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Pain, fatigue, function and transcutaneous electrical nerve stimulation in individuals with fibromyalgia

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PAIN, FATIGUE, FUNCTION AND TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION IN INDIVIDUALS WITH FIBROMYALGIA

by

Dana Leigh Dailey

An Abstract

Of a thesis submitted in partial fulfillment
of the requirements for the Doctor of
Philosophy degree in Physical Rehabilitation Science
in the Graduate College of
The University of Iowa

May 2013

Thesis Supervisor: Professor Kathleen A. Sluka

ABSTRACT

The American College of Rheumatology (ACR) 1990 criterion classifies fibromyalgia as a clinical syndrome characterized by chronic widespread muscular pain and tenderness with hyperalgesia to pressure over 11/18 tender points of at least 3 months duration. Fibromyalgia is characterized by chronic widespread musculoskeletal pain and is associated with fatigue and cognitive dysfunction. The cause of fibromyalgia is unknown, but it has been shown to demonstrate sensitization of the central nervous system pain pathways by demonstrating lower pain pressure thresholds and reduced conditioned pain modulation (CPM).

Pain and fatigue associated with fibromyalgia can interfere with daily function, work, and social activities. Without greater understanding of the interaction of pain, fatigue and function, we are limited in our ability to improve these symptoms for individuals with fibromyalgia. We designed three experiments to examine the relationship of pain, fatigue and function in individuals with fibromyalgia.

Regression analyses demonstrated significant models that included pain, fatigue and fear of movement for prediction of function and quality of life in individuals with fibromyalgia and healthy controls. The fatigue study (cognitive fatigue, physical fatigue and dual fatigue task) demonstrated that people with fibromyalgia show enhanced pain and fatigue to both cognitive and physical fatigue tasks and reduced function in the physical fatigue task in comparison to healthy controls. Our final study showed active TENS restores CPM, decreases deep tissue pressure pain, decreases pain and fatigue during movement for individuals with fibromyalgia.

Abstract Approved: _____
Thesis Supervisor

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Date

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Iowa City, Iowa

CERTIFICATE OF APPROVAL

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PH.D. THESIS

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This is to certify that the Ph. D. thesis of

Dana Leigh Dailey

has been approved by the Examining Committee
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To my family, friends and Marshall for all the love and support.

To accomplish great things, we must not only act, but also dream; not only plan, but also believe.

Anatole France

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ABSTRACT

The American College of Rheumatology (ACR) 1990 criterion classifies fibromyalgia as a clinical syndrome characterized by chronic widespread muscular pain and tenderness with hyperalgesia to pressure over 11/18 tender points of at least 3 months duration. Fibromyalgia is characterized by chronic widespread musculoskeletal pain and is associated with fatigue and cognitive dysfunction. The cause of fibromyalgia is unknown, but it has been shown to demonstrate sensitization of the central nervous system pain pathways by demonstrating lower pain pressure thresholds and reduced conditioned pain modulation (CPM).

Pain and fatigue associated with fibromyalgia can interfere with daily function, work, and social activities. Without greater understanding of the interaction of pain, fatigue and function, we are limited in our ability to improve these symptoms for individuals with fibromyalgia. We designed three experiments to examine the relationship of pain, fatigue and function in individuals with fibromyalgia.

Regression analyses demonstrated significant models that included pain, fatigue and fear of movement for prediction of function and quality of life in individuals with fibromyalgia and healthy controls. The fatigue study (cognitive fatigue, physical fatigue and dual fatigue task) demonstrated that people with fibromyalgia show enhanced pain and fatigue to both cognitive and physical fatigue tasks and reduced function in the physical fatigue task in comparison to healthy controls. Our final study showed active TENS restores CPM, decreases deep tissue pressure pain, decreases pain and fatigue during movement for individuals with fibromyalgia.

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LIST OF ABBREVIATIONS

BMI	Body Mass Index
CES-D	Center for Epidemiologic Studies – Depression
CF	Cognitive Fatigue (Perceived)
CFT	Cognitive Fatigue Task
COWAT	Controlled Oral Word Association Test (Cognitive Fatigue Task)
CPM	Conditioned Pain Modulation
DFT	Dual Fatigue Task
FIQ	Fibromyalgia Impact Questionnaire
FTSTS	Five Time Sit to Stand
MAF	Multidimensional Assessment of Fatigue
MFIS	Modified Fatigue Impact Scale
MMSE	Mini Mental State Exam
PF	Physical Fatigue (Perceived)
PFT	Physical Fatigue Task
PPT	Pressure Pain Threshold
ROM	Range of Motion
SLS	Single Leg Stance
6MWT	Six Minute Walk Test
TENS	Transcutaneous Electrical Nerve Stimulation
TSK	Tampa Scale of Kinesiophobia
VALPAR	Upper Extremity Peg Task (Physical Fatigue Task)
VAS	Visual Analog Scale (0-10 cm)

CHAPTER 1

INTRODUCTION

Overview

Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [102]. Pain is the body's way of signaling potential danger for tissue damage or injury. Chronic pain, on the other hand, does not serve as a warning signal for injury and is considered the disease itself. Chronic pain has clear pathological changes in the peripheral and/or central pain processing systems. Chronic pain has been defined as pain that lasts more than three months, continues beyond the normal tissue healing time, or occurs in the absence of clear tissue damage. In addition, the dysfunction is greater than expected from an injury or physical examination would reveal. With chronic musculoskeletal pain sensitization can occur in both the peripheral and central nervous systems. The peripheral nervous system shows enhanced nociceptive activity that is manifested clinically as localized pain and primary hyperalgesia (decreased pain thresholds). The central nervous system displays central sensitization characterized by increased excitability and increased receptive field sizes of spinal cord neurons that is manifested clinically as temporal summation, widespread decreases in pain thresholds (i.e. secondary hyperalgesia), and widespread pain. Chronic musculoskeletal pain can involves muscles, tendons, ligaments and bone with the most prevalent regions being low back pain (30-40%) and neck pain (15-20%) followed by knee and temporomandibular joint pain (10-15%) [89,102]. Pain is often diffuse and spreads beyond the original site of pain to multiple pain areas [246]. In fact few people

show a single pain site [115] and the resulting disability is linked with a significant loss of productivity and elevated healthcare expenditures [187]. Chronic widespread pain is defined as pain both above and below the waist, involving both sides of the body and lasting for at least 3 months and comprises approximately 10-15% of the population. Of the most common examples of chronic widespread pain is fibromyalgia. In individuals with fibromyalgia, chronic widespread pain is associated with tender points and somatic symptoms [253].

Definition and Epidemiology of Fibromyalgia

Fibromyalgia affects 3 to 6% worldwide [21,35] and is more prevalent in women than men. The diagnosis of fibromyalgia typically occurs during middle age and occurs in a ratio of female to male of 7:1 [4]. Medical costs are higher for patients with fibromyalgia [35,234] than in the general population; with the CDC estimating people with fibromyalgia have total annual utilization costs of $5945 per person for medications, complementary and alternative medicine and diagnostic tests [35]. The diagnosis of fibromyalgia is based on patient history and physical examination. The American College of Rheumatology (ACR) 1990 criterion classifies fibromyalgia as a clinical syndrome defined by chronic widespread muscular pain and tenderness with hyperalgesia to pressure over 11/18 tender points of at least 3 months duration [250]. Fibromyalgia is characterized by chronic widespread musculoskeletal pain and is associated with fatigue, sleep disturbance and cognitive dysfunction [250]. The cognitive dysfunction, often called “fibro fog”, manifests as cognitive deficits and memory problems [21,198]. Fibromyalgia is also associated with other co-morbidities such as depression, anxiety, dysmenorrhea, other rheumatic conditions of rheumatoid arthritis and systemic lupus

erythematosis, chronic fatigue syndrome, irritable bowel syndrome, interstitial cystitis, and temporomandibular disorder [102,250,251].

Pathophysiology

The pathophysiology of fibromyalgia involves genetic predispositions, neuroendocrine changes, neurotransmitter and neurosensory changes. Evidence has shown genetic polymorphisms with changes in the serotoninergic system (5HT1A receptor polymorphism T/T phenotype and SLC6A4 serotonin transporter) and dopaminergic system (Dopamine D4 receptor exon II repeat polymorphism and the catecholaminergic system (catechol-O-methyl transferase (COMT) gene) [26,27,43]. Although several hypotheses about the pathogenesis of fibromyalgia exist (e.g., altered central pain processing, stress-induced, neuroendocrine disruption, and sleep deprivation), altered central pain processing is supported best by the literature and is commonly accepted [172,255]. There are increases in the pain producing substances of substance P and nerve growth factor, and decreases in the pain inhibiting neurotransmitter serotonin in the cerebrospinal fluid [83,190-192,237]. The hypothalamus-pituitary adrenal (HPA) axis has shown dysfunction in individuals with fibromyalgia. The HPA axis assists the body in responding to physical and emotional stress and regulating the sleep wake cycle. Studies have indicated reduced total cortisol levels but normal active free cortisol levels [48,82,91] and possible pituitary dysfunction related to a diminished stress response [159]. Individuals with fibromyalgia have exhibited variable levels of pro-inflammatory and anti-inflammatory cytokines. Cytokines assist in regulating the human body's response to infection, immune response, inflammation, and trauma. Cytokines are thought to have two roles: 1) make disease

response worse (pro-inflammatory) or 2) assist in reducing inflammation and promote healing (anti-inflammatory). A meta-analysis by Úç eyler [236] summarized that individuals with fibromyalgia have higher serum or plasma levels of cytokines IL-6 and IL-8 and normal levels pro-inflammatory cytokines IL-1, TNF (tumor necrosis factor) and IL-2. Thus, alterations in the nervous system, HPA-axis, or immune system may contribute to the pathophysiology of fibromyalgia.

Imaging studies of the brain have been done with SPECT (Single Photon Emission Computed Tomography), PET (Positron Emission Tomography) and fMRI (functional Magnetic Resonance Imaging) to examine changes in the brain and response to pain in individuals with fibromyalgia [44-46,88,122,157]. They have shown changes of baseline regional cerebral blood flow (rCBF) [122,157] with decreased rCBF in the thalamus and caudate nucleus, and an absence of rCBF in the PAG (periaqueductal gray). With fMRI, reduced dopamine and opioid receptor levels have been noted in the basal ganglia, amygdala and insula. In addition, pain sensitivity to heat and mechanical stimuli have been examined and reveal pain sensitivity in the brain consistent with verbal report of pain and not the intensity of the stimulus [44-46,88]. In these studies, the threshold levels for heat and mechanical stimuli were much lower in fibromyalgia subjects compared to healthy controls – these lower threshold stimuli still activated the same brain area as healthy controls with higher pain stimuli. More recent fMRI studies have focused on gray matter atrophy in individuals with fibromyalgia and these studies revealed smaller global gray matter compared to healthy controls with changes seen in the left posterior thalamus, the mid- and anterior cingulate cortex bilaterally, the left insular and medial temporal cortex, the right superior temporal gyrus and the medial parietal cortex

[21,94,121,200,201]. Thus, using a variety of imaging methods a number of brain areas involved in pain processing, pain inhibition, and the affective dimension of pain are altered when compared to controls.

Autonomic disturbances associated with sympathetic hyperactivity and parasympathetic hypoactivity have been noted in individuals with fibromyalgia [112,117,145,218,219]. These authors propose that autonomic dysfunction may explain many of the symptoms of fibromyalgia: fatigue, difficulty sleeping, anxiety, orthostatic hypotension, cold hands and feet, dizziness and faintness. The two most studied areas in autonomic disturbance are heart rate and blood pressure. Heart rate variability (HRV) is evaluated by electrocardiogram (ECG) and demonstrates the fluctuation of heart rate and the intervals between heartbeats. Martinez-Levin demonstrated that in a 24 hour period, individuals with fibromyalgia have decreased HRV and nocturnal sympathetic hyperactivity compared to healthy controls [145]. Staud [219] proposed that this may be a way to measure the variations in the autonomic nervous system and be a potential biomarker for individuals with fibromyalgia. Ribeiro demonstrated that individuals with fibromyalgia experienced a delayed heart rate recovery and possible chronotropic incompetence in response to a graded treadmill exertion test [52]. High resting heart rate is common in individuals with fibromyalgia and might be a result of sympathetic hyperactivity [219] or may be due to a more sedentary lifestyle or deconditioning [180,181]. Orthostatic intolerance has also been shown in individuals with fibromyalgia during tilt table testing [218].

Thus, the pathophysiology of fibromyalgia is complex and may involve multiple systems. Further, the complexity and heterogeneity of symptoms in fibromyalgia makes

assessment and treatment challenging. The diagnostic criteria for fibromyalgia have evolved with a greater understanding of the pathophysiology of fibromyalgia.

Diagnostic Criteria for Fibromyalgia

1990 diagnostic criteria from the ACR include widespread pain for at least 3 months, pain on both sides of the body, above and below the waist and abnormal response to 11 of 18 predefined tender points with 4kg of pressure (blanching of a fingernail)(Figure 1.1). In 2010, new criteria for diagnosis of fibromyalgia were proposed to include a widespread pain index (WPI) and symptom severity (SS) [251]. WPI is determined by the number of areas the patient has had pain over the last week with a possible score of 0-19. Symptom severity is determined by ratings of fatigue, waking unrefreshed, cognitive symptoms and severity of somatic symptoms with a possible score of 0-12. Three primary criteria must be met for a diagnosis of fibromyalgia: 1) widespread pain index (WPI) $\geq$ 7 and symptom severity scale (SS) score $\geq$ 5 or WPI 3-6 and SS scale score $\geq$9. 2) Symptoms must have been present for at least 3 months and 3) the patient does not have a disorder that would otherwise explain the pain. The 2010 proposed criteria represent a change in the diagnosis of fibromyalgia however are not widely used at this time.

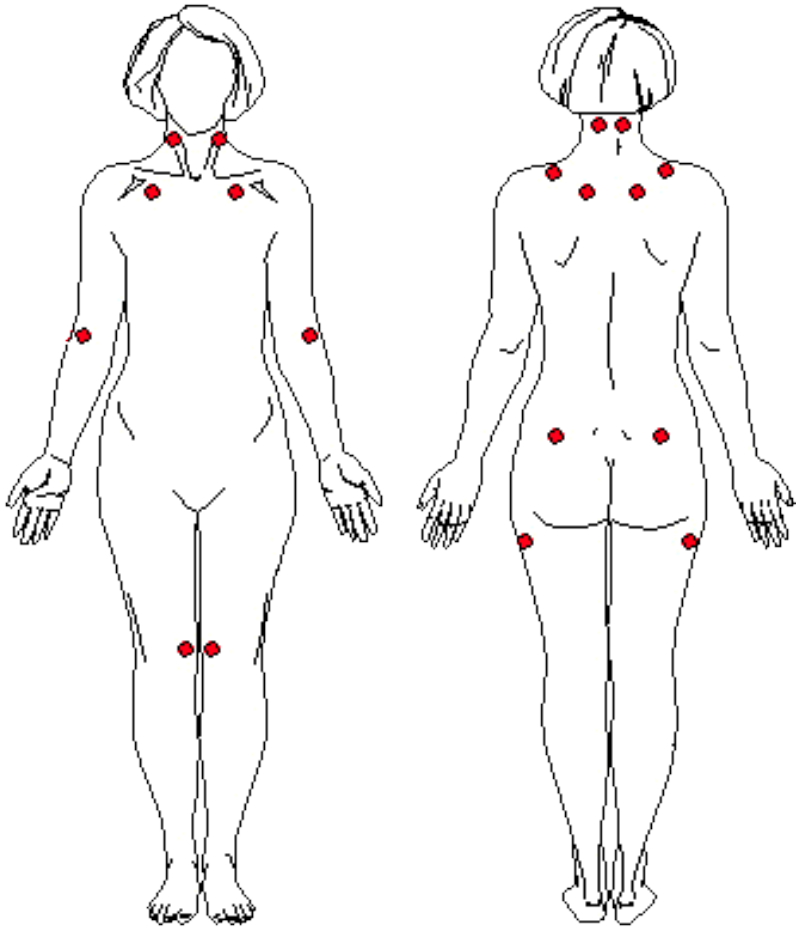

Figure 1.1: 18 tender points for diagnosis of fibromyalgia

Pain Characteristics

One of the most challenging aspects of fibromyalgia is the variable nature of pain among individuals with fibromyalgia [199]. When we attempt to describe the experience of pain, we may consider several descriptors of pain by having individuals with fibromyalgia rate pain levels, in addition to the location and description of the pain, pain aggravating factors and pain relieving factors. The pain associated with fibromyalgia is chronic (at least 3 months), diffuse and widespread (above and below the waist) [250]. Pain for individuals with fibromyalgia may be associated with morning stiffness as well as pain increases throughout the day [16]. Average daily pain ratings may vary in individuals with fibromyalgia. Okifuji reported on daily symptoms in individuals with fibromyalgia (81 females) and shows a mean pain rating (over a 30 day period) of 2.73 ±1.28 (mean ± SD) on a 0-6 low to high scale with greater pain in the morning and evening [166]. In a survey with more than 2500 subjects, Bennett reported individuals with fibromyalgia noted the most common pain aggravating factors as mental stressors, weather changes, sleeping problems and strenuous activity [16]. Henriksson found that many people with fibromyalgia describe activities that aggravate the symptoms of fibromyalgia include carrying and holding objects and these activities are perceived as strenuous [97]. Bennett also found that individuals with fibromyalgia reported the most effective pain relieving factors were rest, heat modalities, prescription pain medications, prescription antidepressants, sleep medications, prayer, massage, and pool therapy [16].

Pain processing occurs by ascending and descending pathways in the nervous system. In individuals with fibromyalgia, these two pathways process pain abnormally resulting in central sensitization [42]. Individuals with fibromyalgia experience diffuse

hyperalgesia (an increased response to painful stimuli) with quantitative sensory testing and allodynia (a heightened sensitivity to stimuli that are not normally painful) [171]. There is a generalized decrease in pressure thresholds in people with fibromyalgia and enhanced temporal summation to repeated noxious stimuli [225,226,231]. Temporal summation in individuals with fibromyalgia also requires a lower threshold of stimulus to induce compared to healthy controls [224,230]. There is also a loss of central inhibitory mechanisms as measured by ineffective conditioned pain modulation [120,126,133,228]. Together these data suggest that there is enhanced excitability in the central nervous system accompanied by decreased inhibition.

Fatigue Characteristics

The impact of fatigue on overall quality of life is significant and yet is currently not understood for individuals with fibromyalgia [16]. In regards to individuals with fibromyalgia, there is no clear definition of fatigue and fatigue has been defined in many different ways: central versus peripheral, pathological versus non-pathological, subjective physical and emotional complaints or perceived physical fatigue versus perceived cognitive fatigue.

The experience of fatigue in individuals with fibromyalgia has been reported in a manner similar to that of pain. Fatigue may be described by rating the level of fatigue and giving descriptors of fatigue. Okifuji reported that daily fatigue levels for 81 women with fibromyalgia, over a 30 day period, reported fatigue ratings 3.50 ± 1.49 (mean ± SD) on a 0-6 low to high scale. Greater levels of fatigue were noted in the evening in a 24 hour time period [166]. In a survey of rheumatologic patients, Wolfe reported fatigue was present in 76% of patients with fibromyalgia [253]. Subjective descriptors of fatigue vary

among individuals with fibromyalgia and fatigue impacts the overall quality of life through limitations in the ability to perform activities at work, home or social activities [3]. Research suggests fatigue may have both physical and cognitive components that are related yet distinct [58] and may vary depending on the specific measure, particularly in patients with fibromyalgia. However, fatigue as described by people with fibromyalgia is a subjective whole-body experience that can be physical and/or mental.

If we consider the question of components of fatigue, in individuals with fibromyalgia, previous studies have directly examined muscle fatigue, i.e. decreased capacity to perform a maximum voluntary muscle action [34,70,143,155,155,164]. Muscle fatigue can be defined as a decreased capacity to perform a maximum voluntary muscle action or a series of repetitive muscle actions [58]. Muscle fatigue is a non-pathological response to muscle activity, is temporary, recovers after rest, and can be due to changes in the peripheral muscle or to loss of central drive. In general these prior studies have examined static contractions of a single muscle in the upper extremity or the lower extremity, or a bicycle exercise task. When compared to sedentary controls, there are no differences in peripheral or central fatigue indices for the quadriceps muscle [105,105,143,152,154,164], but there were differences in central fatigue indices for the biceps muscle [34]. Direct measures of muscle fatigue could be task-dependent or muscle dependent. On the other hand, consistently, people with fibromyalgia rate their perceived fatigue significantly higher than healthy subjects before and during exercise tasks – bicycle task or single muscle contractions [137,154,155]. Thus, subjective fatigue responses in people with fibromyalgia may not reflect changes in the muscle's response to contraction.

For the purposes of the current study we are defining fatigue as perceived physical and/or perceived mental exhaustion that can be triggered by stress, medication, overwork, or mental and physical illness or disease. We will further sub-classify fatigue into perceived physical fatigue and perceived cognitive fatigue to distinguish these two different entities of the fatigue experience in fibromyalgia. Thus clinically described fatigue is distinctly different from muscle fatigue.

People with fibromyalgia typically describe perceived physical fatigue as an overall feeling of tiredness or exhaustion, fatigue while completing functional tasks (e.g. folding laundry, drying hair or getting dressed), sleepiness, or feeling of heaviness [35]. Perceived physical fatigue also may be defined as failure to initiate or sustain physical activities [58]. The Multidimensional Assessment of Fatigue (MAF) has been used frequently as a subjective questionnaire to describe fatigue in research for individuals with fibromyalgia [3,5,49,149]. Humphrey developed a conceptual model of fatigue in fibromyalgia based on patient interviews [100]. Participants described fatigue as on overwhelming tiredness not relieved by rest or sleep. The subjects also gave descriptors of lack of energy, feeling of weakness or heaviness [100]. The perception of fatigue has been noted in relation to exercise capacity in a study by Bacchason [8] in a maximal incremental cycling test in individuals with fibromyalgia and healthy controls. During the cycling task, the individuals with fibromyalgia had lowered maximal exercise capacity and an increase rate of perceived exertion (RPE) compared to controls. Bandak demonstrated less time to exhaustion during isometric muscle contractions, and a doubling of pain in individuals with fibromyalgia compared to healthy controls [10].

Perceived cognitive fatigue is distinctly different from perceived physical fatigue and can be defined as failure to initiate and/or sustain attentional tasks [58] or cognitive dyscognition. Subjectively, individuals with fibromyalgia often use the phrase “fibro fog” to describe short term memory problems, mental clarity disturbances and dissociative symptoms [74]. Research into the area of “fibro fog” has focused on cognitive performance during neuropsychological testing rather than testing specifically with a cognitive fatigue task. Neuropsychological testing has been used to measure intelligence, memory or cognitive processing or the impact of physical performance on cognitive performance as opposed to perceived cognitive fatigue [37,84,85,87,129,130,169]. These studies show decreased memory, attention deficits, decreased verbal fluency and difficulty with information processing. However, cognitive performance is not perceived cognitive fatigue. Like the difference between muscle function and perceived physical fatigue, perceived cognitive fatigue can occur without a deficit in cognitive performance. To date few studies have examined perceived cognitive fatigue in fibromyalgia subjects. However, in other conditions such as Parkinson's, multiple sclerosis, stroke and brain injury, patients report greater mental/perceived cognitive fatigue than controls [40,99,107,140].

In Summary, there is a wide range of variability in the measurement of perceived physical fatigue and little to no measurement of perceived cognitive fatigue in individuals with fibromyalgia. The relationship between perceived cognitive fatigue and perceived physical fatigue in fibromyalgia patients is currently not well understood. There is also a gap in the understanding of how pain and fatigue affect function in individuals with fibromyalgia.

Function and Fibromyalgia

Pain and fatigue associated with fibromyalgia can interfere with daily function [3]. Patients with fibromyalgia report difficulty with strenuous physical activities, cognitive tasks such as paying bills and self-care activities such as pouring a cup of coffee and getting dressed [100]. Individuals with fibromyalgia also report having to take things slower in order to accomplish tasks [100]. Cardosos reported significant differences in functional capacity in women with fibromyalgia as defined by the six minute walk test, grip strength, one repetition maximum of knee flexors and extensors [31]. Goes et al. reported women with fibromyalgia have deficits in lower limb muscle strength in isometric test, balance and agility in functional tasks compared to healthy controls [86].

Physical activity and exercise clearly improve pain, fatigue and function in people with fibromyalgia and include aerobic exercise (land and aquatic) [22,23,95,110,197], tai chi [111,238,248], and yoga [32,33,51,123,124]. This exercise research shows strong evidence that aerobic cardiovascular exercise improves symptoms of fibromyalgia as well as improves quality of life [22,23]. However, exercise itself may be painful, and the pain may prevent a person from exercising [243]. In general, individuals with fibromyalgia are less physically active than sedentary, healthy controls. [147,148]. Thus, treatments aimed at decreasing pain will improve a person's ability to exercise and participate in activities of daily living. Fatigue may also impact function as fatigue may limit participation in work and social activities [3]. Okifuji developed a predictor model in individuals with fibromyalgia based on the patient's report of pain, fatigue and emotional distress over a 30 day period [166]. The model showed 1) emotional distress and pain increased fatigue;

2) fatigue, but not emotional distress increased pain and 3) pain but not fatigue increased emotional distress.

Fear of Movement (Kinesiophobia)

The fear of pain negatively correlates with function and positively correlates with pain intensity in patients with osteoarthritis, fibromyalgia and low back pain [185,245]. Pain-related fear is a concept which is part of the fear avoidance model proposed by Vlaeyen et al. [245]. It is a model to describe the relationship between pain related to movement and the fearful anticipation of the consequences. A simplified summary of this model follows. Following injury, the individual may follow one of two paths 1) experience no fear or 2) pain catastrophizing. For those with no fear following the pain experience they are able to reach recovery without difficulty. For those with increased pain catastrophizing, the pain leads to pain related fear and subsequently to avoidance behaviors resulting in disuse, depression and disability all which further impact the pain experience. For many individuals with fibromyalgia, the fear of pain and symptom exacerbation limits physical activity, function and participation in exercise [118]. The fear of movement (kinesiophobia) may be measured by the Tampa Scale of Kinesiophobia (TSK). The TSK measures of fear of movement or re injury in chronic pain patients in multiple scenarios (e.g., physical and work activity). It is possible that if we decrease pain intensity in individuals with fibromyalgia, we will concomitantly decrease fear of movement, and subsequently increase participation in exercise.

Transcutaneous Electrical Nerve Stimulation (TENS)

One treatment aimed at reducing central excitability, increased in fibromyalgia, and increasing central inhibition, reduced in fibromyalgia, is transcutaneous electrical nerve stimulation (TENS). TENS is a "non-pharmacological" treatment for pain that is inexpensive, safe, and easy to use. Prior studies show that TENS utilizes opioid receptors both spinally and supraspinally to produce inhibition of nociceptive dorsal horn neurons, reduce excitatory neurotransmitter release and reduce hyperalgesia [114,141,209,210]. TENS produces this effect by activating central inhibitory pathways that involve the periaqueductal gray and the rostral ventromedial medulla and the spinal cord [60,114,141,208]. Thus, TENS reduces central sensitization and central excitability by increased central inhibition [60,114,142,206] and decreased central excitability [114,138,141,208,212].

Although TENS is shown to be effective for several pain conditions such as osteoarthritis, chronic musculoskeletal pain, and postoperative pain [18,108,167], its effectiveness in treatment of people with fibromyalgia is virtually unknown. Four randomized controlled-trials have investigated the effectiveness of TENS on pain in people with fibromyalgia with mixed results. One compared effectiveness to s-adenosyl-l-methionin (SAMe), one to warmth therapy, one to massage therapy or sham TENS, and one to a placebo TENS. When compared to SAMe, TENS was not effective; however, TENS application was being applied at minimal intensities that caused a tingling sensation over 4 tender points [63]. We, and others, have previously shown that TENS

applied at inadequate intensities does not reduce pain or increase pressure pain thresholds (PPTs) [18,178,179]. When compared to warmth therapy TENS effectiveness was similar, with approximately a 1/10 decrease in pain for both treatments [139]. The treatments in this case were not compared to a placebo or a no-treatment control and thus specific effects could not be concluded [139]. Subjects were also simultaneously enrolled in a multidisciplinary treatment program consisting of exercise and cognitive behavioral therapies [139], both effective treatments for fibromyalgia [95]. Thus "effectiveness" of these interventions could be related to the multidisciplinary treatment and not to TENS or warmth therapy. Another study showed that both TENS and massage therapy were better than sham TENS for resting pain [233] which is in direct contrast to my study of TENS and individuals with fibromyalgia that active TENS had no effect on resting pain. It is possible that repeated TENS used in the prior study had a cumulative effect as compared to the study that used a one-time treatment [233]. In contrast, a fourth study [158] used TENS in combination with an exercise program. However TENS was given in the morning for 30 minutes 5 times per week for 3 weeks, and exercise was done in the afternoon and not during TENS. If TENS reduces pain during movement, the use of TENS during exercise should be more beneficial. Further, effectiveness of TENS is greater during the stimulation versus after it has been removed [61,179]. Like most pharmaceutical agents with a limited duration of action, TENS has a limited duration of action. Thus TENS studies should be designed to test efficacy during peak response. Lastly, all the above studies used resting pain as their primary measure for pain. In my study of TENS and individuals with fibromyalgia, resting pain was unaffected by TENS

while movement pain was significantly reduced. Thus, measurement of resting pain in this population may provide conflicting results on effectiveness of the treatment.

Conditioned Pain Modulation

Conditioned pain modulation (CPM) can be used to examine descending inhibition. CPM is a spinal-medullary-spinal pathway that is activated when two concomitant painful stimuli are applied at the same time [240]. In CPM, the first painful stimulus is applied (the conditioning stimulus) and then a second painful stimulus is applied outside the conditioning stimulus site (the test stimulus) in order to stimulate the descending inhibitory pathway. In healthy subjects, there is an increase in pressure pain threshold during CPM; this increase is reduced in individuals with fibromyalgia [119,126,133,228]. In animal studies, prior work shows that TENS activate descending inhibitory pathways [60,114] and inhibits sensitization of dorsal horn neurons [141]. Thus, TENS may be particularly useful in people with fibromyalgia for its ability to activate descending inhibitory pathways (reduced in patients with fibromyalgia) and to inhibit central excitability (increased in patients with fibromyalgia).

Hypothesis and Aims

Fibromyalgia is described as chronic widespread musculoskeletal pain and as such is frequently seen in clinical settings by physical therapists. Treatments aimed at decreasing pain and fatigue is expected to improve a person's ability to exercise and participate in activities of daily living. Without greater understanding of the interaction of pain, fatigue and function, we are limited in our ability to improve these symptoms for patients with fibromyalgia. The goal of these studies is to understand pain, fatigue, function and the interactions of these variables in patients with fibromyalgia. Three

experiments were designed to address pain, fatigue and function in individuals with fibromyalgia.

Study 1

Hypothesis 1: Higher levels of fatigue are associated with higher levels of pain and pain-related fear of movement, decreased function and decreased quality of life in individuals with fibromyalgia compared to healthy controls

Aim 1.1**:** To determine if pain, fatigue and fear of movement in individuals with fibromyalgia are different from healthy subjects.

Aim 1.2*:* To determine the degree to which fatigue, pain, and fear of movement are predictors of function and quality of life.

Overview: We will test this hypothesis by examining pain, fatigue, quality of life and function in individuals with fibromyalgia and compare these results to healthy controls.

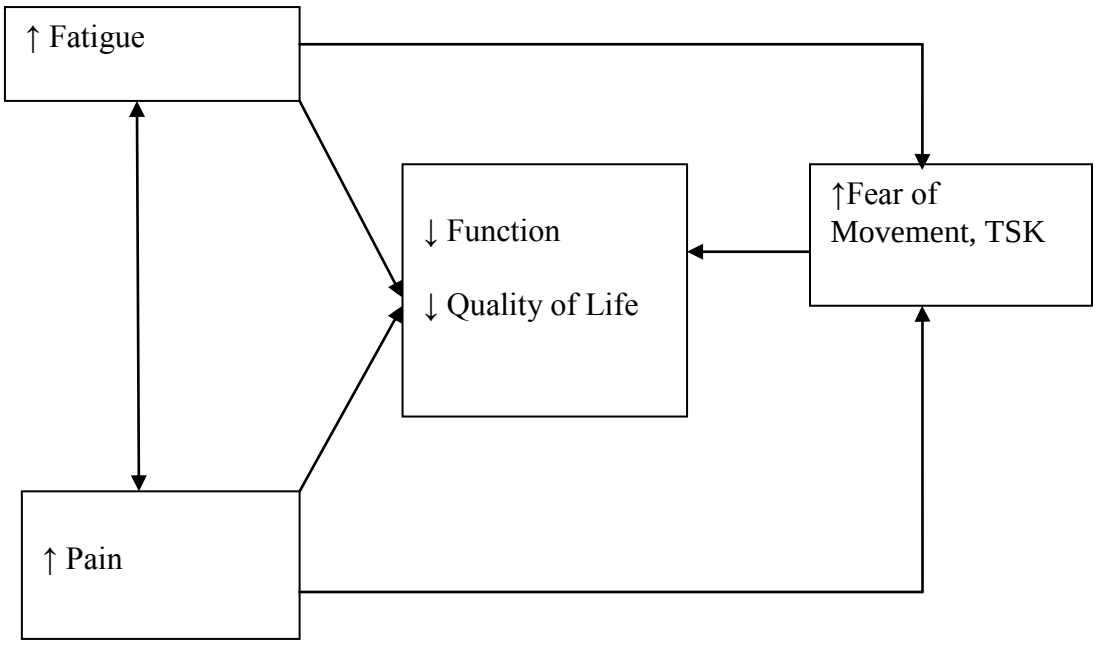

Figure 1.2: Model for Study 1

Study 2

Hypothesis 2.1: There will be greater perceived cognitive fatigue and perceived physical fatigue during fatigue tasks (cognitive fatigue task, physical fatigue task, dual fatigue task) in individuals with fibromyalgia compared to healthy controls. Perceived cognitive fatigue and perceived physical fatigue will occur to a greater degree in the dual fatigue task than in the single fatigue task.

Aim 2.1: To determine if perceived cognitive fatigue and perceived physical fatigue are enhanced during a cognitive fatigue task, physical fatigue task and dual fatigue task in individuals with fibromyalgia compared to healthy controls.

***Overview*:** I will test this hypothesis by examining perceived physical and perceived cognitive fatigue in response to physical fatigue task, cognitive fatigue task and dual fatigue tasks in individuals with fibromyalgia and compare to healthy controls.

Hypothesis 2.2: There will be greater pain and reduced function during fatigue tasks (cognitive fatigue task, physical fatigue task, dual fatigue task) in individuals with fibromyalgia compared to healthy controls.

Aim 2.2*:* To determine the impact of fatigue (perceived cognitive fatigue and perceived physical fatigue) on pain and function in individuals with fibromyalgia compared to healthy controls.

Overview: I will test this hypothesis by examining pain and function in individuals with fibromyalgia in response to a perceived physical fatigue, perceived cognitive fatigue and dual physical and cognitive fatigue task and compare to healthy controls.

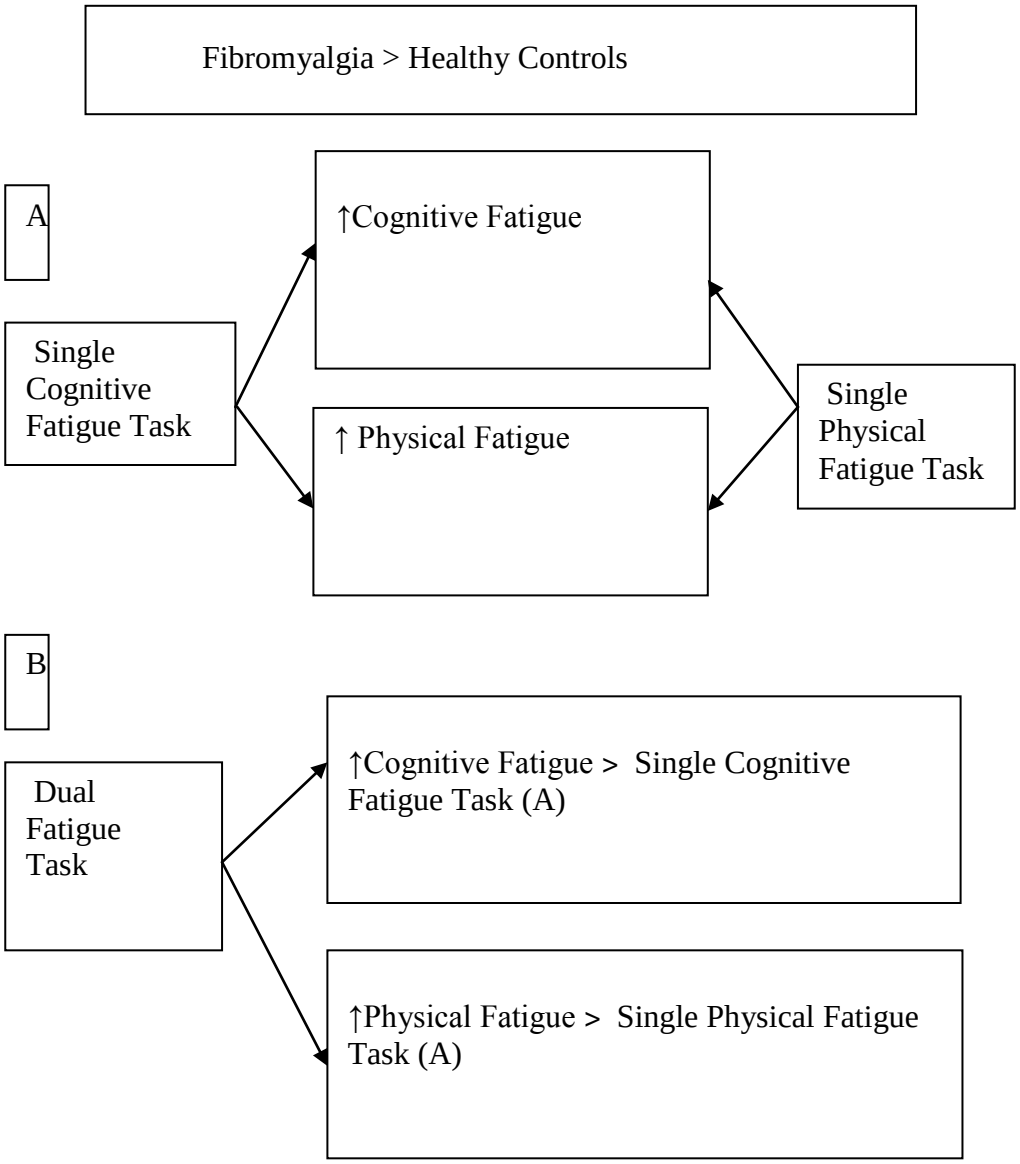

Figure 1.3: Model for Study 2, Hypothesis 2.1

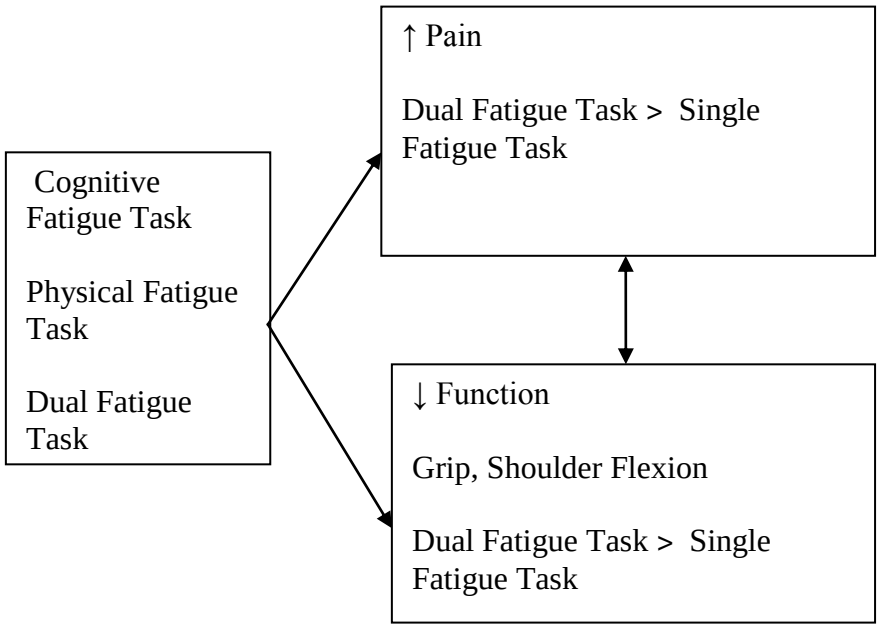

Figure 1.4: Model for Study 2, Hypothesis 2.2.

Study 3

Hypothesis 3.1: The application of TENS to people with fibromyalgia (FM) will reduce pain and fatigue, reduce central excitability and restore conditioned pain modulation (CPM) which will be manifested as improved function

Aim 1*:* To test the effectiveness of TENS on pain, fatigue and function in a crossover design study for patients with fibromyalgia with random assignment to three treatments: no TENS control, placebo TENS and active high frequency TENS.

Aim 2: To test the effect of TENS on central inhibition and hyperalgesia as an indicator of central excitability.

Overview: I will test this hypothesis by examining pain, fatigue and function before and after three treatments of TENS in individuals with fibromyalgia. I will further examine effects of TENS on PPTs (outside the site of testing) and central pain modulation as indicators of central excitability and central inhibition.

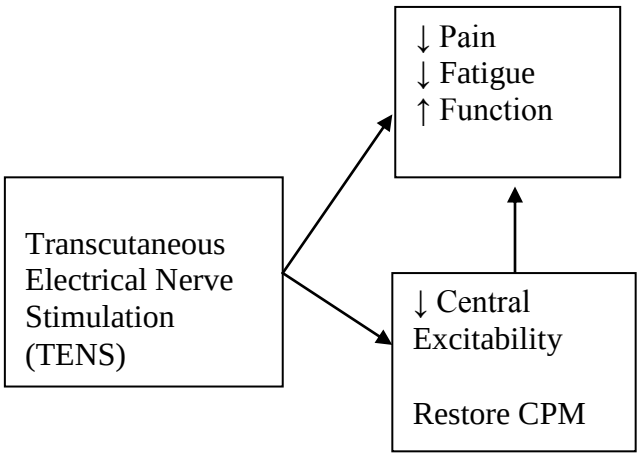

Figure 1.5: Model for Study 3

CHAPTER 2

PREDICTORS OF REDUCED FUNCTION AND QUALITY OF LIFE IN INDIVIDUALS WITH FIBROMYALGIA AND HEALTHY SUBJECTS

Abstract

Fibromyalgia is a condition characterized by chronic widespread muscular pain that interferes with function and quality of life. Fatigue is a symptom that affects the majority of people with fibromyalgia and can also interfere with daily activities and quality of life. People with fibromyalgia also have significantly higher fear of movement that could contribute to function and quality of life. The first aim of this study was to determine if pain, fatigue and fear of movement in individuals with fibromyalgia are different from healthy subjects. The second aim of the study was to determine the degree to which pain, fatigue and fear of movement are predictors of function and quality of life in individuals with fibromyalgia and healthy subjects. Pain was assessed with a visual analog scale (VAS) and pressure pain thresholds (hyperalgesia). Fatigue was assessed with a VAS, Multidimensional Assessment of Fatigue (MAF) and the Modified Fatigue Impact Scale (MFIS). Fear of movement was examined with the Tampa Scale of Kinesiophobia (TSK). Function was assessed with the six minute walk test, five time sit to stand, single leg stance and quality of life was assessed with the Fibromyalgia Impact Questionnaire (FIQ). Comparisons between groups (FM, HC) revealed significant differences between the groups for all variables ($p<0.01$). There were moderate and significant correlations between pain measures (VAS, PPT), fatigue measures (VAS, MAF, MFIS) and fear of movement (TSK) ($r=0.32$ to 0.89, $p\leq0.01$). Hierarchical linear

regression analyses were completed demonstrating significant models (p=0.001) that each included pain, fatigue and fear of movement as predictors of function (6WMT, FTSTS, SLS) and quality of life (FIQ) in individuals with fibromyalgia and healthy controls. These models show the strongest predictors to be pain and fatigue for function outcomes with TSK showing minimal effects on function: 6MWT (R^2=0.53, p=0.001); FTSTS (R^2=0.54, p=0.001); and SLS (R^2=0.51, p=0.001). For quality of life, pain, fatigue and fear of movement were all significant predictors (R^2=0.82, p=0.001). Thus, pain and fatigue alone can explain about 50% of the variability in function, pain, fatigue and fear of movement can explain 82% of quality of life in individuals with fibromyalgia and healthy controls.

Introduction

Fibromyalgia is a condition characterized by chronic widespread muscular pain. The 1990 diagnostic criterion from the American College of Rheumatology includes widespread pain for at least 3 months, pain on both sides of the body, above and below the waist and abnormal response to 11 of 18 predefined tender points with 4kg of pressure [250]. Fibromyalgia affects 4-10% of the US population [35,250] with 3.4% of women and 0.5% of men.

Individuals with fibromyalgia experience pain, fatigue and fear of movement that can interfere with function and quality of life [3,185,245] and the experience of fibromyalgia can impact quality of life [2,17,50,168,198,202,252]. Based on a survey, Silverman reports physicians' rate greater severity of fibromyalgia based on the subject's pain, functional disability and fatigue ratings [204]. Further, a survey of 203 individuals with fibromyalgia reported disease severity levels of fibromyalgia as mild (10%),

moderate (24%), or severe (66%) [198]. Thus, the majority of people with fibromyalgia rate the disease as severe and physicians suggest that this severity is based on ratings of perceived pain, fatigue and disability. It is unclear the degree to which pain, fatigue and fear of movement contribute to decreases in function and quality of life in people with fibromyalgia.

One of the most challenging aspects of fibromyalgia is the variable nature of pain among individuals with fibromyalgia [199]. Henriksson found that many people with fibromyalgia describe activities that aggravate the symptoms of fibromyalgia include carrying and holding objects and these activities are perceived as strenuous [97]. Individuals with fibromyalgia report difficulty with strenuous physical activities, cognitive tasks such as paying bills and self-care activities such as pouring a cup of coffee and getting dressed [100]. Individuals with fibromyalgia also report having to take things slower in order to accomplish tasks [100]. Thus, pain is a significant symptom that may contribute to participation in physical function.

Subjective descriptors of fatigue vary among individuals with fibromyalgia and fatigue impacts the overall quality of life through limitations in the ability to perform activities at work, home or socially [3]. People with fibromyalgia typically describe perceived physical fatigue as an overall feeling of tiredness or exhaustion, fatigue while completing functional tasks (e.g. folding laundry, drying hair or getting dressed), sleepiness, or feeling of heaviness [35]. Perceived physical fatigue also may be defined as failure to initiate or sustain physical activities [58]. Fatigue could contribute to decreased function and quality of life in individuals with fibromyalgia.

Fear of movement (kinesiophobia) is a concept which is part of the fear avoidance model proposed by Vlaeyen et al [245]. Fear of movement negatively correlates with function and positively correlates with pain intensity in patients with osteoarthritis, fibromyalgia and low back pain [185,245]. In an exercise induced shoulder injury model fear of movement was associated with pain and disability [170]. In people with low back pain, fear movement contributed to self-reported reported disability with walking and overall disability, but not flexibility [244]. Thus, fear of movement could contribute directly to function and quality of life in individuals with fibromyalgia.

Based on the changes in function and quality of life in individuals with fibromyalgia, we hypothesized that higher levels of fatigue are associated with higher levels of pain and pain-related fear of movement, decreased function and decreased quality of life in individuals with fibromyalgia compared to healthy controls. A prediction model was developed and is represented in Figure 2.1. The first aim of this study was to determine if pain, fatigue and fear of movement in individuals with fibromyalgia are different from healthy subjects. The second aim of the study was to determine the degree to which pain, fatigue and fear of movement are predictors of function and quality of life in individuals with fibromyalgia and healthy subjects.

Methods

Following completion of written consent, demographic information was gathered for the participants with respect to age, gender, ethnicity, marital status, education, income, body mass index, and length of diagnosis of fibromyalgia (Table 2.1). The order of testing included questionnaires for the clinical presentation of the individuals with fibromyalgia in comparison to healthy subjects. The questionnaires included the

Fibromyalgia Impact Questionnaire (FIQ), Multidimensional Assessment of Fatigue (MAF), Modified Fatigue Impact Scale (MFIS) and Tampa Scale of Kinesiophobia (TSK). Results for the participant's clinical characteristics are presented in Table2.1.

Subjects

Following approval by the Institutional Review Board at the University of Iowa, fibromyalgia subjects and healthy controls were recruited from the staff and students of the University of Iowa. Fibromyalgia subject information was gathered from a previously completed study which included 43 subjects (42F, 1M) ages 25-76 years (mean 49.1 ± 12.9 yr). The healthy age and sex matched control group included 38 subjects (37F, 1M) ages 25-76 years (mean 46.5 ± 2.5 yr). Subjects were matched in age by decade. Inclusion criteria for the individuals with fibromyalgia included: 1) diagnosis of fibromyalgia by a physician and 2) ability to walk for six minutes. Inclusion for healthy controls included 1) sex and age-matching by decade to the group of individuals with fibromyalgia and 2) no history of a chronic pain condition by a physician. Subjects in both groups were excluded if they had: 1) active inflammatory condition; 2) pacemaker; 3) pregnancy 4) uncontrolled hypertension or 5) significant cognitive deficits. Questionnaires were completed followed by pain measures, fatigue measures and function measures. Order of testing is shown in 2.2.

Pain Measures

Visual Analogue Scales (VAS): A visual analogue scale was used for measurement of pain at rest and pain with movement. Resting pain and pain with movement (during the 6 minute walk test) was assessed using a 10 cm visual analogue scale. Pain VAS has good test-retest reliability (ICC 0.71-0.99) and convergent validity

of 0.30 -0.95 [113]. The subject was instructed to place a single mark through the line at the appropriate point on the scale. Each scale consisted of a 10-cm horizontal line with descriptors at the far left and far right as “no pain” and “worst pain imaginable”, respectively.

Pressure Pain Threshold (PPT): Deep tissue hyperalgesia was measured using PPTs. Previous studies demonstrate that anesthetic blockade of the skin under the algometer has no effect on the PPT, thus this is a measure of deep tissue hyperalgesia [227]. A digital pressure algometer (Somedic AB, Farsta, Sweden) was used to measure pain threshold to deep mechanical stimuli. A $1cm^2$ algometer probe applied pressure at a rate of 40 kPa/sec. Subjects were instructed to activate a button when the sensation of pressure clearly became one of painful pressure and this value was recorded. PPTs were assessed over the cervical spine, lumbar spine, forearm and anterior tibialis muscle. Two bilateral cervical areas were tested for primary to assess primary hyperalgesia: 1) 2 cm lateral to the C3 spinous processes and 2) 2 cm lateral to C5 spinous processes. Two bilateral lumbar areas were tested: 1) 2 cm lateral to L3 spinous processes and 2) 2 cm lateral to the L5 spinous processes. The left forearm was assessed at 3, 4, 5 cm from mid elbow crease. The left leg was assessed at 5, 6, 7 cm below the inferior patellar pole, bisecting the anterior tibialis musculature. The PPT scores for the four areas were averaged to create a composite PPT score. Each subject had a practice trial on the non-testing forearm prior to data collection. PPT has excellent test-retest reliability (r=0.79-0.94) and is a valid measure of deep tissue hyperalgesia [227].

Fatigue Measures

Visual Analogue Scale (VAS): A visual analogue scale was used for measurement of fatigue at rest and fatigue with movement. Resting fatigue and fatigue with movement (during the 6 minute walk test) was assessed using a 10 cm visual analogue scale. Fatigue VAS has internal consistency (Cronbach's alpha 0.91-0.96) and concurrent validity (Pearson's correlation >.0.30 with $p<0.01$). Each scale consisted of a 10-cm horizontal line with descriptors at the far left "no fatigue" and far right as "worst fatigue imaginable" [131].

Multidimensional Assessment of Fatigue (MAF): The MAF is a 16-item self report measure of fatigue used in chronic illness according to four dimensions: degree and severity, distress, timing (over the past week, when it occurred and any changes), and impact on various activities of daily living (household chores, cooking, bathing, dressing, working, socializing, sexual activity, leisure and recreation, shopping, walking, and exercising). The MAF has been shown to have internal consistency $r=0.93$; and convergent validity with a fatigue VAS $r=.80$, $p<0.05$ [11].

Modified Fatigue Impact Scale (MFIS): The MFIS is a modified form of the Fatigue Impact Scale (Belza). This 21-item instrument that provides an assessment of the effect of fatigue in terms of physical, cognitive, and psychosocial functioning domains. Test retest reliability is 0.72-0.93 and the convergent validity is 0.48-0.80 [76,182].

Function and Quality of Life Measures

6 Minute Walk Test (6MWT): The 6MWT is a function test that measures the maximum distance a person can walk as fast as comfortable in 6 minutes. The test includes time, distance and speed of walking may be calculated – we used distance

walked as our outcome for the 6MWT. VAS for pain and fatigue were rated at the 3 minute time frame for ratings of pain with movement and fatigue with movement, respectively. The 6MWT is a sub-maximal test of aerobic capacity with indications for endurance [183]. The subjects completed the walk test in a 200 foot lap turning around at 100 feet. The 6MWT has excellent test-retest reliability (ICC=0.95-0.97) and construct validity (r=0.63-0.79) [131,232] .

Five Time Sit to Stand Test (FTSTS): The FTSTS is a test of lower body strength. The time it takes to complete five repetitions of sit to stand completed as quickly as possible is recorded. The FTSTS has good reliability (ICC >0.95) and validity (r=0.59-0.88) [165].

Single Leg Stance (SLS): SLS is a measure of balance. It was measured with a three trial average to a 30 second maximum with alternating testing of lower extremities. The inter-rater reliability for the best of 3 trials is excellent (0.994 with 95% confidence interval 0.989-0.996 [213].

Fibromyalgia Impact Questionnaire (FIQ): The FIQ is a standard measure in assessing quality of life and was used to measure each subject's ability to complete functional tasks at home, work and social areas of life. The test-retest reliability for the FIQ is r=0.56-0.92 concurrent validity is 0.46-0-0.96 [13].

Pain-Related Fear of Movement

Tampa Scale of Kinesiophobia (TSK): The TSK 17-item measure of fear of movement or re-injury in chronic pain patients in multiple scenarios (e.g., physical and work activity). Test retest reliability is r=0.64-0.91 with internal consistency with Cronbach's alpha 0.70-0.81 [185,186].

Data Analysis

The Statistical Package for the Social Sciences (SPSS v.21) was used for all statistical analysis. Clinical characteristics are listed in Table 2.1. Descriptive statistics (mean, standard error) were calculated for each study variable. Kolmogorov-Smirnov was used to test for normality of data. T-tests were performed to compare the measures (pain, fatigue and function) between the individuals with fibromyalgia and the healthy controls (Table 2.2). Data (mean $\pm$ S.E.M and 95% confidence intervals) for all measures are represented as a difference score ($p \leq 0.01$) for all outcome variables between groups. Cohen's d was calculated for effect size with each variable (Table 2.2).

Correlation analyses were completed with Pearson's correlation for study variables to review correlation matrix for the regression analysis for all variables with all subjects (Table 2.3). Upon analysis, high co-linearity was noted between pain at rest and pain with movement ($r=0.80$, $p \leq 0.01$) and fatigue at rest and fatigue with movement ($r=0.89$, $p \leq 0.01$) and for further analysis, pain was represented by the pain at rest measure and fatigue was represented by fatigue at rest measure. Pearson's correlation by group (Fibromyalgia, Healthy Controls) for each study variable and body mass index (BMI) was also calculated and is represented in Table 2.4.

To test the predictive model of pain, fatigue and fear of movement on function and quality of life, hierarchical linear regression (controlling for BMI) was performed separately by group (Fibromyalgia, Healthy Controls) for the effects of each independent variable of pain (pain, PPT average), fatigue (fatigue, MAF and MFIS) and fear of movement (TSK) on the dependent variables of function and quality of life (6MWT, FTSTS, SLS, and FIQ) (Models Ia - If, 2.5-2.12). Hierarchical linear regression analysis,

as a statistical method, allows for several independent variables to predict the dependent variable. It is the best method based on allowing entry of data based on a hypothesis and scientific theory and has the ability to view the predictive influence of a variable on the outcome because known predictors are held constant in the model as compared to stepwise regression which allows the statistical package to select the entry of the variables based on a mathematical equation.

Further hierarchical linear regressions (controlling for BMI) were performed for the predictive model with all subjects for pain, fatigue and fear of movement, function and quality of life (Models IIa-IIf, Tables 2.5-2.12).

Results

Clinical Characteristics

Eighty one age and sex matched adults participated in the study (FM=43, HC 38). Clinical characteristics of each sample are presented in Table 2.1. The average age for each group was FM= 49.1±12.9 years and HC= 46.5 ± 2.5 years. The majority of subjects were female with percentages of 97.6% (FM) and 97% (HC). These percentages are consistent with the population estimates for the diagnosis of fibromyalgia. The majority of the subject sample was Caucasian (87.7% FM and 73% HC), married (61%FM and 61.76%HC), income less than $60, 000 (63.4% FM and 82.35% HC). Education level varied between the FM and HC group with a majority of the FM group with some college or above (75.6%) compared to less than half of the HC group with some college or above at (48.82%).

Outcome Variable Comparison between Groups (FM, HC*)*

In comparing the group with fibromyalgia to healthy controls, all variables (pain, PPT average, fatigue, MAF, MFIS, BMI, TSK, 6MWT, FTSTS, SLS and FIQ) were significantly different ($p \leq 0.01$)(Table 2.2). In general, people with fibromyalgia had more pain, lower pain thresholds, greater fatigue, worse function and reduced quality of life. Cohen's d calculations demonstrated effect size for the difference between those with fibromyalgia and healthy controls was from -2.1 to 5.7, in ascending order (smallest to largest for all measures (Table 2.2).

Correlation Analysis

All Subject Analysis

Pearson's correlations for all subjects for all study variables (pain, fatigue, MAF, MFIS, TSK, PPT) demonstrated low to high correlations as shown in Table 2.3. All were significant ($p \leq 0.01$) except for 2 correlations: PPT with TSK ($r=-0.19$, $p>0.05$) and PPT with BMI ($r=-0.19$, $p>0.05$). The higher correlations for all subjects were for pain and fatigue ($r=0.89$, $p \leq 0.01$), followed by MAF and MFIS ($r=0.82$, $p \leq 0.01$).

Cohort Analysis (FM, HC)

Pearson's correlations by cohort (FM or HC, Table 2.4) demonstrated strong relationships in the individuals with fibromyalgia for the relationships of pain and fatigue ($r=0.82$, $p \leq 0.01$), MAF and MFIS ($r=0.66$, $p>$ $p \leq 0.01$) and moderate relationships for pain and MAF ($r=0.34$, $p \leq 0.01$), MFIS and TSK ($r=0.34$, $p \leq 0.01$) with weak negative associations for BMI and TSK ($r=-0.04$, $p \leq 0.05$) and BMI and PPT ($r=-0.04$, $p \leq 0.05$). In the healthy control group, strong relationships were noted for pain and fatigue ($r=0.49$, $p \leq 0.01$) and MAF and MFIS ($r=0.48$, $p \leq 0.01$).

Hierarchical Linear Regression Analyses

Tables 2.5-2.12 present the results of the hierarchical linear regression models used for the analyses (controlling for BMI) arranged by function variables and the quality of life variable: 6MWT, Table 2.5 and 2.6; FTSTS, Table 2.7 and 2.8; SLS, Table 2.9 and 2.10; and FIQ, Table 2.11 and 2.12. Two models were used in the analysis: (I) Model I: each independent variable by cohort (FM, HC) (Ia - If) and II) Model II: independent variables of pain, fatigue, fear of movement with all subjects (IIa - IIf). Independent variables used in the regression analysis included pain measures (pain VAS and PPT), fatigue measures (fatigue VAS, MAF and MFIS) and fear of movement (TSK). Interactions for FM and HC ($p<0.05$) are noted in each of the function and quality of life measures (Table 2.5, 2.7, 2.9, 2.11 Cohort FM/HC). Six of twenty four possible interactions for the cohorts were noted to be significant ($p<0.05$): 6MWT (fatigue, MAF); FTSTS (PPT, fatigue, MAF) and FIQ (MAF).

Six minute walk test (6MWT)

For the cohort analysis of Models Ia-If, the predictors in the groups with FM were significant for pain, PPT, fatigue, MAF and MFIS. The HC group demonstrated significance for the variable of fatigue. In Model II: IIa-IIf, all models were significant ($p=0.001$) with R^2 showing good strength (0.40 to 0.53). The strongest predictors were pain or fatigue for all subjects with TSK showing minimal effects. The strongest model was for PPT, fatigue and TSK ($R^2=0.53$, $p=0.001$) for the 6MWT.

Five times sit to stand (FTSTS)

In the cohort analysis for FTSTS, the predictors of pain and fatigue were significant ($p=0.01$) for the group with FM and no significance was found for the HC

group. Model II (IIa-IIf) demonstrated significance for all models with moderate strength with R^2=0.39 to 0.54, p=0.001. Coefficient p-values were significant for pain, MFIS, MAF and fatigue, p=0.01. The strongest predictors were pain or fatigue, with minimal contributions from the TSK, for all subjects with the FTSTS. The strongest model for FTSTS was pain, MFIS and TSK (R^2=0.54, p=0.001).

Single leg stance (SLS)

In the cohort analysis, each group of predictors for FM and HC were all significant at the p=0.01 level. Each predictor was moderate in strength. R^2 values for each predictor were: pain R^2 (FM=0.31 and HC=0.23); PPT R^2 (FM=0. 34 and HC=0.23); fatigue R^2 (FM=0.0.36 and HC=0.23); MAF R^2 (FM=0.30 and HC=0.23); MFIS R^2 (FM=0.38 and HC=0.24); TSK R^2 (FM=0.30 and HC=0.23). The group models (IIa-IIf) showed significance (p=0.001) for all models with moderate strength (R^2=0.45 to 0.51). The strongest predictive model was PPT average, MFIS and TSK (R^2=0.51, p=0.001), with pain and fatigue as the strongest predictors.

Fibromyalgia Impact Questionnaire (FIQ)

In the cohort analyses for FIQ, the predictors of pain and fatigue revealed a significant model value for the FM group for pain (R^2=0.30, p=0.01), PPT average (R^2=0.23, p=0.01); fatigue (R^2=0.44, p=0.01); MAF (R^2=0.48, p=0.01) and MFIS (R^2=0.32, p=0.01). The HC group revealed significant models for MAF (R^2=0.48, p=0.01) and MFIS (R^2=0.25, p=0.01). The group model (IIa-IIf) demonstrated significant models (p=0.001) with good strength R^2 =0.69 to 0.82. The strongest model (R^2=0.82, p=0.001) was for pain, MAF and TSK, all of which were strong contributors to the model.

Discussion

We were able to show a significant difference between individuals with fibromyalgia and healthy controls ($p \leq 0.01$) with the variables of pain, fatigue, fear of movement, function and quality of life which agree with prior studies [10,81,98,221]. Our results extend these prior findings and propose a prediction model for function and quality of life by using a combination of individuals with fibromyalgia and healthy subjects. Individuals with fibromyalgia and healthy controls were all used in the predictor model as the healthy control group demonstrated some pain, fatigue or fear of movement and thus was applicable to inclusion in a predictor model of predictor model for pain, fatigue and fear of movement and function.

Specifically our model used the independent variables of pain, fatigue and fear of movement to determine the degree to which pain, fatigue and fear of movement are predictors of function using several measures (6MWT, FTSTS, SLS) and quality of life (FIQ). In our model, these variables contribute about 50% to function outcome measures and as high as 82% to quality of life. These data therefore suggest that pain, fatigue and fear of movement are critical contributors to overall quality of life and ability to perform functional tasks in individual with fibromyalgia.

In the literature, prediction models for individuals with fibromyalgia have focused on predictions for pain, fatigue, function and quality of life. Prediction models for pain have shown that pain was predicted by number of body pain areas, negative affect, and quantitative sensory testing pain aftersensation [2,176,215]. Przekop reported in a community sample of women with fibromyalgia (n=238) that greater physical pain was reported by women who were older, less educated, more depressed, demonstrated higher

BMI and had been treated for fibromyalgia in the past 12 months. Staud and Anderson demonstrated the combination of tender point count, negative affect and wind-up aftersensations accounted for 50% of the variance in clinical pain intensity with windup aftersensation contributing up to 27%. Staud also demonstrated that the sum of local body areas of pain on a body diagram, tender point count and pain related negative affect accounted for 45% of the variance of clinical pain intensity in a study of 280 individuals with fibromyalgia.

Further, fatigue was predicted by the previous day of pain and sleep quality [162]. Nicassio demonstrated that greater depression and lower sleep quality were associated with higher fatigue in a study of 105 individuals with fibromyalgia. In addition, poor sleep quality fully accounted for the positive relationship between pain and fatigue in a cross sectional sample of 63 individuals with fibromyalgia who completed a diary for one week with daily assessment of pain, sleep quality and fatigue [162]. Thus, sleep may play a significant role in the symptom of fatigue in people with fibromyalgia.

Function measures in the literature for prediction models in individuals with fibromyalgia have focused on the assessment of physical functioning by questionnaires or by physical performance measures. Function measure questionnaires have included the FIQ and physical functioning subscale of the FIQ, physical ability impact scale and the SF-36 physical functioning subscale [30,50,194,239]. Physical performance measures for assessment of function in individuals with fibromyalgia have included the 6MWT, five time sit to stand test and bicycling. [30,54,98,235,239]. Homann demonstrated that individuals with fibromyalgia (n=19) walked shorter distances compared to healthy controls (n=20) and that there was a negative correlation between distance walked and

the FIQ score (lower distance and higher FIQ). Carbonell-Baeza examined the association between pain and functional capacity levels in a group of individuals with fibromyalgia (n=123). These subjects demonstrated an inverse association of tender point count with a chair stand test and distance walked in a 6MWT. A positive association of pressure pain threshold was noted with the chair stand, 6MWT distance and upper extremity range of motion. Van Liew analyzed questionnaires from 462 participants and found that self-efficacy was the only significant predictor of physical functioning ratings across time. Torma examined questionnaires from 224 individuals with fibromyalgia and developed predictor model that accounted for 48% of variance in physical function by age, income, education, depressive symptoms, body mass index, and physical activity levels accounted for 31%; pain added 14%; and resilience contributed an additional 3%. Thus, prior studies show activity levels, self-efficacy and pain are major contributors to functional deficits in people with fibromyalgia.

Quality of life has been most commonly assessed in individuals with fibromyalgia by the FIQ as a disease specific questionnaire, [13-15,17] but also included additional questionnaires for self- efficacy [50,196], sleep [198], and self-report of severity [204,252]. Culos-Reed found the importance of perceived control and ratings of well-being were predictive of higher levels of physical activity. Sanchez found in a study of individuals with fibromyalgia (n=74) that physiological anxiety was the best predictor of the sensory dimension of pain and fear of pain was a significant predictor of the pain intensity. Helplessness was the best predictor of the affective dimension of pain, however depression was a predictive variable of self-efficacy expectation. Schaefer found subjects (n=203) with worse severity of self-reported fibromyalgia showed significantly increased

pain severity, quality of life, fatigue, sleep disturbance, anxiety and depression. Silverman reported greater severity of fibromyalgia was significantly associated with higher levels of current pain and sleep interference. De Bruijn completed a study of 18 individuals with fibromyalgia and found that a reduced walking distance in the 6MWT correlated with higher self-reported pain on the FIQ. Wolfe found that the primary determinants of global severity and quality of life were pain, fatigue and function in individuals with fibromyalgia, and agrees with our study showing a significant contribution of pain and fatigue to quality of life.

Fear of movement as a predictor of function or quality of life in individuals with fibromyalgia has not been previously studied. The inclusion of healthy controls, as well as combining pain, fatigue and fear of movement likely underlie the moderate to high levels of our ability to detect functional deficits and reduced quality of life. Future studies should include sleep, physical activity levels, self-efficacy and/or pain catastrophizing as these factors have shown to contribute to pain and fatigue in fibromyalgia and thus contribute to the loss of function and quality of life.

Prediction models have been examined in other chronic pain conditions such as chronic musculoskeletal pain, chronic neck and low back pain, and shoulder pain. In chronic musculoskeletal pain, self-efficacy, pain catastrophizing and pain-related fear of movement impacted disability scores [59]. In chronic neck pain, disability was predicted by previous neck pain, intensity of neck pain, pain-related fear of movement and neck range of motion [195]. In chronic low back pain, fear of movement was predictive of disability and pain [12], and depression, non-physical pain symptoms, obesity and medication use were predictive of long term pain in women with chronic low back pain.

Presence of symptoms greater than 3 months, average pain intensity, range of motion of the shoulder and pain-related fear of movement all contributed to baseline shoulder function [134]. Thus, in several chronic pain conditions, fear of movement and pain contribute to function and disability. Our studies similarly show a contribution of pain and fear of movement to function and quality of life and add fatigue as a significant contributor.

In comparing our study to other prediction models in individuals with fibromyalgia and other chronic pain conditions we demonstrated the importance of pain and fatigue as strong contributors to each model of function (6MWT, FTSTS, SLS) and quality of life (FIQ). The TSK as a measure of pain-related fear of movement had a weaker contribution to the prediction model for function as compared to pain and fatigue. Our study utilized several domains as recommended by OMERACT. OMERACT (Outcome Measures in Rheumatology) is an independent initiative of international health professionals interested in outcome measures in rheumatology and includes a core domain set for fibromyalgia assessment in clinical trials and practice [149,150]. This domain set includes pain, tenderness, fatigue, patient global impressions, multidimensional function and sleep disturbance. Our study is also consistent with Wolfe's findings for domains of assessment for individuals with fibromyalgia. Wolfe completed a patient data study (n=5884) of RA patients with and without FM to determine patient severity of FM and health-related quality of life to determine whether 9 of the OMERACT variables were valued differently in FM compared with non-FM states. Wolfe found the three main determinants of severity of FM and health-related quality of life were pain, fatigue and function [252].

Limitations in our study may include our sample of subjects, lack of a physical activity survey and our definition of function. Our analysis further controlled for BMI and depression, which prior studies have found as contributors to severity of pain, function, and disability. Further studies should also include sleep, self-efficacy, and pain catastrophizing as prior studies show these play a significant role in pain, function and disability. With respect to our subject sample of age and sex matched individuals with fibromyalgia and healthy controls, they demonstrated similar clinical characteristics of age, sex, marital status, ethnicity and income but not education. Another possible limitation of our study is a lack of a physical activity survey or objective measure of activity outside the function measures of 6MWT, FTSTS and SLS. A physical activity survey may have captured self perception of function or given us a clearer rating of activity level for our subjects. The definition of function from a research perspective or in a clinical practice setting may differ from an individual's functional level or perception of function at home, work or social situations.

The impact of pain, fatigue and pain-related fear are important considerations in the assessment and treatment of individuals with fibromyalgia in a clinical setting. As these three domains have a relationship that impacts function and quality of life, it would be important to assess these symptoms during clinical and therapeutic activities. Pain during an exercise regime or education session can impact performance and participation. In addition, fatigue may impact the ability to perform a task as pain or pain-related fear of movement increases. Another consideration in a clinical setting would be the timing of these assessments. As pain and fatigue can vary with rest and movement, it would be important to assess before, during and after activities in the clinic and at home. All three

of these domains (pain, fatigue and pain-related fear) may impact patient performance, participation and follow through at home, work or social situations.

The proposed prediction model for pain, fatigue and fear of movement as we defined it in our study is a strong model for predicting function and quality of life in individuals with fibromyalgia. We were able to demonstrate that pain, fatigue and pain-related fear of movement contribute to a model of function and quality of life. Our model is consistent with other prediction models of chronic pain and highlights the importance of multiple assessments such as pain, fatigue and pain-related fear to capture the heterogeneity of the experience of fibromyalgia.

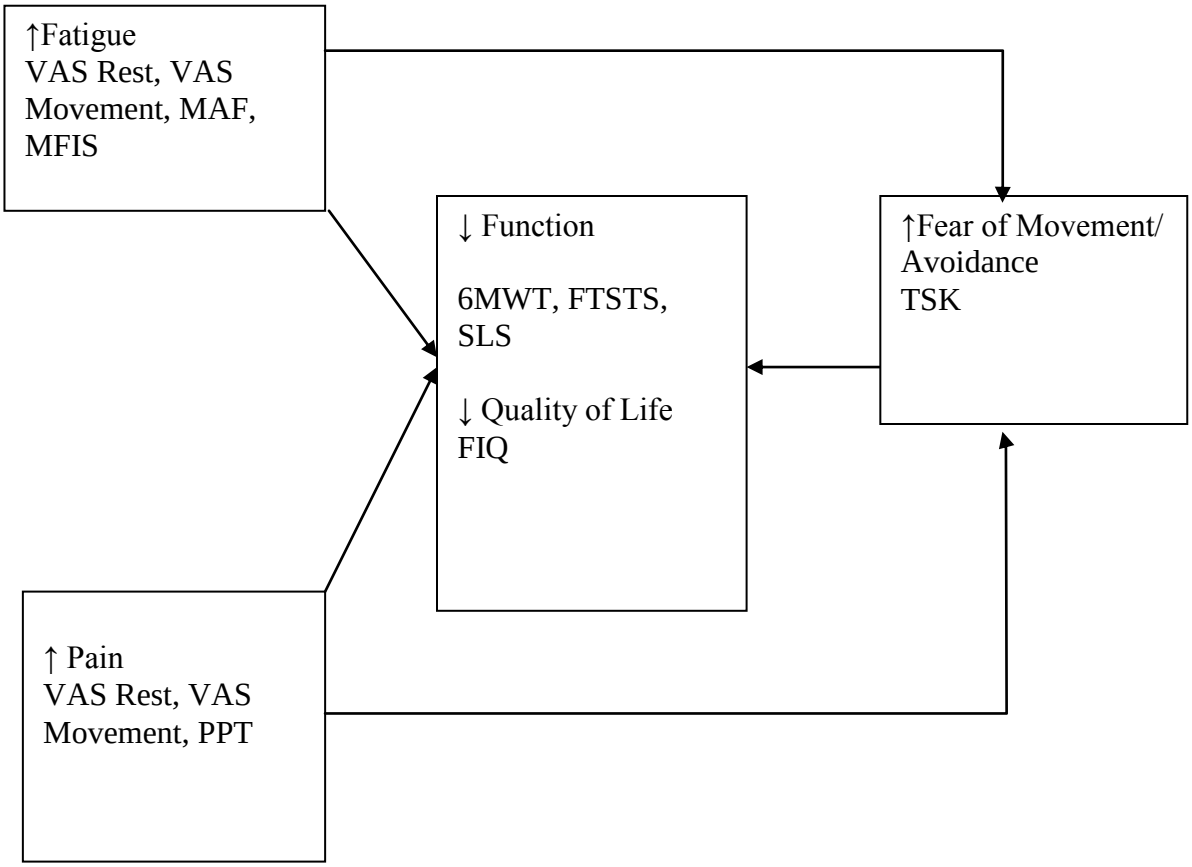

Figure 2.1: Prediction Model for pain, fatigue, fear of movement and function

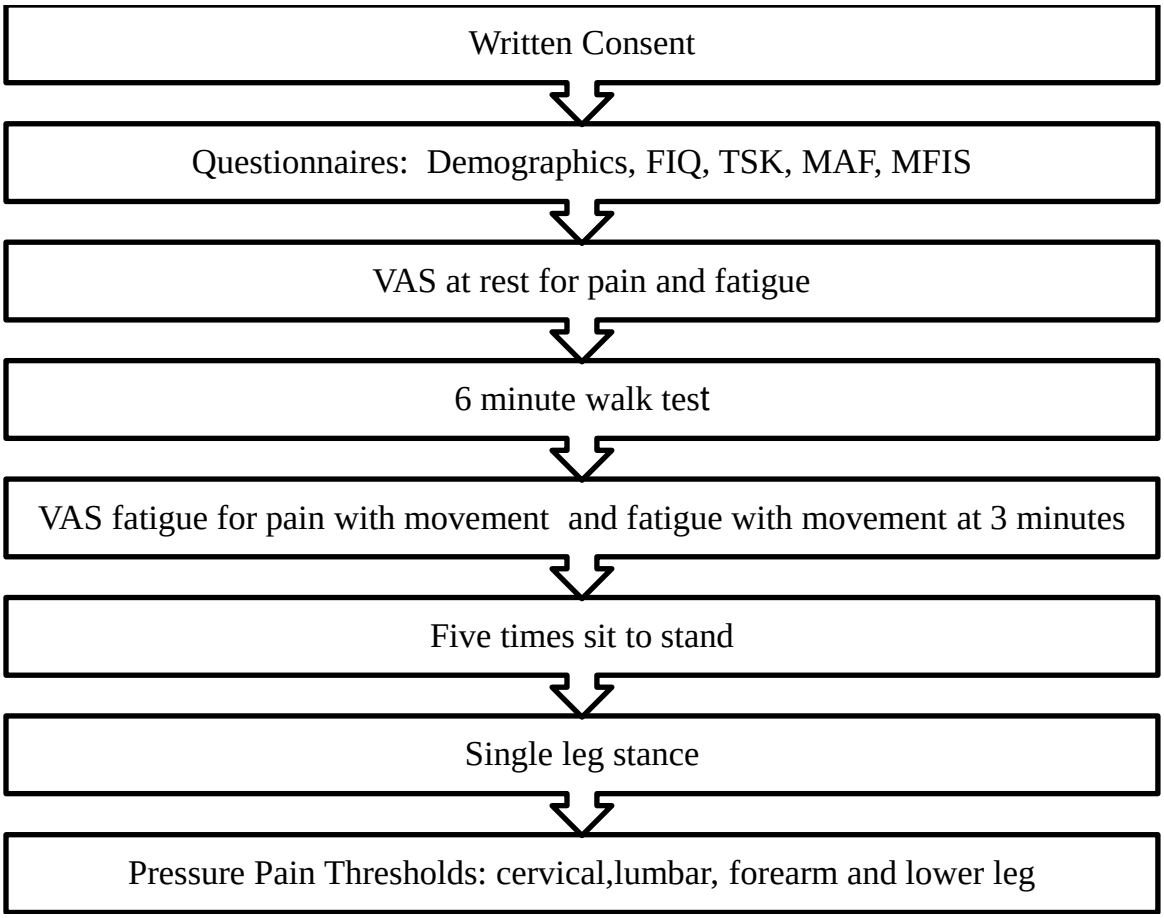

Figure 2.2: Order of Testing Study 1

Table 2.1: Demographics and clinical characteristics.

Total (N=81)	Fibromyalgia (n=43)	Healthy Subjects (n=38)	P Value
Age, years (female and male) (mean ± SEM)	49.1±12.9	46.5 ± 2.5	0.19
Female (% sample)	40 (97.6%)	37(97%)	0.87
Ethnicity (% sample)			
Caucasian	36 (87.7%)	25 (73.53%)	3.2
Others	5 (12.2%)	9 (26.47%)	3.2
Marital status (% sample)			
Married/co-habitating	25 (61.0%)	21 (61.76%)	1.2
Single/widowed/divorced	16 (39.0%)	13 (38.24%)	1.2
Education (% sample)			
High school or less	10 (24.4%)	14 (41.18%)	1.2
Some college or above	31 (75.6%)	20 (48.82%)	1.2
Income (% sample)			
< $ 60,000	26 (63.4%)	28 (82.35%)	2.1
≥ $60,000	15 (36.6%)	6 (17.65%)	2.1
Length of Fibromyalgia diagnosis, years	7.4±5.6	Not Applicable	

Data are mean + S.E.M.

Table 2.2: Data for all outcome measures are represented as a difference score.

Total n=81	Fibromyalgia n=43	Healthy Controls n=38	P Value	Effect Size Cohen's d
FIQ (0-100)	59.85 ± 2.25 (55.31 to 64.38)	9.86 ±1.53 (6.76 to 12.94)	p≤0.01	5.7
MAF	34.51 ± 1.46 (31.54 to 37.47)	10.87 ± 1.74 (7.33 to 14.41)	p≤0.01	4.5
MFIS	50.36 ± 2.37 (45.55 to 55.18)	15.89 ±1.798 (15.89 to 19.53)	p≤0.01	3.7
Pain (0-10cm)	4.54 ± 0.38 (3.78 to 5.43)	0.20 ± 0.08 (0.04 to 0.35)	p≤0.01	3.4
Fatigue (0-10cm)	4.64 ± 0.43 (3.73 to 5.47)	0.67 ± 0.18 (0.29 to 1.04)	p≤0.01	2.8
FTSTS (seconds)	14.84 ± 0.82 (13.49 to 16.91)	7.53 ± 0.41 (6.69 to 8.37)	p≤0.01	2.5
TSK	35.34 ± 1.59 (32.01 to 38.44)	22.92 ± 1.28 (20.32 to 25.52)	p≤0.01	1.9
BMI	33.75 ±1.464 (30.79 to 36.70)	26.62 ± 1.010 (23.94 to 28.63)	p≤0.01	1.2
PPT Average	340.34.81 ± 22.67 (294.59 to 286.10)	487.09 ± 21.36 (443.81 to 530.38)	p≤0.01	-1.4
SLS (seconds)	16.85 ± 1.57 (13.28 to 19.99)	26.61 ± 1.01 (21.34 to 31.88)	p≤0.01	-1.6
6MWT (feet)	1348.72 ± 55.52 (1259.34 to 1470.41)	1910.63 ± 36.67 (1835.85 to 1985.40)	p≤0.01	-2.1

Data are mean + S.E.M and 95% confidence intervals. PPT=Pressure pain threshold, MAF=Multidimensional Assessment of Fatigue, MFIS=modified fatigue impact scale, BMI=body mass index6MWT=six minute walk test, FTSTS=five time sit to stand, SLS=single leg stance, FIQ=Fibromyalgia Impact Questionnaire, TSK=Tampa scale of Kinesiophobia

Table 2.3: Correlation Matrix Variables in the Regression Analysis

		1	2	3	4	5	6	7
1	Pain	-						
2	Fatigue	0.89**	-					
3	MAF	0.67**	0.66**	-				
4	MFIS	0.69**	0.70**	0.82**	-			
5	TSK	0.55**	0.53**	0.43**	0.53**	-		
6	PPT average	-0.43**	-0.44**	-0.50**	-0.44**	-0.19	-	
7	BMI	0.36**	0.33**	0.32**	0.39**	0.34**	-0.19	-

* $p \leq 0.05$, ** $p \leq 0.01$

Table 2.4: Pearson correlations coefficients by cohort: FM (lower) and HC (upper)

		1	2	3	4	5	6	7
1	Pain	-	0.49**	-0.04	-0.03	0.17	0.12	-0.03
2	Fatigue	0.82**	-	0.01	0.09	0.05	-0.07	-0.01
3	MAF	0.34**	0.44	-	0.48**	-0.29	-0.27	-0.07
4	MFIS	0.28	0.41	0.66**	-	-0.23	-0.03	-0.15
5	TSK	0.28	0.25	0.31	0.34**	-	0.12	-0.04
6	PPT average	-0.20	0.29	-0.29	-0.31	0.01	-	-0.06
7	BMI	0.13	0.10	0.16	0.28	-0.26*	-0.04	-

* $p \leq 0.05$, **$p \leq 0.01$

Table 2.5: Cohort (FM, HC): (6MWT) Hierarchical Linear Regression Model***

Level	Predictors	Cohort	β	Std β	Coefficient p value	R^2	Model p value	FM/HC Group p<0.05
Ia.	Pain VAS Rest	FM	-46.41	-0.32	***0.04**	0.10	***0.04**	
		HC	43.73	0.06	0.72	0.00	0.72	
Ib.	PPT	FM	0.85	0.35	****0.01**	0.29	****0.01**	
		HC	-0.04	-0.01	0.94	0.01	0.78	
Ic.	Fatigue VAS Rest	FM	-58.25	-0.46	****0.01**	0.40	****0.01**	*
		HC	-196.31	-0.64	****0.01**	0.42	****0.01**	
Id.	MAF	FM	-10.20	-0.28	0.06	0.27	****0.01**	
		HC	1.75	0.06	0.75	0.02	0.74	*
Ie.	MFIS	FM	-8.26	-0.36	***0.02**	0.31	****0.01**	
		HC	-0.57	-0.02	0.92	0.02	0.77	
If.	TSK	FM	1.10	0.03	0.83	0.18	0.21	
		HC	-5.48	-0.13	0.45	0.03	0.59	

FM=Fibromyalgia, HC=Healthy Controls***controlled for BMI, *p≤0.05, **p≤0.01

Table 2.6: All Subjects: (6MWT) Hierarchical Linear Regression Model***

Level	Predictors	Cohort	β	Std β	Coefficient p value	R^2	Model p value	FM/HC Group p<0.05
IIa.	Pain VAS	All	24.43	0.16	0.37	0.51	****0.001**	
	Fatigue VAS		-110.15	-0.69	****0.01**			
	TSK		-1.64	-0.04	0.67			
IIb.	Pain VAS	All	-54.27	-0.36	****0.01**	0.41	****0.001**	
	MAF		-4.07	-0.14	0.24			
	TSK		-1.75	-0.05	0.68			
IIc.	Pain VAS	All	-45.16	-0.30	***0.02**	0.44	****0.001**	
	MFIS		-11.60	-0.25	****0.01**			
	TSK		-0.46	-0.01	0.91			
IId.	PPT	All	0.63	0.23	***0.03**	0.40	****0.001**	
	MAF		-6.15	-0.21	0.06			
	TSK		-6.18	-0.16	0.13			
IIe.	PPT	All	0.59	0.21	***0.03**	0.44	****0.001**	
	MFIS		-6.91	-0.33	****0.01**			
	TSK		-3.80	-0.10	0.34			
IIf.	PPT	All	0.43	0.16	0.08	0.53	****0.001**	
	Fatigue VAS		-79.90	-0.50	****0.01**			
	TSK		-0.95	-0.02	0.80			

FM=Fibromyalgia, HC=Healthy Controls***controlled for BMI, *p≤0.05, **p≤0.01

Table 2.7: Cohort (FM, HC): (FTSTS) Hierarchical Linear Regression Model***

Level	Predictors	Cohort	β	Std β	Coefficient p value	R^2	Model p value	FM/HC Group p<0.05
Ia.	Pain VAS Rest	FM	0.96	0.45	****0.01**	0.20	***0.01**	
		HC	0.22	0.04	0.81	0.01	0.82	
Ib.	PPT	FM	-0.01	-0.27	0.08	0.08	0.21	*
		HC	0.01	0.35	***0.03**	0.14	0.08	
Ic.	Fatigue VAS F	FM	1.01	0.50	****0.01**	0.26	****0.01**	*
		HC	-0.32	-0.14	0.42	0.03	0.61	
Id.	MAF	FM	0.23	0.38	*0.02	0.14	0.06	*
		HC	-0.03	-0.14	0.41	0.03	0.60	
Ie.	MFIS	FM	0.13	0.37	***0.03**	0.14	0.07	
		HC	0.02	0.08	0.64	0.02	0.76	
If.	TSK	FM	0.08	0.16	0.34	0.02	0.61	
		HC	-0.06	-0.17	0.59	0.04	0.51	

FM=Fibromyalgia, HC=Healthy Controls***controlled for BMI, *p≤0.05, **p≤0.01

Table 2.8: All Subjects: (FTSTS) Hierarchical Linear Regression Model***

Level	Predictors	Cohort	β	Std β	Coefficient p value	R^2	Model p value	FM/HC Group p<0.05
IIa.	Pain VAS	All	0.93	0.47	****0.01**	0.50	****0.001**	
	Fatigue VAS		0.46	0.22	0.19			
	TSK		0.01	0.02	0.83			
IIb.	Pain VAS	All	1.06	0.54	****0.01**	0.51	****0.001**	
	MAF		0.08	0.21	0.06			
	TSK		0.01	0.01	0.89			
IIc.	Pain VAS	All	0.96	0.49	****0.01**	0.54	****0.001**	
	MFIS		0.09	0.33	****0.01**			
	TSK		-0.01	-0.03	0.80			
IId.	PPT	All	0.00	-0.11	0.28	0.39	****0.001**	
	MAF		0.16	0.43	****0.01**			
	TSK		0.09	0.18	0.08			
IIe.	PPT	All	0.00	-0.12	-1.27	0.44	****0.001**	
	MFIS		0.14	0.53	4.80			
	TSK		0.06	0.11	1.09			
IIf.	PPT	All	0.00	-0.11	0.24	0.46	****0.001**	
	Fatigue VAS		1.13	0.55	****0.01**			
	TSK		0.05	0.09	0.36			

FM=Fibromyalgia, HC=Healthy Controls***controlled for BMI, *p≤0.05, **p≤0.01

Table 2.9: Cohort (FM, HC): (SLS) Hierarchical Linear Regression Model***

Level	Predictors	Cohort	β	Std β	Coefficient p value	R^2	Model p value	FM/HC Group p<0.01
Ia.	Pain VAS Rest	FM	-0.54	-0.13	0.32	0.31	**0.01	
		HC	0.92	0.07	0.65	0.23	**0.01	
Ib.	PPT	FM	0.02	0.21	0.11	0.34	**0.01	
		HC	0.00	-0.04	0.78	0.23	**0.01	
Ic.	Fatigue VAS R	FM	-1.12	-0.28	*0.05	0.36	**0.01	
		HC	0.25	0.04	0.77	0.23	**0.01	
Id.	MAF	FM	-0.15	-0.14	0.35	0.30	**0.01	
		HC	0.02	0.03	0.84	0.23	**0.01	
Ie.	MFIS	FM	-0.24	-0.33	*0.02	0.38	**0.01	
		HC	-0.05	-0.09	0.57	0.24	**0.01	
If.	TSK	FM	-0.02	-0.02	0.90	0.30	**0.01	
		HC	0.00	0.00	0.98	0.23	**0.01	

FM=Fibromyalgia, HC=Healthy Controls***controlled for BMI, *p≤0.05, **p≤0.01

Table 2.10: All Subjects: (SLS) Hierarchical Linear Regression Model***

Level	Predictors	Cohort	β	Std β	Coefficient p value	R^2	Model p value	FM/HC Group p<0.05
IIa.	Pain VAS	All	-1.36	-0.38	*0.03	0.48	**0.001	
	Fatigue VAS		0.20	0.06	0.75			
	TSK		-0.02	-0.02	0.82			
IIb.	Pain	All	-0.74	-0.21	0.10	0.45	**0.001	
	MAF		-0.06	-0.09	0.43			
	TSK		-0.02	-0.02	0.82			
IIc.	Pain	All	-0.31	-0.09	0.45	0.50	**0.001	
	MFIS		-0.49	-0.46	**0.01			
	TSK		0.02	0.02	0.84			
IId.	PPT	All	0.01	0.16	0.11	0.45	**0.001	
	MAF		-0.08	-0.13	0.24			
	TSK		-0.08	-0.09	0.34			
IIe.	PPT	All	0.01	0.10	0.24	0.51	**0.001	
	MFIS		-0.16	-0.33	**0.01			
	TSK		-0.01	-0.01	0.95			
IIf.	PPT	All	0.01	0.12	0.20	0.49	**0.001	
	Fatigue VAS		-1.02	-0.28	**0.01			
	TSK		-0.02	-0.02	0.85			

FM=Fibromyalgia, HC=Healthy Controls***controlled for BMI, *p≤0.05, **p≤0.01

Table 2.11: Cohort (FM,HC): (FIQ) Hierarchical Linear Regression Model***

Level	Predictors	Cohort	β	Std β	Coefficient p value	R^2	Model p value	FM/HC Group p<0.05
Ia.	Pain VAS Rest	FM	2.79	0.48	**0.01	0.30	**0.01	
		HC	-0.78	-0.04	0.82	0.05	0.42	
Ib.	PPT	FM	-0.04	-0.39	**0.01	0.23	**0.01	
		HC	-0.01	-0.12	0.48	0.06	0.33	
Ic.	Fatigue VAS R	FM	3.38	0.58	**0.01	0.44	**0.01	
		HC	1.79	0.21	0.20	0.09	0.19	
Id.	MAF	FM	1.03	0.64	**0.01	0.48	**0.01	*
		HC	0.51	0.59	**0.01	0.39	**0.01	
Ie.	MFIS	FM	0.50	0.48	**0.01	0.32	**0.01	
		HC	0.39	0.46	**0.01	0.25	**0.01	
If.	TSK	FM	0.23	0.16	0.30	0.10	0.12	
		HC	-0.23	-0.19	0.25	0.08	0.22	

FM=Fibromyalgia, HC=Healthy Controls***controlled for BMI, *p≤0.05, **p≤0.01

Table 2.12: All Subjects: (FIQ) Hierarchical Linear Regression Model***

Level	Predictors	Cohort	β	Std β	Coefficient p value	R^2	Model p value	FM/HC Group p<0.05
IIa.	Pain VAS	All	4.48	0.46	**0.01	0.69	**0.001	
	Fatigue VAS		2.90	0.28	*0.04			
	TSK		0.25	0.10	0.20			
IIb.	Pain VAS	All	3.79	0.39	**0.01	0.82	**0.001	
	MAF		0.96	0.52	**0.01			
	TSK		0.19	0.08	0.21			
IIc.	Pain VAS	All	4.20	0.43	**0.01	0.80	**0.001	
	MFIS		0.68	0.51	**0.01			
	TSK		0.07	0.03	0.67			
IId.	PPT	All	-0.03	-0.17	0.72	0.77	**0.001	
	MAF		1.18	0.63	**0.01			
	TSK		0.50	0.20	**0.01			
IIe.	PPT	All	-0.04	-0.23	**0.01	0.76	**0.001	
	MFIS		0.84	0.63	**0.01			
	TSK		0.38	0.15	*0.03			
IIf.	PPT	All	-0.05	-0.25	**0.01	0.70	**0.001	
	Fatigue VAS		5.52	0.54	**0.01			
	TSK		0.39	0.13	0.06			

FM=Fibromyalgia, HC=Healthy Controls***controlled for BMI, *p≤0.05, **p≤0.01

CHAPTER 3

COGNITIVE, PHYSICAL OR DUAL FATIGUE TASKS ENHANCE PAIN, PERCEIVED COGNITIVE FATIGUE AND PERCEIVED PHYSICAL FATIGUE IN PEOPLE WITH FIBROMYALGIA WHEN COMPARED TO HEALTHY CONTROLS

Abstract

Fibromyalgia is a condition characterized by chronic widespread muscle pain and fatigue. The primary objective of this study was to determine if pain, perceived cognitive fatigue, and perceived physical fatigue were enhanced in participants with fibromyalgia compared to healthy controls during a cognitive fatigue task, a physical fatigue task and a dual fatigue task. Twenty four individuals with fibromyalgia and 32 healthy controls completed pain, fatigue and function measures. A cognitive fatigue task (Controlled Oral Word Association Test) and physical fatigue task (Valpar peg test) were done individually and combined for a dual fatigue task. Resting pain, perceived cognitive fatigue and perceived physical fatigue were assessed during each task using visual analogue scales. Function was assessed with shoulder range of motion and grip. People with fibromyalgia had significantly higher increases in pain and fatigue when compared to healthy subjects with all fatigue tasks ($p<0.01$). For the physical fatigue task, people with fibromyalgia performed less well when compared to healthy controls during transfer of pegs from waist to overhead ($p<0.001$). These data show that people with fibromyalgia show larger increases in pain and fatigue to both cognitive and physical fatigue tasks and reduced function in a physical fatigue task. Thus, how physical and cognitive activity might impact pain and fatigue is an important consideration for the clinician in terms of

clinical instruction and education, clinical performance and exercise performance in treatment of individuals with fibromyalgia.

Introduction

Fibromyalgia affects 4-10% of the US population [35,89] with 3.4% of women and 0.5% of men. The 1990 American College of Rheumatology diagnostic criteria for fibromyalgia includes chronic widespread pain on both sides of the body and above and below the waist as well as pain in 11 of 18 specified sites (tender points) with digital palpation [250]. Fatigue is an extremely common symptom in fibromyalgia with up to 100% of individuals with fibromyalgia reporting fatigue and is greater in severity compared to other arthritic conditions[151,256] Fatigue, as described clinically, is a subjective experience may have both physical and cognitive components that are related yet distinct [3,58,223]. While the pain associated with fibromyalgia contributes to significantly reduced function, the relationship between pain, fatigue and function is currently not well-understood.

Muscle fatigue has been previously measured in people with fibromyalgia using a variety of techniques. Voluntary muscle strength and endurance are decreased in people with fibromyalgia [103-105,143,152,153,164]. In general these prior studies have examine static contractions of a single muscle in the upper extremity or the lower extremity, or a bicycle exercise task. When compared to sedentary controls, there are no differences in central fatigue indices for the quadriceps muscle [152,164] but there were for the biceps muscle [34]. Direct measures of muscle fatigue could be task-dependent or muscle dependent. On the other hand, consistently, people with fibromyalgia rate their perceived fatigue significantly higher before and during exercise tasks – bicycle task or

single muscle contractions [137,152-155]. Thus, subjective fatigue responses in people with fibromyalgia may not reflect changes at the muscle level. People with fibromyalgia typically describe fatigue as an overall feeling of tiredness or exhaustion, fatigue while completing functional tasks (e.g. folding laundry, drying hair or getting dressed), decreased attention, sleepiness, or feeling of heaviness [35].Thus, examination of perceived physical fatigue in response to functional task may be distinctly different than that to a fatiguing exercise task using a single muscle.

Perceived cognitive fatigue is distinctly different from perceived physical fatigue and is often referred to as decreased performance during acute but sustained mental effort or cognitive dyscognition [85] – referred to as "fibro fog". 'Fibro fog' is a self-reported perception of cognitive difficulties such as mental confusion, memory difficulties, memory decline or speech difficulties [1,74,85,129,130]. Cognitive performance is typically measured by verbal fluency, memory, concentration, automatic processing [37,38,84,85,169], and is also commonly decreased in people with fibromyalgia [74]. Performing both a physical and a cognitive fatigue task simultaneously exacerbates both physical and cognitive performance when done as individual tasks in people with neurological diseases, i.e. stroke, multiple sclerosis and Parkinson's [19,20,68,116]. However, it is unclear if a decrease in performance is noted in people with fibromyalgia during a simultaneous dual fatigue task.

Therefore, we developed the current study to examine the interactions between pain, perceived cognitive fatigue, and perceived physical fatigue in individuals with fibromyalgia in comparison to healthy controls. We specifically used a perceived physical fatigue task that is clinically relevant, examined effects of perceived cognitive

fatigue, examined a dual fatigue task (physical and cognitive fatigue task simultaneously) and measured changes in pain, perceived physical fatigue, and perceived cognitive fatigue. We tested the following aims: 1) To determine if perceived cognitive fatigue and perceived physical fatigue are enhanced during a cognitive fatigue task, physical fatigue task and dual fatigue task in individuals with fibromyalgia compared to healthy controls and 2) determine the impact of fatigue (perceived cognitive fatigue and physical fatigue) on pain and function in individuals with fibromyalgia compared to healthy controls.

Methods

Subjects

Following approval by the Institutional Review Board at the University of Iowa, healthy subjects and individuals with fibromyalgia were recruited through a university advertisement from the staff and students of the University of Iowa and a laboratory database of interested participants with fibromyalgia. To be included, subjects had to be between the ages 18-86, be able to reach overhead, be able to stand for at least 5 minutes, and have no history of shoulder injury or surgery. Additional inclusion criteria for the subjects with fibromyalgia included diagnosis of fibromyalgia as described by the 1990 American College of Rheumatology criterion for fibromyalgia [250]. Criteria for exclusion were: 1) uncontrolled hypertension, 2) active inflammatory condition, 3) cognitive deficits, 4) shoulder injury or surgery or unable to reach overhead, 5) pregnancy, or 6) unable to stand for at least 5 minutes. Power analysis for the sample size for this study was based on a previous study by Cherry [37] which revealed that decreased physical performance levels coincided with decreases in cognitive performance [37]. The effect size in the study by Cherry was 1.73. Sample size calculations using the

power and sample size calculator by DuPont and Plummer [67] alpha = .05, power at 80%, two treatment groups, it was calculated that 24 participants were required per group. In the current study 24 individuals with fibromyalgia (23 female, 1 male) aged 25-72 (female mean 51.87, SD11.11; male 65) and 34 healthy controls (33 female, 1 male) aged 25-77 years (female mean 45.03, SD 14.62, male 47) participated in the study.

Demographic information was gathered for age, gender, ethnicity, marital status, education, income, body mass index, and length of diagnosis of fibromyalgia (Table 3.1). Several questionnaires were completed to assist in the clinical presentation of the individuals with fibromyalgia in comparison to healthy subjects and included the Mini-Mental State Exam (MMSE), Fibromyalgia Impact Questionnaire (FIQ), Center for Epidemiological Studies – Depression (CES-D), Multidimensional Assessment of Fatigue (MAF), Modified Fatigue Impact Scale (MFIS) and Tampa Scale of Kinesiophobia (TSK). Results for the participant's clinical characteristics are presented in Table 3.1.

Mini-Mental State Exam (MMSE): The mini mental state exam is an 11-item measure of cognitive function: orientation, registration, attention and calculation, recall and language. Test-retest reliability for the MMSE is r=0.64 to 0.85 and construct validity of 0.69-0.78 [184].

Fibromyalgia Impact Questionnaire (FIQ): The FIQ was used to measure each subject's ability to complete functional tasks at home, work and social areas of life. The test-retest reliability for the FIQ is r=0.56-0.92 concurrent validity is 0.46-0-0.96 [13].

Center for Epidemiological Studies – Depression (CES-D): The CES-D is a 20 item self-report scale regarding the symptoms of depression in the last week. Higher

scores indicate more depressive symptoms. The CES-D has been shown to be a reliable measure of depressive symptom with high internal consistency with Cronbach's alpha 0.85-0.90 and construct validity of r=0.69 - 0.75 [177].

Multidimensional Assessment of Fatigue (MAF): The MAF is a 16-item self-report measure of fatigue according to four dimensions: degree and severity, distress, timing (over the past week, when it occurred and any changes), and impact on various activities of daily living (household chores, cooking, bathing, dressing, working, socializing, sexual activity, leisure and recreation, shopping, walking, and exercising). The MAF has been shown to have internal consistency r=0.93; and convergent validity with a fatigue VAS r=.80, $p<0.05$ [11].

Modified Fatigue Impact Scale (MFIS): The MFIS is a modified form of the Fatigue Impact Scale This 21-item instrument provides an assessment of the effects of fatigue in terms of physical, cognitive, and psychosocial functioning. Test retest reliability is 0.72-0.93 and the convergent validity is 0.48-0.80 [76,182].

Tampa Scale of Kinesiophobia (TSK): The Tampa Scale of Kinesiophobia 17-item measure of fear of movement or re injury in chronic pain patients in multiple scenarios (e.g., physical and work activity). Test retest reliability is r=0.64-0.91 with internal consistency with Cronbach's alpha 0.70-0.81 [185,186].

Fatigue Tasks

Cognitive fatigue task (CFT): Controlled oral word association test (COWAT) was used to induce perceived cognitive fatigue. The controlled word association test involves having the participant list as many words as possible in one minute for a given letter. The traditional COWAT is given for 3 letters for a total of 3 minutes with three

primary sets of letters 1) CFL 2) PRW and 3) FAS. For this study, the COWAT was modified to last 18 minutes to approximate perceived cognitive fatigue. The subjects completed word listing for eighteen letters for a total of 18 minutes with the same 9 letters repeated twice. The order of letters was as follows: C, F, L, P, R, W, F, A, S. The test was scored by the total number of words listed in 18 minutes. The participant was instructed not to use words that were proper names or repeat words. The COWAT has test-retest reliability for total word score is r=0.84 and validity is 0 .6 to 0.4 for scoring of clusters, and switch scores [188,189]. For the purposes of our study, we scored the COWAT using the total number of words over the entire 18 minute time period and was used a measure of inducing perceived cognitive fatigue.

Physical fatigue task (PFT): The physical fatigue task involved an upper extremity task utilizing the Valpar component work sample 9 whole body range of motion work panels and pegs (Figure 3.1) (VCWS09), Valpar International. Each panel has 22 pegs and 3 shapes. The heights of the panel are adjusted so that the subject must reach 4 to 6" above his/her head height for transfer 1. The physical task was divided into two segments: 1) transferring pegs and shapes from shoulder height to overhead and 2) transferring pegs and shapes overhead to waist height. The subject utilized the dominant arm for the peg activity. The non-dominant arm was allowed to assist in moving the shapes or stabilize the panel. The ability to perform the physical fatigue task was assessed by the time to complete transfer one (shoulder height to overhead) and transfer two (overhead to waist height) and total time for both transfers.

Dual fatigue task (DFT): The dual fatigue task involved a combined (dual) cognitive fatigue task and physical fatigue task completed at the same time as described

above. The DFT will be measured by total words and total time for transfer completion. The subject was allowed to stop the test if unable to continue due to pain or fatigue.

Outcome Measures

Pain Measure

Visual analogue scale (VAS): Pain was assessed at rest using a 10 cm visual analogue scale. The subject was instructed to place a single mark through the line at the appropriate point on the scale. Each scale consisted of a 10-cm horizontal line with descriptors at the far left and far right as "no pain" and "worst pain imaginable", respectively. Pain VAS has good test-retest reliability with ICC 0.71-0.99 and convergent validity of 0.30 -0.95 [113].

Fatigue Measure

Fatigue visual analogue scale (VAS): Perceived cognitive fatigue and perceived physical fatigue were assessed using a 10 cm visual analogue scale. For perceived cognitive fatigue anchors were "no mental fatigue" and "worst mental fatigue imaginable". For perceived physical fatigue anchors were "no physical fatigue" and "worst physical fatigue imaginable". The subject was instructed to place a single mark through the line at the appropriate point on the scale. Fatigue VAS has internal consistency with Cronbach's alpha 0.91-0.96 and concurrent validity with Pearson's correlation >.0.30 with $p<0.01$ [65,90].

Function Measures

Range of motion (ROM): Active shoulder flexion was measured for both shoulders with a goniometer with the subject in standing. Goniometric measurements were taken for one measurement before and after each task for the cognitive fatigue task,

physical fatigue task and dual fatigue task. Shoulder flexion range of motion has an inter-rater reliability of 0.69 and r=0.53-0.58 with a standard error of measurement of 17 degrees [96].

Grip strength: Bilateral grip strength measurements were taken for both hands with a hand dynamometer at setting 2 (Jamar®) before and after the cognitive fatigue task, physical fatigue task and dual fatigue task. Measurements were recorded in pounds. For grip strength, test-retest reliability is 0.82-0.85 [146].

Protocol

Each session began by obtaining consent, completing demographic and clinical characteristic questionnaires, measuring height and weight. Visual analogue scales were completed for pain, perceived cognitive fatigue and perceived physical fatigue at baseline followed by PPT's for cervical region and left forearm. Subjects were then randomized to a testing order by selecting one of two testing orders for the three fatigue tasks. The testing order was selected by pulling a slip of paper of testing out of an envelope, each containing one of the two testing orders. Fatigue task testing orders were: 1) CFT/PFT/DFT (11 FM, 16HC) or (2) PFT/CFT/DFT. (13FM, 18 HC). Pre-task and post-task measurements were taken for grip, ROM, pain, perceived cognitive fatigue and perceived physical fatigue. A 10 minute rest was given between each fatigue task (3.2).

Statistical Analysis

Descriptive statistics (mean, standard error) were determined for each study variable. Normality of data was confirmed with Kolmogorov-Smirnov goodness of fit test ($p< 0.05$). Difference scores were compared using a multivariate analysis (controlling for BMI and depression) for pain, perceived cognitive fatigue, perceived physical fatigue,

function and performance measures. Performance measures were evaluated using a multivariate analysis (controlling for BMI and depression) for the fatigue tasks (cognitive, physical and dual). Percent decrement (single task-dual task)/single task was calculated for the fatigue tasks (cognitive, physical and dual). Resulting means are provided with 95% confidence intervals.

Results

Cognitive Fatigue Task

During the cognitive fatigue task there was a significant increase in pain, perceived cognitive fatigue, and perceived physical fatigue for those with fibromyalgia compared to healthy controls (Table 3.2, 3.3). Fibromyalgia subjects showed an increase in pain of 0.85 ± 0.47 cm compared to -0.50 ± 0.38 cm for the healthy controls ($p<0.01$). Perceived cognitive fatigue significantly increased during the cognitive fatigue task by 2.76 ± 0.65 cm in fibromyalgia subjects compared to 0.78 ± 0.54 cm for healthy controls ($p<0.01$). Perceived physical fatigue significantly increased during the cognitive fatigue task by 1.48 ± 0.48 cm compared to -0.15 ± 0.39 cm for healthy controls ($p<0.01$). However, functional outcome measures (grip force and range of motion) and performance on the cognitive fatigue task (total number of words and words per minute) were unchanged by the cognitive fatigue task (Table 3.3).

Physical Fatigue Task

During the physical fatigue task there was a significant greater increase in pain, perceived cognitive fatigue, and perceived physical fatigue for those with fibromyalgia than healthy controls (Table 3.2, Figure 3.3). Subjects with fibromyalgia had a significantly greater increase in pain of 2.73 ± 0.51cm compared to 0.52 ± 0.42 in healthy

controls ($p<0.01$). During the physical fatigue task, perceived cognitive fatigue increased 1.56 ± 0.45 cm in people with fibromyalgia compared to 0.01 ±0.37 in the healthy controls ($p<0.01$), and perceived physical fatigue increased by 3.14 ± 0.54 cm in people with fibromyalgia 1.37 ± 0.44 cm in healthy controls ($p<0.01$). Functional outcome measures, grip and shoulder range of motion, were unchanged after the physical fatigue task. In contrast, physical performance on the physical fatigue task was reduced in people with fibromyalgia when compared to healthy controls. Performance on the physical fatigue task was measured by time to complete transfer 1 (shoulder to overhead), transfer 2 (overhead to waist) and total transfer time. Total transfer time for was not significantly different in people with fibromyalgia (949.51 ± 49.27 s) compared to the healthy control group (871.41 ± 49.27 s)($p=0.09$). However, the first transfer, that involved moving objects from shoulder height to overhead, took 492.28 ± 27.19 s in people with fibromyalgia and was significantly greater than healthy controls (470.82 ± 22.41 s)($p<0.001$). There was no significant difference in the second transfer overhead to waist between people with fibromyalgia (443.90 ± 38.19 s) and healthy controls (414.99 ± 31.47 s)($p=0.82$).

Dual Fatigue Task

Pain during the dual fatigue task demonstrated results similar to the single physical fatigue tasks with increases of 2.45 ± 0.42 cm in the fibromyalgia group compared to 0.68 ± 0.34 cm in the healthy controls ($p<0.01$). Perceived cognitive fatigue during the dual fatigue task demonstrated results similar to the single cognitive fatigue task with the increases of 2.13 ± 0.53 cm for those with fibromyalgia compared to 0.89 ± 0.44 cm for healthy controls ($p<0.01$). Perceived physical fatigue during the dual fatigue

task demonstrated similar results to the single physical fatigue task with 2.96 ±0.54 cm for those with fibromyalgia compared to 1.21 ± 0.44 cm for healthy controls ($p<0.01$). Shoulder range of motion and grip during the dual fatigue task was not different between groups (Table 3.2). There was no significant difference in cognitive performance or perceived physical fatigue performance in the dual fatigue task between those with fibromyalgia and healthy controls. Performance on the dual task was significantly less than the single task performance for both fibromyalgia and healthy control groups for both cognitive and physical performance. Specifically, all subjects performed less well during the dual task with transfer 1 on the physical fatigue task ($p<0.01$) and transfer 2 on the physical fatigue task ($p<0.01$) (Table 3.4, Figure 3.5, 3.6). However, the magnitude of change in the dual task compared to the healthy controls between those with fibromyalgia and those with healthy controls was not significantly different.

Discussion

The current study shows, for the first time that a physical fatigue task not only increased perceived physical fatigue, but also increased perceived cognitive fatigue. Conversely a cognitive fatigue task not only increased perceived cognitive fatigue but also increased perceived physical fatigue. We further show that both physical and cognitive fatigue tasks significantly increase pain in fibromyalgia when compared to healthy controls. The effects of the fatigue tasks were enhanced in people with fibromyalgia. This suggests there is a direct interaction between perceived physical fatigue, perceived cognitive fatigue and pain, and that chronic pain results in enhanced fatigue to both physical and cognitive tasks.

The physical fatigue task used in the current study involved multiple upper extremity joints: shoulder, elbow, wrist and hand in order to simulate a functional activity. This physical fatigue task therefore would be similar to screwing in a light bulb, reaching for dishes in a cupboard, an item in a closet or doing laundry. Previous tasks examining physical fatigue in people with fibromyalgia have typically used a single muscle (biceps or quadriceps) and show significant deficits in overall strength and endurance [103-105,143,152-154,164]. In general these studies have shown that for upper extremity muscles there are deficits in central fatigue measures, but not for lower extremity muscles [34,152,164]. Interestingly, examination of EMG responses of the biceps muscle between healthy controls and fibromyalgia revealed changes consistent with muscle remodeling to a larger population of fatigue-resistant type I fibers [34] consistent with a sedentary population. Thus, muscle fatigue in people with fibromyalgia may have a central component but this is likely dependent on the task performed, the muscle examined, or muscle fiber type.

This measurement of perceived fatigue in people with fibromyalgia in response to a physical task is significantly increased compared to healthy controls [8]. The current study extended these prior findings by separately examining perceived cognitive and perceived physical fatigue and showing significant increases in both fatigue measures in response to physical fatigue task. Similarly, in people with chronic fatigue syndrome, a physical fatigue task (bicycling) significantly increased both perceived physical fatigue and perceived cognitive fatigue [137]. In people with central nervous system diseases such as multiple sclerosis, Parkinson's, stroke and traumatic brain injury, also show significant increases in both physical and perceived cognitive fatigue with a walking

physical fatigue task [9,69,101,106,107,135,214]. This change in perceived cognitive fatigue and perceived physical fatigue is viewed as central effect. Thus, in people with conditions associated with fatigue, a physical fatiguing task enhances both physical and perceived cognitive fatigue.

Previous studies show that physical activity and exercise increase pain in people with fibromyalgia [112,119,120,163,222]. Our study similarly showed increases in pain with physical activity in people with fibromyalgia – these increases were 3/10 points on a visual analogue scale. The underlying mechanisms for this may relate to interactions in central nervous system pathways that mediate both motor and pain responses. In particular animal studies show that combining a fatiguing exercise task with a low-dose muscle insults enhances measures of hyperalgesia (pain-like behaviors) [207,211,254] through activation of neurons in the caudal raphe nuclei of the brainstem [207]. Basic research also shows that systemic increases in pro-inflammatory cytokines can initiate fatigue, and in parallel increase expression of pro-inflammatory cytokines [53,93]. Conversely, in a mouse model of chronic fatigue syndrome, there is increased expression of cytokines in the central nervous system both cortex and brainstem [203]. People with fibromyalgia clearly have significant pain, pain with movement, and increases in circulating levels of pro-inflammatory cytokines [236]. Similarly, there are increased levels of pro-inflammatory cytokines in other conditions associated with significant fatigue including multiple sclerosis and chronic fatigue syndrome, both of which also have significant pain [28,29,56,57,249]. Thus, it is possible that the enhanced fatigue in response to physical fatigue is related to neuro-immune interactions that affect brain areas that modulate pain and motor responses.

Physical performance in response to the physical fatigue task was significantly reduced particularly for the task that involved moving objects in an overhead transfer. This agrees with prior studies showing reduced strength and reduced endurance during exercise tasks [8,86]. It is unclear if the reduction in physical performance on the VALPAR test is a result of pain, physical deconditioning, and/or physical fatigue. A recent study, however, shown that pain explains 35-42% of the variance in functional performance in people with fibromyalgia [86]. Since fibromyalgia subjects in the current study not only had ongoing pain but also had significant increases in pain during the physical task, we suggest that the reductions in physical performance in the current study are related to pain.

We also show for the first time that performing a cognitive fatiguing task increases pain and perceived physical fatigue, as well as perceived cognitive fatigue, in people with fibromyalgia, and these increases are greater than healthy controls. Further we show increases in perceived cognitive fatigue during a physical fatigue task in people with fibromyalgia that were greater than healthy controls. Few studies have differentiated physical and perceived cognitive fatigue in fibromyalgia, and none have asked if perceived cognitive fatigue can impact pain, perceived physical fatigue, and function. However, studies in other conditions with significant cognitive and mental fatigue have begun to evaluate these interactions. For people with chronic fatigue syndrome, perceived physical fatigue increases perceived cognitive fatigue [137]. In people with multiple sclerosis, traumatic brain injury, cancer and perceived cognitive fatigue syndrome both cognitive fatiguing tasks and physical fatiguing tasks increase perceived cognitive fatigue [39,40,45,92,106].

Despite enhanced perceived cognitive fatigue we show that cognitive performance on the COWAT was similar to healthy controls. This is in contrast to prior studies that show reduced cognitive performance in people with fibromyalgia. Studies showing deficits in cognitive performance show difficulties with working memory, episodic memory, attention, processing speed and verbal fluency using sophisticated cognitive function tests [37,38,41,42,64,75,84,85,87,130,169,205,242]. We specifically designed the cognitive task to induce perceived cognitive fatigue, and this particular test (COWAT) has not been examined to our knowledge in people with fibromyalgia.

All subjects, regardless of group, showed significantly reduced physical and cognitive performance during the dual fatigue task when compared to the single fatigue task. Similar results have been found in multiple conditions such as stroke and Parkinson's [55,174]. However, fibromyalgia and healthy controls both showed significant reductions in performance. Furthermore, the increases in pain, perceived physical fatigue and perceived cognitive fatigue were similar to the single fatigue task, suggesting that there is not an enhanced symptomatic effect of doing both tasks simultaneously. This may be that maximal deficits were found with the single fatigue task or that there was a practice effect when completing the dual task following the single task.

Together, these data show that people with fibromyalgia performing a fatiguing task, either physical or cognitive, show significant increases in pain and fatigue and decreases in function. Understanding these changes in fatigue and pain with fatiguing tasks will be important toward designing an appropriate activity-based treatment strategy, participation in daily activity, and return to work. Strategies aimed at decreasing pain and

fatigue during movement could improve participation in regular activities. Physically fatiguing tasks, such as exercise and regular activity, may impact not only pain but also perceived physical fatigue and perceived cognitive fatigue. Cognitive fatiguing tasks such as education or verbal instruction may impact pain not only perceived cognitive fatigue but also perceived physical fatigue. Thus, clinicians should be aware of the impact fatiguing tasks can have on pain, perceived cognitive fatigue, and perceived physical fatigue and modify both physical activity but also cognitive activity accordingly in this population.

Table 3.1: Demographics and clinical characteristics

Total (N=58)	Fibromyalgia (n=24)	Healthy Subjects (n=34)	P Value
Age, years (female and male) (mean ± SEM)	52.42 ± 2.3	46.5 ± 2.5	**0.05**
Female (% sample)	23 (96%)	33(97%)	0.74
Ethnicity (% sample)			
Caucasian	19 (79.17%)	25 (73.53%)	0.28
Others	5 (20.83%)	9 (26.47%)	0.28
Marital status (% sample)			
Married/co-habitating	12 (50%)	21 (61.76%)	0.66
Single/widowed/divorced	12 (50%)	13 (38.24%)	0.66
Education (% sample)			
High school or less	6 (25%)	14 (41.18%)	0.54
Some college or above	18 (75%)	20 (48.82%)	0.54
Income (% sample)			
< $ 60,000	19 (79.17%)	28 (82.35%)	0.98
≥ $60,000	5 (20.83%)	6 (17.65%)	0.98
Length of Fibromyalgia diagnosis, years	10.04 ± 1.6	Not Applicable	Not Applicable
Body Mass Index (mean ± SEM)	34.22 ± 1.88	26.10 ± 1.30	**≤0.01**
MMSE (mean ± SEM)	28.42 ± .26	28.84 ± .30	0.44
FIQ (mean ± SEM)	55.20 ± 2.88	9.55 ± 1.64	**≤0.01**
CES-D (mean ± SEM)	20.58 ± 2.16	6.66 ± 1.01	**≤ 0.01**
MAF (mean ± SEM)	65.6 ± 6.45	11.16 ± 1.94	**≤0.01**
MFIS (mean ± SEM)	51.71 ± 3.81	15.72 ± 2.07	**≤ 0.01**
TSK (mean ± SEM)	36.04 ± 1.85	22.72 ± 1.42	≤0.01

[a] MMSE=Mini Mental State Exam, FIQ=Fibromyalgia Impact Questionnaire, CES-D=Center for Epidemiology Studies-Depression, MAF=Multidimensional Assessment of Fatigue, MFIS=Modified Fatigue Impact Scale, TSK=Tampa Scale of Kinesiophobia

Table 3.2: Pain, fatigue and function difference score baseline

Variable	Cognitive Fatigue Task (COWAT)		Physical Fatigue Task (Valpar)		Dual Fatigue Task (COWAT and Valpar)	
	FM	HC	FM	HC	FM	HC
Pain	0.85 ± 0.47[b] -0.08 to 1.79	-0.50 ± 0.38 -1.26 to-0.28	2.73 ± 0.51[b] 1.71 to 3.75	0.52 ± 0.42 -0.32 to 1.35	2.45 ± 0.42[b] 1.61 to 3.28	0.68 ± 0.34 0.01 to 1.37
Perceived cognitive fatigue	2.76 ± 0.65 [b] 1.45 to 4.07	0.78 ± 0.54 -0.30 to 1.86	1.56 ± 0.45[b] 0.66 to 2.47	0.01 ± 0.37 -0.74 to 0.75	2.13 ±0.53[b] 1.50 to 3.47	0.89 ± 0.44 -0.01 to 1.77
Perceived physical fatigue	1.48 ± 0.48[b] 0.53 to 2.43	-0.15 ± 0.39 -0.94 to 0.63	3.14± 0.54[b] 2.06 to 4.22	1.37 ± 0.44 0.48 to 2.26	2.96 ± 0.54[b] 1.88 to 4.03	1.21 ± 0.44 0.32 to 2.09
Grip right hand	-0.80 ± 1.92 -4.65 to -3.05	3.32 ± 1.58 0.15 to 6.49	-1.96 ± 2.03 -6.03 to 2.12	1.94 ± 1.67 -1.42 to 5.30	1.95 ± 3.02 -4.10 to 8.00	-7.71 ± 2.48 -12.70 to -2.73
Grip left hand	-3.11 ± 1.94 -7.00 to 0.78	0.93 ± 1.60 -2.28 to 4.13	-1.89 ± 1.74 -5.38 to 1.60	1.58 ± 1.43 1.30 to 4.45	-2.41 ± 2.55 -7.53 to 2.70	-2.91 ± 2.10 -7.13 to 1.31
ROM right shoulder	-4.67 ± 4.41 -13.51 to 4.18	-2.10 ± 3.63 -9.38 to 5.20	1.68 ± 6.28 -10.92 to 14.27	6.84 ± 5.17 -3.54 to 17.22	0.60 ± 2.13 -3.62 to 4.94	-1.71 ± 1.76 -5.24 to 1.82
ROM left shoulder	-0.38 ± 1.63 -3.64 to 2.88	0.41 ± 1.34 -2.28 to 3.10	0.25 ± 1.60 -2.96 to 3.46	1.15 ± 1.32 -1.49 to 3.80	-0.40 ± 1.88 -4.17 to 3.38	-0.27± 1.55 -3.38 to 2.84

Controlled for BMI and depression (CESD). Data are mean ± S.E.M. and 95% confidence intervals. [a]S.E.M. =standard error of measure, COWAT=Controlled Oral Word Association Test, Valpar=Valpar Peg Test, VAS=visual analogue scale, ROM=range of motion, ROM=Range of motion, CFT=Cognitive fatigue performance task, PFT=physical fatigue performance task, DFT=dual fatigue performance task

[b] $p<0.01$Significant difference between fibromyalgia group and healthy control

Table 3.3: Fatigue Task Performance FM and HC

Fatigue Task	Performance Measure	FM n=24	HC n=34	*P Value*
CFT	Total Words	144.36 ± 8.18 127.93 to 160.78	140.14 ± 6.74 126.61 to 153.67	0.79
PFT	Transfer 1 (seconds) (waist to overhead)	492.28 ± 27.19 437.72 to 546.85	470.82 ± 22.41 425.86 to 515.78	**p=0.001****
	Transfer 2 (seconds) (overhead to waist)	443.90 ± 38.19 366.97 to 520.24	414.99 ± 31.47 351.84 to 478.13	0.82
	Total Transfer (seconds)	949.51 ± 49.27 850.6 to 1048.43	871.41 ± 41.45 788.20 to 954.62	0.09
DFT	Total Words	116.07 ± 8.38 99.26 ± 132.88	117.54 ± 6.90 103.69 to 131.39	0.63
	Transfer 1 (seconds) (waist to overhead)	509.2 ± 31.50 445.98 to 572.41	501.98 ± 25.96 449.89 to 554.07	0.48
	Transfer 2 (seconds) (overhead to waist)	503.53 ± 39.08 425.11 to 581.94	469.54 ± 32.2 404.93 to 534.15	0.09
	Total Transfer (seconds)	1013.58 ± 68.17 876.73 to 1150.43	943.29 ± 57.35 828.17 to 1058.42	0.31
Percent Decrement: (Single Task - Dual Task)/Single Task		FM	HC	*P Value*
Total Words		18.72 ± 4.62% 9.45 to 27.98%	15.9 ± 3.8% 8.27 ± 23.53%	0.82
Transfer 1 (seconds) (overhead to waist)		-5.37 ± 3.91% -13.22 to 2.48%	-6.76 ± 3.22% -13.23 to -2.9%	0.12
Transfer 2 (seconds) (waist to overhead)		-8.00 ± 4.10% -16.23 to 2.22%	-9.96 ± 3.38% -16.74 to -3.18%	0.77
Total Transfer (seconds)		-6.48 ± 4.48% -15.47 ± 2.52%	-5.67 ± 3.69% -13.08 to 1.75%	0.71

Data for fatigue task performance during single and dual fatigue tasks with covariates of BMI and Depression (CESD). Data are mean ± S.E.M. and 95% confidence intervals. BMI=Body mass index, CESD=Center for Epidemiology – Depression, S.E.M. =standard error of measure, FM=fibromyalgia group, HC=healthy control group, CFT=Cognitive fatigue performance task, PFT=physical fatigue performance task, DFT=dual fatigue performance task,** p<0.01Significant difference between fibromyalgia group and healthy control group

Table 3.4: Fatigue Task Performance all subjects, SFT and DFT

Fatigue Task		Mean ± S.E.M.	Confidence Interval 95%	P value
CFT	Total Words CFT	256.21 ± 7.071	242.03 to 270.396	0.80
DFT	Total Words DFT	183.31 ± 6.81	169.64 to 196.97	0.13
PFT	Transfer 1 (seconds)	480.02 ± 13.70	452.546 to 507.49	**0.01
DFT	Transfer 1 (seconds)	505.071 ± 15.163	474.659 to 535.48	**0.01
PFT	Transfer 2 (seconds)	427.25 ± 19.40	388.34 to 266.16	0.37
DFT	Transfer 2 (seconds)	484.11 ± 19.84	444.32 to 523.89	0.60
PFT	Total Transfer (seconds)	907.26 ± 24.11	858.92 to 955.62	0.18
DFT	Total Transfer (seconds)	1390.79 ± 30.10	1330.50 to 1451.07	0.10

Data for fatigue task performance during single and dual fatigue tasks with covariates of BMI and Depression (CESD). Data are mean ± S.E.M. and 95% confidence intervals. SEM=error of measure, FM=fibromyalgia group, HC=healthy control group, CFT=Cognitive BMI=Body mass index, CESD=Center for Epidemiology – Depression, S.E.M. =standard fatigue performance task, PFT=physical fatigue performance task, DFT=dual fatigue performance task, SFT=single fatigue task, ** p<0.01Significant difference between fibromyalgia group and healthy control group

Figure 3.1: Valpar Peg Task Equipment

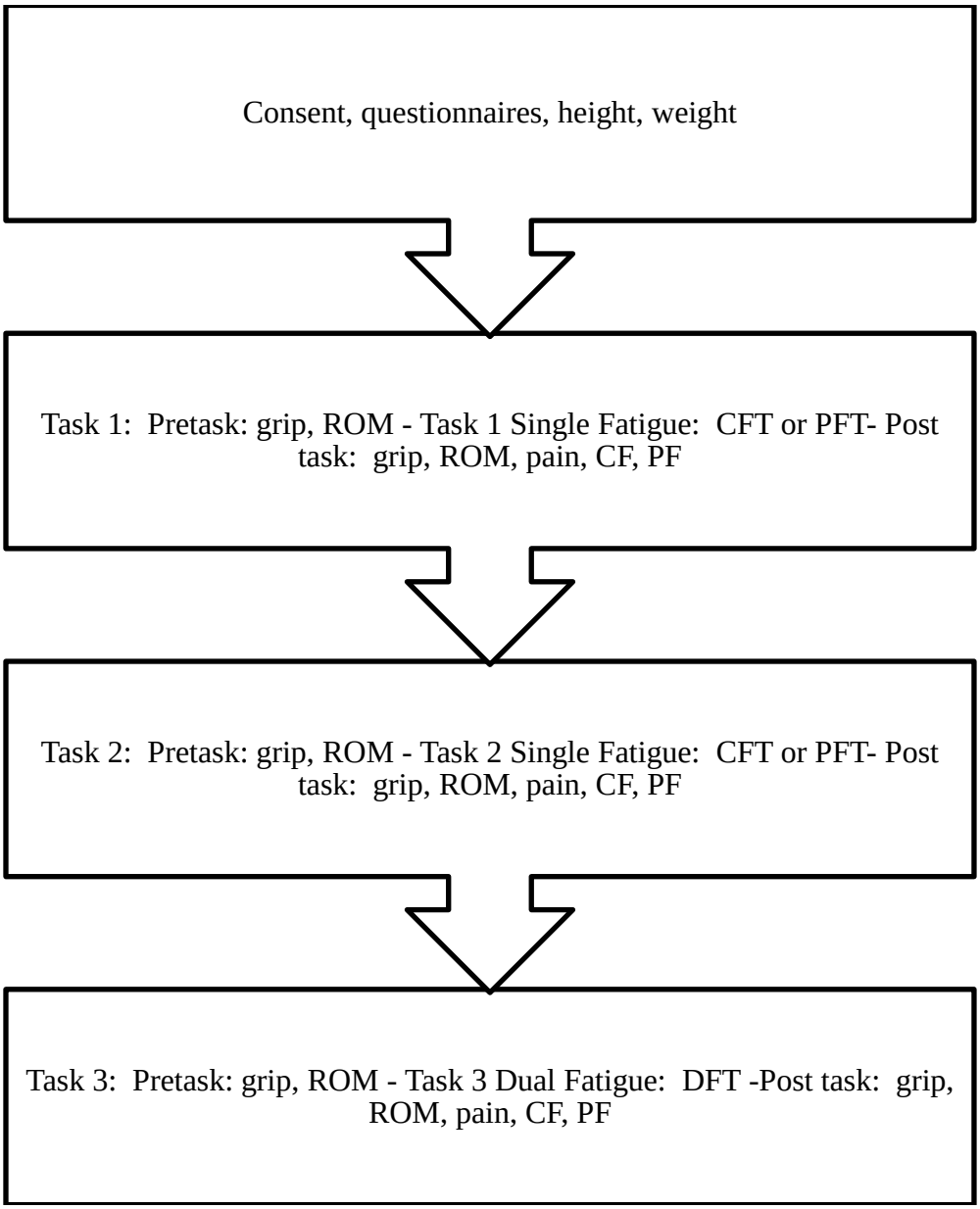

Figure 3.2: Order of Testing, Study 2

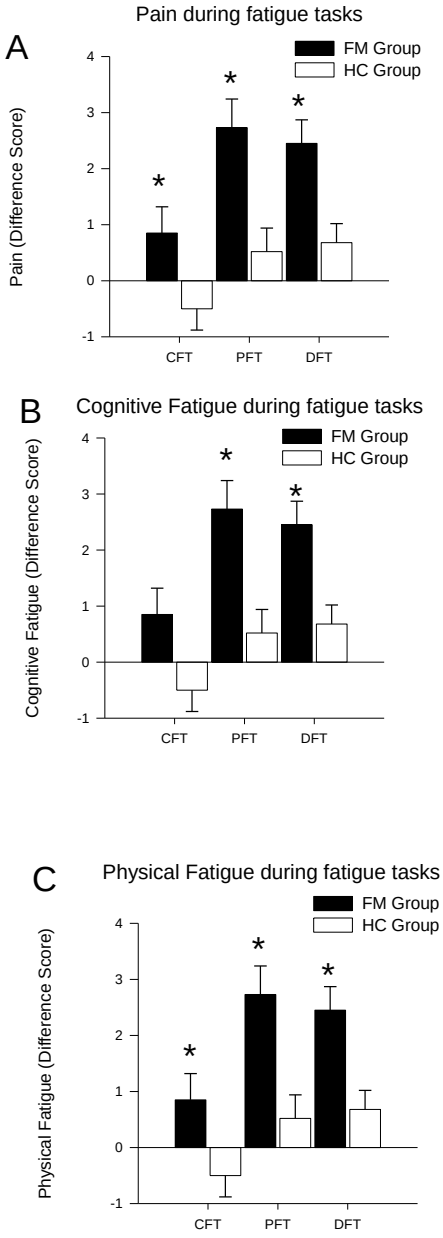

Figure 3.3: Pain, CF, and PF during fatigue tasks

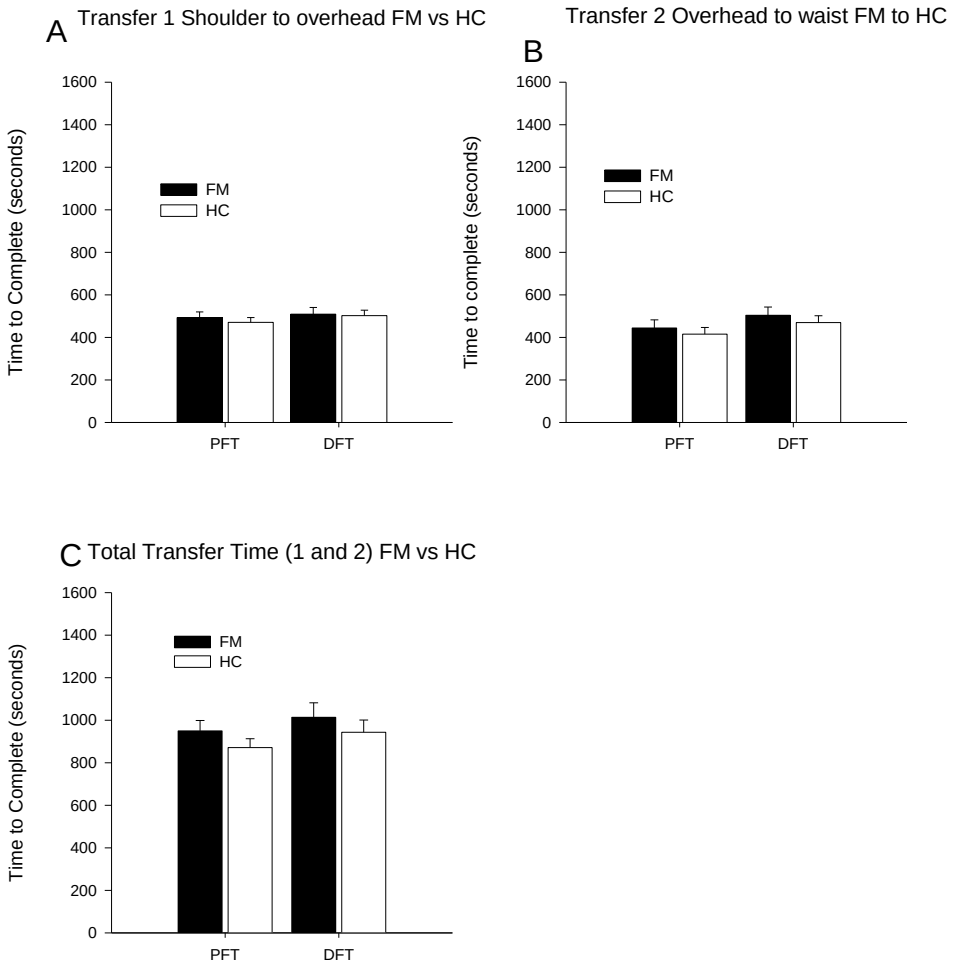

Figure 3.4: Transfer Time FM vs HC Physical Fatigue Task

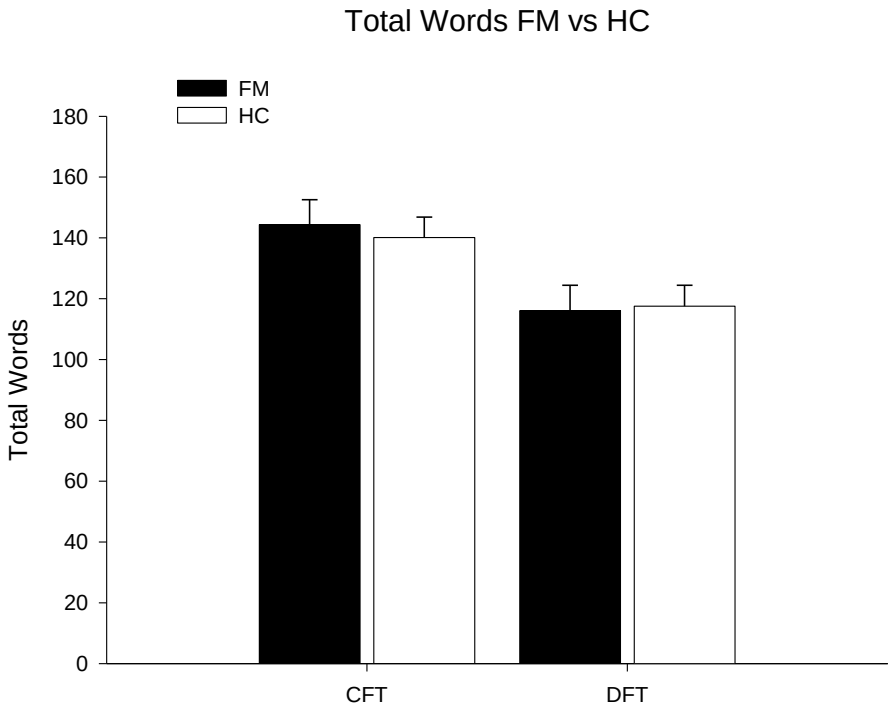

Figure 3.5: Total Words FM vs HC Single Fatigue Task

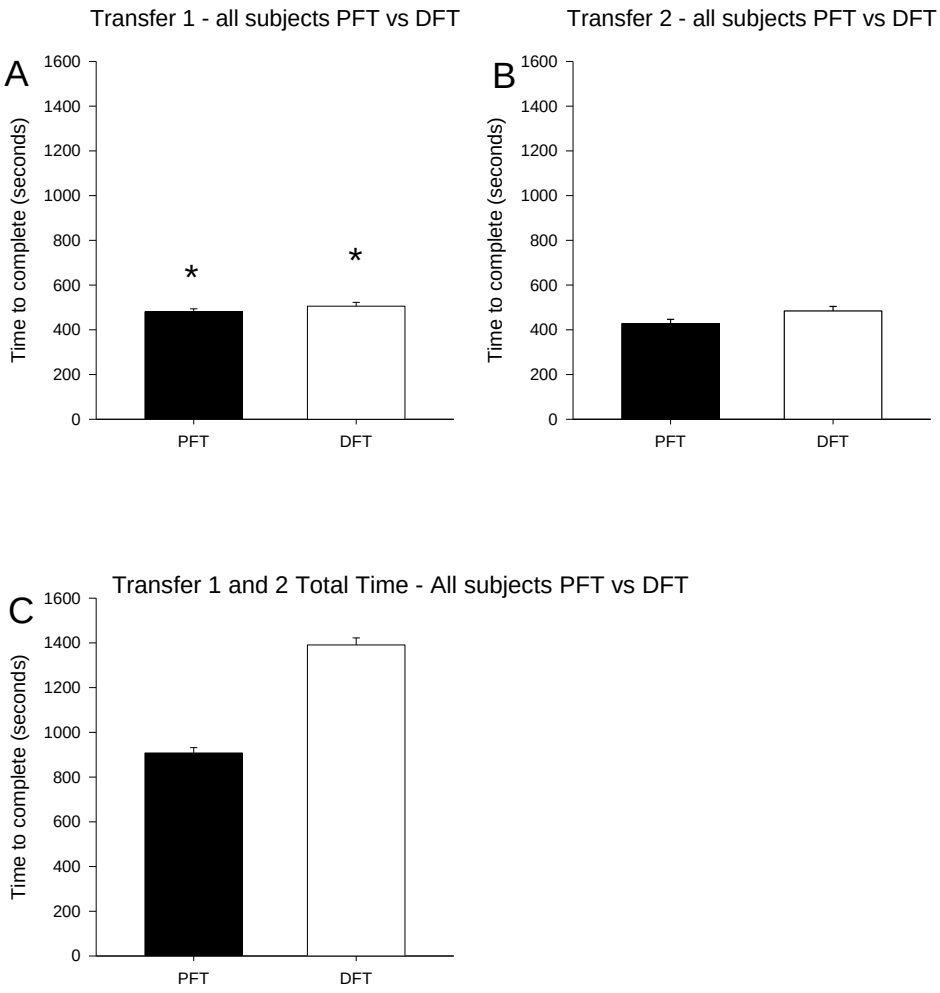

Figure 3.6: Transfer time all subjects

CHAPTER 4

TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS) REDUCES PAIN, FATIGUE AND HYPERALGESIA WHILE RESTORING CENTRAL INHIBITION IN PRIMARY FIBROMYALGIA[A]

Abstract

Because TENS works by reducing central excitability and activating central inhibition pathways, we tested the hypothesis that TENS would reduce pain and fatigue and improve function and hyperalgesia in people with fibromyalgia who have enhanced central excitability and reduced inhibition. The current study used a double-blinded randomized, placebo controlled cross-over design to test effects of a single treatment of TENS in people with fibromyalgia. Three treatments were assessed in random order: active TENS, placebo TENS, no TENS. The following measures were assessed before and after each TENS treatment: pain and fatigue at rest and movement, pressure pain thresholds (PPTs), 6 minute walk test (6MWT), range of motion (ROM), five time sit to stand test (FTSTS), and single leg stance (SLS). Conditioned pain modulation (CPM) was completed at end of testing. There was a significant decrease in pain and fatigue with movement for active TENS compared to placebo and no TENS. PPTs significantly increased at site of TENS (spine) and outside site of TENS (leg) when compared to placebo TENS or no TENS. During Active TENS CPM was significantly stronger compared to placebo TENS and no TENS. No changes in functional tasks were observed with TENS. The results of our study show active TENS restores CPM, decreases deep

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tissue pressure pain, decreases pain and fatigue during movement. TENS may be an effective treatment for people with fibromyalgia by restoring central inhibition and reducing central excitability.

Introduction

The American College of Rheumatology (ACR) classifies fibromyalgia as a clinical syndrome defined by chronic widespread muscle pain, fatigue and tenderness with hyperalgesia to pressure over tender points [250]. Pain and fatigue associated with fibromyalgia can interfere with daily function, work and social activities [6]. The etiology of fibromyalgia is unknown, but it is generally accepted that there is enhanced central excitability [175,220,225] and reduced pain inhibition [120,126,133,225,229]. Thus, one of the main treatments for patients with fibromyalgia must focus on pain relief to allow the person to function more independently both at home and at work. Research into the treatment of fibromyalgia has demonstrated strong evidence that aerobic cardiovascular exercise improves symptoms of fibromyalgia as well as improves quality of life [22]. However, exercise itself may be painful, and the increase in pain may potentially prevent a person from exercising [119,216,243]. Thus, treatments aimed at decreasing pain during movement should improve a person's ability to participate in activities of daily living. Transcutaneous electrical nerve stimulation (TENS) is a non-pharmacological treatment modality that delivers electrical stimulation through the skin and is used for both acute and chronic pain control [7,61,62,72,173,179,193,247].

Transcutaneous electrical nerve stimulation (TENS) activates central inhibitory pathways [60,114,142,206] and decreases central excitability [114,138,141,208,212]. TENS activates descending inhibitory pathways from the midbrain and brainstem to

inhibit excitability of nociceptive neurons in the spinal cord. Although TENS is shown to be effective for several pain conditions such as osteoarthritis, chronic musculoskeletal pain, and postoperative pain [18,108,167], its effectiveness in treatment of people with fibromyalgia is virtually unknown. The primary aim of the study was to test the effectiveness of TENS on pain, fatigue and function in a crossover design study for patients with fibromyalgia with random assignment to three treatments: no TENS control, placebo TENS and active high frequency TENS. A secondary aim was to test the effect of TENS on central inhibition and hyperalgesia as an indicator of central excitability. We hypothesized that the application of TENS to people with fibromyalgia (FM) would reduce pain and fatigue, reduce central excitability and restore conditioned pain modulation (CPM) which would be manifested as improved function.

Methods

The current study used a randomized, placebo controlled cross-over design to test the effects of a single treatment of TENS in people with primary fibromyalgia (NCT00932360, C9366). Three treatments were assigned in random order: active TENS, placebo TENS and no TENS with a washout period of one week between treatments. The outcomes assessor remained blinded to the all treatments: active TENS, placebo TENS, and no TENS. The subject was blinded to the active TENS and placebo TENS treatments. The study was approved by the Institutional Review Board at the University of Iowa.

Subjects

Sample size was calculated using a prior study comparing the effect of active TENS to placebo-TENS for chronic pain and effect sizes ranging between 1.56-1.93

[144]. In the Marchand study, the mean VAS pain intensity rating for each of 16 sessions of active TENS was 2.6 to 3.6 on a 0-10 cm scale and placebo TENS was 2.05 to 3.2. Using a significance level of .05 and power of .80, a sample size of 40 subjects was calculated for this current study. Subjects were recruited from the University of Iowa's Rheumatology clinic, local rheumatologists and staff of the University of Iowa. The CONSORT diagram is shown in Figure 4.1. Subjects were screened by telephone with Inclusion criteria of 1) diagnosis of fibromyalgia by a physician and 2) history of cervical or lumbar pain. The 1990 ACR criteria for diagnosis of fibromyalgia were used for this study which includes axial pain above and below the waist as part of the diagnostic criteria [250]. Subjects were not required to restrict other treatments (pharmaceutical of non-pharmaceutical) but were required to be on a stable pharmaceutical management plan for 1 month prior and during study to entering the study. Thus, effects of TENS will be tested as a supplement to standard care. Subjects were excluded if they had: 1) prior use of TENS in the last five years; 2) active inflammatory condition; 3) pacemaker 4) pregnancy 5) uncontrolled hypertension or 6) significant cognitive deficits. A total of 125 subjects were screened for eligibility with 82 people unable to participate and 43 people were eligible and agreed to participate with 2 withdrawing after the first session. Of the 82 people unable to participate, we were unable to contact 45 people, 15 declined and 22 were ineligible. The primary reason for ineligibility was prior TENS use. Forty three subjects with fibromyalgia (42F; 1M), aged 25-76 years (mean 49.2 ± 12 yr) participated in this study. Demographic information was gathered for age, gender, ethnicity, marital status, education, income, body mass index and length of diagnosis of fibromyalgia (see Table 4.1). The Fibromyalgia Impact Questionnaire (FIQ) was completed to help

describe clinical presentation of the subjects. The FIQ was used to measure each subject's ability to complete functional tasks at home, work and social areas of life. The reliability for the FIQ is r=0.72-0.92 and validity is 0.46-0.96 [13] .

Subjects were randomized to treatment group after providing written consent. The order of active TENS, placebo TENS and no TENS was randomized in the sequentially numbered opaque sealed envelopes [66] that were not available to the outcomes assessor. The order of TENS treatment was randomized by drawing the order out of a hat and were stored in a secure area that was accessed only by the TENS allocator. The envelopes were signed, dated and opened by the TENS allocator before the TENS application and after the outcomes assessor had left the room.

Outcome Measures

We used a series of pain measures to examine resting and evoked pain as well as pain processing. We added a measure of fatigue since it is a common co-morbid symptom in fibromyalgia. Lastly, we examined several functional measures aimed at endurance, strength, flexibility and balance.

Pain Measures

Visual Analogue Scales (VAS): A visual analogue scale was used for measurement of pain at rest, pain with movement, fatigue at rest and fatigue with movement. Resting pain and pain with movement (during the 6 minute walk test (6MWT) was assessed using a 10 cm visual analogue scale. Pain VAS has good test-retest reliability (ICC 0.71-0.99) and convergent validity of 0.30 -0.95 [113]. The subject

was instructed to place a single mark through the line at the appropriate point on the scale. Each scale consisted of a 10-cm horizontal line with descriptors at the far left and far right as “no pain” and “worst pain imaginable”, respectively

Pressure Pain Threshold (PPT): PPTs measured deep tissue hyperalgesia using a digital pressure algometer (Somedic AB, Farsta, Sweden). Previous studies demonstrate that anesthetic blockade of the skin under the algometer has no effect on the PPT, thus this is a measure of deep tissue hyperalgesia. A $1cm^2$ algometer probe applied pressure at a rate of 40 kPa/sec. Subjects were instructed to activate a button when the sensation of pressure clearly became one of painful pressure and this value was recorded. PPTs were assessed over the cervical spine, lumbar spine to assess for effects of TENS at the site of stimulation and over the anterior tibialis muscle to assess for widespread effects of TENS outside the site of stimulation. Two bilateral cervical areas were tested at the site of treatment: 1) 2 cm lateral to the C3 spinous processes and 2) 2 cm lateral to C5 spinous processes. Two bilateral lumbar areas were tested: 1) 2 cm lateral to L3 spinous processes and 2) 2 cm lateral to the L5 spinous processes. The left leg was assessed at 5, 6, 7 cm below the inferior patellar pole, bisecting the anterior tibialis musculature. Each area was averaged for a composite PPT score at each site. Each subject had a practice trial on the non-testing forearm prior to data collection. PPT has excellent test-retest reliability (r=0.79-0.94) and is a valid measure of deep tissue hyperalgesia [217].

Conditioned Pain Modulation (CPM): The ability of subject’s to engage their descending inhibitory system was tested using CPM. Assessment of CPM was completed using an ice water bath at $4^{\circ}C$. The subject’s left foot up to the ankle was placed into the cold water and pressure pain thresholds were measured proximal to the electrode in the

cervical or lumbar area dependent on the area of TENS application: cervical or lumbar region.

Fatigue Measure

Visual Analog Scales (VAS): A visual analogue scale was used for measurement of fatigue at rest and fatigue with movement. Resting fatigue and fatigue with movement (6MWT) was assessed using a 10 cm visual analogue scale. Fatigue VAS has internal consistency (Cronbach's alpha 0.91-0.96) and concurrent validity (Pearson's correlation >0.30 with $p<0.01$). Each scale consisted of a 10-cm horizontal line with descriptors at the far left "no fatigue" and far right as "worst fatigue imaginable".

Function Measures

6 Minute Walk Test (6MWT): The 6MWT is a function test measures the maximum distance a person can walk as fast as comfortable in 6 minutes. The test measures time, distance, speed of walking and pain. The 6MWT is a sub maximal test of aerobic capacity with indications for endurance [183]. The subjects completed the walk test in a 200 foot lap turning around at 100 feet. The subjects rated pain and fatigue at the 3 minute time frame. The 6MWT has excellent test-retest reliability (ICC=0.95-0.97) and construct validity (r=0.63-0.79) [232].

Range of Motion (ROM): Range of motion was completed using the two inclinometer method for cervical and lumbar flexion and extension. The measurement was taken using the method described by the American Medical Association (AMA) in The Guide to the Evaluation of Permanent Impairment [73]. ROM measures have good

intrarater reliability for the cervical spine (r=0.864-0.866) and good intratester reliability lumbar spine(r=0.90)[125,161].

Five Time Sit to Stand Test (FTSTS): The FTSTS is a test of strength for the lower body. The time it takes to complete five repetitions of sit to stand completed as quickly as possible is recorded. The FTSTS has good reliability (ICC >0.95) and validity (r=0.59-0.88)[165].

Single Leg Stance (SLS): SLS is a measure of balance. It was measured with a three trial average to a 30 second maximum with alternating testing of lower extremities. The inter-rater reliability for the best of 3 trials is excellent (0.994 with 95% confidence interval 0.989-0.996 [213].

Transcutaneous Electrical Nerve Stimulation (TENS)

The study used a crossover design with random assignment to three treatments: active TENS, placebo TENS and no TENS (Figure 4.2). Testing was completed by two assessors: the outcomes assessor and the TENS assessor. The randomization of treatments was completed by the TENS assessor in order to maintain blinding of the outcomes assessor. Each treatment was completed once a week over a three week period. The skin was cleansed with an alcohol swab and a butterfly shaped electrode (Stimcare Premium Electrode, Empi Inc, St. Paul, MN) was applied to the skin (Figure 4.3). The placement of the electrode was based on patient preference for one of two locations: cervical thoracic junction (n=19) or lumbar-sacral junction (n=24). Instructions to the subject by the TENS assessor were: "You will receive one of three treatments: strong sensation TENS, no sensation TENS and no TENS. The strong sensation will feel like a twitching or tapping. The no sensation TENS will be subtle and you many not feel

anything at all. The no TENS treatment means a TENS unit will be attached to the electrodes but not turned on. Neither you nor the outcomes assessor will know which study treatment you are receiving. Today, I will gradually increase the intensity until you fell a strong but tolerable, non-painful sensation. Every 5 minutes I will ask you if the sensation decreased and if needed. I will make adjustments". Previous studies show the greatest analgesic effect of TENS with the highest intensities including those described as maximal tolerable intensity [156,179]).

The TENS treatment consisted of a 30 minute session while the subject rested comfortably and continued to be worn throughout the last half of the testing session for a total of 60-75 minutes. Per standard procedure [136,179,241], the TENS unit was left on during the pain assessments to assess the effect of TENS during its maximally effective period. Once the TENS unit was applied, every 5 minutes, the TENS assessor asked the subject "Are you feeling comfortable?" Adjustments to intensity were made as needed. All TENS devices were Rehabilicare Maxima TENS units (Empi Inc., St Paul, MN). The active TENS settings were 100 Hz, 200 μs at maximal tolerable intensity. The average peak amplitude used in the active TENS treatment group averaged 39.93 ± 13.79 mA. Maximal tolerable intensity was the highest intensity the subject tolerated that was not painful. With some subjects, this intensity produced a motor contraction. An adhesive cloth was placed over the TENS electrode to prevent visual inspection of motor contraction and maintain blinding of the outcome assessor. In addition, the TENS unit was placed in a pouch to maintain blinding for the subject and the outcomes assessor. The placebo TENS unit applied TENS at 100 Hz, 200 μs for 30 seconds and then the current ramped off over a 15 second time frame. Intensity was turned up until the subject

reported feeling the stimulation. The no TENS control was completed with the TENS unit turned off to blind the outcome assessor.

Perceived effectiveness: Since all subjects were told they were getting an active treatment, a no sensation treatment and no TENS, we asked them to determine the relative effectiveness of each condition. Upon completing each session of testing, the subject was asked, “On a 0-10 scale, how effective was your treatment today?” Each scale consisted of a 10-cm horizontal line with anchor points “not effective” and “very effective”.

Blinding: To assess blinding of the outcomes assessor, the outcomes assessor was asked “What treatment did the subject receive today? Choices for the outcome assessor were: active, placebo or no TENS”? The responses to these questions was recorded and compared by Chi-square statistical analysis to assess blinding of the subject and outcomes assessor.

Protocol

Each visit began with questionnaires followed by measurement of height and weight. The outcomes assessor completed testing in the order of: 6MWT, ROM, FTSTS, SLS, PPT, and TENS electrode application. A second assessor completed TENS application and every 5 minutes during the TENS treatment would ask the subject, "Is the TENS treatment comfortable?" and make adjustments to intensity as needed. Following the 30 minute resting TENS treatment, the outcomes assessor completed the final testing with the TENS unit on. Thus the TENS unit continued to be worn throughout the testing session for a total of 60-75 minutes. The order of testing following with the TENS on was: PPT, 6MWT, ROM, FTSTS, SLS and CPM.

Data Analyses

Descriptive statistics (mean, standard error) were determined for each study variable. Chi-square tests were used to make comparisons on categorical variables such as investigation for assessor blinding. The primary analysis was the comparisons between TENS treatment groups which was completed using a mixed model approach which accounts for the repeated measures collected through the crossover design. When group differences were identified, post-hoc comparisons between groups were made. To reduce the chance of a Type 1 error in multiple comparisons, Tukey's adjusted p-values were used. Resulting least squares means are provided with 95% confidence intervals. Percent improvement calculations demonstrate zero as no change and positive numbers indicate positive change.

Results

Table 4.1 shows the demographic and clinical characteristics for all subjects with fibromyalgia as well as by area of TENS application (cervical or lumbar). There were not significant differences between cervical and lumbar treatment groups except for body mass indexes ($p<0.05$) which was incorporated in the mixed model analysis as a potential confounder. The peak amplitude used in the active TENS treatment group was 39.93 ± 13.79 mA. The peak amplitude computed from the initial 45 seconds of stimulation for the placebo treatment group was 7.81 ± 2.21 mA.

Pain at rest and with movement

The average pain intensity at rest (0-10 scale) before TENS was similar between treatments: active TENS was 5.0 ± 0.5, placebo TENS was 5.0 ± 0.4, no TENS treatment

group was 5.2 ± 0.4. Pain at rest showed no significant difference between treatments who received active TENS, placebo TENS or no TENS (Figure4.4A). Average pain with movement before TENS is reported in 4.2. Pain with movement (during the 6MWT) was significantly less during active TENS (4.0 ± 0.4) when compared to placebo (4.7 ± 0.4) ($p<0.05$) or no TENS (5.0 ± 0.4) ($p<0.05$) (Figure 4.4A).

Fatigue at rest and with movement

The average fatigue intensity at rest before TENS was similar between treatments. Fatigue at rest was not significantly different between treatments who received active TENS (Figure 4.4B). Average fatigue with movement before TENS is reported in Table 4.2. Fatigue with movement (during the 6MWT) was significantly different between active (4.4 ± 2.3) and placebo TENS (5.5 ± 2.6) ($p<0.05$) and no TENS (5.0 ± 2.7)($p<0.01$). (Figure 4.4A)

Pressure Pain Thresholds

Average PPT in the cervical, lumbar and leg prior to TENS are reported in Table 4.2. In the cervical region (n=41), PPTs were significantly increased during active TENS when compared to no TENS ($p<0.05$) but not placebo TENS (Figure45A). In the lumbar region (n=41), PPTs were significantly increased in the active TENS when compared to either placebo TENS or no TENS ($p<0.05$)(Figure 4.5A). Outside the site of TENS, PPTs (n=36) over the anterior tibialis muscle were significantly increased during active TENS when compared to placebo TENS ($p<0.01$) or no TENS ($p<0.05$) (4.5A).

Conditioned Pain Modulation

To test if TENS modified central inhibition we examined the effects of TENS on CPM. During active TENS PPTs in response to CPM were significantly greater than

those in the placebo TENS ($p<0.05$) or no TENS ($p<0.01$) treatment groups (Figure 4.5B).

Function

There were no significant changes in function when examining the ROM, SLS, FTSTS and 6MWTduring active TENS when compared to the placebo TENS or no TENS treatment group (Table 4.2). While there appeared to be a difference in the distance walked during active TENS, this measure showed significant variability and did not reach statistical significance ($p=0.26$).

Blinding

The outcomes assessor was able to state the treatment (active, placebo, no TENS) correctly between 34% and 58% of the time. For the cervical region, correct treatment was active 54%, placebo 50% and no TENS 58%. For the lumbar region, correct treatment was active 53%, placebo 34% and no TENS 50%. No significant difference was noted between treatments when assessed with a chi squared test ($p=0.75$).

Perceived Effectiveness

Effectiveness ratings (0-10 scale) by the subject after each treatment was significant between active 6.31 ± 0.34 and placebo 3.96 ± 0.39 ($p<0.01$) and active and no TENS 3.25 ± 0.41 ($p<0.01$). There was no significant difference in effectiveness rating between placebo and TENS no TENS treatments.

Discussion

The current study shows for the first time that TENS may be an effective non-pharmacological treatment for pain in individuals with fibromyalgia. Specifically we show that both pain and fatigue during movement, but not at rest, are reduced by a one-

time 30 minute treatment with active TENS in individuals with fibromyalgia. Additionally, we also show for the first time that active TENS showed differences in pain sensitivity and inhibition. PPTs increased not only at the location of TENS application (spine) but also outside the site of TENS (leg) suggesting widespread effects of TENS to reduce central excitability. Further, we showed increased CPM in the active TENS treatment group suggesting that TENS restores central inhibition. Based on this study with a one-time use of TENS, we suggest that a more comprehensive clinical trial test effects of TENS over a prolonged treatment period in people with fibromyalgia. This should include use of TENS during physical activity and exercise since TENS reduces movement pain, daily home-use of TENS, and measurement of multiple outcomes including resting and movement pain movement, physical activity and function, quality of life, and pain physiology.

Four randomized controlled-trials have investigated the effectiveness of TENS on pain in people with fibromyalgia with mixed results. One compared effectiveness to s-adenosyl-l-methionin (SAMe), one to warmth therapy, one to massage therapy or sham TENS, and one to placebo. When compared to SAMe, TENS was not effective; however, TENS application was being applied at minimal intensities that caused a tingling sensation over 4 tender points [63]. We, and others, have previously shown that TENS applied at inadequate intensities does not reduce pain or increase pressure pain thresholds (PPTs) [18,178,179]. When compared to warmth therapy TENS effectiveness was similar, with approximately a 1/10 decrease in pain for both treatments [139]. The treatments in this case were not compared to a placebo or a no-treatment control and thus specific effects could not be concluded [139]. Subjects were also simultaneously enrolled

in a multidisciplinary treatment program consisting of exercise and cognitive behavioral therapies [139], both effective treatments for fibromyalgia [95]. Thus "effectiveness" of these interventions could be related to the multidisciplinary treatment and not to TENS or warmth therapy. Another study showed that both TENS and massage therapy were better than sham TENS for resting pain [233] which is in direct contrast to the current study showing no effect on resting pain. It is possible that repeated TENS used in the prior study had a cumulative effect as compared to the study that used a one-time treatment [233]. In contrast, a fourth study [158] used TENS in combination with an exercise program. However TENS was given in the morning 5 times per week for 3 weeks, for 30 minutes, and exercise was done in the afternoon and not during TENS. If TENS reduces pain during movement, the use of TENS during exercise should be more beneficial. Further, effectiveness of TENS is greater during the stimulation versus after it has been removed [61,179]. Like most pharmaceutical agents, TENS has a limited duration of action and thus studies should be designed to test effectiveness during peak response. Lastly, all the above studies used resting pain as their primary measure for pain. In the current study, resting pain was unaffected by TENS while movement pain was significantly reduced. Thus, measurement of resting pain in this population may provide conflicting results on effectiveness of the treatment.

Our study extended the prior findings by examining pain during movement, fatigue at rest and during movement, and function. We show that pain and fatigue during movement, but not at rest, are significantly reduced during TENS. This change in movement pain, but not resting pain, was also shown in a prior study by Rakel and Frantz [179] in people with postoperative pain. Further in people with osteoarthritis, pain during

movement is also significantly reduced [127,128]. A reduction in pain with movement would be expected to increase physical activity levels and improve quality of life. Movement pain in people with fibromyalgia is a significant barrier to exercise and leads to a sedentary lifestyle [109,118,147].

Surprisingly, the current study showed that TENS reduced fatigue during movement. Fatigue is a significant symptom in fibromyalgia and is associated with decreased physical activity [47,71,160]. Prior work in animal shows that fatiguing exercise can enhance pain through central mechanisms including those classically involved in inhibition of pain [207,211,254]. Future studies should examine the relationship between pain and fatigue both at rest and with movement to further understand this interaction.

It has become clear that fibromyalgia is associated with enhanced central excitability [175,231] in the pain pathways and loss of pain inhibition [120,126,133,225]. Basic science studies show that TENS reduces enhanced excitability of neurons in the pain pathways [79,80,132] and activates pain inhibitory mechanisms to reduce hyperalgesia [61,114,208]. The current study showed that TENS increased PPTs not only at the site of TENS application (spine) but also outside the area of TENS (leg) - consistent with reduced central excitability. We further show that PPTs during CPM were greater during active TENS when compared to placebo TENS or no TENS–consistent with an increase in inhibition. Thus the current study suggests that TENS may begin to normalize pain processing in the central nervous system in people with fibromyalgia. While we only tested a single application of TENS, repeated use, as done clinically, could have more widespread and longer effects, and should be investigated.

The current study showed a lack of change in function during a single TENS treatment. While there was a trend towards an increase in distance walked (6MWT) this was not significant. As a secondary measure, we may not have had significant power to observe changes in the 6MWT - power analysis of the current data shows we would need 299 subjects per treatment to obtain statistical significance. Previous studies show that increasing physical activity by 30 minutes per day was sufficient to decrease pain in fibromyalgia [77,78]. Repetitive treatment with TENS reduces pain in a cumulative manner in people with musculoskeletal pain [36,144]. Thus, future studies should examine if longer term use of TENS decreases pain with movement, increases physical activity and increases function in fibromyalgia.

Intensity of TENS is critical for producing a reduction in pain [156,178] in healthy controls, and in postoperative pain [18]. In fact, Moran et al [156] show dose-dependent increase in pressure pain thresholds with increasing intensity from no change at sensory perception thresholds to significant increases at a "strong, but comfortable intensity". In the current study we used the maximal tolerable intensity which was above sensory threshold and below pain thresholds, and described to subjects as 'strong, tolerable and non-painful" to promote the greatest potential relief of pain during active TENS. It should also be noted that we tested the effectiveness of the TENS by keeping the TENS unit on during the second half of the testing during movement and study activities since the greatest effect of TENS occurs while the unit is on.

We have previously validated the transient placebo used in the current study [241] showing complete blinding of the outcome and TENS applicator, and adequate blinding of the subject (approx. 50% guessed correctly) allowing us to deliver a true placebo

treatment [178,241]. However, in prior studies we show that subjects identify the active TENS correctly the majority of the time (close to 100%)[178]. This lack of ability to blind the active treatment is an inherent problem in TENS trials - when TENS is applied at adequate intensities to produce analgesia the subject is aware of receiving an active treatment. To improve blinding, the current study modified the instructions so that subjects thought all 3 treatments were "real". Thus, subject expectation is likely not an explanation for TENS effectiveness in the current study.

Clinically, in people with fibromyalgia, TENS may be a helpful adjunct treatment to their current management plan particularly to reduce pain and fatigue during movement. Future studies should examine if long term use of TENS decreases pain with movement, increases physical activity and increases function in individuals with fibromyalgia. We demonstrated in this current study that a one-time use of TENS facilitated a change in pain with movement. Often in the clinic setting, a reduction in pain is viewed as significant by patients might not match what is statististically significantly in the research setting. Importantly, the current study used TENS as an addition to ongoing pharmacological treatment and was able to show a reduction in pain and fatigue with movement. It is expected that TENS is not a "cure" for fibromyalgia but rather an adjunct treatment aimed at reducing pain so that physical activity will be increased. The reduction in movement-pain with TENS is an important consideration as pain during movement can impact treatment recommendations for exercise, pacing and physical activity. Therefore the use of TENS during exercise or physical activity could engage people with fibromyalgia in a more active lifestyle leading to longer term changes in central sensitization

Table 4.1: Demographics and clinical characteristics

	Total (N=41)	Cervical (n=17)	Lumbar (n=24)
Age, years (mean ± SEM)	49.1±12.9	48.1±13.0	49.9±13.0
Female (% sample)	40 (97.6%)	17 (100%)	23 (95.8%)
Ethnicity (% sample)			
Caucasian	36 (87.7%)	14 (82.4%)	22 (91.7%)
Others	5 (12.2%)	3 (17.7%)	2 (8.3%)
Marital status (% sample)			
Married/co-habitating	25 (61.0%)	8 (47.1%)	17 (70.8%)
Single/widowed/divorced	16 (39.0%)	9 (52.9%)	7 (29.2%)
Education (% sample)			
High school or less	10 (24.4%)	4 (23.5%)	6 (25.0%)
Some college or above	31 (75.6%)	13 (76.5%)	18 (75.0%)
Income (% sample)			
< $ 60,000	26 (63.4%)	13 (76.5%)	13 (54.2%)
≥ $60,000	15 (36.6%)	4 (23.5%)	11 (45.8%)
Body mass index* (mean ± SEM)	33.6 ± 9.4	37.3 ±11.7	31.0 ± 6.3
Length of Fibromyalgia diagnosis, years (mean ± SEM)	7.4 ± 5.6	6.4 ± 5.0	8.1 ± 6.0
FIQ (0-100) (mean ± SEM)	60.05 ± 2.3	60.04 ± 4.0	60.06 ± 2.6
Pain at Rest (0-10cm scale) (mean ± SEM)	5.0 ± 0.5	4.8 ± 0.6	5.1 ± 0.5
Pain with Movement (0-10cm scale) (mean ± SEM)	5.3 ± 0.4	5.6 ± 0.6	5.1 ± 0.7

Table 4.1: continued

	Total (N=41)	Cervical (n=17)	Lumbar (n=24)
Fatigue at Rest (0-10cm scale) (mean ± SEM)	4.97 ± 0.4	5.3 ± 0.6	4.7 ± 0.6
Fatigue with Movement (0-10cm scale) (mean ± SEM)	5.41 ± 0.4	6.0 ± 0.6	4.9 ± 0.6
Pressure Pain Threshold Cervical (kPa) (mean ± SEM)	260.90 ± 22.81	265.88 ± 36.28	355.49 ± 47.89
Pressure Pain Threshold Lumbar (kPa) (mean ± SEM)	365.98 ± 31.45	257.37 ± 29.92	373.42 ± 42.64
Pressure Pain Threshold Anterior Tibialis (kPa) (mean ± SEM)	421.97 ± 29.45	423.91 ± 36.28	420.41 ± 44.50

* *p*-value < 0.05

Table 4.2: Outcome measure difference score before and during TENS

Variable			
	Active TENS	Placebo TENS	No TENS
Pain at rest (0-10cm)	-0.38 ± 0.26 (-0.9 to 0.13)	-0.74 ± 0.25 (-1.25 to -0.25)	-0.47 ± .26 (-0.98 to 0.04)
Pain with movement (0-10cm)	1.11 ± 0.26 (0.59-1.63)	0.23 ± .26[b] (0.24 to 0.77)	0.26 ± 0.25[c] (-0.28 to 0.75)
Fatigue at rest (0-10cm)	-0.09 ± 0.21 (-0.52 to 0.33)	-0.14 ± 0.21 (-0.56 to 0.28)	0.12 ± .22 (-0.31 to 0.54)
Fatigue with movement (0-10cm)	0.94 ± 0.23 (0.47 to 1.41)	0.39 ± .24[b] (-0.43 to 0.5)	0.04 ± 0.23[d] (-0.41 to 0.49)
PPT Cervical (kPa)	-53.15 ± 10.09 (-73.17 to -33.13)	-26.42 ± 10.02 (-46.29 to -6.55)	-19.39 ± 10.06[c] (-39.34 to 0.57)
PPT Lumbar (kPa)	-86.97 ± 15.97 (-118.76 to -55.18)	-34.89 ± 15.91[b] (-66.58 to -3.2)	-33.23 ± 15.95[c] (-64.97 to -1.48)
PPT Ant Tib (kPa) n=36	-56.77 ± 17.27 -(91.3 to -22.23)	-48.92 ± 17.88[b] (-84.63 to -13.21)	-0.48 ± 17.28[c] (-35.03 to 34.07)
PPT with CPM (kPa) n=39	467.01 ± 36.95 (392.47 to 541.56)	416.42 ± 36.71[b] (-342.3 to 490.53)	423.12 ± 36.83 (648.78 to 497.45)
6MWT Average Change (feet)	-25.28 ± 35.5 (-95.67 to 45.1)	54.68 ± 34.92 (-14.56 to 123.92)	-16.85 ± 35.34 (-86.9 to 53.21)
FTSTS (seconds)	-.07 ± -0.46 (-1.01 to 0.86)	-0.46± 0.46 (-1.39 to 0.47)	-0.10 ± 0.46 (-1.04 to 0.83)
SLS Left (seconds)	-0.48 ± 0.73 (-1.93 to 0.97)	-1.02 ± 0.72 (-0.41 to 2.44)	-0.68 ± 0.73 (-2.13 to 0.78)
SLS Right (seconds)	-0.45 ± 0.74 (-1.91 to 1.02)	-1.24 ± 0.73 (-2.69 to 0.21)	1.83 ± 0.74 (-3.3 to -0.36)
ROM Cervical (degrees)	1.99 ± 2.37 (-2.66 to 6.64)	-0.39 ± 2.75 (-5.78 to 5.0)	-3.12 ± 2.6 (-8.22 to 1.98)
ROM Lumbar (degrees)	-0.54 to 2.6 (-5.64 to 4.56)	2.94 ± 2.15 (-1.27 to 7.15)	-0.41 to 2.04 (-4.41 to 3.59)

CPM score is the % increase in PPT during CPM above TENS effect. Data are mean ± S.E.M and 95% confidence intervals. N=41 unless otherwise stated.

[a] TENS=Transcutaneous electrical nerve stimulation, VAS=visual analogue scale, PPT=pressure pain threshold, CPM=conditioned pain modulation, 6MWT=six minute walk test, SLS=single leg stance, ROM=range of motion.

[b] Significant difference between active and placebo

[c] Significant difference between active and no TENS

[d] Significant difference between placebo and no TENS

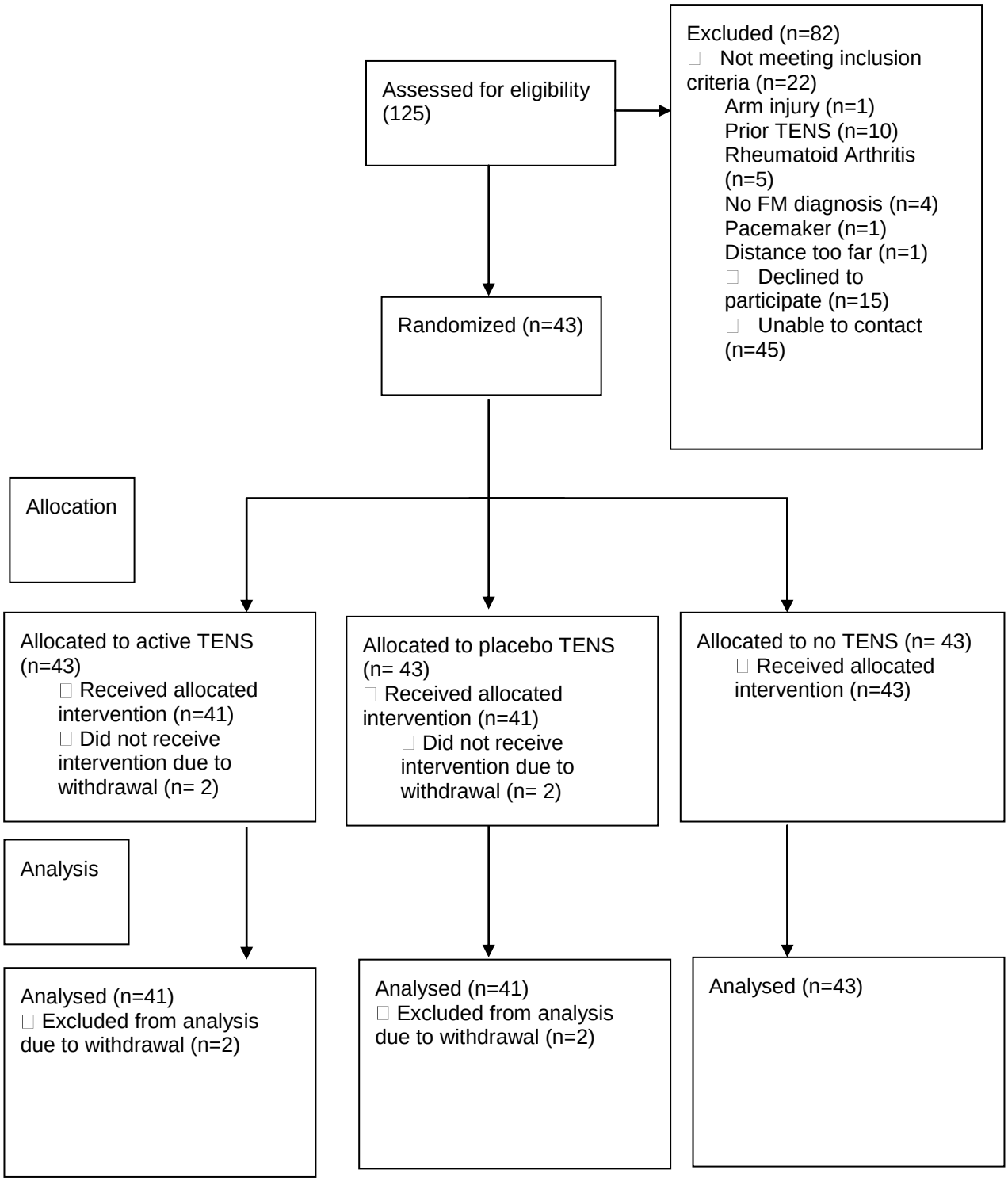

Figure 4.1: Consort diagram for the study

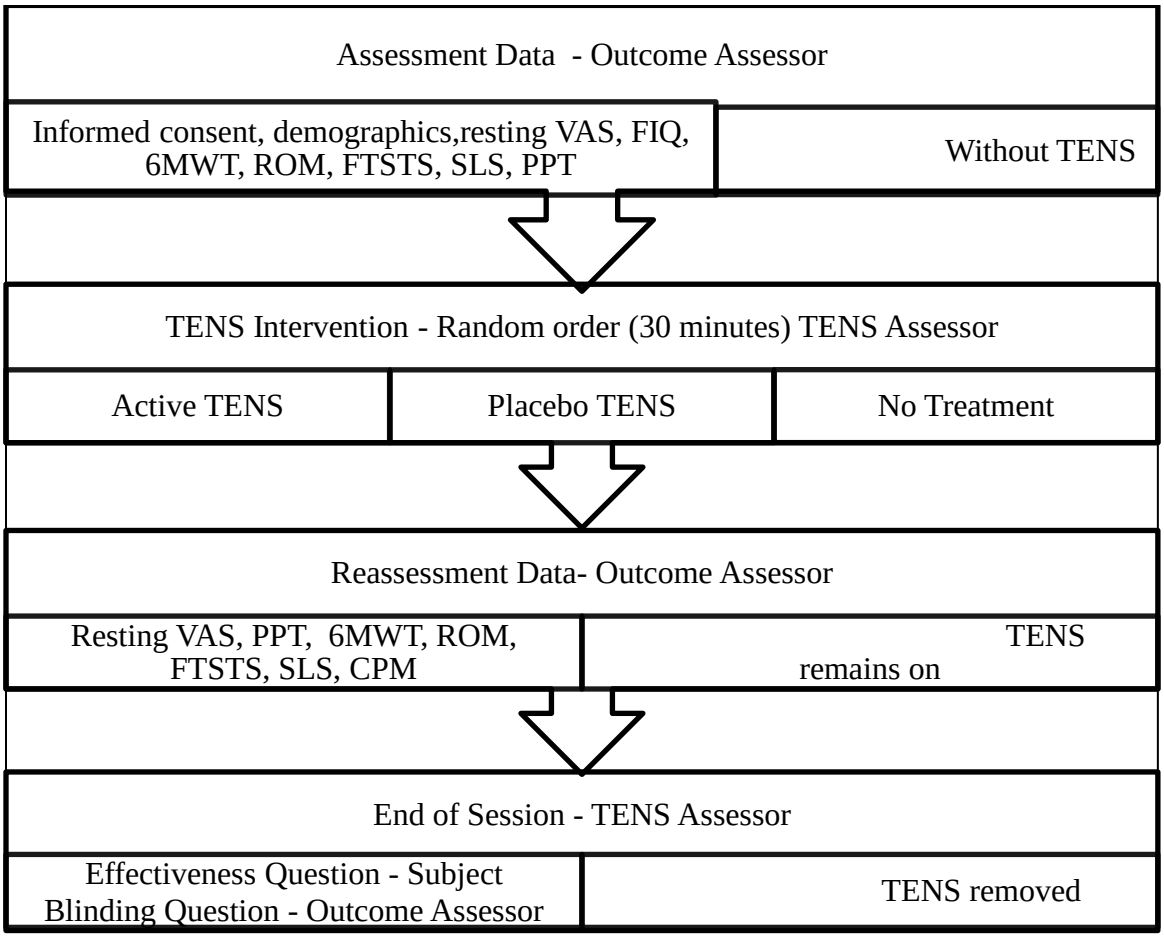

Figure 4.2: Order of Testing, Study 3

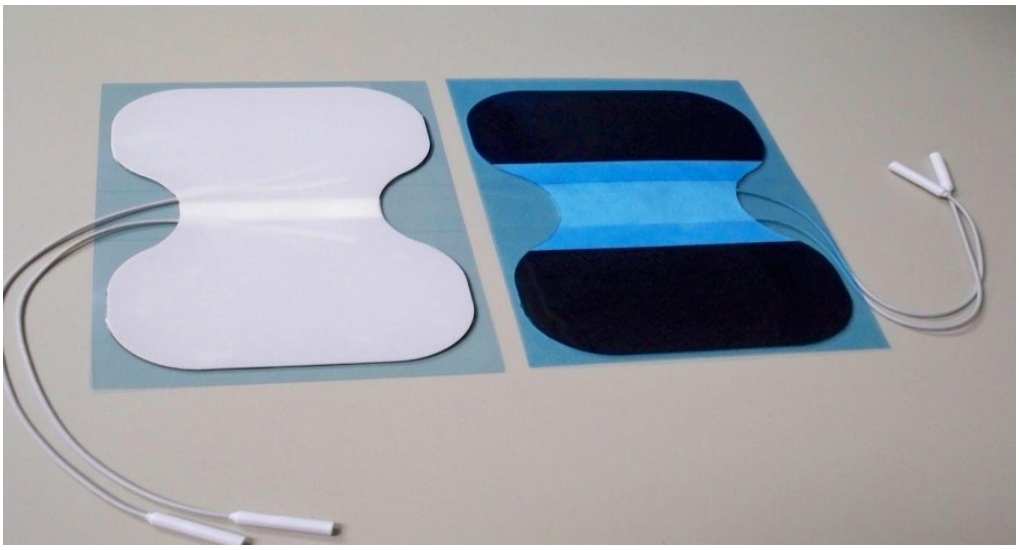

Figure 4.3: Picture of electrode used in the study (Empi Inc, St. Paul, MN)

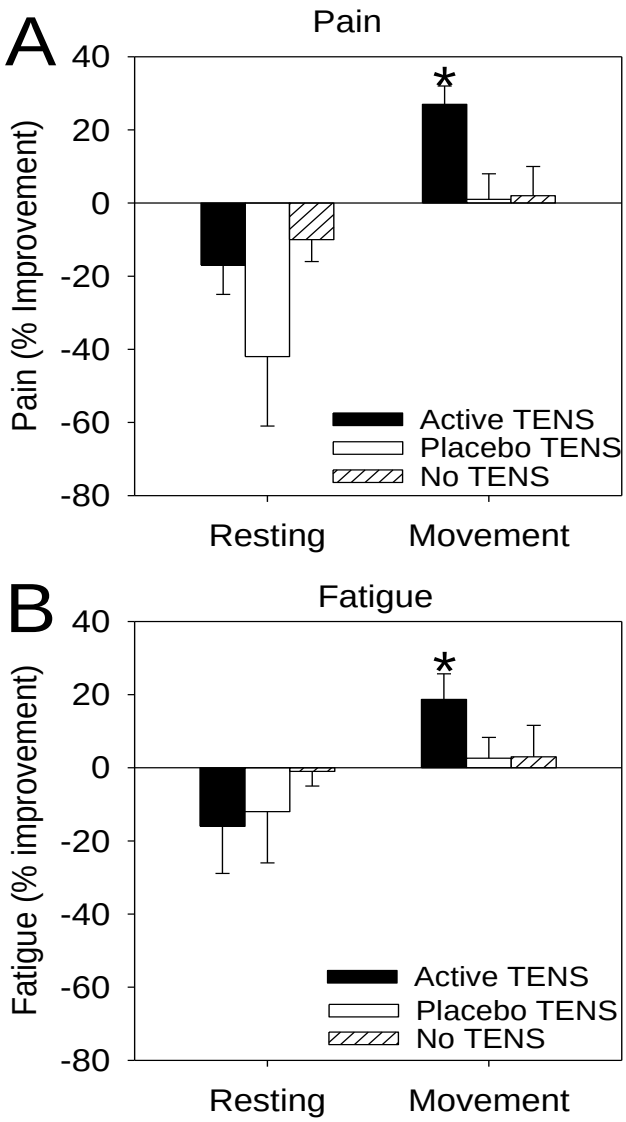

Figure 4.4: Percent improvement in pain and fatigue.

Graphs represent the percent improvement in pain (A) and fatigue (B) at rest and during movement (6MWT) during active TENS, placebo TENS, or no TENS. Significant differences were seen between active TENS and placebo TENS and no TENS for pain with movement and fatigue with movement. * Significantly different from active and no TENS

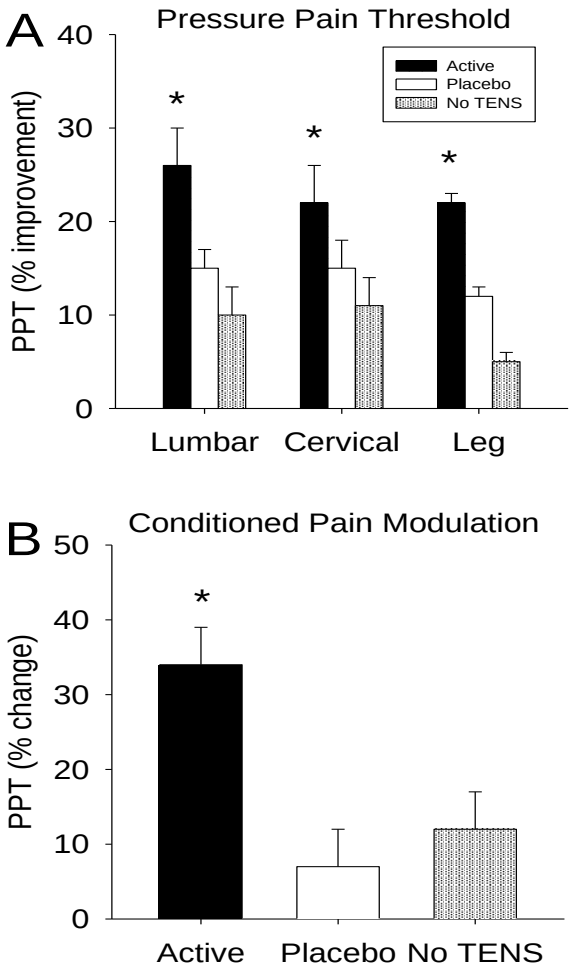

Figure 4.5: Percent improvement in PPT and PPT % change during CPM

A. Graphs represent percent improvement in pressure pain thresholds (PPTs) in the lumbar region, cervical region, and leg after active TENS, placebo TENS, or no TENS. Significant increases in PPTs were observed in all areas (*p<0.05). B.

Changes PPTs during conditioned pain modulation (CPM) during active TENS, placebo TENS or no TENS when compared to the TENS condition alone. A significantly greater change in PPTs occurred in the treatment group that received active TENS when compared to placebo TENS or no TENS treatment group (*p<0.05).

CHAPTER 5

DISCUSSION

Conclusions

The American College of Rheumatology (ACR) 1990 criterion classifies fibromyalgia as a clinical syndrome characterized by chronic widespread muscular pain and tenderness with hyperalgesia to pressure over 11/18 tender points of at least 3 months duration [250]. Fibromyalgia is characterized by chronic widespread musculoskeletal pain and is associated with fatigue and cognitive dysfunction [250]. Without greater understanding of the interaction of pain, fatigue and function in individuals with fibromyalgia, we are limited in our ability to examine these associated symptoms of fibromyalgia in clinic and research settings and we are limited in the ability to improve the symptoms associated with fibromyalgia which can limit function at work, home and in social situations.

To examine the relationship of pain, fatigue and function in individuals with fibromyalgia, we designed three experiments. The experiments focused on three areas of the experience of fibromyalgia: (1) fatigue, pain and pain-related fear and relationship to function and quality of life in individuals with fibromyalgia and healthy controls (2) interaction of pain and fatigue in three fatigue tasks (perceived cognitive fatigue, perceived physical fatigue and dual fatigue) in individuals with fibromyalgia and healthy controls (3) effect of a one-time treatment of transcutaneous electrical nerve stimulation (TENS) on pain, fatigue and function in individuals with fibromyalgia. The hypotheses and conclusions from each study are discussed in this chapter.

Hypotheses

Hypothesis 1

Higher levels of fatigue are associated with higher levels of pain and pain-related fear of movement, decreased function and decreased quality of life in individuals with fibromyalgia. *Aim 1.1*: To determine if pain, fatigue and fear of movement in individuals with fibromyalgia are different from healthy subjects. *Aim 1.2:* To determine the degree to which pain, fatigue and fear of movement are predictors of function and quality of life in patients with fibromyalgia and healthy subjects.

In our first study, we were able to support our hypothesis and both aims 1 and 2. Comparisons between the individuals with fibromyalgia and healthy controls were significantly different for the variables assessed for pain, fatigue and function. The individuals with fibromyalgia demonstrated higher pain at rest and lower pressure pain thresholds. The individuals with fibromyalgia demonstrated higher fatigue at rest, higher scores on two fatigue questionnaires, the MAF and MFIS. BMI was also significantly higher in the individuals with fibromyalgia compared to the healthy controls. In function tasks, the individuals with fibromyalgia walked less distance in the 6MWT, took longer to complete a sit to stand test and stood on one leg for a shorter time.

The proposed prediction model for pain, fatigue and fear of movement as we defined it in our study is a strong model for predicting function and quality of life in individuals with fibromyalgia. We were able to demonstrate that pain, fatigue and pain-related fear of movement contribute to a model of function and quality of life. Our model is consistent with other prediction models of chronic pain [12,59,134,195] and highlights

the importance of multiple assessments such as pain, fatigue and pain-related fear to capture the heterogeneity of the experience of fibromyalgia.

Hypothesis 2.1

There will be greater perceived cognitive fatigue and perceived physical fatigue during fatigue tasks (cognitive fatigue task, physical fatigue task, dual fatigue task) in individuals with fibromyalgia compared to healthy controls. Enhanced perceived cognitive fatigue and perceived physical fatigue will occur in the dual fatigue task compared to the single fatigue task. *Aim 2.1:* To determine if perceived cognitive fatigue and perceived physical fatigue are enhanced during a cognitive fatigue task, physical fatigue task and dual fatigue task in individuals with fibromyalgia compared to healthy controls.

Our results partially support this hypothesis and aim. Significant increases in pain and fatigue occurred in people with fibromyalgia when compared to healthy subjects with all fatigue tasks (perceived cognitive fatigue, perceived physical fatigue and dual fatigue). In all the fatigue tasks, subject ratings for pain, perceived cognitive fatigue and perceived physical fatigue increased from baseline in both groups however a significant difference as noted between the individuals with fibromyalgia and the healthy control group. In the physical fatigue task, the ratings of pain and perceived physical fatigue were the highest when comparing all three tasks in the individuals with fibromyalgia. Perceived cognitive fatigue ratings were the highest in the cognitive fatigue task for the individuals with fibromyalgia and the healthy control group. The dual fatigue task did not show a higher rating of pain and fatigue compared to the single fatigue tasks (perceived cognitive fatigue and physical fatigue task) as expected in either group.

Hypothesis 2.2

There will be greater pain and reduced function during fatigue tasks (cognitive fatigue task, physical fatigue task, dual fatigue task) in individuals with fibromyalgia compared to healthy controls. *Aim 2.2:* To determine the impact of fatigue (perceived cognitive fatigue and perceived physical fatigue) on pain and function in individuals with fibromyalgia compared to healthy controls.

Our results partially support this hypothesis and aim. In the cognitive fatigue task, functional outcome measures (grip force and range of motion) and performance on the cognitive fatigue task (total number of words) were unchanged. For the physical fatigue task, people with fibromyalgia performed less well when compared to healthy controls during transfer of pegs from waist to overhead. No significant differences were noted with the transfer shoulder to overhead or when we compared the total time for transfer of pegs for both transfer 1 and 2. Functional outcome measures, grip and shoulder range of motion, were unchanged after the physical fatigue task. Physical performance (time for transfer of pegs) was reduced in people with fibromyalgia when compared to healthy controls.

In the dual fatigue task, there was no significant difference in cognitive performance or perceived physical fatigue performance between those with fibromyalgia and healthy controls. Performance on the dual task was significantly less than the single task performance for both fibromyalgia and healthy control groups for both cognitive and physical performance. All subjects performed less well during the dual task with transfer 1 on the physical fatigue task and transfer 2 on the physical fatigue task. However, the

magnitude of change in the dual task compared between those with fibromyalgia and those with healthy controls was not significantly different.

These data show that people with fibromyalgia show enhanced pain and fatigue to both cognitive and physical fatigue tasks and reduced function in the physical fatigue task. We also show for the first time that performing a cognitive fatiguing task increases pain and perceived physical fatigue, as well as perceived cognitive fatigue, in people with fibromyalgia, and these increases are greater than healthy controls. Further we show increases in perceived cognitive fatigue during a physical fatigue task in people with fibromyalgia that were greater than healthy controls. Few studies have differentiated physical and perceived cognitive fatigue in fibromyalgia, and none have asked if perceived cognitive fatigue can impact pain, perceived physical fatigue, and function. Thus, a consideration of how physical and cognitive activity might impact pain and fatigue is an important consideration for the clinician in terms of clinical instruction and education, clinical performance and exercise performance in treatment of individuals with fibromyalgia.

Hypothesis 3

The application of TENS to people with fibromyalgia (FM) will reduce pain and fatigue, reduce central excitability and restore conditioned pain modulation (CPM) which would be manifested as improved function. *Aim 1:* To test the effectiveness of TENS on pain, fatigue and function in a crossover design study for patients with fibromyalgia with random assignment to three treatments: no TENS control, placebo TENS and active high frequency TENS. *Aim 2*: To test the effect of TENS on central inhibition and hyperalgesia as an indicator of central excitability.

Our results partially support this hypothesis and partially support aim 1 and 2. There was a significant decrease in pain and fatigue with movement for active TENS compared to placebo and no TENS. PPTs increased at site of TENS (spine) and outside site of TENS (leg) when compared to placebo TENS or no TENS. During Active TENS CPM was significantly stronger compared to placebo TENS and no TENS. No changes in functional tasks were observed with TENS for the 6MWT, FTSTS, ROM or SLS.

This third study shows for the first time that TENS may be an effective non-pharmacological treatment for pain in individuals with fibromyalgia. Specifically we show that both pain and fatigue during movement, but not at rest, are reduced by a one-time 30 minute treatment with active TENS in individuals with fibromyalgia. Additionally, we also show for the first time that active TENS showed differences in pain sensitivity and inhibition. The results of our study show active TENS restores inhibition (CPM), reduced central excitability (increased leg PPT), decreases deep tissue pressure pain (spine PPT), decreases pain and fatigue during movement. Thus, TENS may be an effective treatment for pain and fatigue in people with fibromyalgia producing its effects by restoring central inhibition and reducing central excitability.

Summary

The purpose of these experiments was to examine the relationship of pain, fatigue and function in individuals with fibromyalgia. We were able to examine these three variables in a prediction model, a functional task and a pain control intervention. We were also able to support hypothesis 1, and partially support hypothesis 2.1, 2.2 and hypothesis 3. We were able to show the contribution of pain, fatigue and pain-related fear on function and quality of life in individuals with fibromyalgia. We were able to show for

the first time the effect of a cognitive fatiguing task on pain and fatigue and the effect of TENS on pain and fatigue, but not function. The interaction of pain, fatigue and function is a complex and multidimensional relationship.

Future Directions

Further exploration into the relationship between pain and fatigue is needed to better explain the heterogeneity of the experience of fibromyalgia and how pain and fatigue impact function. A consideration to explore is the relationship between rest and movement when we examine both pain and fatigue. A working definition of fatigue, both perceived cognitive fatigue and perceived physical fatigue is needed to assist in the comparison of research and further studies. The impact of fatigue (both cognitive and physical) in the daily activities of individuals with fibromyalgia needs to be explored in order to develop treatment strategies to assist in reducing fatigue and its impact on function and disability in individuals with fibromyalgia. Function is a multidimensional aspect of the experience of fibromyalgia and may differ in clinical settings, research settings, work and home environments. Measurement of function needs to include both objective and subjective components to evaluate the actual performance in comparison to the experience or perception of the functional activity.

With respect to TENS, a longer trial of the effect of TENS in individuals with fibromyalgia is needed to further assess the possible benefits to this population of patients. My initial study is a one-time use of TENS and positive changes were seen in individuals with fibromyalgia. Most studies with TENS in individuals with fibromyalgia have been of short term use and not focused on movement pain. It is possible with

repetitive use of TENS over a longer period of time to see further changes in movement pain, decreasing central sensitization and improving descending inhibition, thus "rewiring" the ability of the central nervous system to process pain in a different manner for individuals with fibromyalgia. The possibility of rewiring an individual's pain processing system would lead to greater improvements in pain, fatigue and function in this population.

Clinical Implications

The impact of pain, fatigue and fear of movement, function and quality of life are important considerations in the assessment and treatment of individuals with fibromyalgia in a clinical setting. In my three studies I have shown that pain, fatigue, and fear of movement can predict function and quality of life. In addition, perceived cognitive fatigue and perceived physical fatigue can both be induced during a physical fatigue task, a cognitive fatigue task and a dual fatigue task. In addition, a one-time treatment of TENS was able to reduce pain and fatigue with movement in individuals with fibromyalgia.

The three domains of pain, fatigue and function have a relationship that impacts quality of life, and thus it would be important to assess these symptoms during clinical and therapeutic activities. Pain during an exercise regimen or education session can impact performance and participation. According to current literature, physical activity and exercise clearly improve pain, fatigue and function in people with fibromyalgia and includes aerobic exercise, both land and aquatic [22,23,95,110,197]. This exercise research shows strong evidence that aerobic cardiovascular exercise improves symptoms

of fibromyalgia as well as improves quality of life [22,23]. However, exercise itself may be painful, and the pain may prevent a person from exercising [243].In addition, fatigue may impact the ability to perform a task as pain or pain-related fear of movement increases. Physically fatiguing tasks, such as exercise and regular activity, may impact not only pain but also perceived physical fatigue and perceived cognitive fatigue. Cognitive fatiguing tasks such as education or verbal instruction may impact pain and not only perceived cognitive fatigue but also perceived physical fatigue.

Clinically, in people with fibromyalgia, TENS may be a helpful adjunct treatment to their current management plan particularly to reduce pain and fatigue during movement. Often in the clinic setting, a reduction in pain is viewed as significant by patients might not match what is statististically significantly in the research setting. Importantly, the current study used TENS as an addition to ongoing pharmacological treatment and was able to show a reduction in pain and fatigue with movement. It is expected that TENS is not a "cure" for fibromyalgia but rather an adjunct treatment aimed at reducing pain so that physical activity will be increased. The reduction in movement-pain with TENS is an important consideration as pain during movement can impact treatment recommendations for exercise, pacing and physical activity. Therefore the repetitive use of TENS during exercise or physical activity could engage people with fibromyalgia in a more active lifestyle leading to longer term changes inhibition and in central sensitization.

Another consideration in a clinical setting would be the timing of these assessments. As we have demonstrated in our TENS and FM study (Chapter 4), pain and fatigue can vary with rest and movement, it would be important to assess pain and fatigue

before, during and after activities in the clinic and at home. Understanding these changes in pain fatigue and function will be important toward designing an appropriate activity-based treatment strategy, participation in daily activity including work, family and social situations.

Other considerations for clinical practice would be to include the domains recommended by the OMERACT which list a core domain set for fibromyalgia assessment in clinical trials and practice [149,150]. This domain set includes pain, tenderness, fatigue, patient global impressions, multidimensional function and sleep disturbance. Additional recommendations outside the core domain to consider for some, but not all individuals with fibromyalgia for include depression and dyscognition. The FIQ, in its original or revised form, has been shown to be a valuable tool in examining the impact of the experience of fibromyalgia in a clinical setting version [13-17,24,25].

In summary, pain, fatigue and function and the impact on quality of life in individuals with fibromyalgia are important considerations for research and clinical practice. It is important to progress toward translating research regarding pain, fatigue and function in individuals with fibromyalgia into the clinical practice setting as well as home, work and social environments.

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