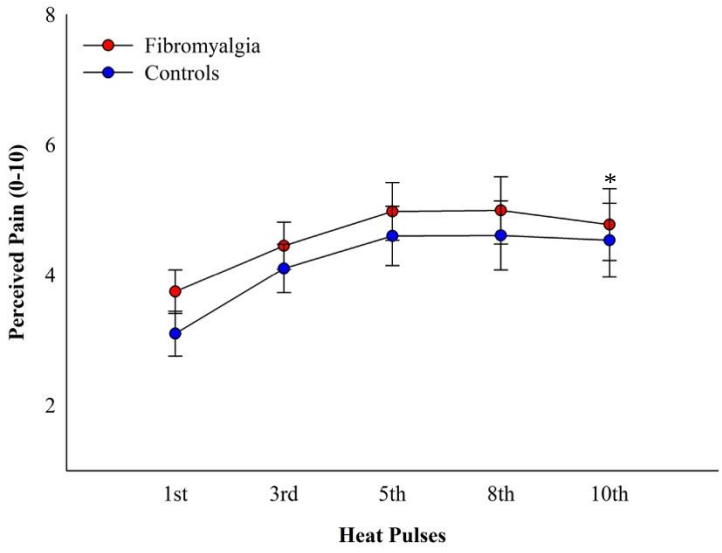

Figure 2.4: The change in pain rating during the temporal summation protocol.
(*) indicates significant increase in pain over time (temporal summation of pain). The data are presented as mean ±SEM. Both groups experienced similar temporal summation of pain.

Cardiovascular Assessment at Rest and During Temporal Summation of Pain

The blood pressure signal was lost during TS for two participants with FM due to excessive left hand movement. During TS, there was significant increase in heart rate [main effect of time, (F (1, 35) = 6.1, P= .02, η_p^2 = .15)], systolic blood pressure [main effect of time, systolic pressure (F (1, 33) = 11.1, P< .01, η_p^2 = .25)] and

diastolic pressure [main effect of time, (F (1, 33) = 26, P< 0.01, η_p^2 = .44)] with no group differences. HRV did not change during TS (Figure 2.5).

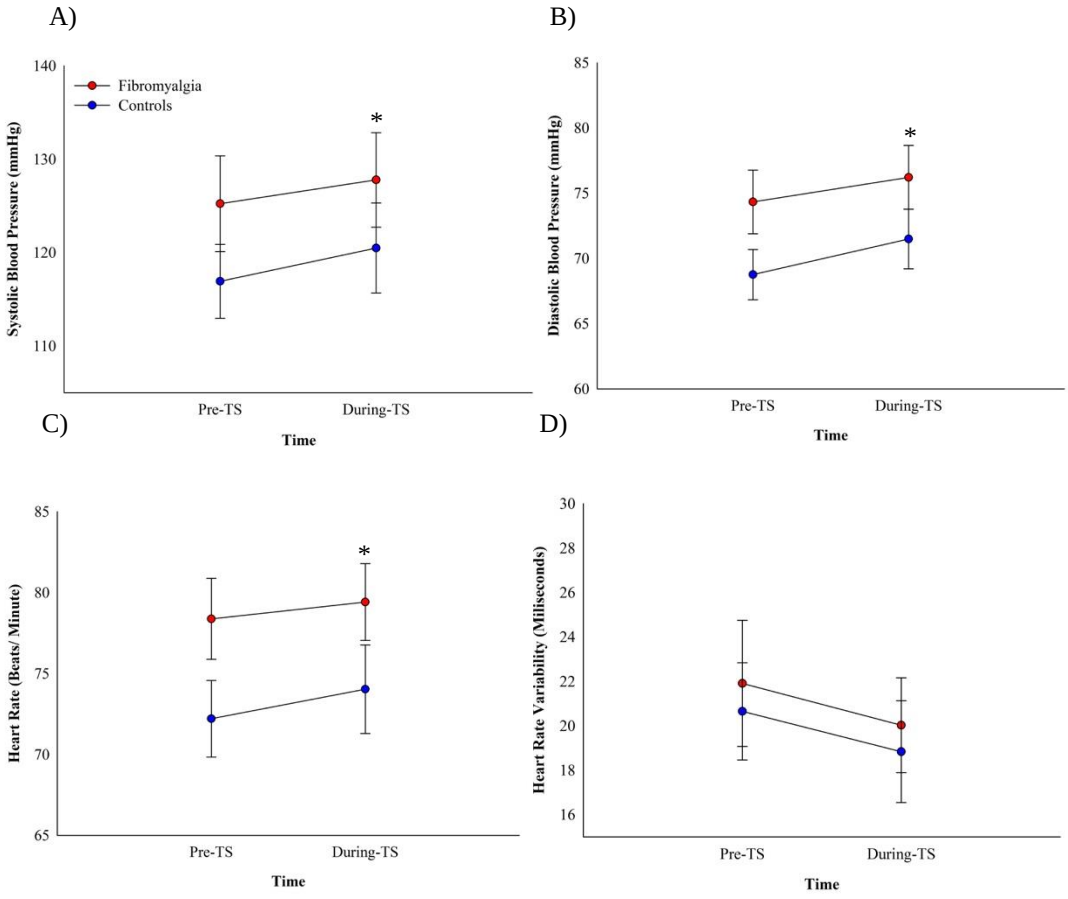

Figure 2.5: Cardiovascular response at rest (pre-TS) and during TS.
(*) indicates significant difference from baseline. Data are presented as mean ±SEM. Both groups had similar increase in systolic, diastolic blood pressure, and heart rate. Heart rate variability did not significantly change during TS.

Relation Between CPM and TS With Autonomic Function

Among the FM group, greater CPM at the forearm was associated with lower Valsalva recovery time (greater sympathetic function) (r_s = - .53, p= .02) (Table 3). Therefore, greater sympathetic function at baseline among people with FM was associated with greater CPM at the forearm, which was the only site they experienced CPM.

Among controls, there were no significant associations between autonomic function and CPM.

In regard to TS of pain, no significant correlations were noted with any autonomic outcome in people with FM. Among controls, greater TS was associated with greater increase in diastolic blood pressure ($r_{partial=}$ .65, $p< .01$), and a trend towards greater increase in systolic blood pressure ($r_{partial=}$ .59, $p= .012$).

The associations between CPM and TS with other baseline outcomes such as age, physical activity, and body composition were assessed. No significant correlations were noted.

Table 2.3: Correlations Between Conditioned Pain Modulation and Baseline Autonomic Outcomes Among People With FM.

	1. Deep Breathing Test	2. Valsalva Recovery Time	3. Pre-CPM HRV	4. COMPASS 31	5. CPM at Forearm
1. Deep Breathing Test					
2. Valsalva Recovery Time	-.26				
3. Pre-CPM HRV	.36	-.06			
4. COMPASS 31	.09	.16	.16		
5. CPM at Forearm	.01	**- .53***	.40	.18	
6. CPM at Quadriceps	-.13	-.22	.37	.13	**.72****

COMPASS 31= composite autonomic symptoms score; *CPM*= conditioned pain modulation; *HRV*= heart rate variability. * $p < 0.05$, ** $p < 0.01$

Discussion

The main aim of the study was to investigate the relation between baseline cardiovascular autonomic function and endogenous pain modulation measured by CPM and TS in people with and without FM. Our study was unique in that the people with FM and control participants were of similar age, sex, BMI, and physical activity. The major findings of the study were: 1) people with FM had lower sympathetic function and greater autonomic symptoms but comparable parasympathetic function and cardiac autonomic balance at baseline, 2) people with and without FM had similar TS and CPM at the forearm, but only people without FM reported CPM at the quadriceps muscle, 3) higher sympathetic function was associated with greater CPM at the forearm in people with FM. These findings suggest that modulation of autonomic function and particularly sympathetic function is related to central pain inhibition.

Participant Characteristics and Baseline Autonomic Function

On average, participants in this study were middle-aged, overweight, and physically active individuals. People with and without FM had similar deep breathing test scores and HRV which indicates similar cardiovascular parasympathetic function and cardiac autonomic balance. However, people with FM had longer Valsalva recovery time indicating a reduced cardiovascular sympathetic function compared to controls. Despite reduced sympathetic function in people with FM, the average score was within normal ranges (Huang et al., 2007; Lee et al., 2017). Our results are consistent with the study of Vincent et al., 2016 that showed people with FM have reduced cardiovascular sympathetic function but similar cardiovascular parasympathetic function compared to control participants that were matched by BMI and physical activity (Vincent et al., 2016). In addition, people with FM had greater

autonomic symptoms (COMPASS 31) which was consistent with previous research (Solano et al., 2009; Vincent et al., 2016). The reduction in autonomic function involved other non-cardiovascular domains including gastrointestinal function, bladder function and pupillomotor. Therefore, people with FM had reduced cardiovascular sympathetic function and greater autonomic symptoms compared to control participants.

Conditioned Pain Modulation in People With and Without FM

Both groups reported CPM at the forearm which had similar magnitude. Only controls experienced CPM at the quadriceps. Although CPM is a systemic phenomenon and in some research studies it is assessed at one site, a number of studies have suggested that CPM magnitude may vary by site (Gajsar et al., 2018; Oono et al., 2011). Gajsar et al. 2018 showed that healthy individuals experienced CPM in two out of the three sites that were assessed (Gajsar et al., 2018). Moreover, in an animal model of pain, greater diffuse noxious inhibitory control occurred on the inflamed side compared to the contralateral side (de Resende et al., 2011). One explanation for CPM variability between sites among people with FM is related to differences in baseline pain sensitivity. People with FM had similar pain threshold at the quadriceps compared with control participants, and only the control participants reported CPM at the quadriceps. In contrast, people with FM reported lower pain threshold at the forearm compared to the controls, but both groups reported CPM at the forearm. Thus, CPM only occurred at the site of greater pain sensitivity (i.e., forearm) compared with control participants. Future studies particularly those investigating CPM in people with FM should assess CPM in more than one site.

Valsalva Recover Time and Conditioned Pain Modulation

Among people with FM, reduced sympathetic function (i.e., longer Valsalva recovery time) was related to lower CPM at the forearm but not the quadriceps. Previous studies have suggested a relation between CPM and sympathetic nervous system mediated by noradrenergic mechanisms. In an animal study by Bannister et al., 2015, DNIC was significantly reduced by $\alpha 2$ adrenergic receptors antagonist in the spinal cord and can be restored by a norepinephrine reuptake inhibitor in the spinal cord (Bannister et al., 2015). In humans, Parent et al., 2015 found a positive association between norepinephrine levels and CPM in people with chronic pain (Parent et al., 2015).

The lack of association with the quadriceps was not surprising given the lack of CPM at this site. One potential reason for the lack of CPM at the quadriceps could be due to differences in the sympathetic response between the upper and lower extremity during the cold water bath. For example, Jacob et al. 2000 found that vascular resistance increased in the arm and decreased in the leg during the cold pressor test on the hand (Jacob et al., 2000). Therefore, people with FM already had lower sympathetic function and the lack of CPM at the quadriceps could be due to difference in sympathetic responses in the extremities; there may have been less sympathetic response in the lower extremities than the upper extremities resulting in no CPM in the lower extremity (quadriceps). Furthermore, the lower sympathetic function in people with FM that was within normal ranges may explain why people with FM had some degrees of CPM (i.e., CPM at one site).

Future mechanistic studies may investigate the variability in sympathetic responses during CPM by assessing muscle sympathetic nerve activity in the upper and lower limbs. Furthermore, among controls, there was no relation between CPM

and baseline sympathetic function which could be explained by the lack of heterogeneity in CPM and baseline cardiovascular sympathetic function in this cohort of control participants which mainly consisted of middle-aged women.

Blood Pressure and Conditioned Pain Modulation

Although people with FM had lower sympathetic function at baseline, the change in blood pressure during the cold water bath was similar between the groups. There was only a significant increase in diastolic blood while systolic blood pressure did not change. The minimal changes in blood pressure may be explained by certain factors. First, the temperature of the cold water bath that was used in this study was 6˚C ± 1˚C which is higher than the temperature that is typically used in a cold pressor task (0 – 3 ˚C). The temperature in our study was selected because the recommendation for CPM protocol suggests the use of a temperature equal to or below 12˚C and to improve tolerance to the cold water bath (Kennedy et al., 2016). Even with this higher temperature, one participant with FM removed her foot secondary to pain. Another factor is that the sample consisted of mainly women (89%); studies in cold pressor test show that women can have similar muscle sympathetic nerve activity as men but have up to 55% less increase in mean arterial pressure (Miller et al., 2019; Stone et al., 2019). This can be explained by the fact that some women experience vasodilatation during the cold pressor test that limits the increase in the blood pressure even though they have similar muscle sympathetic nerve activity levels during the cold pressor test as men (Miller et al., 2019). Therefore, the change in blood pressure during the cold water bath in women may not reflect the sympathetic changes. Lastly, the assessment of PPTs during the cold water may have affected the change in blood pressure given that participants were focusing on reporting pain threshold. Distraction during painful stimulus is associated with less

increase in blood pressure (Furman et al., 2009). Moreover, despite no change in systolic blood pressure, one important finding in our study is that both groups had CPM. This finding may suggest that the magnitude of CPM is not dependent on changes in systolic blood pressure as suggested by previous studies (Chalaye et al., 2013; Chalaye et al., 2014).

Autonomic Function and Temporal Summation

The TS protocol in this study involved using an individualized temperature which was the temperature that resulted in a pain rating of 6 out of 10 (i.e., known as pain60) (Granot et al., 2006). Many control participants (61%) and people with FM (37%) did not report pain60 during the individualization task, and the highest temperature (50 °C) was used with those participants during the TS protocol. During TS protocol, both groups experienced an increase in pain ratings with repetitive pulses of heat indicating the summation of pain. The magnitude of TS was similar between people with and without FM. There are several potential explanations for this unexpected finding. One explanation is the use of heat stimuli for the TS protocol. While heat is a commonly used stimulus in assessing TS, a recent meta-analytic study showed that people with FM have higher TS when using mechanical stimuli compared to thermal stimuli (O'Brien et al., 2018). The second explanation is the use of individualized temperature for the TS protocol. Potvin et al. 2012 used an individualized heat protocol and showed no difference in TS between people with and without FM (Potvin et al., 2012). Staud et al., 2014 used different temperatures (44 ˚C, 46 ˚C, and 48 ˚C) and found that people with FM experienced greater increase in TS as the temperature increases compared to controls (Staud et al., 2014). The third explanation is that both groups had similar regional lean mass and physical activity.

These factors have been shown to predict the magnitude of TS when using an individualized protocol (Awali et al., 2018; Naugle & Riley, 2014).

Baseline cardiovascular autonomic function did not correlate with TS, and both groups had similar increase in heart rate, systolic and diastolic blood pressure during the TS protocol. Among control participants, the TS was associated with greater increase in diastolic blood pressure and a trend towards greater increase in systolic blood pressure. This finding is consistent with previous research that showed that blood pressure reactivity is associated with the increase in pain ratings during experimental pain (Peckerman et al., 1991). Therefore, TS is not associated with baseline cardiovascular autonomic function, however it is associated with blood pressure reactivity in control participants only.

Clinical Implications

There are several clinical implications regarding the results of our study. First, CPM is used in clinical practice and in research to evaluate the severity of central sensitization in people with chronic pain. Our results suggest that CPM should be assessed in more than one body site to better evaluate descending pain inhibition. Second, our results that baseline sympathetic function was correlated with CPM may help explain why medications that increase the levels of norepinephrine can improve CPM in people with chronic pain including duloxetine and tapentadol (Niesters et al., 2014; Yarnitsky et al., 2012). Yarnitsky et al., 2012 showed that duloxetine, serotonin and norepinephrine reuptake inhibitor, improved CPM only in individuals with reduced baseline CPM among people with painful neuropathic neuropathy (Yarnitsky et al., 2012). Third, our results suggest that interventions that increase sympathetic function may improve CPM in people with reduced sympathetic function such as FM. One of the interventions that improve sympathetic function is handgrip exercise

training. Saito et al., 2009 showed that handgrip exercise training has been shown to increase muscle sympathetic responsiveness to a fatiguing handgrip exercise (Saito et al., 2009). Thus, exercise training may improve CPM in people with reduced CPM. It is important to note that when these interventions are administered, they should be carefully monitored as excessive increase in sympathetic function may lead to cardiovascular diseases such as hypertension. For example, the use of duloxetine can cause hypertension in some people with FM (Smith et al., 2010). Further research is needed to study the efficacy of the interventions that increase sympathetic function on CPM in people with FM.

Conclusion

In conclusion, people with FM had reduced cardiovascular sympathetic function that was within normal ranges and greater autonomic symptoms measured by COMPASS 31 compared to control participants. Importantly, these group differences in autonomic function at baseline occurred despite the groups having similar age, sex, BMI and physical activity levels. Furthermore, both groups experienced similar TS and CPM at the forearm while only people without FM reported CPM at the quadriceps muscle. Baseline cardiovascular sympathetic function was associated with CPM at the forearm in people with FM. Lastly, baseline cardiovascular autonomic function did not explain the variability in TS when using an individualized TS of heat pain.

CHAPTER THREE

THE RELATION BETWEEN AUTONOMIC FUNCTION AND PAIN MODULATION FOLLOWING EXERCISE AND COGNITIVE TASK IN PEOPLE WITH FIBROMYALGIA

Introduction

Fibromyalgia (FM) is a chronic pain condition that affects 2-8 % of the population and includes symptoms such as widespread pain, fatigue, anxiety, depression, sleep difficulties and others (Clauw, 2014; Queiroz, 2013; Schaefer et al., 2011). FM is a condition that is difficult to treat, and it has been reported that the majority of people of FM take two or more medications for their symptoms (Knight et al., 2013; Skaer, 2014). Exercise training is one of the most recommended interventions for the treatment of FM since it has been shown to decrease pain, fatigue, sleep difficulties and improve the quality of life (Bidonde et al., 2017; Burckhardt et al., 2005; Busch et al., 2013).

Although exercise is strongly recommended by a number of FM treatment guidelines (Macfarlane et al., 2017), some people with FM report an increase in pain and worsening symptoms following acute exercise while others experience pain relief [exercise-induced hypoalgesia (EIH)] (Daenen et al., 2015; Hoeger Bement et al., 2011; Naugle et al., 2012; Nijs et al., 2012). Why some people with FM report hyperalgesia while others report hypoalgesia following acute exercise is not known. Understating the factors and the mechanisms that contribute to the pain variability in people with FM may result in better exercise prescription and consequently more adherence to exercise training.

Similar to the exercise response, some people with FM often experience an increase in pain following a cognitive task (Coppieters et al., 2016; Crettaz et al.,

2013). The reduction in pain sensitivity following cognitive stress is known as stress-induced hypoalgesia (SIH). Both exercise and cognitive task are forms of stress, and the increase of pain following these tasks could indicate that people with FM have a general abnormal stress response to physical and cognitive stressors, respectively (Crettaz et al., 2013; Daenen et al., 2015). Furthermore, some researchers have proposed that the variability in the pain response following exercise could be explained by an abnormal stress response or autonomic dysfunction (Daenen et al., 2015; Nijs et al., 2012). There is evidence that people with FM have reduced autonomic reactivity in response to exercise and cognitive task (Giske et al., 2008; Kadetoff & Kosek, 2010; Nilsen et al., 2007; Reyes Del Paso et al., 2010). However, these findings are not consistent in the literature and have not been studied in relation to EIH and SIH in people with FM (Kadetoff & Kosek, 2007, 2010). Understanding how stress and autonomic function contribute to the pain response following exercise and cognitive task is essential to better understand the factors that explain symptoms exacerbation in response to physical and cognitive stress.

The aim of this study was to investigate the relation between cardiovascular autonomic function and endogenous pain modulation following physical and cognitive tasks (submaximal isometric exercise and mental math, respectively) in participants with FM and age- and sex-matched pain-free participants. The hypotheses of this study include: 1) perceived stress and cardiovascular response would increase during both isometric exercise and mental math for both groups, 2) people with FM would have altered cardiovascular autonomic response at baseline and during isometric exercise and mental math task compared to controls, 3) people with altered cardiovascular autonomic function would report an increase of pain following exercise and mental math, which would be comparable between the two tasks.

Methods

This study was part of a larger study investigating the relation between autonomic function and pain modulation in people with and without FM. Twenty people with FM (2 men) and 18 age- and sex-matched pain-free individuals (2 men) participated in the study. All participants were initially screened for the following exclusion criteria: cardiovascular disease, pulmonary disease except controlled asthma, autonomic disease, cancer, diabetes, neurological disorder, cancer, pulmonary disease, recent surgery, psychiatric conditions, or taking medications that directly affect autonomic nervous system. Additionally, people without FM had no current acute or chronic pain. The study was reviewed and approved the institutional review committee at Marquette University.

Research Design

Participants completed an autonomic function assessment session (first session) and two randomized sessions (exercise and mental math task) (Figure 3.1). At the beginning of the first session, participant signed the consent form and completed composite autonomic symptoms score 31 (COMPASS 31). Then, cardiovascular data were collected for 10 minutes which was used for HRV analysis. Next, participants performed two autonomic tests (deep breathing test and Valsalva maneuver). Lastly, participants were familiarized to the pressure pain threshold (PPT) assessment and performed six-minute walk test.

At the beginning of the exercise session, all participants completed the short-form McGill pain questionnaire (SF-MPQ), and people with FM completed the revised fibromyalgia impact questionnaire (FIQR). Then, maximal voluntary isometric contraction (MVIC) was assessed followed by 45 minutes of quiet rest (washout period) to eliminate the effect of MVIC on EIH. The exercise consisted of

the performance of submaximal isometric exercise at 30% of MVIC for four minutes (Naugle et al., 2014; Naugle, Naugle, et al., 2016); this duration matched the mental math task. Electrocardiogram (ECG) and beat-to-beat blood pressure were recorded before and during the exercise while PPTs were assessed before and after exercise. Participants were asked to rate their pain intensity, ratings of perceived exertion (RPE), and perceived stress before, at the middle, and at the end of the exercise. State anxiety questionnaire was completed before and after the exercise.

The mental math task session consisted of a similar protocol as the exercise session except, instead of the submaximal isometric exercise, participants performed mental math task that consisted of serial subtractions by 13 from a four-digit number as fast as possible for four minutes (Caceres & Burns, 1997; Hoeger Bement et al., 2010).

Some tasks in this study occurred in the second or third session regardless of whether it was exercise or mental task session. At the beginning of the second session, participants completed the international physical activity questionnaire (IPAQ) and body composition was assessed using dual-energy x-ray absorptiometry (DXA) at the end of the session. At the beginning of the third session, participants completed pain anxiety symptoms scale (PASS-20) and depression, anxiety, and stress scale (DASS-21).

Other tasks performed in the study that were part of a larger study included conditioned pain modulation (CPM) at the beginning of the second session and temporal summation of pain (TS) at the beginning of the third session. The 45-minute quiet rest was to minimize the effect of these tasks on EIH or SIH.

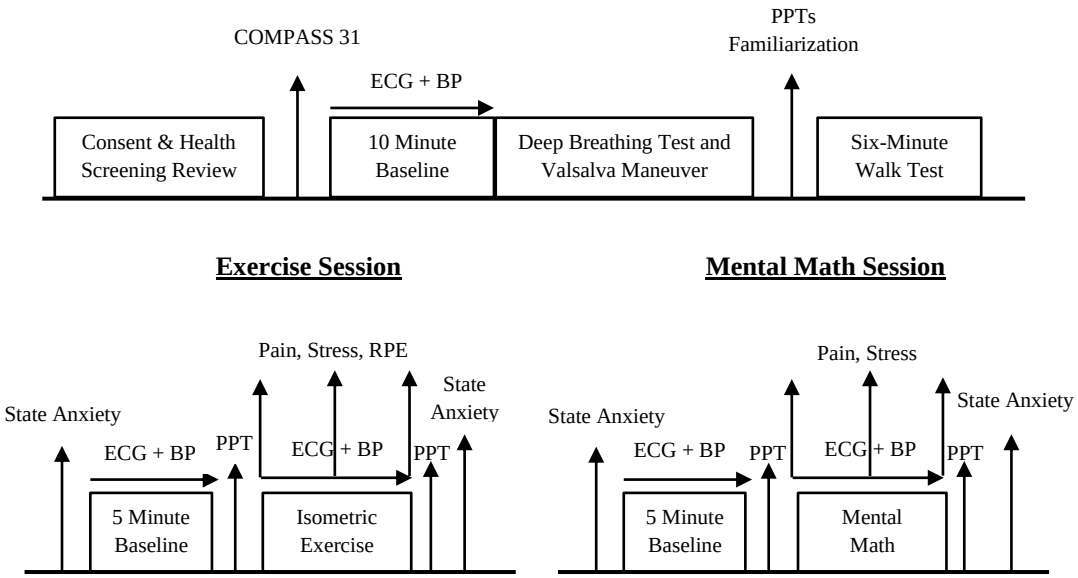

Figure 3.1: Protocol of the study.
Participants completed an autonomic function assessment session and two randomized sessions (exercise and mental math task). *COMPASS 31*= Composite autonomic symptom score 31; *ECG*= electrocardiogram, *BP*= blood pressure; *PPT*= pressure pain threshold; *RPE*= ratings of perceived exertion.

Isometric Handgrip Exercise

Isometric handgrip exercise was done with a hand dynamometer (Biopac, Goleta, California) while the participant was seated with the elbow flexed at around 90° and unsupported. Participants performed three MVIC with each lasting for 3 – 5 seconds and separated by one minute of rest. The highest MVIC value was used for the exercise. For the submaximal isometric exercise, participants were asked to match a target force (30% MVIC) displayed on a monitor for four minutes. Verbal encouragement was provided during the exercise. Participants were instructed to rate their pain using a numerical pain rating scale from 0 (no pain) to 10 (worst pain), to provide RPE from 0 (Nothing at all) to 10 (extremely strong), and to rate their

perceived stress from 0 (not stressed at all) to 10 (extremely stressed). All ratings were provided before, at the middle, and at the end of the exercise.

Mental Math Task

Mental math task, also known as serial subtraction test, is a commonly used method to induce stress in research (Caceres & Burns, 1997; Hoeger Bement et al., 2010). Participants performed serial subtractions by 13 from a four-digit number within 3 seconds for four minutes. In case of error or not providing an answer within 3 seconds, the participant was asked to start from the first number of the series. In case of 3 errors, participant was asked to start from a new four-digit number. In addition, participants were frequently asked to go faster and discouragement comments were provided regardless of the participant's performance (Hoeger Bement et al., 2010). Participants were asked to rate pain intensity and perceived stress at baseline, at the middle, and at the end of the task using the same scales as in the exercise task.

Pressure Pain Threshold

PPTs were evaluated using pressure algometer with a 1 cm^2 diameter rubber tip (Somedic, Sweden). Participants were instructed to say "pain" when they first felt the pain. The pressure was applied twice in a randomized order to right quadriceps (middle portion of the quadriceps) and right ventral forearm (proximal 1/4 the distance between cubital fossa and wrist joint) at a rate of 50 kPa/Sec. The average of the two trials at each site was used in statistical analysis. PPTs were assessed before and after isometric exercise and mental math task. EIH was calculated for each site (quadriceps and forearm) as [post-exercise PPT – pre-exercise PPT], and SIH was calculated as [post-mental math PPT – pre-mental math PPT].

Heart rate and Blood Pressure

ECG and beat-to-beat blood pressure data were collected before and during isometric exercise and mental math task. ECG data was collected using the Biopac ECG amplifier (ECG 100C) with a gain of 2000. The low pass filter and high pass filter were set at 35 Hz and 1 Hz, respectively. The ECG setup involved the application of three electrodes on the chest (right clavicle, left clavicle and left lower rib) using lead II configuration method. Beat-to-beat blood pressure data were collected using finger cuff sensors placed on the left hand and blood pressure monitor (NIBP100D, CNSystems, Austria) which was calibrated with every usage. The blood pressure amplifier (Biopac DA100C) setup included a gain of 1000 and low pass filter of 300 Hz. For all cardiovascular and autonomic assessment, Biopac MP150 (Biopac, Goleta, California) was utilized as the data acquisition system and sampling rate was 2000 samples/second. Participants were instructed to avoid moving the left arm or change positions to avoid causing artifacts in the blood pressure and/or ECG signals.

Cardiovascular Autonomic Function Tests

Heart rate variability (HRV), deep breathing test, and Valsalva were used to evaluate baseline cardiovascular autonomic function. HRV was used to evaluate cardiac autonomic control at rest and during exercise and mental math. Deep breathing assesses the parasympathetic function mediated by vagus nerve innervation to the heart. The Valsalva maneuver can assess cardiovascular sympathetic adrenergic function (Jones & Gibbons, 2015; Low, 2004; Low et al., 2013).

Heart Rate Variability

ECG data was used to calculate HRV using Kubios software. ECG data was collected in the first session at rest as well as before and during exercise and mental math in the second and third sessions. As part of the HRV analysis, a correction

algorithm was used to automatically detect and correct physiological artifacts such as missing or ectopic beats (Lipponen & Tarvainen, 2019). Root mean square of successive differences of R-R intervals (RMSSD) was used in the statistical analysis given that it is the common outcome used to represent HRV ("Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology," 1996).

Deep Breathing

In the first session, participants were instructed to perform a breathing task for 1 minute involving 5-second inhalation and 5-second exhalation (6 respiratory cycles/minute). All participants performed practice trials before performing the actual test. Respiration data were collected to identify peak inspiration and peak expiration using Biopac respiratory transducer (TSD 201) and Biopac respiratory amplifier (RSP 100). The main outcome of deep breathing test was calculated by first calculating the difference of heart rate at peak inspiration and peak expiration in every respiration cycle and averaging the scores of all respiratory cycles (Jones & Gibbons, 2015; Low, 2004; Low et al., 2013).

Valsalva Maneuver

In the first session, participants were instructed to perform forceful expiration by blowing into a syringe while maintaining the force of expiration at a pressure of 40 mmHg for 15 seconds. The syringe had a small leak to maintain open glottis and was connected to a pressure gauge which was placed in front of the participants for visual feedback. All participants performed practice trials before performing two Valsalva maneuvers. The results were rejected if the maneuver was performed for less than 10 seconds or at pressure less than 30 mmHg. Beat-to-beat blood pressure data was

collected during the maneuver. The main outcome for sympathetic cardiovascular function was Valsalva recovery time, which was the time it took for the systolic blood pressure to recover to baseline after the drop in blood pressure at the end of the maneuver (Jones & Gibbons, 2015; Low, 2004; Low et al., 2013; Vogel et al., 2005).

Composite Autonomic Symptom Score 31

This questionnaire consists of 31 items and it evaluates autonomic symptoms. The items of COMPASS 31 cover 6 domains which are orthostatic tolerance, secretomotor function, vasomotor function, bladder function, gastrointestinal function, and pupillomotor function. Total scores of the questionnaire ranges from 0-100 with higher scores indicating greater autonomic symptoms.

Revised Fibromyalgia Impact Questionnaire

The FIQR has three domains which assess symptoms, function, and overall impact of the FM. Higher scores indicate more severe symptoms (Bennett et al., 2009; Burckhardt et al., 1991).

Short Form McGill Pain Questionnaire

This is a questionnaire that evaluates different pain dimensions including sensory and affective pain (Melzack, 1987).

State-Anxiety Version of State-Trait Anxiety Inventory

The state-anxiety inventory consists of 20 questions to evaluate current anxiety levels (Spielberger et al., 1983).

Depression, Anxiety and Stress Scale

DASS-21 is a questionnaire that assesses symptoms of psychological distress via three main subscales: depression, anxiety and stress subscale. DASS-21 has been validated in chronic pain patients and non-clinical sample (Henry & Crawford, 2005;

Wood et al., 2010). In people with FM, DASS-21 is associated with the FIQR symptom severity (Alok et al., 2011).

Pain Anxiety Symptom Scale

PASS-20 is a 20-item scale that assesses pain-related fear or anxiety through four domains: cognitive anxiety, avoidance, fearful thinking, and physiological anxiety (McCracken & Dhingra, 2002). PASS-20 has been validated in patients with chronic pain and pain-free individuals (Abrams et al., 2007; Roelofs et al., 2004). High PASS-20 scores indicate greater pain-related anxiety. Low PASS-20 scores have been shown to correlate with greater pain tolerance in athletes (G.S. et al., 2018).

International Physical Activity Questionnaire

IPAQ assesses physical activity levels over the previous week. The questionnaire has different domains that assess physical activity performed in leisure time, transportation, work, or home-related physical activity such as gardening. The questionnaire is valid and reliable (Craig et al., 2003). The outcomes used in the study include moderate and vigorous physical activities. Greater time spent in moderate and vigorous physical activity is associated with greater baseline parasympathetic function (O'Brien et al., 2020) and greater HRV (Rennie et al., 2003).

Six-Minute Walk Test

Participants were instructed to walk as fast as they can for six minutes on a straight 30 meters walking course which its start and end points were marked with cones. After each minute, participants were informed of the time left and standardized encouragement were provided. Participants were asked at the beginning, middle, and end of the test to rate their pain and RPE. At the end of the six minutes, participants were asked to stop and the distance walked was measured (Laboratories, 2002).

Body Composition

Body composition was assessed using DXA and then analyzed by encore software (Lunar iDXA, GE Healthcare, Madison, Wisconsin). The main outcome used in the study was total fat percentage (%) because previous research has shown that higher fat percentage is associated with lower HRV (Millis et al., 2010).

Statistical Analysis

Statistical analysis was performed using SPSS (Version 25, IBM, Armonk, NY). For baseline group comparisons, Independent *t* test or Mann-Whitney *U* test was used based on normality results. Data in text and tables are presented as mean ± standard deviation (SD), and in figures as mean ± standard error of the mean (SEM). The p-value was set at $p \leq 0.05$ for analyses related the main aim and hypothesis. For other analyses, the p-value was set at $p < 0.01$ (Field, 2013).

To evaluate the change in PPTs following exercise and mental math, separate repeated measure analysis of variance (RM ANOVA) models were conducted for each session with trial (pre and post) and site (forearm and quadriceps) as within-group variables, and group (FM and controls) as a between-group variable.

To evaluate the change in pain, RPE and stress during exercise and mental math session, separate RM ANOVA models were conducted for each session and for each variable with time (baseline, 2nd minute, and end) as within-group variable and group (FM and controls) as a between-group variable.

Similarly, to assess the change in state anxiety following isometric exercise and mental math task, separate RM ANOVA models were conducted for each session with time (pre and post) as within-group variable and group (FM and controls) as a between-group variable.

Cardiovascular outcomes during exercise and mental math task were analyzed using 1-minute windows in the second minute and the last minute in addition to baseline. These time points were selected to match pain, RPE and stress analysis. Separate RM ANOVA models for each session and for each cardiovascular variable were conducted with time (baseline, 2nd minute, and end) as within-group variable and group (FM and controls) as a between-group variable.

Because the differences in the change of PPTs between people with and without FM only existed following isometric exercise, additional RM ANOVA models were conducted for pain, stress, state anxiety and cardiovascular outcomes in order to investigate the differences in the change with isometric exercise and mental math task. These RM ANOVA models had session (exercise and mental math task) and time as within-group variables and group as between-group variable.

For all RM ANOV analyses, follow-up group comparisons were conducted by using Independent *t* test or Mann-Whitney *U* test. Paired t test or Wilcoxon test was used to determine if the change within-group was significant.

Pearson or spearman rank correlation was done to determine the association between the change of PPTs following exercise and mental math task with autonomic outcomes or other baseline measures. The correlations were performed for the entire sample and for each group separately. Furthermore, because there were no site-specific differences in EIH or SIH, we reported correlations for average EIH and average SIH. Average EIH was calculated as [(EIH at forearm + EIH at quadriceps)/2] and average SIH was calculated as [(SIH at forearm + SIH at quadriceps)/2].

Sample Size Analysis

The power analysis for determining sample size was performed using G*power 3.1. The effect size was taken from studies that showed an association between the change of autonomic function and pain during exercise and mental math, and studies that showed differences between people with and without FM following exercise and mental math (Kingsley et al., 2009; Oosterwijck et al., 2017; Reyes Del Paso et al., 2010). The sample size needed was 16 participants per group for 80% power at $\alpha = 0.05$.

Results

The data of one participant with FM was excluded from the analysis because the participant dropped out after the first session and did not perform the main tasks of the study (i.e., isometric exercise and mental math task). In addition, because FIQR, SF-MPQ, MVIC were similar in the two sessions, we reported the data of the exercise session in table 1.

The characteristics of the groups are reported in Table 1. Participants in both groups were middle-aged women except two men in each group. Both groups were physically active and exceeded the minimum requirement for moderate and vigorous physical activity which is 600 met-minute/week (WHO, 2010). Body fat percentage was similar between the groups, and both groups were overweight based on body mass index. People with FM had greater pain levels measured by SF-MPQ, greater pain-related anxiety measured by PASS-20, and greater depression, anxiety, and stress measured by DASS-21. The scores of PASS-20 and DASS-21 exceeded the clinical cutoffs, 30 and 33, respectively. Participants with FM had a lower handgrip strength. During the six-minute walk test, people with FM had greater increase in pain and walked shorter distance, but reported similar change in RPE as controls.

For baseline cardiovascular autonomic function, people with FM had greater Valsalva recovery time, indicating lower sympathetic function, but had similar deep breathing scores and HRV as controls. People with FM also had greater autonomic symptoms measured by COMPASS 31.

Table 3.1: Baseline Differences Between People With Fibromyalgia and Controls

		FM (n= 19) Mean ±SD	Controls (n= 18) Mean ± SD	p-value
Sex (Men)		2	2	
Age (years)		49.8 ±11.4	49.4 ±11.9	.92
SF-MQP		**11.9 ±10.3****	.33 ±1	< .01
FIQR		41.3 ±21.2	-	
DASS-21				
	Depression	**10.6 ±8.9****	1.3 ±2.7	< .01
	Anxiety	**10.2 ±10.2****	1.1 ±2.4	< .01
	Stress	**16.8 ±8.8****	4.6 ±6.6	< .01
	Total Score	**37.7 ±24.8****	7 ±10.4	
PASS-20		**36.7 ±21.6****	16.6 ±14.8	< .01
Cardiovascular Autonomic Function				
	Deep Breathing Test (beats)	13.1 ±5.6	10.5 ±5	.13
	Valsalva Recovery Time (sec)	**2.8 ±2.4****	1.3 ±1.2	< .01
	Heart Rate Variability RMSSD (ms)	23.2 ±13.2	26.5 ±15.3	.69
Self-report Autonomic Function (COMPASS 31)		**31.6 ± 15.2****	5.5 ± 5.2	< .01
Body Composition				
	Total Fat Percentage (%)	39.7 ±10.7	34.3 ±9.3	.11
MVIC (kg)		**21.3 ±8.5****	28.4 ±6.2	< .01
Physical Activity and Fitness				
a) IPAQ	Moderate Physical Activity (met-minute/week)	3542.4 ±4864.2	2023.1 ±2016	.34
	Vigorous Physical Activity (met-minute/week)	3821.1 ±5825.8	1180 ±1398.4	.50
b) Six-Minute Walk Test				
	Pain Change Relative to Baseline (0-10)	**2.8 ±2.2****	.8 ±.9	< .01
	RPE Change Relative to Baseline (0-10)	4.1 ±1.5	4.6 ±2.6	.51
	Distance Covered (m)	**539.4 ±81.7****	624.5 ±61.3	< .01

SF-MPQ= short-form McGill pain questionnaire; *FIQR*= revised fibromyalgia impact questionnaire; *DASS-21*= depression, anxiety, and stress scale 21, *PASS-20*= pain anxiety symptom scale, *Sec*= Second; *RMSSD*= root mean square of successive RR interval differences; *ms*= millisecond, *kg*= kilogram, *COMPASS 31*= composite autonomic symptoms score 31; *MVPA*= moderate to vigorous physical activity; *RPE*= rating of perceived exertion; *m*= meter. Data are presented as mean ± SD. * p <0.05, ** p < 0.01.

Pressure Pain Thresholds Changes Following Isometric Exercise and Mental Math

One participant with FM did not perform the exercise task. Exercise duration was similar between the groups (FM: 3.8 minutes ± .5; controls: 3.8 minutes ± 0.6; p= .99). Three participants in each group did not complete the entire four minutes of exercise due to inability to maintain contraction at the target force due to fatigue and/or pain. Before exercise, people with FM had lower PPT at the forearm (FM: 241.8 ±126; controls: 327.3 ±112.2; p= .04) and trended to have lower PPT at the quadriceps (FM: 324 ±174.8; controls: 417.3 ±121.5; p= .07). Following exercise, there were group differences in the change of PPTs [trial x group interaction (F (1, 34) = 5.1, P= .03, η_{ϱ}^2= .13)] (Figure 3.2A). Only control participants reported an increase in PPTs following exercise (p< .01) that was similar across the sites [trial x group x site interaction (F (1, 34) = .30, P= .59, η_{ϱ}^2= .01)]. Participants with FM had no change in PPTs (p= .995), however, there was variability in the change of PPTs with nine participants experiencing an increase (i.e., EIH) and nine participants experiencing a decrease in PPTs (hyperalgesia) (Figure 3.5).

Before mental math, people with FM had lower PPT at the forearm (FM: 223 ±118.1; controls: 322.6 ±103.3; p= .01) and lower PPT at the quadriceps (FM: 293.1 ±141.6; controls: 417.6 ±142; p= .01). Following mental math, there was no change in PPTs [main effect of trial, (F (1, 35) = 3.1, P= .09, η_{ϱ}^2= .08)] for both groups [trial x group interaction (F (1, 35) = .2, P= .67, η_{ϱ}^2= .01)] (Figure 3.2B). The no change in PPTs could be caused by the variability in PPTs changes in both groups. Twelve control participants and ten participants with FM had an increase in PPTs (SIH) while six control participants and nine participants with FM had a decrease in PPTs (hyperalgesia).

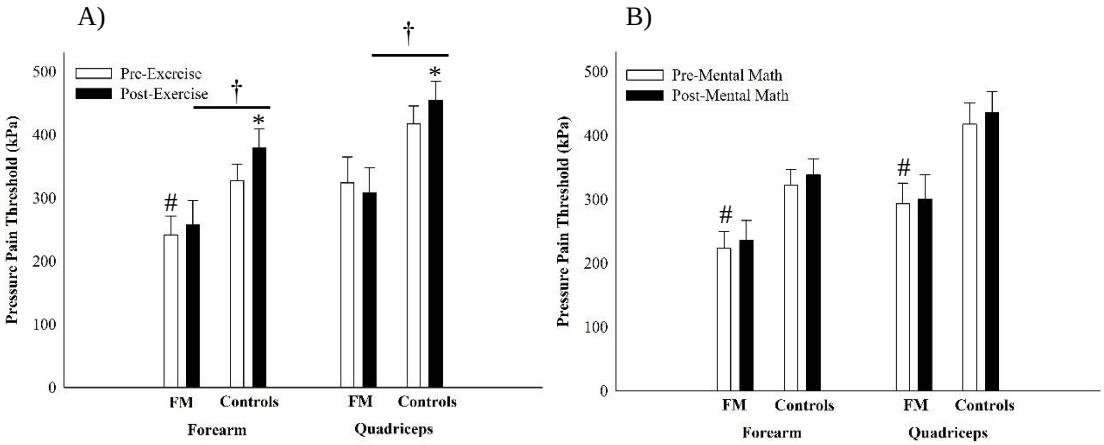

Figure 3.2: The change of PPTs following: A) isometric exercise and B) mental math task.
(#) indicates group differences at baseline. (*) indicates significant increase in PPTs following exercise (EIH). (†) indicates significant group differences in the change of PPTs. Only controls experienced increase in PPTs (EIH) at both sites following exercise. Following mental math, there was no change in PPTs for both groups.

Cardiovascular Changes During Isometric Exercise and Mental Math

Mean Arterial Pressure

The blood pressure data collected during exercise for one participant with FM was excluded from statistical analysis due to excessive arm movement. During exercise, there was a significant group difference in the change of mean arterial pressure [trial x group interaction, ($F(1.7, 54.3)= 4.2$, $p= .03$, $\eta_p^2 = .11$)]. Post hoc showed that controls had greater increase in mean arterial pressure at the end of exercise compared to people with FM ($p= .02$) (Figure 3.3A).

During mental math, there was a significant increase in mean arterial pressure [main effect of time, ($F(1.2, 42.7)= 23.7$, $p< .01$, $\eta_p^2 = .40$)] with no group differences (Figure 3.3A). When the exercise and mental math were compared, there were differences in the magnitude of increase of mean arterial pressure [session x time

interaction, ($F(2, 66)= 21.5$, $p< .01$, $\eta_p^2 = .39$)] with post hoc showing that the increase was greater at the end of exercise compared to mental math ($p< .01$).

Heart Rate

Before exercise, people with FM had higher heart rate compared to control participants (FM: 76.3 ±10.1; controls: 69.3 ±8; $p= .03$). Exercise led to significant increase in heart rate [main effect of time, ($F(1.4, 48.4)= 47.4$, $p< .01$, $\eta_p^2 = .58$)] with no group differences (Figure 3.3B).

Before mental math, people with FM had higher heart rate (FM: 73.8 ±9; controls: 66 ±8.9; $p= .01$). Mental math led to an increase in heart rate [main effect of time, ($F(1.4, 49.7)= 33$, $p< .01$, $\eta_p^2 = .49$)] with no group differences. When isometric exercise and mental math were compared, there was a significant difference in the change of heart rate between the tasks [session x time interaction, ($F(1.6, 54.2)= 17.2$, $p< .01$, $\eta_p^2 = .34$)]. Post hoc showed a greater increase in heart rate at the end of exercise compared to mental math task ($p< .01$).

Heart Rate Variability

The change of HRV was different between people with and without FM during exercise [trial x group interaction, ($F(2, 33)= 4.1$, $p= .025$, $\eta_p^2 = .20$)]. Post hoc showed that only controls had a significant reduction in HRV ($p= .01$) (Figure 3.3C). During mental math, HRV did not change. When isometric and mental math task were compared, there was no significant difference in the change in HRV between the tasks.

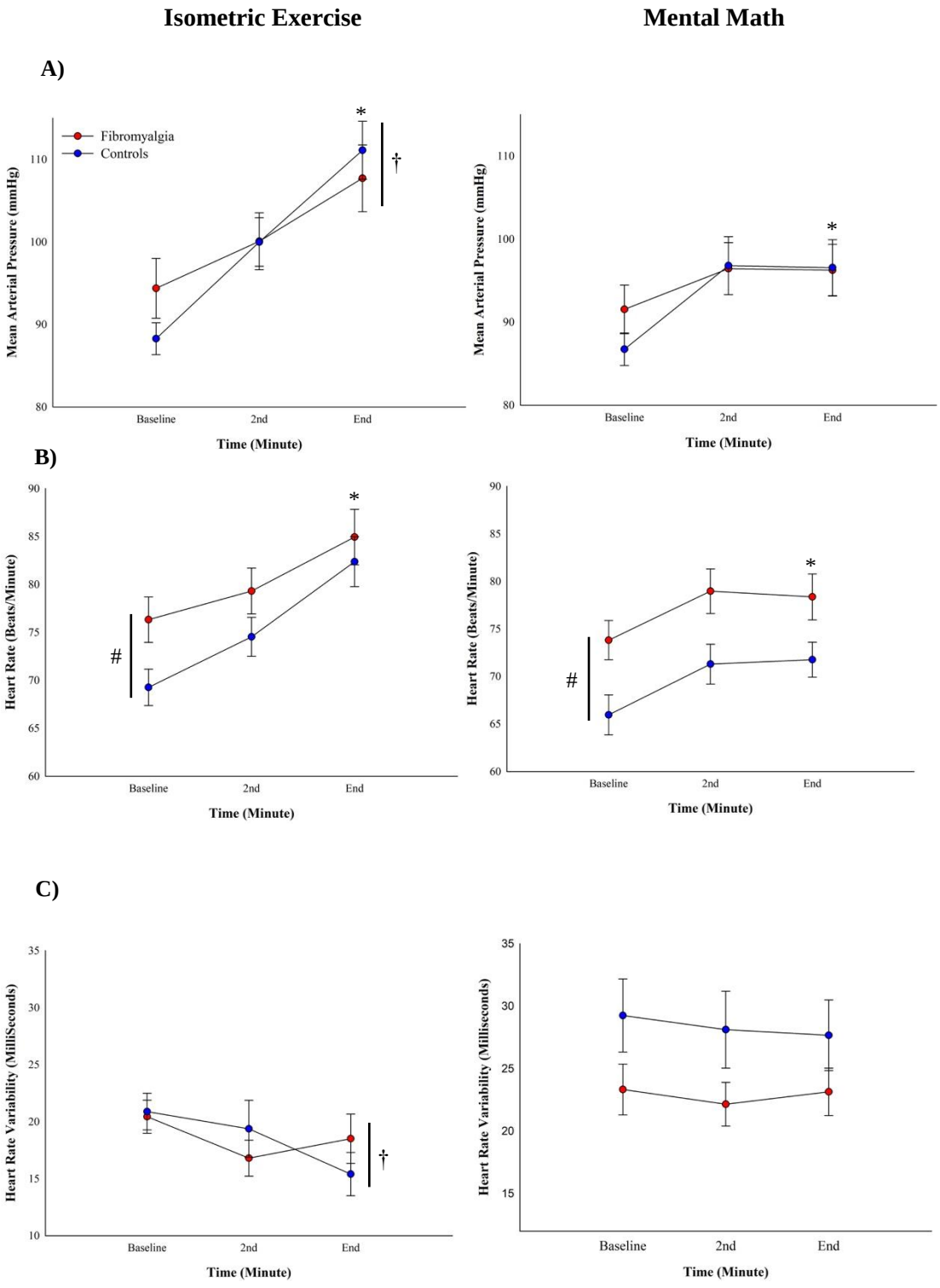

Figure 3.3: The change of A) mean arterial blood pressure, B) heart rate, and C) heart rate variability during isometric exercise and mental math task.
(#) indicates group differences at baseline. (*) indicates significant increase relative to baseline. (†) indicates significant group differences in the change relative to baseline. A) People with FM had less increase in mean arterial pressure during exercise while both groups had similar increase during mental math. B) Both groups had similar increase in heart rate following exercise and mental math. C) Only control participants had a reduction in HRV following exercise compared to people with FM while both groups had no change during mental math.

Self-Report Pain and Exertion

Perceived Pain

Before exercise, people with FM reported higher baseline pain (FM: 1.3 ±1.2; controls: 0 ±0; p< .01). During exercise, there was a significant increase in pain [main effect of time, (F (2, 31) = 79.5, P< .01, η_p^2= .84)] with no group differences (Figure 3.4A).

Before mental math, people with FM reported higher pain (FM: 2.4 ±2.6; controls: 0 ±0; p< .01). During mental math, pain did not change. When exercise and mental math were compared, there was a significant difference in the change of perceived pain between the tasks [session x time interaction, (F (2, 31) = 72.8, P< .01, η_p^2= .82)]. Post hoc showed that exercise led to greater increase of pain compared to mental math (p< .01).

Perceived Exertion

Before exercise, there were no significant group differences in RPE levels (FM: .4 ±.8; controls: 0 ±0; p= .15). Exercise led to significant increase in RPE [main effect of time, (F (2, 31) = 165.3, P< .01, η_p^2= .91)] with no group differences.

Changes in Stress and Anxiety

Perceived Stress

Before exercise, there were no significant group differences in stress levels (FM: .5 ±.7; controls: 0 ±0; p= .08). During exercise, stress significantly increased [main effect of time (F (2, 31) = 38.8, P< .01, η_p^2= .72)] with no group differences (Figure 3.4B).

Before mental math, people with FM reported higher stress (FM: 1.7 ±2.1; controls: .4 ±1.7; p= .02). During mental math, stress significantly increased [main

effect of time, (F (2, 34) = 37.4, P< .01, η_p^2= .69)] with no group differences. When isometric exercise and mental math task were compared, there were differences in the change of stress between the tasks [session x trial interaction, (F (2, 31) = 9.8, P< .01, η_p^2= .39)]. Post hoc showed that a greater increase in stress in the first two minutes during mental math task compared to exercise (p< .01), however, both tasks led to similar levels of stress at the end.

State Anxiety

Before exercise, people with FM had higher state anxiety (FM: 30 ±7.8; controls: 22.4 ±4.4; p< .01). Following exercise, there was a significant increase in state anxiety [main effect of time, (F (1, 33) = 14.6, P< .01, η_p^2= .31)] with no group differences.

Before mental math, people with FM had higher state anxiety (FM: 30.1 ±9.7; controls: 23.1 ±4.6; p< .01). Following mental math, there were group differences in the change of state anxiety [group x time interaction, (F (1, 35) = 5.4, P= .03, η_p^2= .13)], however, post hoc did not show significant group differences. When the change of anxiety following exercise and mental math were compared, there was a trend for differences in the increase of anxiety levels but did not reach statistical significance [session x time interaction, (F (1, 33) = 3.98, P= .054, η_p^2= .11)].

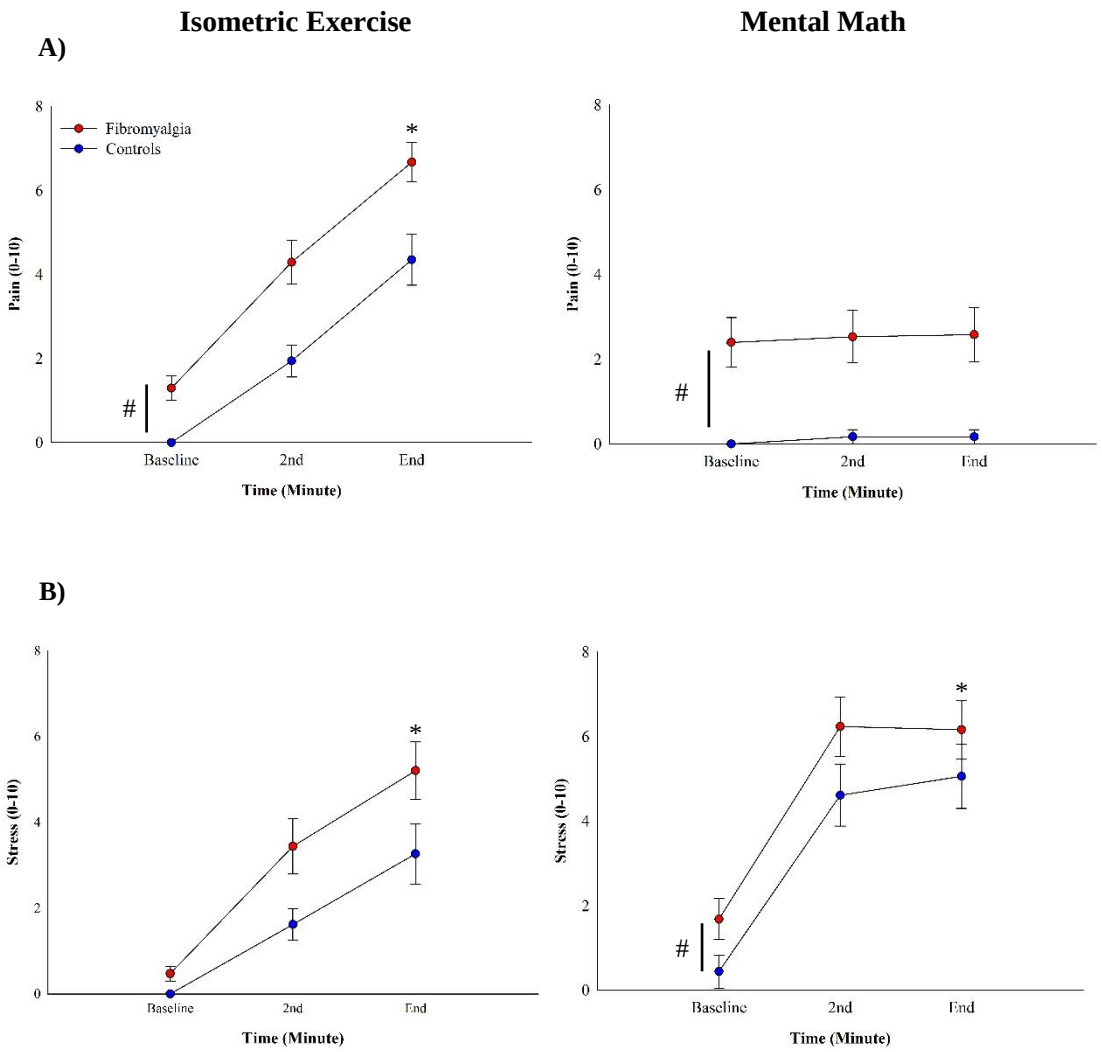

Figure 3.4: The change of A) perceived pain, and B) perceived stress during isometric exercise and mental math task.
(#) indicates group differences at baseline. (*) indicates significant increase relative to baseline. Isometric exercise led to significant increase in pain and stress whereas mental math only led to an increase in stress.

Correlations Between Autonomic Outcomes and the Pain Modulation Following Isometric Exercise and Mental Math

Correlations Among the Entire Sample

Among the entire sample, individuals with shorter Valsalva recovery, indicating greater sympathetic function, reported greater EIH (Table 2). Individuals with lower COMPASS 31 scores (i.e., lower autonomic symptoms) trended to have

greater EIH. The increase in mean arterial pressure during exercise was associated with greater EIH (r= .48, p< .01).

The change of PPTs following mental math was positively associated with the change of PPTs following isometric exercise; those participants that reported greater SIH also reported greater EIH (Figure 3.5). Higher HRV before the mental math task was correlated with greater SIH (r= .39, p= .019). Greater increase in heart rate during mental math was associated with greater SIH (r= .39, p= .018). Also, individuals with greater pre-mental math task HRV had lower pre-mental math heart rate (r= - .61, p< .01), and trended to have greater increase in heart rate during the mental math task (r= .37, p= .025).

Correlations Among the FM Group

Among people with FM, participants with greater sympathetic function reported greater EIH (r_s = - .48, p= .045) and trended to have less increase in self-report pain during exercise (r_s = .50, p= .043). The change of PPTs following isometric exercise was positively correlated with the change of PPTs following mental math (r= .68, p< .01).

Correlations Among the Control Group

Among controls, greater baseline HRV before the mental math was correlated with greater SIH (r= .56, p= .015). Greater increase in heart rate during mental math was associated with greater SIH (r= .75, p< .01).

Correlations Between Pain Following Exercise and Mental Math With Other Baseline Measures

Among in the entire sample, individuals with lower PASS-20 scores (i.e., lower pain-related anxiety) had greater EIH (r_s = -.42, p= .01) and trended to have lower COMPASS 31 scores (r_s = .35, p= .033). Individuals with lower DASS-21

scores trended to have greater EIH (r_s = - .36, p= .03), shorter Valsalva recovery time (r_s = .41, p= .011), and lower COMPASS 31 scores (r_s = .57, p< .01).

There were no significant correlations among FM group only or control group only when correlations were run separately.

Table 3.2: Correlations Between Baseline Autonomic Function and Pain Following Exercise and Mental Math

	1. Deep Breathing Test	2. Valsalva Recovery Time	3. COMPASS 31	4. Pre-Exercise HRV	5. Pre-Mental Math HRV	6. EIH
1. Deep Breathing Test						
2. Valsalva Recovery Time	-.16					
3. COMPASS 31	.14	**.54****				
4. Pre-Exercise HRV	.06	-.16	-.05			
5. Pre-Mental Math HRV	.10	-.30	-.11	.25		
6. EIH	.10	**-.50****	-.39*	-.11	.03	
7. SIH	-.08	**-.34***	-.04	.04	**.39***	**.40****

COMPASS 31= composite autonomic symptoms score; *HRV*= heart rate variability, *EIH*= exercise-induced hypoalgesia, *SIH*= stress-induced hypoalgesia. * $p < .05$, ** $p < .01$. Significant correlations are bolded

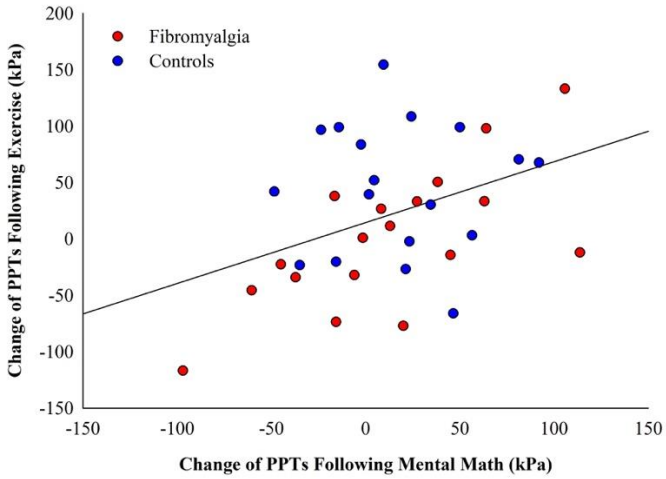

Figure 3.5: Correlation between the change of PPTs following exercise and mental math. Positive numbers in the axes indicate an increase in PPTs following exercise (EIH) and mental math (SIH) whereas the negative numbers indicate a decrease in PPTs (hyperalgesia).

Discussion

One of the findings in our study was that only control participants reported EIH while people with FM had variable responses to exercise. Following mental math, people with and without FM had variable responses with some reporting SIH and others reporting hyperalgesia. One of the novel findings of this study was that the change of PPTs following exercise was associated with the change of PPTs following mental math; participants that reported greater EIH also reported greater SIH. Additionally, greater EIH and greater SIH were associated with greater baseline sympathetic function. Thus, the findings showed the modulation of pain following physical and cognitive tasks are related, and both are related to baseline sympathetic function.

Participants Characteristics

People with FM had similar age, sex, body fat percentage, and physical activity levels as controls participants. Thus, any group differences cannot be attributed to these potential confounding factors. Despite these similarities, people

with FM had greater autonomic symptoms (COMPASS 31) and lower cardiovascular sympathetic function (Valsalva recovery time) which is in line with previous research (Solano et al., 2009; Vincent et al., 2016). The reduction in sympathetic function and the increase in autonomic symptoms were associated with greater pain-related anxiety measured by PASS-20 and greater depression, anxiety and stress measured by DASS-21. Previous studies showed that higher PASS-20 and higher DASS-21 are correlated with higher pain-related disability and lower quality of life (Alamam et al., 2019; Geelen et al., 2017).

Exercise-Induced Hypoalgesia and Autonomic Function

Only Controls participants had EIH following isometric handgrip exercise. People with FM had variables responses which is consistent with previous studies (Hoeger Bement et al., 2011). Previous research has suggested that baseline autonomic function and cardiovascular reactivity during exercise may explain the variability in EIH response in people with FM (Daenen et al., 2015; Nijs et al., 2012). One of novel findings in this study was that baseline sympathetic function was associated with EIH in people with and without FM. The correlation was also significant among the FM participants which suggests that baseline sympathetic function may explain some of the variability in EIH in people with FM. This finding may be explained through shared mechanisms between the sympathetic adrenergic system and EIH. First, there are areas in the brain that are known to modulate sympathetic response and EIH. For example, locus coeruleus modulates the sympathetic function and inhibits pain following exercise. In animal model of neuropathic pain, noradrenergic mechanism through the locus coeruleus contributed to the hypoalgesia following treadmill exercise (Lopez-Alvarez et al., 2018). In humans, many studies have suggested that exercise may inhibit pain through CPM

especially if the exercise is painful or performed to task failure (Alsouhibani et al., 2018; Fingleton et al., 2017; Lemley et al., 2015; Stolzman & Bement, 2016). It is known that noradrenergic mechanism contributes to CPM (Bannister et al., 2015; Parent et al., 2015). The isometric exercise in our study resulted in significant increase in pain which may have activated CPM and noradrenergic pain inhibitory system. In addition, locus coeruleus also receive projections from areas that modulate the cardiovascular response during isometric exercise and also known to modulate pain such as PAG and NTS (Bruehl & Chung, 2004; Green et al., 2007; Iwamoto & Kaufman, 1987; Macefield & Henderson, 2015; Sander et al., 2010). Williams et al. 1990 showed that lesions to the PAG resulted in significant reduction in exercise pressor during isometric contraction (Williams et al., 1990). Therefore, the relation between baseline sympathetic systems and pain following exercise could be driven by the shared areas in the brain that modulate both systems.

Another finding was that individuals with lower autonomic symptoms measured by COMPASS 31 trended to have greater EIH. Moreover, individuals with greater autonomic symptoms had greater psychological distress. These findings demonstrate the interaction between EIH, autonomic symptoms and psychological symptoms such as stress or pain-related anxiety. The findings also show that COMPASS 31 can potentially be utilized in clinical settings prior to exercise prescription to help identify how patients may respond to exercise.

The increase in mean arterial pressure during exercise was also associated with EIH magnitude. Similarly, Black et al. 2016 showed that the change in mean arterial blood pressure was associated with systemic EIH in young men (Black et al., 2016). This relation between blood pressure and EIH is not consistent in the literature. Umeda et al. 2006 compared different doses of isometric exercise and found that

blood pressure increases as the dose increases while EIH stayed the same (Umeda et al., 2010). In our study, people with FM had less increase in mean arterial pressure and no change in HRV during isometric exercise. This is consistent with studies showing that people with FM experience lower sympathetic response during exercise. For example, Giske et al., 2008 found that people with FM had lower levels of plasma epinephrine after performing an isometric exercise to task failure compared to healthy participants that were matched in age, sex and physical activity levels (Giske et al., 2008).

Stress-Induced Hypoalgesia and Autonomic Function

People with and without FM reported similar variability in the pain following mental math with some participants reporting SIH and others reporting hyperalgesia. Baseline sympathetic function was correlated with SIH. This finding suggests shared mechanisms between sympathetic modulation and modulation of pain following mental math such as noradrenergic mechanisms. Previous animal research studies have supported the role of noradrenergic mechanisms in SIH through the activation of α adrenergic receptors (Binder et al., 2004; Bodnar et al., 1983) and the involvement of locus coeruleus (Nakamoto et al., 2017).

SIH was also correlated with baseline (pre-mental math) HRV. Individuals with greater pre-mental math HRV had lower baseline heart rate and trended to have greater increase in heart rate during the mental math. One explanation for this finding is that individuals who had higher HRV could have had more parasympathetic dominance at rest and greater sympathetic response during mental math task which led to greater increase in heart rate and greater pain inhibition.

Stress-Induced Hypoalgesia and Exercise-Induced Hypoalgesia Comparisons

For people with and without FM, the change of pain sensitivity following isometric exercise was positively associated with the change of pain sensitivity following mental math; both were correlated with baseline sympathetic function. Interestingly, exercise led to significant increase in stress and anxiety indicating that it was a stressful task. Animal studies showed that when the exercise is stressful, it activates the noradrenergic pain inhibitory system. For example, Bondar et al., 1983 showed the involvement of α adrenergic receptor in the analgesic response following cold swimming stress (Bodnar et al., 1983). Future mechanistic studies are needed to understand the mechanisms that explain the relation between sympathetic function and pain following physical and cognitive tasks.

In this study, the difference in hypoalgesia between people with FM and control participants only existed following exercise. Following exercise, only the control participants reported hypoalgesia, and neither group experienced hypoalgesia following mental math. There are some potential factors may have contributed to this finding. First, exercise led to an increase in pain while pain did not change during mental math. Previous studies suggested that the increase in pain during isometric exercise may activate CPM leading to greater inhibition in people without FM given that they have intact CPM response. Ellingson et al., 2014 compared painful exercise (exercise + occlusion) and non-painful exercise and found grater EIH with painful exercise suggesting that the pain during exercise has an additive effect (Ellingson et al., 2014). Second, another difference between the isometric exercise and the mental math task is that isometric exercise resulted in greater increase in heart rate and blood pressure compared to mental math. One potential hypothesis is that tasks that result in greater cardiovascular pressor response may have greater hypoalgesic effect in

healthy participants. A meta-analytic review of EIH showed that among healthy individuals, isometric exercise produces the greatest EIH response which could be potentially due to a greater pressor response (Naugle et al., 2012). Thus, this finding suggests that the difference in the pain response between people with and without FM could be more prominent in tasks that result in greater increase in pain and greater cardiovascular pressor response.

Clinical Implications

The findings of this research study are important clinically for multiple reasons. First, it can help in identifying people with FM who are more likely to have pain exacerbation following single exercise session; those individuals with reduced sympathetic cardiovascular function, have high psychological distress, and report that stress typically makes their pain worse. Second, our results may help in prescribing exercise for people with FM. Individuals with reduced cardiovascular sympathetic function may benefit from exercises that are known to increase sympathetic function. For instance, Saito et al., 2009 found that 4 weeks of intermittent isometric handgrip exercise training can increase muscle sympathetic nerve activity in response to acute fatiguing handgrip task (Saito et al., 2009). Lastly, the combination of exercise and medications that are known to increase cardiovascular sympathetic function may be beneficial for some people with FM. For instance, duloxetine which is serotonin and norepinephrine reuptake inhibitor has been shown to increase sympathetic function and decrease pain (Chalon et al., 2003; Detke et al., 2002; Goldstein et al., 2002). However, given that interventions that increase sympathetic responsiveness such as duloxetine may cause hypertension (Smith et al., 2010), further research is needed to study the safety and efficacy of these interventions in improving autonomic function and pain following exercise in people with FM.

Conclusion

Both exercise and mental math led to significant increase in heart rate, mean arterial pressure, and stress indicating that both were stressful tasks. Despite both of these tasks increasing stress, only control participants reported EIH while people with FM had variable pain sensitivity responses following exercise. In response to mental math, both groups had variable changes in pain sensitivity. Interestingly, people that reported greater hypoalgesia following exercise also reported greater hypoalgesia following mental math. Lastly, people that reported greater hypoalgesia following physical and cognitive tasks had greater baseline sympathetic function suggesting a shared mechanism between sympathetic function and the change of pain in response to physical and cognitive stress.

CHAPTER FOUR
DISCUSSION AND CONCLUSION

The overall aim of this dissertation is to better understand the relation between cardiovascular autonomic function and endogenous pain modulation in people with FM and age- and sex-matched control participants. Aim one investigated the relation between cardiovascular autonomic function and central pain facilitation and inhibition, measured by TS and CPM, respectively. Aim two examined the relation between cardiovascular autonomic function and endogenous pain modulation following physical and cognitive tasks (submaximal isometric exercise and mental math, respectively). The aims in this dissertation were unique by evaluating several aspects of baseline cardiovascular autonomic function in relation to central pain inhibition and facilitation. The aims also took into consideration factors that could influence autonomic function and pain modulation such as physical activity, body composition, and psychological variables.

Baseline Autonomic Function

At baseline, people with FM had lower sympathetic function quantified by Valsalva systolic blood pressure recovery time compared with the control participants despite both groups being of similar age, sex, BMI, and physical activity levels. Similarly, people with FM reported greater autonomic symptoms using COMPASS 31. These findings of reduced baseline sympathetic function and greater autonomic symptoms are important clinically. For example, interventions prescribed to people with FM should not only focus on pain but also address other issues such as autonomic symptoms reported in COMPASS 31 including orthostatic intolerance, vasomotor symptoms, secretomotor symptoms and others. Exercise is one of the interventions that has been shown to alleviate orthostatic intolerance (Mtinangi &

Hainsworth, 1999; Wieling et al., 2002; Winker et al., 2005), secretomotor symptoms (Okazaki et al., 2002; Thomas et al., 1999), and vasomotor symptoms (Metsios et al., 2014; Mitropoulos et al., 2020).

In contrast to the group differences in baseline sympathetic function, people with and without FM had similar cardiovascular parasympathetic function and HRV. This finding is in contrast with a previous study that showed people with FM had lower HRV and lower parasympathetic function measured by deep breathing test compared with control participants (Zamuner et al., 2016). However, the study by Zamuner et al., 2016 was different from our study in that it excluded individuals who engaged in regular physical activity. In our study, participants were physically active, and physical activity is positively associated with cardiovascular parasympathetic function (Reland et al., 2004). Another factor that might have contributed to similar group responses in HRV and parasympathetic function is that we excluded participants who had cardiovascular conditions or had been taking medications that influence cardiovascular autonomic function (e.g., antidepressants or hypertension medications). Hypertension is associated with reduced HRV and parasympathetic function (Mancia & Grassi, 2014; Schroeder et al., 2003) and twice as common in people with FM compared to the general population (Walitt et al., 2015).

Conditioned Pain Modulation and Relation to Autonomic Function

CPM is a measure of the integrity of descending pain inhibition, and previous studies showed that people with FM have reduced CPM compared to pain-free individuals (O'Brien et al., 2018). In our study, control participants had CPM in the forearm and quadriceps whereas people with FM only had CPM in the forearm. The finding that CPM magnitude varies by body region is important for research and clinical purposes. First, it showed that the assessment of CPM in one site may not

give an accurate representation of overall central pain inhibition. For instance, if CPM was only assessed in the forearm in our study, the result would have been that CPM was similar between the groups which is just partially true. Second, our results provide supporting evidence that body region may contribute to the intra-individual variability in CPM. Previous studies in healthy individuals and animals have shown that CPM magnitude could vary in different body parts (de Resende et al., 2011; Gajsar et al., 2018; Oono et al., 2011). In our study, we found that CPM at the forearm, but not the quadriceps, was correlated with baseline cardiovascular sympathetic function in people with FM. Therefore, future studies should investigate whether sympathetic tone measured by muscle sympathetic nerve activity is different between the upper and lower limbs during CPM. Future studies can also investigate whether sympathetic activity levels in the upper and lower limbs are driven by the location of the conditioning stimulus (cold water bath). In our study, the cold water bath was applied to the left lower limb, and people with FM reported CPM in the upper limb (i.e., forearm) but not the lower limb. It is unknown if CPM would occur at the forearm if the cold water bath was applied to the upper limb in people with FM.

The relation between CPM and sympathetic function could be due to shared central processing including similar activation of brain areas (e.g., locus coeruleus) (Saper, 2002) and receptors in the spinal cord (e.g., alpha 2 adrenergic) (Bannister et al., 2015). Our finding may explain why interventions that increase sympathetic function such as duloxetine can improve CPM (Niesters et al., 2014; van de Donk et al., 2019; Yarnitsky et al., 2012). For instance, Yarnitsky et al., 2012 studied the effect of duloxetine in people with painful diabetic neuropathy. Their results showed that greater improvement in CPM response and clinical pain were associated with less efficient CPM at baseline; these results suggest that patients with reduced CPM would

benefit more from duloxetine compared to patients with more efficient CPM (Yarnitsky et al., 2012). In addition, some types of exercise such as isometric exercise can increase sympathetic reactivity (Saito et al., 2009), and we have previously shown that acute isometric exercise can improve CPM in people with less efficient baseline CPM (CPM non-responders) (Alsouhibani, 2019). Future mechanistic research is needed to understand the mechanisms that explain the relation between sympathetic function and CPM.

Temporal Summation and Relation to Autonomic Function

TS is used to evaluate central pain facilitation (O'Brien et al., 2018), and the TS protocol in our study involved the application of ten noxious heat pulses. People with and without FM experienced a similar increase in pain over time with the noxious pluses indicating similar TS. In addition, we did not find an association between baseline autonomic function and TS. Some studies have shown an association between baseline blood pressure and TS. For instance, Chung et al., 2008 showed that greater baseline systolic blood pressure was correlated with greater TS in people with low back pain (Chung et al., 2008). Among people with FM, a study found no association between baseline HRV and TS, however, greater reduction in the hight frequency HRV during the TS was associated with greater increase in TS (Kim et al., 2015). Moreover, the relation between TS and HRV is not consistent in the literature. Petersen et al., studied whether the increase of HRV by a medication could result in a reduction in TS. The results of their study showed that the use of propranolol increased HRV but did not affect the magnitude of TS (Petersen et al., 2018). One of the factors that might have contributed to these inconsistencies is the characteristics of the participants in these studies. In our study, we assessed baseline factors that are known to influence autonomic function and TS. For example, the

sample in our study were physically active; greater time spent in moderate to vigorous physical activity is associated with greater HRV (Kiviniemi et al., 2016) and lower TS (Naugle & Riley, 2014). Another factor that could explain the inconsistency is the modality of noxious stimuli (pressure or heat) (Kim et al., 2015). Given that people with FM experience greater TS with a mechanical stimulus than thermal (O'Brien et al., 2018), future studies should investigate whether baseline autonomic function is related to TS of pressure pain in people with FM.

Modulation of Pain Following Physical and Cognitive Task

In aim 2, we examined the relation between cardiovascular autonomic function and endogenous pain modulation following physical and cognitive tasks. Following isometric exercise, we found that only the control group experienced hypoalgesia (increase in PPTs) while people with FM had variable responses with some reporting hypoalgesia and others reporting hyperalgesia. This result is consistent with previous studies (Hoeger Bement et al., 2011; Lannersten & Kosek, 2010; Staud, Robinson, et al., 2005) and it supports the notion that people with FM have reduced pain modulation with acute exercise.

Following mental math, both groups had similar variability in the change of PPTs with some participants reporting SIH (increase in PPTs) and others reporting hyperalgesia. The variability in the change of PPTs with mental math has been reported previously even among healthy individuals. Hoeger Bement et al., 2010 found pain threshold and pain ratings did not change following mental math task in young healthy individuals, however, participants had variable responses with some reporting hypoalgesia and others reporting hyperalgesia or no change (Hoeger Bement et al., 2010). One explanation for the similarities between the groups is that both groups had comparable increases in stress, anxiety and cardiovascular response.

These factors have been shown to influence the magnitude of SIH (al'Absi & Petersen, 2003; Geva & Defrin, 2018; Hoeger Bement et al., 2010).

One of the major findings in aim 2 was that the modulation of pain following exercise and mental math were related (i.e., greater EIH was associated with greater SIH). There are several similarities between the isometric exercise and mental math task. Both tasks resulted in increase in heart rate, blood pressure, and stress levels indicating that these tasks were stressful to people with and without FM. This was in agreement with previous studies in healthy individuals showing that both isometric exercise and mental math are types of stress that increase perceived stress, increase anxiety levels and provoke a cardiovascular response (Carter & Ray, 2009; Yoon et al., 2009). Interestingly, animal studies have suggested that the mechanisms of EIH could vary depending on whether the exercise was stressful. Terman et al., 1986 found that naloxone, opioid antagonist, attenuated the hypoalgesic response following swimming in 20˚C water whereas naloxone did not have an effect on the hypoalgesic response following swimming in 10˚C water (Terman et al., 1986). This suggests that non-opioid mechanisms may explain the hypoalgesia following the more stressful exercises whereas opioid mechanisms contribute to EIH following less- or non-stressful exercises. Newcomb et al., 2011compared EIH following 20 minutes of aerobic exercise at moderate intensity to 20 minutes of aerobic exercise at preferred intensity in people with FM (Newcomb et al., 2011). The results showed that preferred intensity had larger EIH effect size compared to prescribed intensity despite that the intensity of preferred exercise was significantly lower. Future mechanistic studies are needed to investigate the mechanisms that explain the relation between the change of pain following isometric exercise and mental math. In addition, it is

unknown whether the pain response following stressful and non-stressful exercise are related in people with FM.

Differences Between People With and Without FM in the Cardiovascular Autonomic Response During Exercise and Mental Math

One of the hypotheses we had in aim 2 was that people with FM would have reduced cardiovascular autonomic response compared to control participants during exercise and mental math. During exercise, controls had greater increase in mean arterial pressure and greater reductions in HRV compared to people with FM. This result may suggest that people with FM had lower sympathetic reactivity to exercise which could be due to lower baseline sympathetic function in people with FM compared to controls. This finding was not surprising given that Giske et al., 2008 showed that following fatiguing isometric exercise, people with FM had lower increase in epinephrine levels compared to control participants (Giske et al., 2008).

In contrast to our hypothesis, we found that the increase in heart rate was similar in both groups. The similarities in heart rate between people with and without FM could have been caused by a few reasons. One explanation is the duration of the exercise task was four minutes and not to task failure. The initial increase in heart rate during isometric exercise is caused by parasympathetic withdrawal (Martin et al., 1974) and subsequent activation of metaboreceptors caused by the accumulation of metabolites leads to an additional increase in heart rate that is sympathetically mediated (Iellamo et al., 1999). In our study, only three participants in each group reached task failure before completing the four minutes. This could have been driven by the fact that the majority of the participants in our study were women. Women are less fatigable compared to men (Hunter, 2014, 2016) and have less increase in heart rate during sustained low to moderate intensity isometric handgrip exercise

(Cauwenberghs et al., 2020). West et al., 1995 showed that women are less fatigable compared to men during sustained isometric contraction performed at 30% of MVC to task failure (West et al., 1995). When the handgrip exercise is performed for 3 minutes, women have less increase in heart rate compared to men (Cauwenberghs et al., 2020). Thus, it is possible that the lack of group differences in heart rate during exercise could be caused by the duration of the exercise and the majority of participants were women.

People with FM had a similar increase in heart rate and blood pressure during mental math compared to controls which was inconsistent with our hypothesis. One factor that could explain this result is that the sympathetic response to cognitive task is highly variable among participants compared to physical stressors like isometric exercise. El Sayed et al., 2016 showed that young healthy participants had different muscle sympathetic nerve responses to mental math task with some participants experiencing increase in sympathetic nerve activities and others experiencing a reduction whereas a task like handgrip exercise led to gradual and consistent increase in sympathetic nerve activity (El Sayed et al., 2016). The increase in blood prerssure and heart rate is lower during mental math task compared with isometric exercise (Wasmund et al., 2002). Thus, the lack of group differences in the cardiovascular response to mental math could have driven by the variability in sympathetic responses to the cognitive task among people with and without FM that were primarily women. Women have lower heart rate and blood pressure reactivity to cognitive task compared to men (Carter & Ray, 2009; El Sayed et al., 2018). Lastly, physical activity is associated with blunted cardiovascular response to psychological stressors (Crews & Landers, 1987; Forcier et al., 2006), and both groups in our study were

physically active. Together, all these factors might have contributed to the lack of differences in cardiovascular response to mental math.

Relation of Autonomic Function and Pain Modulation Following Physical and Cognitive Tasks

One of the novel findings in study 2 was baseline sympathetic function was correlated with the pain response following exercise and mental math. This finding suggests that there could be potential shared mechanisms that explain the relation between sympathetic function and pain following physical and cognitive stress. One of these potential mechanisms could be the activation of areas in the brain that are involved in modulating pain and sympathetic response. For instance, locus coeruleus can modulate sympathetic function and can inhibit pain (Bruehl & Chung, 2004). In addition, locus coeruleus is activated under acute stress (Wood et al., 2017), and both exercise and mental math led to significant increase in stress and anxiety in our study. Locus coeruleus receives projections from other areas that modulate pain and sympathetic function such as PAG (Bruehl & Chung, 2004). Animal studies showed that PAG is involved in SIH (Butler & Finn, 2009) and in the modulation of the cardiovascular response during exercise (Williams et al., 1990). However, further studies are needed to determine the mechanisms that explain the relation between sympathetic function and the pain response following exercise and mental math.

Previous studies have shown an association between CPM and EIH (Fingleton et al., 2017; Lemley et al., 2015; Stolzman & Bement, 2016), and some researchers have suggested that SIH is one of the mechanisms of CPM (Butler & Finn, 2009). In aim 1 and aim 2, we found that baseline sympathetic function was related to CPM and pain following exercise and mental math. These findings are important clinically and for future research studies. Clinically, interventions that have been shown to improve

CPM and increase sympathetic function may improve EIH in people with reduced sympathetic function. Examples of these interventions include duloxetine, serotonin and norepinephrine reuptake inhibitor, (Yarnitsky et al., 2012) and tapentadol, which is an opioid and norepinephrine reuptake inhibitor (Niesters et al., 2014; van de Donk et al., 2019). Van de Donk studied the effect of the use of tapentadol for 3 months in people with FM who had reduced CPM. The results showed that tapentadol led to significant increase in CPM compared to placebo (van de Donk et al., 2019). Future studies may investigate whether interventions like tapentadol can improve sympathetic function and EIH in people with reduced sympathetic function. In addition, isometric exercise has been shown to improve sympathetic reactivity and CPM. Saito et al., 2009 showed that 4 weeks of intermittent isometric training increased sympathetic reactivity to sustained handgrip exercise. Alsouhibani et al., 2019 found that acute isometric exercise led to improvement in CPM in people with reduced CPM (CPM non-responders) (Alsouhibani, 2019). Given that stress may exacerbate pain in people with FM (Fischer et al., 2016), future interventional studies may investigate whether isometric exercise training can improve the ability to cope with physical and cognitive stressors in people with FM.

Conclusion

The results of this dissertation provided evidence regarding the relation between autonomic function and pain modulation in people with and without FM (Figure 4.1). Aim one showed that people with FM had CPM only at the forearm which was associated with baseline sympathetic function (Figure 4.1). This finding suggests that CPM could vary on different body parts in people with FM and variability could be potentially explained by factors such as different sympathetic responses, however, further studies are needed.

Aim two showed that the pain modulation following isometric exercise and mental math were correlated in people with and without FM demonstrating a similarity between the pain modulation following physical and cognitive stress. In addition, greater baseline sympathetic function was associated with greater pain relief following exercise and mental math suggesting a potential shared mechanism between sympathetic function and pain following physical and cognitive stress.

Thus, the findings of this dissertation may help clinicians and researchers in different ways. First, it demonstrated that the assessment of CPM in people with FM should include different body regions, and future studies should investigate whether sympathetic responses in different body regions contribute to differences in CPM magnitudes in different sites. Seconds, our findings suggest that interventions that improve sympathetic function in people with reduced sympathetic function may lead to improvement in pain inhibition and in the ability to cope with physical and cognitive stress.

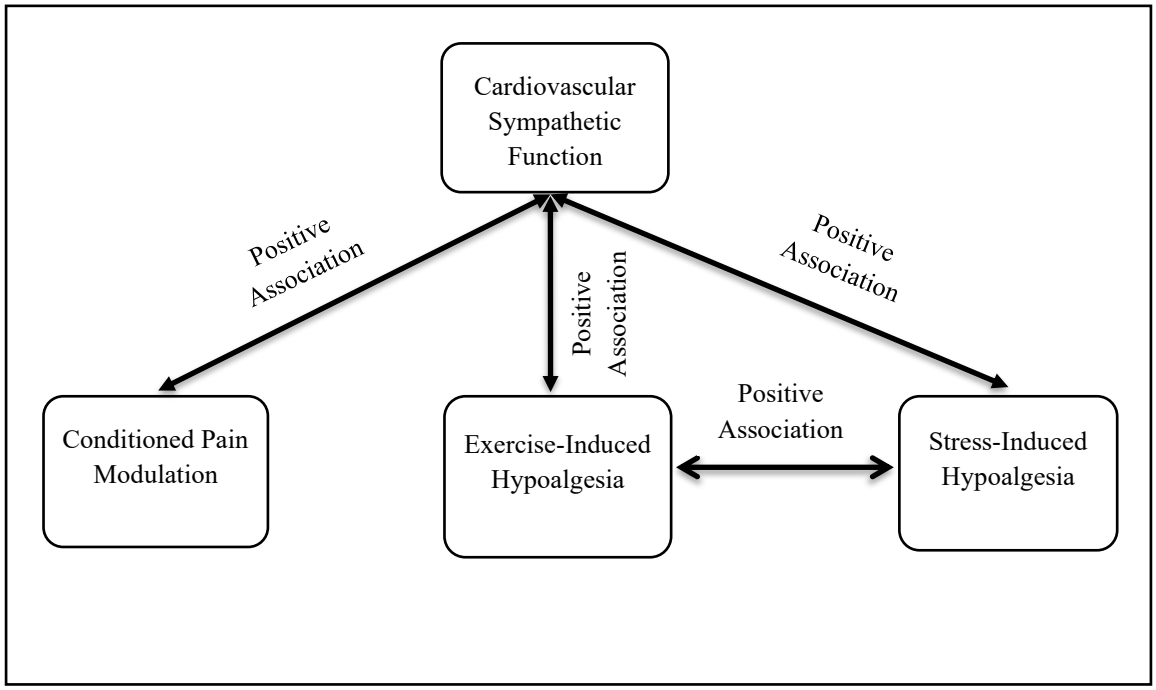

Figure 4.1: The major findings of the study.

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