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MECHANISMS OF ISOMETRIC EXERCISE-INDUCED HYPOALGESIA  
IN YOUNG AND OLDER ADULTS

by

Kathy J. Lemley

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

Milwaukee, Wisconsin

August 2014

ABSTRACT  
MECHANISMS OF ISOMETRIC EXERCISE-INDUCED HYPOALGESIA  
IN YOUNG AND OLDER ADULTS

Kathy J. Lemley

Marquette University, 2014

Pain reduction following exercise (exercise-induced hypoalgesia; EIH) is well-established in young adults. Specific to isometric exercise, the greatest EIH follows low intensity contractions held for long duration. The EIH response of older adults is not known; and the mechanisms for EIH are unclear at any age. This dissertation aimed to address these unknowns through a series of three studies.

In *study one*, repeatability of pressure pain reports (pain threshold and pain ratings) was assessed in healthy older adults, including the impact of psychological factors. Pain reports, measured before and after quiet rest, did not change following quiet rest. Higher state anxiety was associated with greater pain.

*Study two* examined the impact of isometric contractions that varied in intensity and duration on pain relief in healthy older adults. Pressure pain was assessed before and after isometric contractions of the left elbow flexor muscles. Unlike young adults, older adults experienced EIH similarly across different isometric exercise tasks and women experienced greater pain reduction than men. Anxiety did not influence EIH.

Conditioned pain modulation (CPM; a reduction in pain to a test stimulus in the presence of a noxious conditioning stimulus) has been hypothesized to augment EIH when exercise is painful. In *study three*, CPM and EIH were assessed in healthy young and older adults. CPM was measured as the difference in pressure pain with the foot immersed in neutral-temperature water versus noxious ice water. While young adults experienced CPM, older adults experienced a range of responses from hypoalgesia to hyperalgesia with foot immersion in the ice water bath. CPM predicted EIH and was associated with state anxiety; however state anxiety was unrelated to EIH. Results for age and sex-related differences in pain perception varied across studies or sessions.

The results of this dissertation suggest anxiety influences pain sensitivity, but not magnitude of EIH. Older adults, particularly women, experience reductions in pain following isometric exercise and are less dependent upon task than young adults. CPM may predict EIH response following isometric exercise in both young and older adults and may be a useful tool in clinical decision making for adults experiencing pain.

## ACKNOWLEDGEMENTS

Kathy J. Lemley

I would first like to give a very special thank you to my advisor Dr. Marie Hoeger Bement for her support, encouragement, and expert guidance throughout my time in her laboratory. She buoyed me up all those times when I didn't think I could do it, and she celebrated my every success whether big or small along the way. For this and all I have learned from her I will be forever grateful.

I would like to acknowledge committee member Dr. Sandra Hunter who gave freely of her time and knowledge. Her ability to see the big picture has left an incredible impression on me. I would also like to thank my committee Chair Dr. Lawrence Pan, and committee members Drs. Margaret Faut-Callahan and Laura Frey Law for providing the leadership and guidance to allow me to grow, learn and develop a higher understanding of the research process.

Thanks also to Dr. April Harkins for her mentorship in the initial stages of this dissertation and her continued support as I found my path. A special thank you for the friendship and support of my lab colleague Stacy Stolzman who made coming to the lab fun and in whom I knew I could always count on. Soon it will be your turn! Thanks also to the many undergraduate and graduate students and post docs too numerous to name who helped with everything from troubleshooting equipment problems, to data collection and data entry, to help with lit searches and library runs for needed articles. I could not have done this without you.

My husband Jim has lived this dissertation with me. He has taken on the role of chief cook and housekeeper during this journey to allow me to focus on succeeding. He is my pillar and without his unwavering support I would not have reached my goal. I would also like to thank my daughters Erin and Caitlin for their encouragement and most of all for their belief in me.

Finally I would like to recognize my faculty colleagues and administrators at Concordia University Wisconsin whose support and understanding was integral to the completion of this dissertation.

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## LIST OF ABBREVIATIONS

ACC	Anterior Cingulate Cortex
CGRP	Calcitonin Gene-Related Peptide
CPM	Conditioned Pain Modulation
EIH	Exercise-Induced Hypoalgesia
FPQ-9	Fear of Pain Questionnaire
IASP	International Association for the Study of Pain
MVC	Maximal Voluntary Contraction
NRS	Numerical Rating Scale
NTS	Nucleus Tractus Solitarius
PAG	Periaqueductal Gray
PAQ-R	Pain Attitude Questionnaire-Revised
PCS	Pain Catastrophizing Scale
PFC	Prefrontal Cortex
RVM	Rostral Ventromedial Medulla
RPE	Rating of Perceived Exertion
SRD	Subnucleus Reticularis Dorsalis
STAI	State-Trait Anxiety Inventory
tDCS	Transcranial Direct Current Stimulation
VAS	Visual Analog Scale
WDR	Wide Dynamic Range

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## **CHAPTER 1**

### **INTRODUCTION AND LITERATURE REVIEW**

Pain is the primary reason people seek healthcare and more than 100 million Americans suffer from chronic pain (Institute of Medicine: Committee on Advancing Pain Research, Care and Education, 2011). The frequency of pain reports increases with age (Crook et al., 1984; Davis & Srivastava, 2003; Harkins, 2001), with an age-associated increase in the prevalence of both neuropathic pain (pain of neurological origin) and musculoskeletal pain (e.g., osteoarthritis) until approximately the seventh decade of life. At this time pain reports stabilize or even decrease slightly (Bagge et al., 1992; Brattberg et al., 1989; Gibson & Lussier, 2012; Helme & Gibson, 1999; Mobily et al., 1994; Thomas et al., 2004), with the possible exception of osteoarthritis associated pain (Harkins, 1996; Helme & Gibson, 1999; Sternbach, 1986). It is estimated that between 20% and 80% of older adults residing in the community (Blyth et al., 2001; Brattberg et al., 1989; Magni et al., 1993; Mobily et al., 1994; Roy & Thomas, 1987; Thomas et al., 2004) and 45% to 85% of nursing home residents (Fox et al., 1999; Roy & Thomas, 1987) experience some type of pain, with older adults twice as likely as young adults to suffer from persistent pain (Battista, 2002; Crook et al., 1984).

Successful management of pain conditions is limited, resulting in the under-treatment of pain and impaired quality of life. Consequences of poor pain management are numerous and include sleep disturbances, depression, decreased socialization, feelings of helplessness and hopelessness, functional limitations, impaired ambulation, deconditioning, increased fall risk, impaired appetite and physiological functioning, slower rehabilitation progress, and increased healthcare utilization and costs (Battista,

2002; Berry & Dahl, 2000; Ferrell, 1995; Gibson & Lussier, 2012; Herr, 2011; Magni et al., 1993; Parmelee et al., 1991; Roy & Thomas, 1986). Thus, the under-treatment of pain is a major public health concern.

One reason pain is challenging to manage is due to its complex and multidimensional nature (Badura & Grohmann, 2002; Loeser, 2001). The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (International Association for the Study of Pain Taskforce on Taxonomy, 1994). An individual’s perception of pain is an interaction between biological factors, psychological factors and societal context (i.e., biopsychosocial model) (Engel, 1977; Loeser, 2001; Turk & Monarch, 2002).

While pharmacological means are regularly utilized in the management of pain, non-pharmacological interventions have not received as much attention in the literature, particularly in older adults. The increased adverse effects with pharmacological measures seen with age (Cavalieri, 2005; Davis & Srivastava, 2003) and the increasing cost of healthcare make it imperative to determine the efficacy of non-pharmacological, cost-effective means of pain control. Additionally, understanding the interrelationships between the various dimensions of pain, their impact on pain perception, and the mechanisms associated with treatment efficacy is critical to the development of more effective strategies in the management of pain across the lifespan.

This introductory chapter will provide a framework for the dissertation. The topics will highlight the current state of the literature on pain perception, including the

influence of age and sex; the impact of exercise on acute pain perception; and possible mechanisms involved in the alteration of pain perception with an acute bout of exercise.

## **PAIN PERCEPTION**

### **Overview - Anatomy of Pain and Conditioned Pain Modulation**

Nociceptive information is carried on small lightly myelinated A $\delta$  and unmyelinated C-fiber afferents (Almeida et al., 2004; Ringkamp & Meyer, 2009; Treede, 2009) from the periphery to the central nervous system. The nociceptor endings of A $\delta$  fibers are specialized to have a low activation threshold to a single stimulus, typically sharp mechanical or heat stimuli. The more numerous C-fiber afferents may be unimodal, responding to either tonic mechanical stimuli, noxious heat, noxious cold, or chemical mediators such as histamine or substance P, or they may be polymodal responding to all forms of noxious stimuli (Almeida et al., 2004; Mense, 2009; Ringkamp & Meyer, 2009). These two afferent fibers are thought to be responsible for different aspects of the sensory component of acute nociception, with the slightly faster conducting lightly myelinated A $\delta$  fibers providing the initial sharp, localized sense of pain (i.e., first pain) and the slower conducting unmyelinated C-fibers sub-serving the dull or diffuse burning pain that follows (i.e., second pain) (Almeida et al., 2004; Ringkamp & Meyer, 2009).

There is no one pain center in the brain to which nociceptive information is transmitted and interpreted. Instead there is a network of several cortical and subcortical areas that together produce the discriminative, cognitive, and emotional aspects of the pain experience. Some of these structures include the primary and secondary

somatosensory cortices, cingulate cortex, insula, thalamus, hypothalamus, periaqueductal gray, amygdala, and lentiform nucleus (Almeida et al., 2004).

At least five known pathways are involved in the transmission of pain signals to this network. The classic discriminative pathway from the body is the spinothalamic tract. Second order neurons located in the dorsal horn of the spinal cord transmit information to the contralateral thalamus, which in turn transmits information to the primary somatosensory cortex for the localization of the pain stimulus (Almeida et al., 2004; DaSilva et al., 2002). Discriminative noxious stimulation of the facial region is transmitted by the trigeminothalamic pathway. Second order neurons in the spinal trigeminal nucleus of the caudal medulla cross and ascend to the contralateral thalamus and then to the primary somatosensory cortex (DaSilva et al., 2002). Other identified ascending pain pathways include the spinomesencephalic, spinoreticular, spinohypothalamic, and dorsal column pathways transmitting pain information to the limbic system and areas involved in the cognitive appraisal and neuroendocrine response to pain (Almeida et al., 2004).

In addition to ascending pathways there are several descending pathways which may either facilitate or inhibit the transmission of pain (Ren & Dubner, 2009). The activity of these descending pathways is subject to modulation by the previously described ascending inputs as well as by descending input from cortical and subcortical structures. One such pathway which has been associated with a powerful antinociceptive function begins in the periaqueductal gray (PAG) of the midbrain with connections to the dorsal horn of the spinal cord via the rostral ventromedial medulla (RVM) (Ren & Dubner, 2009). The PAG-RVM pathway is an opioid-mediated pathway that has strong

associations with pain inhibition, including the placebo response (Eippert et al., 2009).

There are numerous other nuclei within the brainstem associated with the modulation of pain, including the locus coeruleus, parabrachial nuclei, and the subnucleus reticularis dorsalis (SRD) in the dorsal caudal medulla (Ren & Dubner, 2009).

A second endogenous descending antinociceptive pathway involves a spinal (or trigeminal)-medullary-spinal neural loop for the inhibition of pain (Bouhassira & Danziger, 2006; Le Bars & Willer, 2009; Villanueva & Le Bars, 1995). Specifically, stimulation of nociceptors results in the transmission of ascending input in the spinoreticular tract of the ventrolateral funiculus (De Broucker et al., 1990; Le Bars & Willer, 2009) and activation of neurons in the SRD (Bouhassira et al., 1992; Villanueva et al., 1996; Villanueva & Le Bars, 1995). The SRD, which is preferentially or solely activated by cutaneous and deep noxious input (Villanueva et al., 1996; Villanueva & Le Bars, 1995), transmits inhibitory input to wide dynamic range (WDR) neurons in the dorsal horn of the spinal cord and the trigeminal nucleus caudalis via the dorsolateral funiculi (Cadden, 1993; Cadden & Morrison, 1991; Le Bars et al., 1979a, 1979b; Villanueva & Le Bars, 1995). The resultant effect is a non-segmental reduction in pain (Bouhassira et al., 1992; De Broucker et al., 1990; Le Bars & Willer, 2009; Roby-Brami et al., 1987; Villanueva et al., 1996; Villanueva & Le Bars, 1995). It appears this reduction in pain is dependent upon opioid activity (Bouhassira et al., 1993; de Resende et al., 2011; Le Bars et al., 1981; Willer et al., 1990), while being modulated by serotonergic pathways (Chitour et al., 1982). WDR neurons (i.e., convergent neurons) receive excitatory and inhibitory input from several tissue types, including skin, muscle and viscera (Le Bars & Cadden, 2009). It is thought that this spinal-bulbo-spinal neural



loop may act to reduce input from other tissues thereby amplifying the signals from the original pain stimulus above the “noise” of basic somatosensory activity (Calvino & Grilo, 2006; Le Bars et al., 1979b; Villanueva & Le Bars, 1995).

The functional activation of this spinal-bulbo-spinal pathway can be assessed in humans via conditioned pain modulation (CPM). CPM involves a systemic attenuation of pain in areas outside of the excitatory receptive fields of activated nociceptor afferents (i.e., pain inhibits pain) (Bouhassira & Danziger, 2006; Le Bars & Willer, 2009; Villanueva & Le Bars, 1995). The CPM paradigm involves measurement of pain sensitivity to a test stimulus before and again during or immediately following application of a tonic conditioning stimulus. For example, placing your foot in an ice water bath (conditioning stimulus) decreases the amount of pain you feel if pinched on your arm (test stimulus). The degree of reduction in sensitivity to the test stimulus in the presence of the conditioning stimulus is an indication of the effectiveness of activation of the endogenous inhibitory CPM pathway.

The magnitude of CPM is dependent upon the test and conditioning stimuli used, as well as the duration and intensity of the conditioning stimulus and the body region stimulated (Pud et al., 2009). Additionally, higher centers have a modulating influence on CPM, thus psychosocial mediators such as pain catastrophizing (i.e., magnification of negative thoughts when experiencing or anticipating pain) (Goffaux et al., 2007; Goodin, McGuire, Stapleton, et al., 2009; Granot et al., 2008; Weissman-Fogel et al., 2008), anxiety (Granot et al., 2008) and expectations of the painfulness or impact of the conditioning stimulus on the test stimulus (Bjorkedal & Flaten, 2012; Goffaux et al., 2007; Nir et al., 2012) have also been found to influence response magnitude.

There is a positive association between intensity of the conditioning stimulus and the magnitude of CPM. In general, a stronger conditioning stimulus produces greater CPM (Le Bars et al., 1981; Price & McHaffie, 1988; Tousignant-Laflamme et al., 2008; Villanueva & Le Bars, 1985; Willer et al., 1989) independent of the perceived intensity of the conditioning stimulus (Granot et al., 2008; Lautenbacher et al., 2002; Pud et al., 2005; Weissman-Fogel et al., 2008). Timing of the conditioning and test stimuli is also important, as CPM magnitude is greatest with concurrent application (Pud et al., 2009; Ram et al., 2009). The majority of studies have found that test pain sensitivity returns to baseline within ten minutes (Campbell et al., 2008; France & Suchowiecki, 1999; Kakigi, 1994; Kosek & Ordeberg, 2000; Lewis et al., 2012; Reinert et al., 2000; Serrao et al., 2004), although some studies suggest the effect may persist for longer (Graven-Nielsen et al., 1998; Suzuki et al., 2007; Villanueva & Le Bars, 1995; Washington et al., 2000).

Importantly, CPM does not appear to be solely an effect of distraction. Several authors have shown that distraction likely accounts for only a small amount of the CPM response in healthy adults (Campbell et al., 2008; Edwards, Ness, et al., 2003; Kakigi, 1994; Lautenbacher et al., 2007; Moont et al., 2010; Quiton & Greenspan, 2007). Studies of patients with neurological injuries resulting in contralateral sensory impairment (i.e., thalamic injury, Wallenberg Syndrome) suggest that CPM is not simply a matter of altered attentional focus (De Broucker et al., 1990).

### **Assessment of Pain**

Accurate pain assessment is integral to developing an understanding of the influence of various factors on pain and its sequelae. Laboratory studies of pain typically

focus on acute experimentally-induced noxious stimuli. Frequently employed stimuli include thermal, pressure, electrical, ischemic or chemically-mediated pain (e.g., capsaicin). There is no physiological marker for the presence or magnitude of pain, thus pain assessment relies on self-report whenever possible (Battista, 2002; Chapman & Syrjala, 2001; DeWaters et al., 2008). Typical experimental pain assessments include pain threshold (“the minimum intensity of a stimulus that is perceived as painful”; International Association for the Study of Pain, 2012), pain ratings (the intensity of the pain), and pain tolerance (“the maximum intensity of a pain-producing stimulus that a subject is willing to accept in a given situation”; International Association for the Study of Pain, 2012). These outcome measures provide valuable insight into the acute perception of pain; the impact of a variety of biological, psychological and social factors on pain; and change in pain sensitivity following treatment intervention.

Several self-report scales are available for use in the laboratory setting and are valid for use with healthy adults of all ages. One frequently used scale is a numerical rating scale (NRS), which may be completed verbally (often referred to as a verbal numerical scale) or in written format. An NRS requires a subject to select the number best representing their pain intensity. The scale includes verbal anchors at either end, e.g. 0 = “no pain” and 10 = “worst pain imaginable”. While an 11-point NRS is widely used, scales range from six (0-5) to 101 (0-100) points.

In a study examining the number of levels of a scale providing the best discriminative ability in pain intensity differences, Jensen et al (1994) identified 11- or 21-point scales to provide as much information as a 101-point scale. Additionally, 75% of individuals completing a 101-point scale answered in multiples of 10 effectively

converting the scale to an 11-point scale, while the majority of the remainder used multiples of 5 bringing the scale to 21-points (Jensen et al., 1994). Thus an 11- or 21-point scale appears to be preferred by subjects and provides adequate sensitivity to change. Studies examining the psychometric properties of the NRS have found it to be valid and reliable with cognitively intact adults (Herr & Garand, 2001; Herr et al., 2004; Kremer et al., 1981) while being simple to administer and well-liked by both young and older patients (Herr et al., 2004).

The Visual Analog Scale (VAS) is another commonly used scale in the pain literature. A VAS consists of a continuous 10 cm line with verbal descriptor anchors on each end on which the subject makes a mark to indicate perception of pain intensity. In contrast to the NRS, the VAS has a significantly higher failure rate in older adults (Herr & Garand, 2001; Herr et al., 2004; Kremer et al., 1981), possibly due to its abstract nature (Kremer et al., 1981). An estimated 7% to 30% of cognitively intact older adults have difficulty with the tool, with more incomplete or unscorable responses with increasing age (Chapman & Syrjala, 2001; Gagliese & Melzack, 1997; Herr et al., 2004; Kremer et al., 1981). Additionally, VAS convergent validity has been found to be problematic in several studies, with responses differing significantly from other measures of pain intensity (Chapman & Syrjala, 2001; Gagliese & Melzack, 1997; Gagliese et al., 2005). Thus while appropriate for use with young adults, the VAS is not recommended as a first line tool for older adults (Herr et al., 2004).

One additional factor to consider when using self-report numerical measures of pain intensity may be differences in the underlying pain rating schemas between individuals. Frey Law and colleagues (2013) recently showed that there is great variation

in how individuals interpret the numerical rating of pain using a VAS. Thus a particular number on the scale may not have the same meaning for individuals with different pain rating schemas (Frey Law et al., 2013).

### **Pain Perception and Aging**

Physiological and anatomical changes with aging have the potential to modify pain sensitivity. Skin changes, such as reduced moisture content, reduction of collagen and lipid content, decreased vascular supply, altered inflammatory response and a lessening of the contact area between the dermis and epidermis (Balin & Pratt, 1989; Farage et al., 2008) may affect the intensity of the stimulus required to activate nociceptors. Specific to neurotransmission, there is some evidence for a reduction in intra-epidermal nerve fiber density (Bakkers et al., 2009; Goransson et al., 2004) and altered afferent function with aging (Drac et al., 1991; Lautenbacher & Strian, 1991; Ochoa & Mair, 1969; Parkhouse & Le Quesne, 1988; Verdu et al., 2000). For example, myelin demonstrates altered properties and increased number and magnitude of defects with aging (Ceballos et al., 1999; Drac et al., 1991; Ibanez et al., 2003; Ochoa & Mair, 1969; Peters, 2002; Verdu et al., 2000). These morphological changes may contribute to age-related impairment in saltatory conduction (Ceballos et al., 1999) and reduced nerve conduction velocity in myelinated axons (Eaton et al., 1993; Kakigi, 1987; Trojaborg et al., 1992). Evidence suggests that older adults may rely more on C-fiber transmission than young adults (Chakour et al., 1996). Age-related changes in myelin properties may help to explain the greater reliance on unmyelinated fiber transmission.

Alterations in the release and pharmacodynamics of neurochemicals and systemic hormones associated with nociception may also influence how older adults perceive pain. Studies utilizing animal models have found both substance P and calcitonin gene-related peptide (CGRP), neuropeptides involved in nociception, to be reduced in the dorsal horn of the spinal cord in aged rats (Bergman et al., 1996; Hukkanen et al., 2002); accompanied by an age-associated decline in CGRP transport rate (Fernandez & Hodges-Savola, 1994). Additionally, older adults experience a slower and smaller peak in plasma  $\beta$ -endorphin levels following a cold pressor task (Casale et al., 1985) and lower proportional increase in plasma  $\beta$ -endorphin following high intensity aerobic exercise (Hatfield et al., 1987). Slower or reduced  $\beta$ -endorphin release, an opioid peptide with analgesic properties, could potentially result in an augmentation of pain and attenuation of endogenous pain inhibition.

There is strong consensus that older adults have an impaired ability to activate endogenous inhibitory pain pathways (Edwards, Fillingim, et al., 2003; Riley et al., 2010; Washington et al., 2000) which begins to appear by 40-55 years of age (Lariviere et al., 2007). For example, Washington et al. (2000) found that the magnitude of the analgesic response to cutaneous thermal and electrical pain following a cold pressor task was significantly greater in young adults compared to older adults. Other investigators using a cold pressor task for a conditioning stimulus and a noxious thermal test stimulus have confirmed that CPM magnitude is attenuated or may even result in pain facilitation and hyperalgesia in older adults (Edwards, Fillingim, et al., 2003; Lariviere et al., 2007; Riley et al., 2010). The reduction in CPM with age may be due in part to histochemical changes including reductions in serotonin and norepinephrine (Ko et al., 1997) and loss of

serotonergic and noradrenergic neurons within the dorsal horn (Iwata et al., 2002).

Interestingly, while brain morphology changes are consistently found with aging (e.g., reduction in gray matter volume, neuronal numbers and size, and dendritic spine number; reviewed by Farrell, 2012), the brainstem appears to be relatively spared (Farrell, 2012).

Aging is further associated with altered central control of blood pressure as shown by a generalized elevation of systolic blood pressure in older adults relative to young adults (Burt et al., 1995; Franklin et al., 1997). Elevated blood pressure may impact pain perception as an integration of brainstem structures controlling blood pressure with those involved in pain modulation has been postulated (Ghione, 1996; Randich & Maixner, 1984). For example, the nucleus tractus solitarius (NTS) receives afferent input from peripheral baroreceptors. The NTS in turn projects both directly and indirectly to other regions important in pain modulation including the PAG, RVM with the nucleus raphe magnus, and the locus coeruleus (Bruehl & Chung, 2004; Ghione, 1996).

Experimental evidence supporting an interaction of blood pressure and pain perception is also strong; hypoalgesia has been found to occur following electrical or pharmacological stimulation of baroreceptors (Bruehl & Chung, 2004). Additionally, an association between systolic blood pressure and pain sensitivity has been shown in both normotensive (al'Absi et al., 2000; Bruehl et al., 1992; Bruehl et al., 2002; D'Antono et al., 1999; Fillingim & Maixner, 1996; Page & France, 1997) and hypertensive (Guasti et al., 1995; Randich & Maixner, 1984) individuals. Therefore an age-related increase in resting blood pressure has the potential to mitigate pain sensitivity in older adults.

In addition to anatomical and physiological changes with age, alterations in psychosocial factors and cognitions have the potential to modify pain reports with age.

For example, older adults may underreport pain (DeWaters et al., 2008; Sauaia et al., 2005; Wallace, 1994) despite experiencing increased frequency of painful conditions. The elderly are more likely to believe that pain is a normal part of aging and should be tolerated (Battista, 2002; Yates et al., 1995; Zalon, 1997). Other common beliefs include skepticism about the effectiveness of pain medications (Yates et al., 1995) or fear of medication side-effects, over-medication and addiction (Sauaia et al., 2005; Wallace, 1994; Ward et al., 1993; Zalon, 1997).

Older adults do not wish to be seen as complainers or to worry significant others (Ward et al., 1993; Yates et al., 1995). While older adults may respond negatively regarding the presence of pain; many older adults will respond affirmatively to questions using other pain-related terms such as discomfort or soreness (Battista, 2002; Chibnall & Tait, 2001; Closs & Briggs, 2002; Herr, 2011; Herr & Garand, 2001; Persons, 2002). Older adults have also been found to be more cautious or conservative when labeling a near threshold stimulus as painful (Harkins & Chapman, 1976, 1977), therefore the elderly may need a longer duration of stimulus presentation prior to committing to labeling a stimulus as painful (Gibson & Farrell, 2004). Yet older adults label a strong suprathreshold stimulus with greater pain intensity than young adults (Harkins & Chapman, 1976; Harkins et al., 1986). These variations in the affective and cognitive components of pain processing have the potential to result in alterations in the reporting of pain with aging.

Despite these numerous changes associated with aging, whether or not humans experience age-related changes in pain sensitivity is still not clear. Laboratory-based research findings are mixed with a lack of consensus on the impact of aging on pain. This



may be partly due to the competing nature of the changes. For example, a less efficient endogenous system would be expected to augment pain sensitivity, while diminished A $\delta$  and C fiber density and function and higher systolic blood pressure would be expected to attenuate pain sensitivity. The concurrent nature of these changes may contribute to the variability of study findings. Methodological differences may also account for much of the inconsistency in the literature, such as the instructions given to subjects, location of the noxious stimulus, the age range of subjects, and the stringency of inclusion and exclusion criteria (Gagliese et al., 1999; Gibson & Helme, 2001). Several recent reviews however concluded that overall the weight of the evidence supports a small decrease in pain sensitivity at near threshold stimulus intensities accompanied by a reduction in pain tolerance in older adults (Gibson & Farrell, 2004; Gibson & Helme, 2001; Lautenbacher, 2012).

Evidence indicates that age-related changes in pain perception may be modality specific. The preponderance of evidence suggests that there is an age-related increase in pain threshold with cutaneous heat pain, particularly when utilizing radiant heat as the method of pain induction (Gibson & Farrell, 2004; Gibson & Helme, 2001; Lautenbacher, 2012). These differences are most pronounced in adults over 70 years of age and in the distal extremities (Gibson & Helme, 2001). Likewise pressure pain thresholds have been found to be elevated in older adults (Gibson & Farrell, 2004; Gibson & Helme, 2001; Lautenbacher, 2012), although the weighted effect size is significantly smaller than for radiant noxious heat (Lautenbacher, 2012). In contrast, the vast majority of studies using cutaneous electrical stimulation as the noxious stimulus have failed to identify an age-related difference in pain threshold (Gibson & Farrell,

2004; Gibson & Helme, 2001). Modality differences also become apparent when pain tolerance is used as the outcome measure. While the weight of the evidence points to a reduction in pain tolerance when utilizing pressure pain (Lautenbacher, 2012; Pickering et al., 2002; Woodrow et al., 1972), pain induced by either heat or electrical stimulation shows no age-related change (Lautenbacher, 2012).

Compared to pain threshold data there is a paucity of information on the impact of age on the perception of pain intensity. This is an important gap in knowledge as suprathreshold pain intensity and quality may be more applicable to clinical pain than first recognition of pain (Harkins, 2001). Using a thermal scaling paradigm, Harkins and colleagues (1986) found a trend for both middle-aged and older adults to rate noxious stimuli at near threshold levels as less intense than young adults, yet stronger suprathreshold stimuli as more painful. These findings are consistent with previous findings of conservatism in labeling a noxious stimulus as painful for older adults with noxious electrical stimulation (Harkins & Chapman, 1976, 1977) and heat (Clark & Mehl, 1971). Similarly Edwards and Fillingim (2001) found older adults to rate a train of suprathreshold heat impulses higher and more unpleasant than young adults. These differences disappeared at the highest stimulation temperature. Chao et al. (2007) on the other hand found older adults to rate suprathreshold heat stimuli to the distal extremities lower than young adults, while Kunz et al. (2009) found no age-related differences in intensity ratings of suprathreshold electrical stimulation to the sural nerve. These results suggest that age-related differences in the perception of pain intensity are likely to be small and may wane at the highest levels of stimulation (Gibson & Farrell, 2004).

*Summary:* Experimental evidence for age-related differences in pain perception is mixed and may be modality specific. While conclusions regarding age-related changes in pain perception must be made with caution, overall the current research would suggest that advancing age is associated with a small increase in pain threshold for most noxious stimuli. In contrast, older adults may have a decrease in pain tolerance and may rate suprathreshold stimuli as more painful than young adults. More conservative response criteria and greater stoicism combined with age associated anatomical and physiological changes may account for some of these differences.

### **Sex Differences in Pain Perception**

The majority of reviews of sex differences in laboratory-based pain perception have concluded that overall women have greater pain sensitivity than men (Fillingim et al., 2009; Riley et al., 1998); although a recent systematic review questioned the generalizability of this conclusion as sex differences in pain appear to be modality and outcome measure specific (Racine et al., 2012). While there is general agreement that women are more sensitive to pressure pain than men as noted by lower pain thresholds and/or pain tolerance (Binderup et al., 2010; Dawson & List, 2009; Koltyn et al., 2001; Kroner-Herwig et al., 2012; Matos et al., 2011; Peddireddy et al., 2009; Ravn et al., 2012; Soetanto et al., 2006; Wang et al., 2010), the majority of studies examining pressure pain ratings have found men and women to report comparable pain intensity (Pud et al., 2005; Umeda et al., 2010). When differences are found, women have higher pain ratings than men (Hoeger Bement et al., 2008; Kroner-Herwig et al., 2012). Furthermore, despite women exhibiting lower tolerance for heat and cold pain (Bragdon et al., 2002; Defrin et

al., 2009; Fillingim, Hastie, et al., 2005; Fillingim, Ness, et al., 2005), cold pain thresholds are similar in men and women while the results for heat pain thresholds and pain ratings are mixed (Racine et al., 2012). There is also strong evidence for women to experience similar ischemic pain tolerance than men (Bragdon et al., 2002; Fillingim, Hastie, et al., 2005).

It is unclear why men and women may express different sensitivity to some types of painful stimuli. Several theories have been postulated including hormonal influences, particularly the role of estrogen. Examinations looking at pain sensitivity at different phases of the menstrual cycle initially indicated a small to moderate effect size for menstrual phase differences (Riley et al., 1999). These early studies relied on verbal report of menses regularity to determine timing of sessions. Several recent studies have used objective measures to assess hormone levels and timing of ovulation (i.e., salivary, urine or serum assays) and have failed to find differences in pain sensitivity either across the menstrual cycle (Bartley & Rhudy, 2012; Hoeger Bement et al., 2009; Klatzkin et al., 2010; Rezaii et al., 2012; Tousignant-Laflamme & Marchand, 2009) or with robust differences in  $17\beta$ -estradiol levels in women undergoing in vitro fertilization (Stening et al., 2012). Thus fluctuation in estrogen concentration does not appear to be responsible for the sex-related variability in pain sensitivity.

Another possible factor is sex-related differences in activation of endogenous inhibitory pathways. Research on sex differences in CPM has yielded inconsistent results, with approximately one-half of studies showing a sex-related difference (van Wijk & Veldhuijzen, 2010). One recent review concluded that men experience greater CPM than women (Popescu et al., 2010). Several studies were excluded from this review, however

due to the application of ipsilateral conditioning and test stimuli, thereby limiting the conclusions.

Overall the evidence would suggest that if women do have a reduced ability to activate endogenous inhibitory pathways compared to men, this difference is likely to be small. Furthermore, this difference may be mediated by psychological factors.

Specifically, pain catastrophizing has been found to mediate sex differences in CPM using pressure pain (Goodin, McGuire, Allshouse, et al., 2009). Thus group differences in CPM may have their basis in the cognitive and affective processes involved in pain perception.

Other possible factors postulated to explain sex differences in pain perception include sexual dimorphism in anatomy and functionality of pain processing pathways and structures. These include the PAG-RVM pathway (Lloyd & Murphy, 2006, 2009) and subcortical structures such as the thalamus, amygdala, and nucleus accumbens (Zubieta et al., 2002). Genetic factors such as polymorphisms in the genes encoding ion channels and receptors involved in pain perception have also been implicated (Fillingim et al., 2008; Kim et al., 2004; Mogil et al., 2003). An interaction between the cardiovascular and pain modulating systems has also been theorized to explain sex-related variability. Young women typically have lower systolic blood pressure than young men (Oparil & Miller, 2005) which might account for the greater sensitivity sometimes seen in women. The blood pressure-pain interaction is unlikely to explain sex differences in older adults however, as older women are likely to have systolic blood pressure equal to or higher than men after age 60 (Oparil & Miller, 2005).

There may also be an interaction between sex and age. While the mean weighted effect size for the impact of age on pain threshold appears to be minimally stronger in women (reviewed by Lautenbacher, 2012), there is either no sex difference (Lautenbacher, 2012) or a more marked reduction in pain tolerance with age in men (Pickering et al., 2002; Walsh et al., 1989; Woodrow et al., 1972). Thus age may differentially impact men and women.

*Summary:* Women have greater sensitivity to some, but not all forms of noxious stimuli than men. The sex-based differences vary with the modality applied and the outcome parameter assessed. Women report lower pressure and electrical pain thresholds and a reduced tolerance for noxious pressure or thermal stimuli. Pressure pain ratings and tolerance for ischemic pain appear more comparable between men and women; although women have been found to rate pressure pain higher in some studies. There is little consistency in findings for pain ratings when the stimulus is noxious heat. The mechanisms responsible for sex-related differences in pain perception are as yet unknown.

### **Psychosocial Influences on Pain Perception**

Due to its multidimensional nature, pain perception is influenced not just by biological factors, but also by psychological and sociocultural dynamics. Examinations limited to the biological aspect of pain alone cannot account for the large variability in response to a noxious event. Cognitive and affective elements have been shown to impact pain; such as anxiety, pain catastrophizing, fear of pain, and attitudes regarding pain including stoicism and cautiousness.

## *Anxiety*

A positive relation between state anxiety (a transient state of uneasiness in response to a particular situation) and experimental or procedural pain has been reported in young and middle-aged adults (Chakour et al., 1996; Eli et al., 2003; Hoeger Bement et al., 2010; Kuivalainen et al., 2012; Okawa et al., 2005; Rhudy & Meagher, 2000; Tang & Gibson, 2005; von Graffenried et al., 1978). Those with greater anxiety report greater pain. This relation is most pronounced when the source of the anxiety is directly related to the noxious event (al Absi & Rokke, 1991; Dougher et al., 1987; Weisenberg et al., 1984) and men may be more influenced by anxiety than women (Jones & Zachariae, 2004).

A small number of studies have examined the relation of trait anxiety (i.e., a predisposition to experience anxiety) to pain. High trait anxiety is associated with reduced pain tolerance (James & Hardardottir, 2002), but not reduced pain thresholds (Tang & Gibson, 2005). Additionally, while individuals higher in trait anxiety are likely to experience greater levels of state anxiety under the same experimental conditions than individuals lower in trait anxiety, both high and low trait anxious individuals experience similar increases in perceived pain intensity to an experimental stimulus as state anxiety is increased (Tang & Gibson, 2005).

Whether these relations persist in older adults is not clear. Only a limited number of studies have examined the relation of state anxiety and pain in older adults. These studies have addressed state anxiety either in older individuals with chronic pain (Casten et al., 1995; Smith & Zautra, 2008) or in the acute post-operative phase (Feeney, 2004; Saracoglu et al., 2012). Results of these investigations suggest that a positive relation of

anxiety and pain reports persists beyond middle age. Anxiety has been found to explain up to 27% of the variance in post-operative pain reports in older adults following hip and knee replacement surgery (Feeney, 2004) and anxiety immediately prior to biopsy of the prostate gland is positively correlated with pain intensity associated with the procedure (Saracoglu et al., 2012). To our knowledge the anxiety-pain relation has not been assessed in the context of acute experimental pain in the older adult population.

### *Pain Catastrophizing*

Pain catastrophizing has underlying components of rumination (worry and the failure to end pain-related thoughts), helplessness (feeling helpless to modify pain), and magnification (amplification of the valence of potential negative outcomes of pain) (Quartana et al., 2009; Sullivan et al., 1995). The degree of catastrophic thinking has been linked to greater ratings of pain intensity and unpleasantness, more pain-related distress, and a higher degree of pain-related behaviors in both clinical and healthy populations (Campbell et al., 2012; Forsythe et al., 2011; George & Hirsh, 2009; Nieto et al., 2012; Quartana et al., 2009; Sullivan et al., 2001; Turner et al., 2002). It is also a better predictor of disability than pain intensity in adults experiencing soft tissue injuries (Sullivan et al., 1998). Catastrophizing is stable over time in adults with rheumatoid arthritis (Keefe et al., 1989), predicting pain ratings six months later; and when assessed in the absence of pain may be predictive of reports of pain intensity during a painful stimulus or clinical procedure up to 10 weeks following initial assessment (Sullivan & Neish, 1999; Sullivan et al., 1995).



Age-related declines in pain catastrophizing have been reported in the literature (Jacobsen & Butler, 1996; Sullivan & Neish, 1998). Sex differences have also been noted; women frequently express greater catastrophizing than men (Keefe et al., 2000; Osman et al., 1997; Sullivan et al., 1995; Sullivan et al., 2000; Turner et al., 2002) with the exception of the magnification component (Osman et al., 1997; Sullivan et al., 1995; Sullivan et al., 2000). This has led to the suggestion that catastrophizing may mediate sex differences in pain perception (Forsythe et al., 2011; Keefe et al., 2000; Sullivan et al., 2000; Weissman-Fogel et al., 2008).

Pain catastrophizing is thought to exert its effects by amplifying activity in the prefrontal cortex (PFC), anterior cingulate cortex (ACC), claustrum, and insula (Gracely et al., 2004; Seminowicz & Davis, 2006); brain regions involved in anticipation of and attention to pain as well as the affective dimension of pain. Whether the influence of catastrophizing on pain perception is limited to the cerebral processing of pain is not certain. An absence of a relation between pain catastrophizing and the spinally mediated nociceptive flexion reflex would suggest that pain catastrophizing does not impact descending inhibition on spinal pain processing (Rhudy et al., 2009). Yet higher pain catastrophizing has been found to predict lower CPM in both men and women; and in women diminished CPM was found to partially mediate the relation of catastrophizing and pain intensity (Goodin, McGuire, Allshouse, et al., 2009). Thus pain catastrophizing may impair descending inhibition and in women, the resultant reduction in descending inhibition may partially explain why greater pain catastrophizing is associated with greater pain perception.

In healthy adults situational/state catastrophizing (catastrophizing referencing an ongoing or just experienced noxious event) may show a stronger association to experimental pain than dispositional/trait catastrophizing (catastrophizing based upon recall of previously experienced painful events) (Campbell et al., 2010). The two catastrophizing scores do not appear to be associated with each other in healthy adults or adults with arthritis, although a moderate association has been reported in adults with temporomandibular disorder (Campbell et al., 2010; Quartana et al., 2009). Concern has been expressed, however regarding the use of measures of situational catastrophizing as the validity and reliability of these measures have yet to be established (Quartana et al., 2009).

### *Fear of Pain*

Closely related to pain catastrophizing is fear of pain, another negative pain-related cognitive construct. Fear of pain involves thoughts that pain represents significant harm or injury (Albaret et al., 2004). The three subscales include severe pain (e.g., fracturing a bone), minor pain (e.g., a paper cut), and medical pain (e.g., receiving Novocaine). Fear of pain has been found to predict pain intensity following a cold pressor task (George et al., 2006; George & Hirsh, 2009; Hirsh et al., 2008) and is associated with pain in clinical populations (McNeil & Rainwater, 1998).

Older adults may experience slightly greater fear of pain than younger adults, although the effect size is quite small (Asmundson et al., 2008). In a study examining the factor structure of the Fear of Pain Questionnaire (Albaret et al., 2004), the authors found that older adults differed from young adults on two of the three questionnaire subscales.

Results showed that with increasing age, fear of medical pain lessened while fear of minor pain increased such that for older adults, fear of minor pain exceeded that of fear of medical pain. The opposite was true for young and middle-aged adults (Albaret et al., 2004).

Sex differences may also be present; women have been shown to have greater fear of pain than men in some studies (Asmundson et al., 2008; Carleton & Asmundson, 2009; Roelofs et al., 2005). However similar to age differences the effect size is small (Asmundson et al., 2008) and study results are not always consistent. For example, one study using two samples of healthy adults found sex-related differences in the first sample, but not the second (Roelofs et al., 2005).

While there has been some question as to the uniqueness of fear of pain and pain catastrophizing (Sullivan et al., 2001), studies examining both constructs as predictors of pain reports during a cold pressor task agree that only one contributes unique variance to the regression model. Although agreeing that only one construct uniquely contributes to experimental pain reports, investigators disagree as to which of the two constructs is the most important contributor (George et al., 2006; George & Hirsh, 2009; Hirsh et al., 2008; Sullivan et al., 1995). Interestingly in individuals with shoulder pain, George & Hirsh (2009) found only fear of pain to contribute to the variance in cold pressor pain sensitivity, whereas pain catastrophizing and subject sex contributed to the variance in clinical pain. Additionally, fear of pain and pain catastrophizing appear to be related to activity in overlapping, but different brain regions (Gracely et al., 2004; Ochsner et al., 2006; Seminowicz & Davis, 2006). Together these findings suggest that these two cognitive processes are not redundant.

### *Pain Attitude*

Societal influences in cultures that highly value stoicism may foster more reserved attitudes and behaviors (Hofland, 1992). Attitudes toward pain may therefore impact reports of pain. Two constructs of pain attitude assessed by the Pain Attitude Questionnaire (PAQ; Yong et al., 2001) are stoicism and cautiousness. Factor analysis of the PAQ in healthy community-dwelling adults aged 24-91 years found both stoicism and cautiousness to consist of two subdimensions. Stoicism is comprised of reticism (unwillingness to report pain) and superiority (belief in greater tolerance or ability to control pain than others); whereas cautiousness is comprised of self-doubt (lower self-confidence in the ability to judge sensations as painful or not) and reluctance (reluctant to label a sensation as painful) (Yong et al., 2001). The PAQ was found to have good subscale reliability with Cronbach's alpha coefficients of .75-.86 for internal consistency and .71-.92 for test-retest (Yong et al., 2001). A revised version similarly showed good internal consistency with Cronbach's alpha coefficients of 0.73-0.80 in a sample of individuals with chronic pain (Yong et al., 2003).

In examining for age-related differences in attitudes toward pain, Yong and colleagues (2001) found older adults to be more reticent and more cautious toward reporting pain than young and middle-aged adults, with the greatest differences noted between the oldest old (over 80 years) and the youngest adults (less than 41 years). No age-related differences in attitudes of superiority in control of pain were identified (Yong et al., 2001). These findings are consistent with previous findings using signal detection theory where older adults were noted to have a more conservative response bias than young adults when reporting pain at near-threshold levels (Harkins & Chapman, 1976,

1977); a bias that appears to be absent or reversed at high stimulus intensities (Harkins et al., 1986). Thus while reticence to report pain and cautiousness in labeling lower intensity stimuli as painful appears to be greater in older compared to young adults, attitudes of superiority are not influenced by aging.

### **Summary of Pain Perception**

Pain is a multidimensional phenomenon and pain perception is influenced by emotional and cognitive as well as biological processes (i.e., biopsychosocial model). Appropriate assessment of pain is critical for optimal pain management and a number of pain assessment tools are available. The NRS has been shown to be a valid and reliable tool for cognitively intact adults. The VAS however may be less reliable when used with older adults as there is a progressive increase in failure rate and unscorable responses with age.

Aging may be associated with a small increase in pain threshold and decrease in pain tolerance to most noxious stimuli. Women demonstrate greater pain sensitivity than men for some, but not all forms of noxious stimuli. In particular women appear to be more sensitive to noxious pressure and thermal stimuli than men. There is clear agreement that older adults have a reduced ability to activate the CPM pathway than young adults with thermal and electrical test stimuli. Although there is no consensus on sex differences in CPM; women may have a slightly reduced CPM response compared to men. Additionally, cognitive and emotional factors have been shown to influence pain reports and magnitude of CPM thereby contributing to the variability of findings. State

anxiety, pain catastrophizing, fear of pain, and pain attitudes have all received support in the literature for their influence on the perception of pain.

## **EXERCISE-INDUCED HYPOALGESIA**

One non-pharmacological method of relieving pain is exercise-induced hypoalgesia (EIH), the reduction in pain to a noxious stimulus during or following exercise. Clinically, exercise is used for pain management in a variety of conditions including chronic neck disorders, fibromyalgia, low back pain, osteoarthritis, rheumatoid arthritis and myofascial pain (Hoeger Bement, 2009; Koltyn, 2002b; Loew et al., 2012; Singh, 2002). While the benefits of exercise in these conditions for the reduction of pain and improvement of function has received support in the literature (Hoeger Bement, 2009; Koltyn, 2002b; Loew et al., 2012; Singh, 2002), exercise prescription remains difficult because the optimal exercise parameters, including type and dosage, have yet to be determined (Christmas & Andersen, 2000; Hoeger Bement, 2009; Koltyn, 2002b; Singh, 2002). Additionally, little research has examined isometric (i.e., static) exercise in the management of pain. Isometric exercise with its ease of application has excellent potential to become an effective tool in the relief of pain for a large segment of the population. Specifically, isometric exercise is easy to prescribe and individualize and can be performed by individuals of all ages, including those with limited mobility.

EIH has been demonstrated following aerobic, resistive, and isometric exercise and using a wide variety of pain induction methods. It has been suggested that EIH is actually a methodological artifact in response to repeated pain testing and not a response to the exercise (Padawer & Levine, 1992). An initial attenuation of pain following

exercise with a gradual return to baseline upon repeated pain testing during recovery (Droste et al., 1991; Hoffman et al., 2004; Olausson et al., 1986), as well as similarity in pain reports before and after quiet rest (Hoeger Bement et al., 2008; Hoeger Bement et al., 2009) would argue against this hypothesis.

A number of investigators have examined the presence of attenuated pain perception during or following exercise. Most of these studies have included only men, and the proportion of women in mixed sample studies has been small. Experimental designs are diverse in mode, intensity and duration of exercise; timing of pain assessments; pain perception outcome measures employed (threshold, ratings or tolerance); and method of noxious stimulus induction. Given the extensive variability across studies, direct comparisons and overall recommendations pertaining to exercise prescription is difficult.

### **Aerobic Exercise**

Overall, there is strong evidence supporting a reduction in pain to a variety of noxious stimuli during and following aerobic exercise in healthy adults (reviewed by (Koltyn, 2000; Naugle et al., 2012). The most consistent results occur with a mechanical noxious stimulus (Naugle et al., 2012). There is greater equivocality with noxious heat stimuli and little support for EIH when using a cold pressor test stimulus (Cook & Koltyn, 2000; Hoeger Bement, 2009). One possible reason for the inconsistent thermal results may be the confounding issue of change in skin and body temperature associated with exercise (Koltyn, 2000).

The most consistent EIH results with aerobic exercise are found with exercise of moderate to high intensity ( $> 60\% \text{ VO}_{2\text{max}}$  or 200 W) and longer duration ( $>10$  minutes) (Hoffman et al., 2004; Koltyn, 2002a). Following treadmill running of various intensities and durations, Hoffman et al. (2004) found decreased pressure pain ratings associated with high intensity, longer duration running ( $75\% \text{ VO}_{2\text{max}} \times 30 \text{ min}$ ), but not after shorter duration or lower intensity. Thus it appears that aerobic exercise of sufficient intensity and duration decreases sensitivity to pain.

### **Resistance Exercise**

There is limited research into the impact of resistance exercise on pain perception. To date all studies have utilized a noxious pressure stimulus. Results indicate that EIH does occur as shown by an increase in pain threshold and decrease in pain ratings (Focht & Koltyn, 2009; Koltyn & Arbogast, 1998) or an increase in pain tolerance (Bartholomew et al., 1996). Koltyn & Arbogast (1998) found elevations in pain threshold and reduced elevation in pain ratings over a 2 minute pressure pain test at five minutes following a resistance training session in young men and women. The reductions in pain reports were no longer present at 15 minutes into recovery (Koltyn & Arbogast, 1998). Similar results were found in a group of young men, and the reduction in pain was unaffected by time of day (Focht & Koltyn, 2009).

The impact of resistance training on pain threshold is less clear. Men and women undergoing resistance training using a concentric/eccentric or eccentric only protocol one time per week experienced elevations of pain threshold after four weeks of training. This change in pain was still present one week post-exercise cessation (Slater et al., 2010). In



contrast, Anshel & Russell (1994) found no change in pain thresholds following a 12 week resistance training program in men. Only when aerobic exercise was part of the training protocol did pain thresholds increase.

### **Isometric Exercise**

More recently investigators have begun to examine isometric exercise with several studies identifying reductions in pain ratings (Hirsh et al., 2008; Koltyn et al., 2001; Koltyn & Umeda, 2007; Staud et al., 2005) or increases in pain thresholds (Hoeger Bement et al., 2008; Koltyn et al., 2001; Koltyn & Umeda, 2007; Kosek & Ekholm, 1995; Kosek et al., 1996; Kosek & Lundberg, 2003; Staud et al., 2005). A summary table of results in healthy adults can be found in Table 1.1. For studies examining clinical populations, only the results for healthy control subjects are included in the summary table.

**Table 1.1. Summary of Literature on Isometric Exercise-Induced Hypoalgesia**

Author and Year	Subjects	Exercise	Intensity and Duration	Pain Stimulus	EIH Response	
					PTh	PR
Ge et al. 2012	22 F 0 M	Shoulder Abduction	Sustained to task failure	Pressure	+	1 of 2
Lannersten & Kosek 2010	21 F 0 M	Knee Extension Shoulder Rotation	20%-25% MVC x 5 min	Pressure	+	+
Umeda et al. 2010	25 F 25 M	Handgrip	25% MVC x 1 min 25% MVC x 3 min 25% MVC x 5 min	Pressure	+	+
Umeda et al. 2009	23 F 0 M	Handgrip	25% MVC x 1 min 25% MVC x 3 min	Pressure	-	-
Hoeger Bement et al. 2009	20 F 0 M	Elbow Flexion	25% MVC to task failure	Pressure	+	+
Hoeger Bement et al. 2008 (experiment 1)	14 F 13 M	Elbow Flexion	MVC's x 3	Pressure	+	+
Hoeger Bement et al. 2008 (experiment 2)	11 F 11 M	Elbow Flexion	25% MVC to task failure 25% MVC x 2 min 80% MVC to task failure	Pressure	+	+
Ring et al. 2008	0 F 24 M	Handgrip	15% MVC x 4.5 min 25% MVC x 4.5 min	Electrical (NFR)		+
Koltyn & Umeda 2007	14 F 0 M	Handgrip	40%-50% MVC x 2 min	Pressure	+	+
Kadetoff & Kosek 2007	17 F 0 M	Knee Extension	39 N (~10% MVC) to task failure	Pressure	+	
Staud et al. 2005	11 F 0 M	Handgrip	30% MVC x 90 sec	Pressure Thermal	+	+
Drury et al. 2004	0 F 12 M	Handgrip	Intermittent MVC every 2 s x 1 min	Pressure	+	
Kosek & Lundberg 2003	12 F 12 M	Knee Extension Shoulder Rotation	MVC to task failure	Pressure	+	
Koltyn et al. 2001	16 F 15 M	Handgrip	MVC 40%-50% MVC x 2 min	Pressure	+ F + F	+ + F

**Table 1.1 Continued**

Author and Year	Subjects	Exercise	Intensity and Duration	Pain Stimulus	EIH Response	
					PTh	PR
Persson et al. 2000	25 F 0 M	Shoulder Abduction	Sustained to task failure	Pressure	+	
Kosek et al. 1996	14 F 0 M	Knee Extension	25% MVC to task failure (max 5 min)	Pressure	+	
Kosek & Ekholm 1995	14 F 0 M	Knee Extension	25% MVC to task failure (max 5 min)	Pressure	+	
Paalasmaa et al. 1991	0 F 11 M	Plantarflexion	30% MVC x 2 min 70% MVC x 2 min	Thermal	- -	

*Abbreviations:* F = Female, M = Male; PTh = Pain Threshold, PR = Pain Ratings, PTol = Pain Tolerance, MVC = Maximal Voluntary Contraction; NFR = Nociceptive Flexion Reflex; + = positive EIH (i.e., elevation in PTh or reduction in PR); - = negative EIH (i.e., no change in PTh or PR)

As with aerobic exercise, there appears to be a dose-response relationship for EIH. Specifically, the greatest reduction in pain ratings is seen following exercise of lower intensity held for a long duration (Hoeger Bement et al., 2008; Naugle et al., 2012). This was demonstrated by Hoeger Bement et al. (2008) in a study of similar design as that of Hoffman and colleagues (2004) using aerobic exercise. Young men and women performed isometric elbow flexion at 25% maximal voluntary contraction (MVC) for two minutes, 25% MVC to task failure, 80% MVC to task failure, or three brief MVCs. Pressure pain thresholds and pressure pain ratings were assessed before and immediately after each exercise dose. The greatest increase in pain threshold occurred following the contraction of 25% MVC held to task failure, and this contraction was the only one to result in a decrease in peak pain ratings. No change in pain ratings or pain threshold was found for a contraction of 25% MVC held for two minutes. Fatigue is not required for EIH to occur as participants experienced both an increase in pain threshold and a

decrease in pain ratings following the three brief MVC's without a reduction in force between contractions. It is not known if EIH following isometric contractions persists with advancing age or if the parameters to achieve EIH are altered in older adults.

The vast majority of studies of EIH following isometric exercise have used pressure as the noxious test stimulus. Only two studies have examined response to a thermal stimulus and these studies found conflicting results. Paalasmaa and colleagues (Paalasmaa et al., 1991) failed to find a significant difference in heat pain threshold after isometric plantarflexion contractions of 30% and 70% MVC held for two minutes. In contrast, Staud et al. (2005) found a decrease in thermal pain ratings at end exercise during a 90 second handgrip contraction at 30% of MVC. Inconsistency in the findings of these two studies may be related to the use of different outcome measures of pain perception (i.e., pain ratings vs pain threshold). Additionally, it is possible that task specificity may play an important role in response to a noxious heat stimulus with the exercising muscle group significantly impacting the outcome. Despite the mixed results for noxious thermal stimuli, overall there is strong evidence that isometric exercise results in an EIH response if of sufficient intensity or duration.

### **Exercise-Induced Hypoalgesia and Aging**

Several modes of exercise appear beneficial for pain reduction and functional improvement in older adults with chronic pain (Koltyn, 2002b; Singh, 2002). Yet the optimal prescription for pain relief is not clear, leaving practitioners feeling ill-prepared to provide the most effective exercise prescriptions for their older clients (Christmas & Andersen, 2000; Hoeger Bement et al., 2009; Koltyn, 2002b; Singh, 2002). The majority

of EIH studies have involved young healthy male subjects performing aerobic exercise (Hoeger Bement et al., 2009; Koltyn, 2000). Older adults and women have historically been underrepresented (Beery & Zucker, 2011).

Recently the number of studies including women has risen, yet there remains a paucity of information on EIH in older adults. A handful of studies examining EIH in patient populations have included healthy middle-aged control subjects. These studies reveal that EIH does continue into middle-age (Ge et al., 2012; Hoffman et al., 2005; Kadetoff & Kosek, 2007; Kosek et al., 1996; Meeus et al., 2010; Staud et al., 2005). Thus far no studies have systematically examined EIH during or following an acute bout of exercise in adults aged 60 years and above.

An altered EIH response with aging has received indirect support using an animal model. Specifically, male mice aged 4, 24, and 48 weeks demonstrated a reduction in paw licking in response to a formalin test following six hours of forced walking (Onodera et al., 2001). The analgesia was age-dependent with the oldest mice exhibiting the least analgesia. Clear conclusions regarding aging and EIH cannot be drawn however, as the forced walking paradigm may be a measure of stress-induced analgesia as opposed to EIH (Onodera et al., 2001).

### **Sex-Differences in Exercise-Induced Hypoalgesia**

Little is known about the influence of sex on EIH. A small number of recent studies have reported on sex-related differences with inconsistent results between studies. For example, both men and women experienced increases in pain threshold and decreases in pain ratings following three brief MVCs of the elbow flexor muscles in one study

(Hoeger Bement et al., 2008). In a separate study only women reported an increase in pain thresholds after two brief maximal handgrip contractions. Both men and women reported reductions in pain ratings following the handgrip contractions (Koltyn et al., 2001).

Sex differences following submaximal isometric contractions have also been mixed. Koltyn et al. (2001) found only women to report an increase in pain threshold and decrease in pain ratings following submaximal efforts. While a trend was seen for women to report greater decreases in pain ratings after submaximal exercise in the study by Hoeger Bement and colleagues (2008), this failed to reach statistical significance. Sex-differences are not limited to isometric exercise-induced hypoalgesia as women were also found to be the sole responders in response to treadmill running for 10 minutes at 85% age-predicted maximal heart rate, with reductions in ratings of pain intensity and pain unpleasantness to a cold pressor task (Sternberg et al., 2001).

There is some evidence for men to experience a larger effect size for EIH following isometric exercise (Umeda et al., 2010). Consistent with this response, a recent study by Hoeger Bement et al. (2014) found that when matched for baseline pain, only men experienced a reduction in pain ratings following an isometric contraction to task failure. Thus the presence and direction of sex differences in EIH remains unclear with insufficient evidence to make any definitive conclusions at this time.

### **Summary of Exercise-Induced Hypoalgesia**

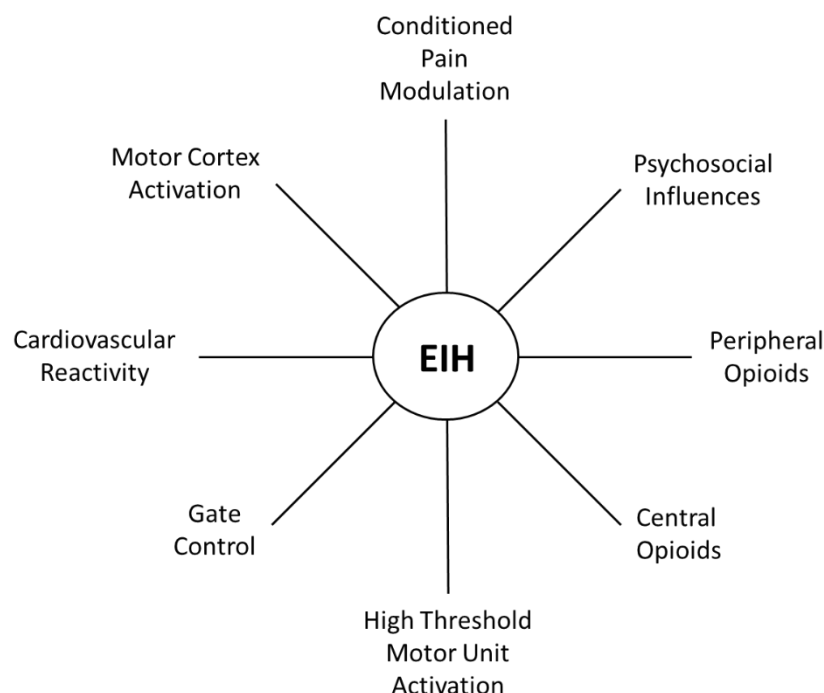
EIH has been found during and following all types of exercise (i.e., aerobic, resistance, isometric). This response is most consistent with higher intensity, longer

duration aerobic exercise or isometric exercise of either high intensity or prolonged lower intensity. Limited data precludes formulation of a conclusion regarding the efficacy of varying doses of resistance exercise on pain perception. The most consistent EIH response is seen with a noxious pressure stimulus regardless of the type of exercise. The responses to painful thermal stimuli are more equivocal with little demonstrable EIH using a cold pressor task. The results may also vary with the outcome measure used to assess pain perception; as pain threshold, pain ratings and pain tolerance do not always respond in an identical fashion even within the same group of subjects. Pain ratings and pain tolerance may be more consistent indicators of EIH than pain threshold.

Historically women and older adults have been underrepresented in the exercise and pain literature. While the inclusion of women into studies of EIH has improved in the last decade, there remains a paucity of information on the effects of aging on EIH. The presence of sex-differences in the pain response to exercise remains inconclusive.

## **POTENTIAL MECHANISMS OF EXERCISE-INDUCED HYPOALGESIA**

The mechanisms responsible for pain reduction following exercise have not been established in either young or older adults; and both opioid and non-opioid systems have been theorized to be involved (Cook & Koltyn, 2000; Hoeger Bement, 2009; Koltyn, 2000). There is likely more than one mechanism producing EIH and the specific mechanism(s) may be task dependent and vary with the pain induction method (e.g., pressure, thermal, chemical, ischemic or electrical), the type of tissue assessed (e.g. bone, muscle or skin), and the environmental conditions. Figure 1.1 illustrates some potential mechanisms resulting in EIH.



**Figure 1.1 Potential mechanisms for EIH**

This figure shows potential mechanisms that may result in exercise-induced hypoalgesia. The contribution of any one potential mechanism likely varies with the exercise task, pain induction method, tissue assessed, and environmental conditions.

It does appear that central (i.e., changes in spinal or supraspinal processing) or systemic (i.e., circulating hormones) mechanisms are at least partly responsible for the reduction in pain due to systemic effects. A change in pain perception would be expected only at the site of exercise if the response was mediated solely by local mechanisms. Several studies using both aerobic and isometric exercise have found a reduction in pain perception at sites distant to the exercising muscle (Anshel & Russell, 1994; Droste et al., 1991; Hoeger Bement et al., 2008; Hoffman et al., 2004; Koltyn et al., 1996; Koltyn & Umeda, 2007; Kosek & Lundberg, 2003; Staud et al., 2005). While a greater EIH response magnitude has been noted on the exercising limb during sustained shoulder external rotation, this limb difference was not identified during prolonged knee extension (Kosek & Lundberg, 2003) suggesting that EIH response magnitude differences may be



limb or muscle dependent. The following discussion will review some of the potential central or systemic mechanisms proposed in EIH.

### **Plasma Beta Endorphins**

The discovery of opioid peptides and receptors in the 1970's with their analgesic properties (Dalayeun et al., 1993; Hartwig, 1991) has led to significant interest in the possible role of these peptides in EIH. Perhaps the best studied has been  $\beta$ -endorphin, an opioid peptide that acts both as a neurotransmitter in the central nervous system and as a hormone after release into the bloodstream from the anterior pituitary gland. Several investigators have examined the plasma  $\beta$ -endorphin response to exercise. As with EIH, the largest body of literature involves aerobic exercise in healthy young adults. Numerous studies consistently show an increase in plasma  $\beta$ -endorphin levels following aerobic exercise of moderate to high intensities ( $> 60\% \text{ VO}_{2\text{max}}$ ; reviewed by Goldfarb & Jamurtas, 1997). Similar to EIH, there is an interaction between intensity and duration for the release of  $\beta$ -endorphin. For moderate or low intensity exercise to induce elevated levels of plasma  $\beta$ -endorphin prolonged durations are necessary. Considering the similarity in the EIH and  $\beta$ -endorphin responses to aerobic exercise, it would be easy to infer a causal relationship between these two responses. Surprisingly little research has looked directly into the relation between them. Only three groups of researchers have measured both plasma  $\beta$ -endorphin levels and pain perception during and following either running (Janal et al., 1984; Oktedalen et al., 2001) or cycling (Droste et al., 1991) in young male athletes. Despite the finding of a parallel increase in plasma  $\beta$ -endorphin

and EIH, all three studies failed to identify an association between these two variables. Therefore, greater levels of  $\beta$ -endorphin were not associated with greater hypoalgesia.

### **Centrally Acting Opioids**

While pituitary  $\beta$ -endorphin release into the plasma may not explain EIH, this does not preclude the involvement of centrally acting opioids or other peripheral opioids such as enkephalins or endomorphins. To further address possible opioid involvement in EIH, studies have utilized naloxone, an opioid receptor antagonist capable of crossing the blood brain barrier. Results thus far have been mixed with studies administering naloxone finding EIH to be attenuated (Haier et al., 1981; Janal et al., 1984; Olausson et al., 1986) or unchanged (Droste et al., 1991; Janal et al., 1984; Olausson et al., 1986). Animal studies evaluating activation of the opioid system in relation to EIH are more supportive of opioid involvement (Galdino et al., 2010; Hoeger Bement & Sluka, 2005), yet animal models also have implicated non-opioid mechanisms (reviewed by Cook & Koltyn, 2000; Koltyn, 2000). Both animal and human models suggest that opioid and non-opioid mechanisms are involved in EIH, and the predominant mechanism may be dependent upon the exercise task as well as the pain induction method.

### **Recruitment of High Threshold Motor Units**

Another proposed mechanism for EIH involves the activation of high threshold motor units (Hoeger Bement et al., 2008). This hypothesis is supported by the findings of Hoeger Bement et al. (2008) where subjects experienced EIH only after contractions of high intensity or low intensity contractions held to task failure, contractions when

recruitment of high threshold motor units is pronounced. In contrast to the findings of Hoeger Bement et al. (2008), pain reduction following low intensity isometric contractions of short duration where few high threshold motor units would be active has been found by others (Staud et al., 2005; Umeda et al., 2010; Umeda et al., 2009). This suggests that while fiber type recruitment may have a role in EIH, it does not fully explain EIH following isometric contractions. Another mechanism is likely responsible when contractions are of low intensity and held for short duration.

### **Motor Cortex Activation**

EIH has also been hypothesized to result from activation of the primary motor cortex and corticospinal tracts (Hoeger Bement, 2009). In animals, the corticospinal tract sends collaterals to regions involved in pain modulation including the PAG and RVM, in addition to pain processing neurons in the dorsal horn of the spinal cord. In the rat model, stimulation of the primary motor cortex results in an intensity-dependent reduction in dorsal horn WDR neuron activity in response to noxious, but not innocuous mechanical stimuli (Senapati et al., 2005). In humans, transcranial direct current stimulation (tDCS) has been shown to increase pain thresholds (Reidler et al., 2012) and has been successfully used in the treatment of intractable pain of central origin, such as thalamic pain, phantom limb pain, and post-stroke pain (Fenton et al., 2009; Fregni et al., 2006).

Although the mode of action of tDCS remains unclear, experiments using tDCS may give some indication as to the means by which motor cortex activation during exercise could induce EIH. An increase in blood flow in the ventrolateral thalamus and several brain areas known to be important in the processing and modulation of pain has

been found following tDCS (Garcia-Larrea et al., 1999). Additionally, tDCS applied to the motor cortex is associated with a reduction in the flexion withdrawal reflex, indicative of reduced spinal excitability (Garcia-Larrea et al., 1999). Activation of the motor cortex as occurs with exercise has the potential to result in both direct dorsal horn inhibition and indirect inhibition via endogenous inhibitory pathways.

### **Interaction of Cardiovascular and Pain Modulating Systems**

An interaction of the cardiovascular and pain modulating systems has been hypothesized to be responsible for EIH (Koltyn & Umeda, 2006). Blood pressure increases with exercise and this rise in blood pressure stimulates baroreceptors. As activation of baroreceptors results in hypoalgesia (Bruehl & Chung, 2004) and blood pressure has been found to be negatively associated with pain (Bruehl et al., 2002), baroreceptor response to exercise-induced changes in blood pressure may result in activation of descending inhibitory pathways and EIH (Koltyn & Umeda, 2006; Ring et al., 2008; Umeda et al., 2009).

Support for an association of blood pressure and EIH was indirectly established with the findings of stepwise elevations in both pain threshold and blood pressure with exercise (Kemppainen et al., 1985; Pertovaara et al., 1984), as well as a positive correlation between change in blood pressure and increase in pain threshold (Kemppainen et al., 1985). Additionally, Koltyn and colleagues (2001) found women to have higher pain ratings and lower blood pressure at rest than men, yet this difference in pain sensitivity was abolished after exercise when blood pressure in women rose to be similar to that of men.

Not all studies are in agreement. Despite a relation of blood pressure with pain sensitivity before and after fatiguing isometric exercise, Hoeger Bement et al. (2009) did not find a relation of blood pressure reactivity with EIH. Furthermore, while Ring and colleagues (2008) identified a mediational relation of blood pressure and reductions in pain ratings with different intensities of isometric contractions in men, this relation was not found to hold for women or a mixed group of men and women following isometric contractions of varied duration (Umeda et al., 2010; Umeda et al., 2009).

### **Conditioned Pain Modulation**

Pain often occurs in the contracting muscles with exercise (Cook et al., 1997; Cook et al., 2000; Frey Law et al., 2010; Weissman-Fogel et al., 2008). It has been postulated that pain within the exercising limb may act as a conditioning stimulus thereby activating the CPM pathway (Cook & Koltyn, 2000; Kosek & Lundberg, 2003; Weissman-Fogel et al., 2008). Repeated maximal handgrip exercise has been used as a conditioning stimulus in an investigation using a CPM paradigm (Weissman-Fogel et al., 2008). Despite frequent use of CPM as an indirect measure of central nervous system pain modulation (France & Suchowiecki, 1999; Lautenbacher & Rollman, 1997; Reinert et al., 2000; van Wijk & Veldhuijzen, 2010), intervention studies utilizing CPM protocols are extremely limited. Two recent interventional investigations have found the magnitude of the CPM response to be associated with pain reduction either with the use of transcutaneous electrical nerve stimulation (TENS) in individuals with fibromyalgia (Dailey et al., 2013) or with pulsed radiofrequency treatment in individuals with cluster headaches (Chua et al., 2011). These results suggest that pain reduction with these

interventional strategies may be mediated by activation of descending inhibitory pathways. Yet few studies of EIH have assessed muscle pain during exercise, and no study has directly examined the relation between CPM and EIH.

As EIH occurs with short duration exercise not generally perceived as painful, CPM is unlikely to serve as a primary mechanism for EIH. It is plausible that CPM may play an additive or synergistic role during painful exercise. Specific to exercise, there is a linear increase in pain during sustained isometric contractions of constant force; a one unit increase in pain intensity is seen for every 10% of maximum holding time (Frey Law et al., 2010). An additive effect of CPM along with another mechanism may therefore explain why in young adults the greatest pain relief with isometric exercise occurs following contractions of low intensity held for long duration (Hoeger Bement et al., 2008; Naugle et al., 2012). As no studies to date have examined the potential relation of CPM with EIH, it is not known if CPM might contribute to the EIH response.

### **Summary of Potential Mechanisms**

The mechanisms behind EIH are quite complex and likely involve activation of both opioid and non-opioid systems. Several potential mechanisms have been proposed including release of  $\beta$ -endorphins into the blood stream, central opioid release, recruitment of high threshold motor units, activation of the primary motor cortex and corticospinal tracts, and conditioned pain modulation. Each of these proposed mechanisms has the potential to be affected by changes in the neuromuscular system which occurs with aging. Mechanisms may vary with the specifics of the exercise task and may be moderated by the age and sex of the individual.

## **SIGNIFICANCE AND PURPOSE**

Better pain assessment and management will promote better quality of life while decreasing suffering (Carr & Goudas, 1999; Dahl & Moiniche, 2004). A clearer understanding of how aging influences acute pain is essential for the identification of alternative pain management techniques for older adults. Exercise is one potential non-pharmacological intervention for the management of pain. There is a paucity of information, however on EIH in older adults and the parameters required to produce optimal pain relief are not known. Isometric exercise, in particular, has the potential for safe use with adults of all ages for the management of pain. Furthermore, the mechanisms underlying the reduction in pain have yet to be elucidated. Understanding the role of intensity and duration of contractions and the mechanisms responsible for EIH following isometric exercise will help healthcare professionals prescribe exercise programs for pain management for both young and older adults.

The purpose of this dissertation is to examine a novel area of research that has received little attention in the literature, but has significant relevance in understanding the role of exercise in pain management in young and older adults. Specifically, this dissertation addresses gaps in our knowledge regarding 1) the dose-response relation between intensity and duration of isometric exercise on pain relief in older adults; 2) our understanding of the relation between EIH with activation of CPM; and 3) psychosocial factors involved in pain perception and EIH. The findings of this dissertation will provide the scientific rationale to more effectively prescribe exercise in the management of pain, especially in regard to older adults. Moreover, it will lay the groundwork for continued research on the effect of isometric exercise in clinical pain populations. The improved

understanding of the influence of aging on pain following exercise and the potential mechanisms and moderating factors involved will have a direct impact on exercise prescription, thus improving patient outcomes in the management of pain conditions.

## **SPECIFIC AIMS AND HYPOTHESES**

**Aim 1: To determine the relation between anxiety and pain attitude with pain perception using a tonic mechanical noxious stimulus in healthy older adults.**

*Hypothesis 1: State anxiety and reticence to report pain will be associated with reports of pain.*

*Hypothesis 2: State anxiety and pain reports will not significantly change with experimental pain testing.*

**Subaim 1: To identify if repeated pain testing influences variability of pain reports in healthy older adults.**

*Hypothesis: Older adults who demonstrate variability in pain reports will have reduced variability on repeated pain testing.*

**Subaim 2: To examine if sex differences in pressure pain perception are present in older adults.**

*Hypothesis: Older women will report greater pain to the same noxious pressure stimulus than older men.*



**Aim 2: To determine the influence of age on exercise-induced hypoalgesia following the performance of sustained isometric contractions of varying intensities and durations.**

*Hypothesis: Older adults will experience exercise-induced hypoalgesia following isometric contractions of both high and low intensity.*

**Subaim: To determine if there are sex-differences in EIH in older adults.**

*Hypothesis: Women and men will experience similar pain relief following isometric contractions of the elbow flexor muscles.*

**Aim 3: To ascertain if there is a relation between CPM and EIH following a submaximal isometric contraction of the elbow flexor muscles that is perceived to be painful in young and older adults.**

*Hypothesis 1: The magnitude of the CPM response will predict the magnitude of EIH following an isometric contraction to task failure in young and older adults.*

*Hypothesis 2: Older adults will have an attenuated conditioned pain modulation response compared to young adults using a mechanical noxious test stimulus.*

*Hypothesis 3: Older adults will have attenuated exercise-induced analgesia compared to young adults following the same exercise protocol.*

**Subaim 1: To determine if there are age-related differences in pain sensitivity to a noxious pressure stimulus.**

*Hypothesis: Older adults will feel pain similarly to young adults using a noxious pressure stimulus to the index finger.*

**Subaim 2: To determine if there are sex-differences in CPM using a noxious pressure stimulus.**

*Hypothesis: Women and men will experience similar CPM using a mechanical noxious test stimulus.*

## **CHAPTER TWO**

### **REPEATABILITY OF PAIN REPORTS AND THEIR RELATION WITH STATE ANXIETY AND PAIN ATTITUDE IN HEALTHY OLDER ADULTS**

#### **INTRODUCTION**

Acute pain serves as a protective mechanism when tissue damage is present or likely to occur. Control of acute pain is important as it may progress to chronic pain and pain related disability (Carr & Goudas, 1999; Dahl & Moiniche, 2004; Vierck, 2006). The most efficacious pain management strategies involve consideration of a multitude of factors that influence pain perception. The age of the individual may be one such factor impacting the pain experience and response to intervention strategies. The role of aging, however on pain perception is unclear.

Clinically, older adults appear to have a reduction in acute pain sensitivity. Elderly adults are more likely than young adults to experience little or no pain with certain painful pathologies such as myocardial infarction (Gagliese, 2009; Gibson & Helme, 2001; Harkins, 1996, 2001; Mehta et al., 2001). Older adults may also report less postoperative pain and require lower doses of analgesics following surgery than young adults (Bellville et al., 1971; Gagliese et al., 2005; Gibson & Helme, 2001; Oberle et al., 1990). A clearer understanding of how aging influences the acute pain experience is an important component in the development of effective treatment strategies for older adults.

Models of acute experimental pain show conflicting results regarding age-related changes. Methodological differences may explain the disparities in pain perception associated with aging such as the type of noxious stimulus employed (Edwards & Fillingim, 2001; Gibson & Farrell, 2004; Hoeger Bement et al., 2014; Lautenbacher,

2012), the pain scale utilized (Gagliese & Melzack, 1997), or the indices of pain assessed (Lautenbacher, 2012). For example, radiant heat pain sensitivity is shown to decrease with age demonstrated by elevated pain thresholds, while pain threshold to an electrical stimulus remains unchanged (Gibson & Farrell, 2004). Equivocal results are also noted when comparing studies using different pain indices with the same noxious modality. Higher pain thresholds have most commonly been reported for thermal and mechanical stimuli, whereas pain tolerance for these modalities either remains unchanged or is decreased (reviewed by Lautenbacher, 2012). The potential age-related changes become more complex given the potential for sex differences in pain perception, particularly for pressure pain (Fillingim et al., 2009; Racine et al., 2012; Riley et al., 1998).

Biopsychosocial influences further enhance the complexity of pain perception through the interaction between the processing of sensory input, psychological dynamics, and societal influences. For example, attitudes toward pain such as stoicism and cautiousness have been suggested to influence pain perception, with older adults more conservative when labeling stimuli as painful and more reticent to report pain than younger adults (Harkins & Chapman, 1976; Yong et al., 2001). In young and middle-aged adults, state anxiety has been shown to be positively related to pain (Chakour et al., 1996; Eli et al., 2003; Hoeger Bement et al., 2010; Kuivalainen et al., 2012; Okawa et al., 2005; Rhudy & Meagher, 2000; Tang & Gibson, 2005; von Graffenried et al., 1978). This relation may be stronger in young men than women (Edwards et al., 2000; Fillingim, Keefe et al., 1996; Frot et al., 2004; Jones & Zachariae, 2004; Soetanto et al., 2006) and is particularly robust when the anxiety is directly related to the noxious event (al Absi & Rokke, 1991; Dougher et al., 1987; Weisenberg et al., 1984).

Little is known, however if the positive relation between anxiety and pain persists beyond middle-age. Only a small number of studies have examined the anxiety-pain relation in older adults, and to our knowledge none have examined the relation in healthy older adults undergoing acute experimental pain. The few studies specifically addressing older adults have examined this relation in individuals with chronic pain (Casten et al., 1995; Smith & Zautra, 2008) or following an acute operative procedure (Feeney, 2004; Saracoglu et al., 2012). Anxiety may continue to play a substantial role in perception of clinical pain intensity with advanced age as demonstrated by Feeney (2004) who found that state anxiety accounted for up to 27% of the variance in reports of acute pain following orthopedic surgery in adults over age 65. Given that in older adults state anxiety has been found to be associated with acute clinical pain, it is plausible that the association between state anxiety and acute experimental pain seen in young and middle-aged adults persists with advancing age. Furthermore, state anxiety may help to explain some of the variability in pain reports demonstrated between individuals experiencing the same noxious stimulus.

If the association of state anxiety with acute pain perception persists with aging, alterations in state anxiety would have the potential to impact pain perception with either single or repeated experimental pain testing. This issue of repeated pain testing is important to understand both from a clinical and research perspective. For example, treatment effectiveness may be assessed by comparing pain threshold and/or pain ratings to an experimental noxious stimulus before and after an intervention (Hoeger Bement et al., 2008; Hoeger Bement et al., 2009; Hoeger Bement et al., 2011; Hoffman et al., 2004; Koltyn et al., 2001; Koltyn & Umeda, 2007; Umeda et al., 2010). It is not known if pain

testing using a tonic noxious pressure stimulus results in alterations in state anxiety or pain reports in older adults or if variability in pain reports is reduced with previous exposure to the pain testing protocol.

The specific aim of this study was to determine the relation between anxiety and pain attitude with pain perception using a tonic mechanical noxious stimulus in healthy older adults. We hypothesized the following: 1) state anxiety and reticence to report pain would be related to pressure pain reports and 2) reports of pain and state anxiety would not significantly change with experimental pain testing. Our secondary aims were to determine if older adults who demonstrate variability in pain reports in session one will have reduced variability with repeated pain testing in a second session, and to examine whether sex differences in pressure pain perception are present in older adults. We hypothesized that repeated testing will decrease within session variability in pain assessment in older adults. As young women appear to have lower pain thresholds to a noxious pressure stimulus than men (Racine et al., 2012), we further hypothesized that older women would report greater pain to the same noxious stimulus than older men.

## **MATERIALS AND METHODS**

### **Participants**

Thirty healthy adults aged 60-85 years (17 females and 13 males, mean age  $72 \pm 6.3$  years) took part in the study. Exclusion criteria included history of a neurological or cardiovascular condition, pain requiring regular use of an analgesic or use of an analgesic 24 hours preceding testing, sensory impairment in the upper extremities, use of a psychotropic medication, uncontrolled hypertension or a Mini Mental State Examination

(MMSE) score of  $\leq 24$  indicating possible cognitive dysfunction. Participants provided written informed consent at the start of the study and were compensated \$15 for each session. The protocol was approved by the Institutional Review Boards at Marquette University and Concordia University Wisconsin.

### **Questionnaires and Measures**

Each participant completed several questionnaires and measures prior to the initial pain assessment including measures of pain attitude (Modified Pain Attitude Questionnaire – Revised, Yong et al., 2003) and state and trait anxiety (State-Trait Anxiety Inventory, Spielberger, 1983). State anxiety was assessed two more times, immediately following each of the pressure pain tests.

*Spielberger State-Trait Anxiety Inventory (STAI).*

The STAI is an assessment of transient (state) and enduring (trait) levels of anxiety (Spielberger et al., 1983). Both the state and the trait subscales consist of 20 questions, each with a 4 point scale. Scale scores range from 20 to 80 with higher values indicative of greater levels of anxiety. The STAI has been shown to have good reliability (Barnes, 2002).

*Modified Pain Attitude Questionnaire-Revised (modified PAQ-R).*

The modified version of the Pain Attitude Questionnaire-Revised is a 23 item scale used for the assessment of stoicism and cautiousness about pain (Yong et al., 2003). Items are rated from 1 (strongly disagree) to 5 (strongly agree). The items fall into one of

four dimensions with an average dimension score determined for each. Dimensions are 1) Stoicism-reticence (e.g., “I keep a ‘stiff upper lip’ when I am in pain”); 2) Stoicism-superiority (e.g., “I think I can tolerate more pain than other people”); 3) Cautiousness-Self Doubt (e.g., “I take a long time to decide whether a sensation is painful or not”); and 4) Cautiousness-Reluctance (e.g., “I take great care to avoid labeling a sensation as painful unless I am certain”).

### **Pressure Pain Procedure**

Participants were seated with their right forearm resting in a comfortable position on a table. Pain perception was measured by placing a 10 N force on a Lucite edge (8 x 1.5 mm) on the dorsal aspect of the middle phalanx of the right index finger for 2 min. Participants were asked to press a timing device with their left hand when they first felt pain (i.e., pain threshold in seconds) and to rate the intensity of their pain every 20 seconds using a 0-10 numerical rating scale (NRS) for a total of six pain ratings over time. The scale was anchored with 0 = no pain, 5 = moderate pain, and 10 = worst pain imaginable (McCaffery & Pasero, 1999). The NRS is a recommended pain assessment tool for older adults with intact cognitive abilities (Herr, 2011).

Participants were informed they could stop the test at any time if the pain became intolerable. Pain threshold and pain ratings were measured twice, once before and again after 30 minutes of quiet rest. Pilot data in our laboratory with young adults indicated that 30 minutes was necessary between the two pressure pain tests because 15 minutes was not adequate recovery for the pilot subjects (Hoeger Bement et al., 2008). Change scores were calculated as the difference in pain threshold and average pain ratings before and



after quiet rest. Variability in pain reports was defined as the absolute value of the change scores for each session.

A subgroup of individuals was asked to return one week later and repeat the pressure pain tests as described above. These subjects were asked to return because they failed to report pain threshold or demonstrated variability in pain reports ( $\geq 15$  second difference in pain threshold or a difference in pain ratings of  $\geq 2$  at two consecutive time points) (Hoeger Bement et al., 2011; Hoeger Bement et al., 2010). The second session was conducted to assess if reporting of pain threshold improved and/or the variability in pain reports decreased with additional exposure to the pain testing. Of the questionnaires administered in session one, only the state portion of the STAI is thought to have transient properties. Therefore only state anxiety was assessed in both sessions. As in session one, state anxiety was assessed in session two prior to the first pain test and again immediately following each of the pressure pain tests.

### **Statistical Analyses**

Data were analyzed using Statistical Package for the Social Sciences (SPSS, version 20, IBM, Chicago, IL) and screened for outliers ( $> 3$  SD from the mean), missing data points, and skewness. If data were significantly skewed, transformations were performed prior to data analysis.

### **Session One Anxiety, Pain Attitude, and Pain Analyses**

To determine if anxiety changed with pain testing, state anxiety scores (before pain testing and immediately following each pressure pain test) were analyzed using

repeated measures ANOVA. To identify if pain reports differed before and after quiet rest and to assess for possible sex differences in pain reports, pain threshold and pain ratings during session one were analyzed using separate mixed-design repeated measures ANOVAs. The within-subjects factor levels differed by variable: pain threshold two levels (trial: pre/post quiet rest), and pain ratings two by six levels (trial: pre/post quiet rest and time: pressure pain rating every 20 s during the 2 min pressure pain test). The Greenhouse-Geiser correction was used when the assumption of sphericity was violated. When a significant effect was found, simple contrasts and Bonferroni corrected pairwise comparisons were used as *post-hoc* tests. Pain ratings during the two minute pain test were averaged across the six time points for each trial to perform *post hoc* testing.

Bivariate Pearson's or Spearman's correlations as indicated by normality were run to assess for associations between state and trait anxiety, dimensions of pain attitude, and pain reports. Separate regression analyses were used to determine if state anxiety was predictive of pain threshold or pain intensity when accounting for the influence of sex. As pain attitude did not significantly correlate with pain threshold or pain ratings, pain attitude was not included in the regression models. Independent *t*-tests or Mann-Whitney U tests as appropriate based on skewness compared average state anxiety and the four dimensions of pain attitude between men and women and were also used to assess for differences in state anxiety, pain attitude and pain perception between the participants who were asked to return for a second session and those who completed only the first session.

## Repeated Testing Analyses

Due to severe positive skewing, anxiety data were analyzed using Friedman's ANOVA. To determine if pain threshold and pain ratings differed before and after quiet rest and to assess for possible sex differences, pain reports were analyzed using separate mixed-design multivariate repeated measures ANOVAs as done during session one. For the cohort that completed both sessions, paired *t*-tests or Wilcoxon Signed Rank Tests as appropriate based on normality of the data were used to identify differences in baseline and average state anxiety, baseline and average pain reports, and variability in pain reports before and after quiet rest between the two sessions.

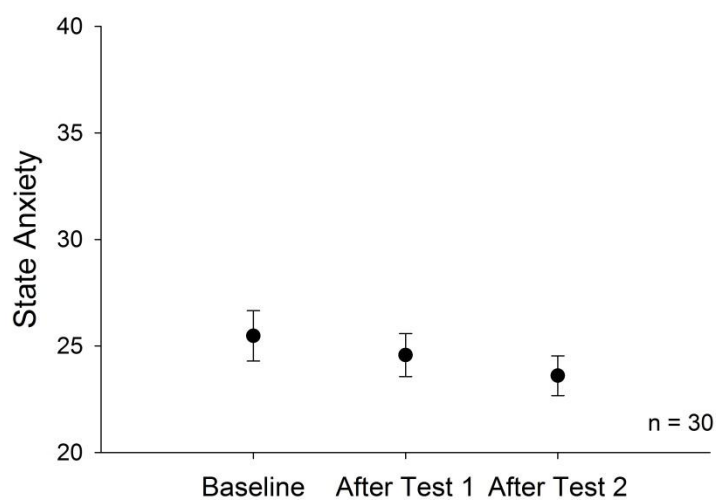
Missing pain threshold values due to failure to push the timing device were imputed using the midpoint between the time of the last pain rating of zero and the first pain rating greater than zero (Lemley et al., 2014). In the absence of pain, test duration of 120 seconds was used as the imputed pain threshold score. For subjects that asked to stop the pain test prior to 120 seconds (e.g., were not able to tolerate the full test duration), pain ratings of 10 were imputed for remaining pain intensity scores. Additionally, one participant skipped an item on the first STAI administration of session one. The average of this item on the remaining two STAI administrations for that session was imputed for the missing item and used in calculation of the initial state anxiety score. A *P*-value of < 0.05 was used for statistical significance. Data are reported as mean  $\pm$  SD within the text and mean  $\pm$  SEM in the figures.

## RESULTS

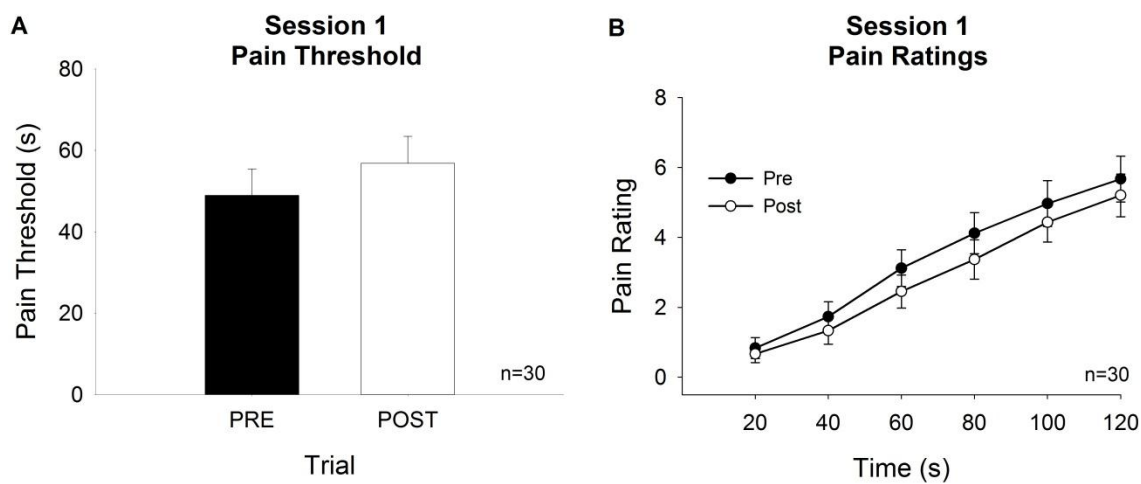
### Session One

Five outliers were identified: one trait anxiety score, one Stoicism-Reticence score, one Cautiousness-Reluctance score, and one state anxiety score following each pressure pain test in session two (total of two). Outliers were altered to the next most extreme score (Field, 2013). A total of 10 missing pain threshold data points (8 before and 2 after quiet rest) were identified due to participants forgetting to push the timing device. No participant forgot to press the timing device both before and after quiet rest. One additional subject indicated they accidentally pressed the timer prior to onset of pain thus a verbal report was used to determine the time of pain threshold. Four participants (2 women, 2 men) reported no pain in at least one trial (1 before, 2 after, 1 both before and after quiet rest). Two women did not complete the full 120 second test duration as they reached their pain tolerance before quiet rest, but all participants completed the full 120 second pain test following quiet rest.

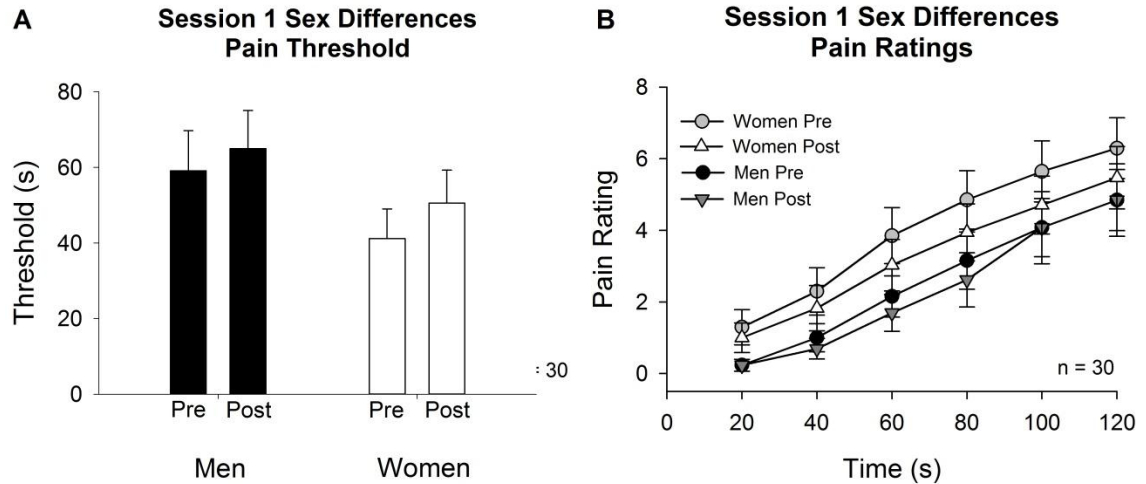
During session one, state anxiety was similar across time (baseline and after each pain test) indicating that the pressure pain test did not change state anxiety ( $p > 0.05$ ; Figure 2.1). Pain threshold and pain ratings were also similar before and after 30-minutes quiet rest ( $p > 0.05$ ; Figures 2.2 A and B). There were no significant main or interaction effects for pain reports with the exception of an increase in pain ratings over the two-minute test ( $p < 0.001$ ,  $\eta_p^2 = 0.72$ ). Furthermore, there were no main or interaction effects for sex for either pain threshold or pain ratings ( $p > 0.05$ ; Figures 2.3 A and B). State anxiety and pain attitude were similar between men and women ( $p > 0.05$ ).



**Figure 2.1 Session One State Anxiety.** State anxiety was similar across time. Data are represented as mean  $\pm$  SEM.

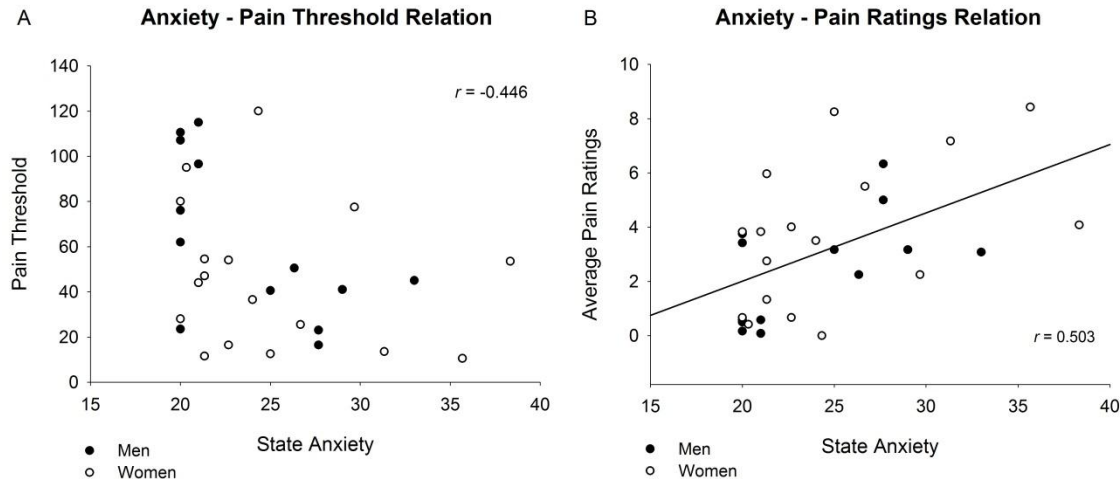


**Figure 2.2 Session One Pain Threshold and Pain Ratings Before and After Quiet Rest.** Pain threshold (A) and pain ratings (B) before and after 30 minutes quiet rest. There was no difference in either pain threshold or pain ratings. Data are represented as mean  $\pm$  SEM.



**Figure 2.3 Session One Sex Differences.** Older men and women reported pain threshold (A) and pain ratings (B) similarly before and after 30 minutes quiet rest. Data are represented as mean  $\pm$  SEM.

As neither state anxiety or pain perception was found to differ across the session, the three state anxiety measures, two pain threshold measures, and the two average pain ratings measures (before and after quiet rest) were averaged to create a single session average of each variable for further analysis. State anxiety was moderately related to pain threshold ( $r = -0.446$ ,  $p = 0.01$ ; Figure 2.4 A), pain ratings ( $r = 0.503$ ,  $p = 0.005$ ; Figure 2.4 B), and Cautiousness-Self Doubt ( $r = 0.392$ ,  $p = 0.03$ ). No significant correlations were found for pain attitude or trait anxiety with pain threshold or pain ratings.



**Figure 2.4 Session One Relations of State Anxiety with Pain Reports.** Relation of state anxiety with pain threshold (A) and average pain ratings (B) for older men and women. Anxiety had a moderate negative association with pain threshold and a moderate positive association with pain ratings.

Because sex may influence pain perception (Fillingim et al., 2009; Racine et al., 2012; Riley et al., 1998) and the anxiety-pain relation (Edwards et al., 2000; Fillingim, Keefe et al., 1996; Frot et al., 2004; Jones & Zachariae, 2004; Soetanto et al., 2006), sex was included in the regression models. Only state anxiety predicted pain ratings [ $F(2, 27) = 6.046, p = 0.007$ , adjusted  $R^2 = 0.26$ ]. Sex did not uniquely contribute to the model ( $p > 0.05$ ). While a trend was seen for state anxiety to predict pain threshold (coefficient  $p = 0.06$ ), the model failed to reach significance ( $p = 0.07$ ).

A total of 19 participants (11 women and 8 men) met criteria to return for a second session: 6 forgot to push the timing device, 2 met criteria for pain ratings (a difference in pain ratings of  $\geq 2$  at two consecutive time points), 4 forgot to press the timing device *and* met criteria for pain ratings, 4 met criteria for pain threshold (difference of  $\geq 15$  seconds), and 3 met criteria for both pain ratings *and* pain threshold. Of these 19 participants that returned, their pain threshold and pain ratings were similar before and after quiet rest during session one ( $p > 0.05$ ).

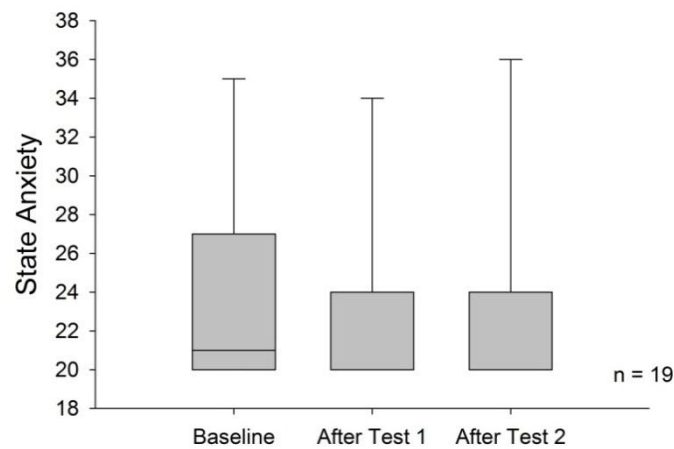
### ***Session One Comparison of Repeating Participants with Non-repeating Participants***

During session one, repeating participants ( $Mdn = 21.0$ ) were less anxious than the non-repeaters ( $Mdn = 26.3$ ;  $U = 50.5$ ,  $p = 0.018$ ,  $r = 0.43$ ). The repeating participants however reported similar pain thresholds, pain ratings, and pain attitude as the non-repeating participants ( $p > 0.05$ ). When examined by sex, repeating women had similar pain reports, average state anxiety, and pain attitude as non-repeating women ( $p > 0.05$ ). Repeating men reported higher pain thresholds ( $Mdn$ : 86.25 s vs. 41 s;  $U = 34.0$ ,  $p = 0.045$ ,  $z = 2.049$ ,  $r = 0.57$ ) and lower average state anxiety ( $Mdn$ : 20.0 vs 27.7;  $U = 0.000$ ,  $p = 0.002$ ,  $z = -3.020$ ,  $r = 0.84$ ) during session one compared with non-repeating men. There were no differences in pain ratings or in pain attitude between the two groups of men.

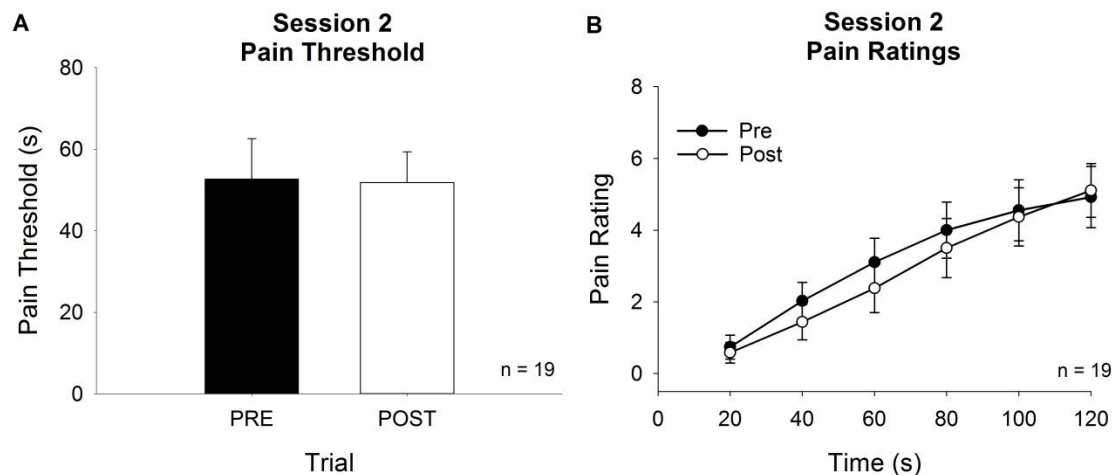
### **Session Two**

There was no change in state anxiety across the second session ( $p > 0.05$ ; Figure 2.5). Pain threshold and pain ratings were similar before and after 30-minutes quiet rest ( $p > 0.05$ ; Figures 2.6 A and B). Pain ratings increased during the 2-minute pain test (time:  $p < 0.001$ ,  $\eta_p^2 = 0.68$ ). There was a significant trial x sex interaction in session two for both pain threshold ( $p = 0.045$ ,  $\eta_p^2 = 0.22$ ) and pain ratings ( $p = 0.02$ ,  $\eta_p^2 = 0.29$ ). Although women trended toward a decrease in pain and men an increase, *post hoc* testing revealed neither change was significant. No significant correlation between session average state anxiety and session average pain threshold or pain ratings was identified ( $p > 0.05$ ).





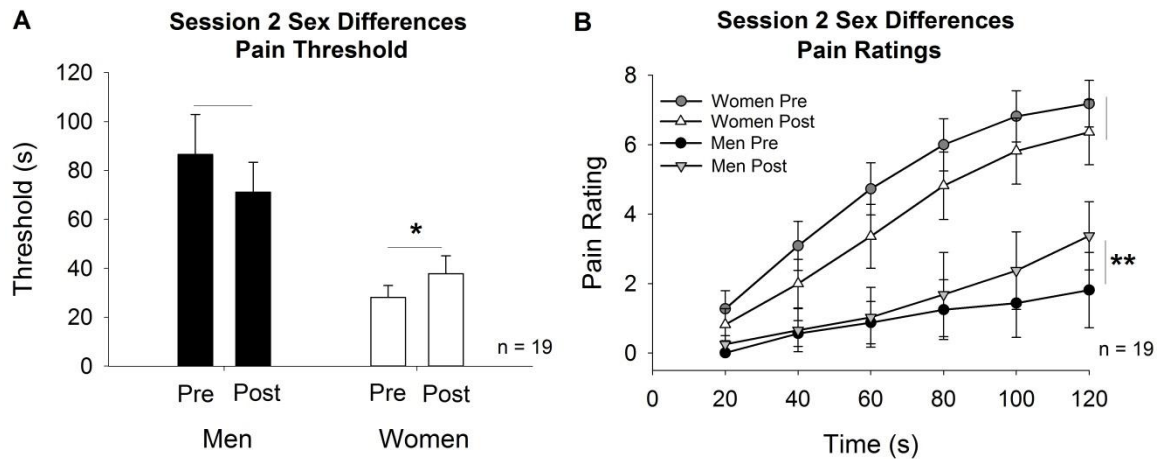
**Figure 2.5 Session Two State Anxiety.** State anxiety was similar across time. Box plots displaying the median, 25<sup>th</sup> to 75<sup>th</sup> percentiles (boxes), and 10<sup>th</sup> to 90<sup>th</sup> percentiles (error bars).



**Figure 2.6 Session Two Pain Threshold and Pain Ratings Before and After Quiet Rest.** Pain threshold (A) and pain ratings (B) before and after 30 minutes quiet rest. There was no difference in either pain threshold or pain ratings. Data are represented as mean  $\pm$  SEM.

Women completing session two trended toward higher state anxiety ( $Mdn = 22.3$ ) than the men ( $Mdn = 20.2$ ), however this was not statistically significant ( $U = 20.5$ ,  $p = 0.051$ ,  $z = -1.97$ ,  $r = 0.45$ ). There was a significant main effect of sex for both pain threshold and pain ratings. During session two, women had lower pain thresholds ( $p =$

0.013,  $\eta_p^2 = 0.31$ ) and higher pain ratings ( $p = 0.006$ ,  $\eta_p^2 = 0.37$ ) than men (Figures 2.7 A and B).



**Figure 2.7 Session Two Sex Differences.** Pain thresholds (A) and pain ratings (B) before and after 30 minutes quiet rest in repeating older men and women. Women had lower pain thresholds and higher pain ratings than men. There was a significant trial by sex interaction, however pain thresholds and pain ratings were similar for both men and women before and after 30 minutes quiet rest. Data are represented as mean  $\pm$  SEM. \*Sex:  $p < 0.05$ . \*\*Sex:  $p \leq 0.01$ .

Fourteen of the 19 participants that returned forgot to press the timing device or continued to demonstrate variability in pain reports in the second session: 2 forgot to push the timing device, 4 met criteria for pain ratings, 2 forgot to press the timing device *and* met criteria for pain ratings, 3 met criteria for pain threshold, and 3 met criteria for both pain ratings *and* pain threshold. Forgetting to press the timing device resulted in 5 missing data points (2 before and 3 after quiet rest), with one participant failing to press the timing device both before and after quiet rest. One-half of the men (4/8) reported no pain before quiet rest. Following quiet rest all four men reported mild pain (NRS range 1-3) during the final 40 s of the pain test. Two women and one man stopped the test prior to 120 seconds due to reaching pain tolerance.

### ***Comparison of Session 1 and Session 2 for Participants Repeating***

We compared session one with session two pain reports and anxiety for the cohort of participants returning for a second session. The variability of pain reports between tests for both pain threshold ( $22 \pm 21$  s vs.  $18 \pm 16$  s) and average pain ratings ( $1.55 \pm 1.48$  vs.  $1.15 \pm 1.02$ ) was similar between the two sessions ( $p > 0.05$ ). Furthermore, average pain reports did not change between sessions and average state anxiety was also similar between sessions for both men and women ( $p > 0.05$ ).

## **DISCUSSION**

Our findings in session one show that state anxiety predicts pressure pain intensity in healthy older adults. There was also a moderate negative relation between pain threshold and state anxiety. Healthy older adults report pain sooner and with greater suprathreshold intensity when state anxiety is greater. This association was present even with the relatively low levels of state anxiety experienced by our participants (Julian, 2011; Kvaal et al., 2005; Potvin et al., 2011). These results are consistent with previous findings in older adults showing a positive relation of anxiety and acute post-operative pain (Feeney, 2004; Saracoglu et al., 2012) and in young and middle-aged adults with experimental (Chakour et al., 1996; Hoeger Bement et al., 2010; Rhudy & Meagher, 2000; Tang & Gibson, 2005; von Graffenried et al., 1978) or procedural (Eli et al., 2003; Kuivalainen et al., 2012; Okawa et al., 2005) pain. When treating older adults with acute pain, minimizing anxiety may be an important intervention. The relation between anxiety and pain also has implications for repetitive pain testing although our results showed no

change in state anxiety within and across sessions using a tonic mechanical noxious stimulus.

Despite the strong relation between anxiety and pain reports in session one, for the participants that returned for session two there was no association between state anxiety and pain reports. The absence of a relation may be due to the extremely low state anxiety scores of the participants in this session, particularly for the men. During session one, repeating men were significantly less anxious than non-repeating men.

As with anxiety, attitudes toward pain may differ among adults and thereby influence the perception of the pain experience. Older adults are thought to be more conservative when labeling stimuli as painful (Harkins & Chapman, 1976) and are likely to report higher suprathreshold pain ratings than young adults (Harkins et al., 1986). Yong and colleagues (2001) found older adults to be more reticent to report pain than younger adults, and this stoic attitude has been found to be a mediator of age-related differences in pain intensity in adults with chronic pain (Yong, 2006). We did not find a relation of pain attitude with either pain threshold or pain ratings in our sample of older adults. One possible reason for this finding may be that beliefs regarding pain attitudes held by an individual may not adequately reflect response to a painful stimulus. Cohort influences on pain attitudes may also have contributed to a lack of association of attitudes with pain reports. The greater the difference in age, the more pronounced the difference in pain attitudes (Yong et al., 2001). Our sample was limited to older adults aged 60 to 85 years. Yong and colleagues (2001) found attitudes to be similar between adults aged 60-80 years and those over 80 years with the exception of stoicism-reticence. Additionally, while healthy adults over age 80 are more reticent to report pain than adults 60-80 years

(Yong et al., 2001), only three of our participants were older than 80 years of age. One limitation of our study is that the results cannot be directly compared to younger adults. Future studies should incorporate participants across the lifespan to further elucidate the relation between pain attitude and pain perception.

Our findings indicate that pressure pain reports are similar before and after quiet rest both within and across sessions in healthy older adults. For those participants completing both sessions, pain reports did not change following quiet rest in either session, and repeated sessions did not alter the variability in pain reports within a session. This has important implications for the use of repetitive testing in intervention studies and suggests that the inherent variability in reporting pain remains even with prior exposure to the testing device. Interestingly, repeating men had lower anxiety and higher pain thresholds during session one than men who did not repeat. Thus for men, those with less anxiety and later onset of pain were more likely to show greater variability in reporting of pain.

When assessing more than one indices of pain, familiarizing participants to the pain testing procedure may help reduce the number of missing pain threshold values due to failure to press the timing device. In the first session, the number of older adults who forgot to press the timing device decreased from 8 prior to quiet rest to 2 following. In the second session, this remained consistent with 2 missed presses before and 3 missed after quiet rest. As variability in pain threshold and pain ratings with repetitive testing was similar between sessions, a single exposure to the pain test may be appropriate for familiarizing participants to the procedure.

The dual task nature of the testing protocol may explain why older adults forgot to press the timing device. Participants were asked to determine change from pressure to pain, press the timing device at the moment of change, and simultaneously monitor the intensity of the painful sensation. While cueing participants to report pain intensity at the designated time points prevented participants from forgetting to indicate pain intensity, no cueing was possible for pain threshold. To our knowledge, previous studies using a single task does not result in participants forgetting to indicate pain threshold in young or older adult populations. Aging has been shown to negatively affect both working memory (Salthouse, 1994) and dual task performance (Hein & Schubert, 2004) which further explains the absent data in this healthy older adult population. Familiarizing older participants to the pain testing procedure may be most critical when performing complex pain assessments.

Sex differences in pain perception were identified only in session two. While pressure stimuli show the greatest magnitude of sex differences in pain perception (Riley et al., 1998), results in the literature have been inconsistent (Racine et al., 2012). Our results in session one along with others indicate that psychosocial factors such as state anxiety influence pain threshold and ratings (Eli et al., 2003; Hoeger Bement et al., 2010; Kuivalainen et al., 2012; Okawa et al., 2005; Rhudy & Meagher, 2000; Tang & Gibson, 2005; von Graffenried et al., 1978), thereby contributing to the variability in pain perception. The significantly lower pain and anxiety scores for the men repeating compared to men not repeating likely contributed to the differing results for sex differences between the two sessions.

Another possible explanation for the inconsistency in study results may be differences in pain rating schemas of the study participants. Frey Law and colleagues (Frey Law et al., 2013) recently showed that there is great variation in how individuals interpret the numerical rating of pain, and individual differences in pain ratings schema may contribute to the variability in study findings. We did not assess underlying interpretation of numerical pain ratings of our participants. In agreement with the recommendations of Frey Law et al (2013), future studies should consider the inclusion of a verbal descriptor scale (e.g., none, mild, moderate, severe) in addition to numerical pain ratings when assessing for group differences in pain intensity.

## **Conclusion**

The positive relation between state anxiety and pain reports in young and middle-aged adults remains in older adults, and anxiety is not altered by testing with a tonic noxious pressure stimulus. Individuals with greater state anxiety report lower pain thresholds and higher pain ratings than less anxious peers. Furthermore, older adults report similar pressure pain before and after quiet rest. Repetitive pain testing improves compliance with reporting pain threshold, but does not improve variability in pain reports.

## CHAPTER THREE

### DOSE-RESPONSE RELATION OF ISOMETRIC EXERCISE-INDUCED HYPOALGESIA IN HEALTHY OLDER ADULTS

This is a non-final version of an article published in final form in *Medicine & Science in Sports & Exercise*. <http://journals.lww.com/acsm-msse/pages/default.aspx>

Lemley, K. J., Drewek, B., Hunter, S. K., & Hoeger Bement, M. K. (2014). Pain relief after isometric exercise is not task-dependent in older men and women. *Med Sci Sports Exerc*, 46(1), 185-191. doi: 10.1249/MSS.0b013e3182a05de8

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## INTRODUCTION

By the year 2030, up to one in five Americans will be age 65 and older (Vincent et al., 2010). Pain is a particularly persistent problem in this age group and it has been estimated that between 40% and 80% of older adults experience pain sufficient to negatively impact daily functioning and overall quality of life (Cavalieri, 2005). While pharmacological means are regularly utilized in the management of pain, the increased adverse effects with pharmacological measures associated with aging (Cavalieri, 2005) and the increasing cost of healthcare make it imperative to examine non-pharmacological, cost effective alternatives for pain relief. One such intervention is exercise, which is frequently used in the management of pain. While most exercise-training programs in older adults with chronic pain demonstrate reductions in pain and improvements in functional status (Koltyn, 2002b; Singh, 2002), the optimal prescription to relieve pain is not clear. This includes lack of knowledge regarding type, intensity and duration of exercise to provide pain relief (Koltyn, 2002b; Singh, 2002). Many practitioners feel ill-



prepared to adequately prescribe exercise for their older clients because of a lack of information on how to individualize programs to best meet the client's needs (Christmas & Andersen, 2000), and so it is vital to understand the impact of age on the change in pain perception following exercise.

Sensitivity to a noxious stimulus has been shown to decrease following exercise, a phenomenon known as exercise-induced hypoalgesia (EIH). EIH has been found following exercise of all types, including aerobic exercise, dynamic resistance exercise, and isometric exercise (reviewed by Naugle et al., 2012). In young healthy adults, the parameters to achieve EIH appear to be specific to the type of exercise performed. Exercise of higher intensity (60-75%  $\text{VO}_{2\text{max}}$  or 200 W) most consistently produces EIH following aerobic exercise (Hoffman et al., 2004; Koltyn, 2002a). In contrast, isometric contractions of high intensity (Hoeger Bement et al., 2008; Koltyn et al., 2001) and low intensity (Hoeger Bement et al., 2008; Hoeger Bement et al., 2009; Koltyn et al., 2001; Kosek & Ekholm, 1995; Umeda et al., 2010) induce an EIH response, with the greatest reduction in sensitivity to a noxious stimulus following low intensity contractions (25% - 50% MVC) held for longer duration (Hoeger Bement et al., 2008; Naugle et al., 2012).

Our knowledge of EIH is based primarily on studies of young adults, and mostly physically active men. Older adults and women have historically been underrepresented in studies of exercise and pain (Beery & Zucker, 2011). In the last decade the pain response following exercise in young women has received more attention in the literature, however there remains a paucity of information on the impact of aging on EIH. Several studies examining EIH in individuals with chronic pain have included control groups consisting of healthy middle-aged adults, with mean age of control subjects

ranging from 34 to 52 years. Results of these studies show that EIH persists in middle-age with reductions in pain sensitivity following both aerobic (Hoffman et al., 2005; Meeus et al., 2010) and low-intensity isometric (Ge et al., 2012; Kadetoff & Kosek, 2007; Kosek et al., 1996; Staud et al., 2005) exercise protocols. To our knowledge no study has examined changes in pain sensitivity immediately following exercise in healthy adults over 60 years of age or the impact of varying the exercise parameters on the magnitude of the EIH response.

There are several factors associated with aging that may impact EIH. For example, older adults experience sarcopenia (a reduction in the number and size of muscle fibers) with greater atrophy of Type II (fast) than Type I (slow) fibers (Hunter & Brown, 2010; Hunter et al., 1999), as well as a reduced ability to activate endogenous descending inhibitory pathways (Lariviere et al., 2007; Riley et al., 2010; Washington et al., 2000). Both recruitment of high-threshold motor units and activation of descending inhibitory pathways have been implicated as potential mechanisms responsible for EIH (Cook & Koltyn, 2000; Hoeger Bement et al., 2008). Thus, the influence of an acute bout of exercise on pain sensitivity may differ in older adults compared with young adults.

Isometric exercise has excellent potential to become an effective pain management tool for a large segment of the population. Individuals of all ages and abilities, including those with limited mobility can perform isometric exercise. Therefore, the purpose of this project was to determine the impact of isometric contractions that varied in intensity and duration on pain relief in adults over 60 years. Because cardiovascular reactivity (Koltyn & Umeda, 2006; Ring et al., 2008) and anxiety (Okawa

et al., 2005) have also been implicated in the modulation of pain perception, we recorded anxiety levels and cardiovascular responses to examine their influence on EIH.

## **MATERIALS AND METHODS**

### **Subjects**

Twelve men ( $72.4 \pm 6.1$  years, mean  $\pm$  SD) and 12 women ( $72.0 \pm 6.6$  years) participated in this experiment. All subjects were healthy and free of any risk factors that would preclude them from participating in exercise. Subjects were excluded if they reported acute or chronic pain, current use of analgesics or psychotropic medications, or if they had a score of less than 25/30 on the Mini Mental Status Examination (MMSE) indicative of possible cognitive impairment. The protocol was approved by the Institutional Review Boards at Marquette University and Concordia University Wisconsin.

### **Experimental Protocol**

Subjects completed four sessions; one familiarization and three experimental. Sessions were separated by approximately one week and experimental sessions were randomized. During the familiarization session, subjects signed informed consent and were familiarized to the experimental procedures and the pressure pain device. Pain thresholds and pain ratings induced by the pressure pain device were determined before and after a 30 minute quiet rest period. Because performance of maximal voluntary contractions (MVCs) has been found to influence pain reports in young adults (Hoeger Bement et al., 2008; Koltyn et al., 2001) MVC force was determined during the

familiarization session following completion of the two pain tests. Specifically, a series of three MVCs were performed with the left elbow flexor muscles with a one-minute rest between contractions. Subjects were verbally encouraged to achieve maximal force. The highest value of the three maximal efforts was recorded and used for calculation of the submaximal target force to be used in the experimental sessions.

During the experimental sessions, pressure pain perception (i.e., pain threshold and pain ratings) was assessed before and after isometric contractions of the left elbow flexors that varied in intensity and duration. Each experimental session consisted of one of three exercise tasks: 1) three brief MVCs separated by a 1-minute rest; 2) 25% MVC sustained for 2 minutes; and 3) 25% MVC sustained until task failure. Measures of blood pressure, heart rate and rating of perceived exertion (RPE) were gathered every 30 seconds during the sustained exercise tasks. The state portion of the Spielberger State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983) was administered at the start of the session and immediately following each of the two pain tests. A 30 minute quiet rest period separated the completion of the first pain test and initiation of isometric exercise.

### **Measurement of Force During Isometric Contractions**

Subjects were seated upright in an adjustable chair with a padded nylon strap placed vertically over each shoulder to minimize shoulder activity and to stabilize the subject. The left shoulder was placed in slight abduction with the elbow flexed to 90 degrees and the forearm held parallel to the floor in a neutral position midway between pronation and supination. The elbow rested on a padded support and the forearm, wrist and hand were placed in a modified wrist-hand-thumb orthosis (Orthomerica, Newport

Beach, CA) which was held in place by Velcro straps. The orthosis was rigidly attached to a force transducer (JR-3 Force-Moment Sensor; JR-3 Inc., Woodland, CA) mounted on a custom-designed adjustable support which measured the forces exerted at the wrist in the vertical direction. A Power 1402 A-D converter and Spike2 software (Cambridge Electronics Design, Cambridge, UK) were used for on-line recording of the vertically directed forces. The force signal was digitized at 500 samples per second.

During performance of the submaximal exercise tasks, subjects were required to match the target force as displayed on a monitor. Subjects were verbally encouraged to sustain the force for as long as possible during the contraction to task failure. A subject was deemed to reach task failure when unable to maintain a force within 10% of the target value for three out of five consecutive seconds (Hoeger Bement et al., 2008). The same investigator (KJL) visually determined task failure for all subjects.

### **Pressure Pain Perception**

A custom-made pressure pain device used frequently in the assessment of EIH (Hoeger Bement et al., 2008; Hoeger Bement et al., 2009; Hoeger Bement et al., 2011) was used to measure pain perception (Forgione & Barber, 1971). An 8 x 1.5 mm Lucite edge (Romus Inc., Milwaukee, WI) was placed on the dorsum of the right index finger midway between the proximal and distal interphalangeal joints for two minutes. A 200-g mass was applied to a second-class lever such that a 10-N force (equivalent to a 1-kg mass) was applied to the Lucite edge. During the two minute test the subject was asked to press a timing device with their left hand when the pressure from the edge first changed to pain (i.e., pain threshold) and to rate the intensity of pain on a 0-10 numerical rating

scale (NRS) every 20-s throughout the test. The NRS anchors were 0 = “No pain”, 5 = “Moderate Pain”, and 10 = “Worst Pain” (McCaffery & Pasero, 1999).

### **Mean Arterial Pressure, Heart Rate and Rating of Perceived Exertion**

Heart rate and blood pressure were monitored continuously throughout the sustained isometric contractions using an automated beat-by-beat blood pressure monitor (Finapres 2300, Madison, WI). The cuff was placed around the middle finger of the right hand. Rating of perceived exertion (RPE) was determined every 30 s throughout the submaximal exercise tasks using a modified Borg CR10 scale (Borg, 1982). The RPE scale ranges from 1 to 10 with scale anchors of 1 = “Not strong at all” and 10 = “So strong I can’t go anymore”.

### **Statistical Analysis**

Data were analyzed using Statistical Package for the Social Sciences (SPSS, version 20, IBM, Chicago, IL) and were screened for outliers ( $> 3$  SD from the mean) and missing data points. Two outliers were identified for state anxiety, one in the MVC session and one in the 25% MVC held to task failure session. Outliers were altered to one unit greater than the next extreme score (Tabachnick & Fidell, 2001). Missing pain thresholds as a result of failure to push the timing device were imputed using the prior knowledge method (Tabachnick & Fidell, 2001). The midpoint between the time of a pain rating of zero and the first pain rating greater than zero was used as the imputed score.

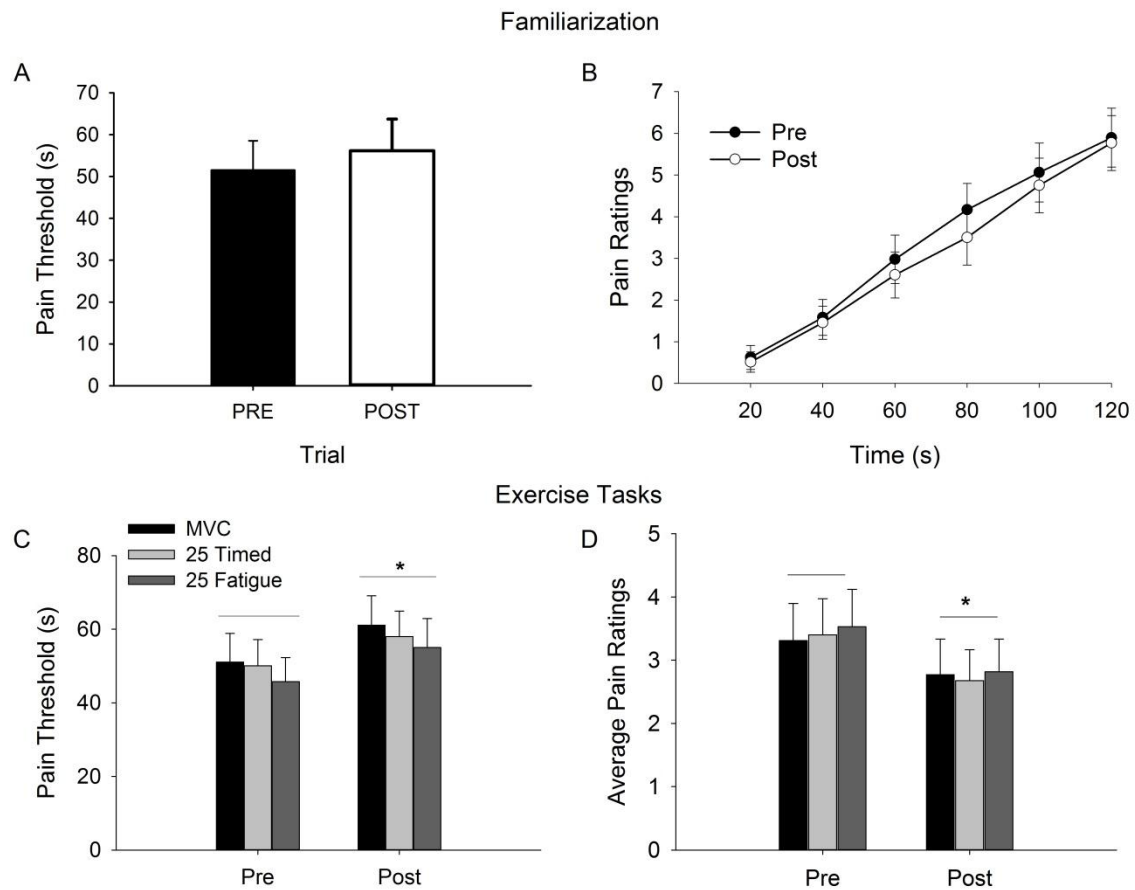
Mixed-design multivariate repeated-measures ANOVA with sex as a between subjects factor was used in the familiarization session to analyze the effect of repeated pain testing on pain threshold (trial) and pain rating (trial x time) and in the exercise sessions to analyze the effect of isometric contractions on pain threshold (task x trial), pain ratings (task x trial x time), and state anxiety (task x time). To assess for learning effects with the pressure pain device across sessions, the first pain test of the four sessions (familiarization and 3 exercise) were identified according to lab visit number. Multivariate repeated measures ANOVA was used to assess for differences in pain threshold (lab visit number) and pain ratings (lab visit number x time). For comparisons across time for each of the submaximal exercise tasks, RPE, heart rate and mean arterial pressure (MAP) were analyzed at quartiles (start of task, 25%, 50%, 75%, and end task) using mixed-design multivariate repeated measures ANOVA with sex as a between subjects factor. When a significant effect was found, simple contrasts and Bonferroni corrected *t*-tests for post hoc multiple comparisons were used to identify differences. Independent *t*-tests assessed for sex differences in time to task failure and strength. Bivariate correlations were run to assess for associations between dependent variables with hierarchical regression analyses assessing for predictive relations between sex (step one) and pre-exercise pain (step two) with relative change in pain (absolute change divided by pre-exercise) following exercise. Pain ratings for the six 20-second time points were averaged for each trial. Averages were used in post hoc testing and in the examination with dependent variables. A *P*-value of  $< 0.05$  was used for statistical significance. Data are reported as mean  $\pm$  SD within the text and mean  $\pm$  SEM in the figures.

## RESULTS

### Familiarization Session

Pain threshold and pain ratings did not change following 30 minutes of quiet rest ( $P = 0.31$  and  $P = 0.40$ , respectively; Figure 3.1 A and B). Additionally, no visit order effect was found for baseline pain threshold ( $P = 0.879$ ,  $\eta_p^2 = 0.03$ ) or pain ratings ( $P = 0.980$ ,  $\eta_p^2 = 0.009$ ) demonstrating no learning effect or effect of session number on baseline pain. Pain ratings increased across the 2-minute pain test (time:  $P < 0.001$ ,  $\eta_p^2 = 0.82$ ) with no difference between trials (trial x time,  $p = 0.12$ ). Women had higher pain ratings, averaged over the two minute pain test ( $4.2 \pm 2.5$  vs  $2.3 \pm 1.7$ ,  $P = 0.034$ ,  $\eta_p^2 = 0.19$ ) and a trend for lower pain threshold ( $41 \pm 32$  s vs  $67 \pm 32$  s,  $P = 0.06$ ,  $\eta_p^2 = 0.15$ ) than men. No trial and sex interaction was identified for either pain threshold ( $P = 0.52$ ) or pain ratings ( $P = 0.74$ ). Women did have a steeper rise in pain ratings than men (time x sex:  $P = 0.04$ ,  $\eta_p^2 = 0.45$ ).





**Figure 3.1 Pain Thresholds and Pain Ratings before and after quiet rest and isometric contractions.** Pain threshold (A) and pain ratings (B) before and after 30 minutes quiet rest. There was no difference in either pain threshold or pain ratings. Pain thresholds (C) and pain ratings (D) before (pre) and after (post) isometric exercise by task. Pain ratings were averaged across the six time points during the 2 minute pain test. Data are represented as mean  $\pm$  SEM. \*Trial:  $p \leq 0.001$ .

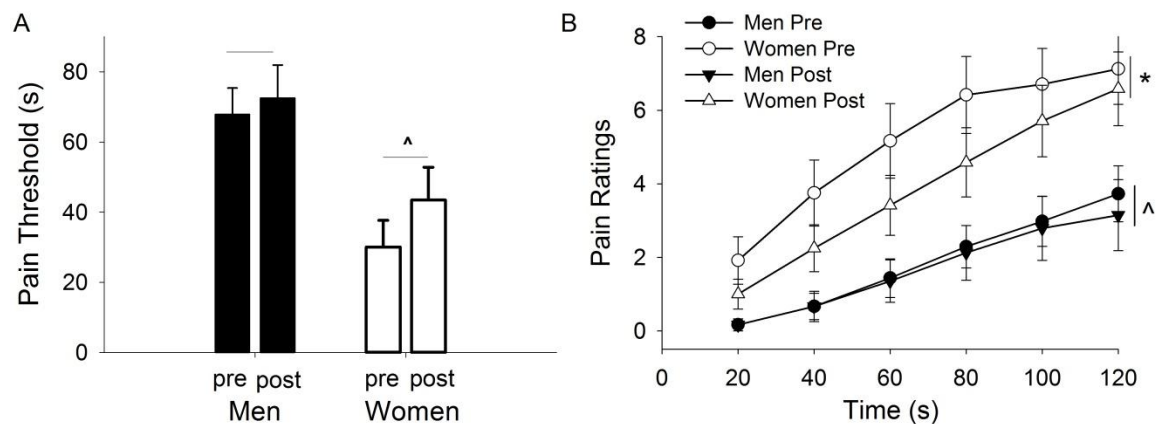
## Exercise Sessions

### Pain threshold and pain ratings

*Task differences.* Pain threshold increased  $\sim 18.5\%$  and pain ratings decreased  $\sim 19\%$  following exercise ( $P < 0.001$ ,  $\eta_p^2 = 0.44$  and  $P < 0.001$ ,  $\eta_p^2 = 0.48$ , respectively) and was similar across exercise tasks (task  $\times$  trial:  $P = 0.94$  and  $P = 0.55$ , respectively; Figure 3.1 C and D). Pre- and post-exercise pain reports and relative change in pain

reports were averaged for the three exercise sessions due to absence of task differences. Average scores were used in subsequent analyses.

*Sex differences.* Women reported lower pain thresholds ( $P = 0.01$ ,  $\eta_p^2 = 0.27$ ) and higher pain ratings ( $P = 0.004$ ,  $\eta_p^2 = 0.31$ ) than men. Women experienced greater reductions in pain ratings after exercise than men (trial x sex:  $P = 0.003$ ,  $\eta_p^2 = 0.34$ ) which was unaffected by task (trial x task x sex:  $P = 0.12$ ). Post hoc analyses revealed that women reported a reduction in pain ratings (23%,  $P = 0.001$ , Cohen's  $d = 0.45$ ) whereas men had no significant change (9%,  $P = 0.28$ , Cohen's  $d = 0.08$ ; Figure 3.2B). There was a trend for an interaction between trial and sex for pain threshold with women reporting greater increases in pain threshold than men, however this failed to reach statistical significance ( $P = 0.06$ ; Figure 3.2A).



**Figure 3.2 – Sex Differences.** Pooled pain thresholds (A) and pain ratings (B) before and after isometric contractions in older men and women. Women had lower pain thresholds and higher pain ratings than men. Women reported lower pain ratings after exercise, whereas men had no change. Data are represented as mean  $\pm$  SEM. \*Trial:  $p = 0.001$ . ^Sex:  $p \leq 0.01$ .

To assess for relations of pre-exercise pain sensitivity and change in pain when controlling for sex, correlation and hierarchical regression equations were completed. There was a negative correlation between pre-exercise pain threshold and relative change

in pain threshold ( $r = -0.59$ ,  $P = 0.001$ ). Hierarchical regression analysis revealed that sex explained 29% of the variance in relative change in pain threshold  $F(1, 22) = 10.49$ ,  $P = 0.004$ . The addition of pre-exercise pain threshold to the equation failed to produce a significant change in  $F$  ( $P = 0.07$ ). While the overall regression model remained significant  $F(2, 21) = 7.66$ ,  $P = 0.003$ , adjusted  $R^2 = 0.37$ ; neither sex ( $P = 0.126$ ) nor pre-exercise pain threshold ( $P = 0.072$ ) were found to provide a unique contribution to the model indicating a high degree of interdependence between these two variables. No predictive association of sex ( $P = 0.213$ ) or sex and pre-exercise pain ratings ( $P = 0.307$ ) with relative change in pain ratings was identified.

### **Strength and Time to Task Failure**

Men were stronger than women ( $P < 0.001$ , Cohen's  $d = 2.8$ ) and MVC force was negatively associated with time to task failure ( $r = -0.419$ ,  $P = 0.042$ ) such that stronger individuals reached task failure more quickly. Time to task failure was similar between men and women for the submaximal contraction ( $610 \pm 176$  s vs  $800 \pm 371$  s respectively,  $P = 0.13$ , Cohen's  $d = 0.66$ ). Strength ( $r = -0.636$ ,  $P = 0.001$ ), but not time to task failure ( $r = 0.392$ ,  $P = 0.06$ ), was associated with the relative change in pain threshold such that stronger individuals experienced smaller threshold increases. Neither strength ( $P = 0.35$ ) nor time to task failure ( $P = .72$ ) was related to relative change in pain rating.

## Anxiety

A time and task interaction ( $P = .04$ ,  $\eta_p^2 = 0.39$ ) and main effect for task ( $P = 0.01$ ,  $\eta_p^2 = 0.35$ ) were found for anxiety. Simple contrasts showed both effects involved differences between the MVC and 25% MVC to task failure sessions, with the interaction occurring between the second (following the pre-exercise pain test) and third (post-exercise) STAI administration. Post hoc comparisons indicated subjects reported a non-significant decrease in state anxiety after exercise in the MVC session ( $P = 0.62$ ) and a small increase in anxiety following exercise to task failure ( $23.4 \pm 5.2$  vs  $25.6 \pm 6.1$ ,  $P = 0.01$ , Cohen's  $d = 0.39$ ). Average state anxiety across the MVC session was slightly less than during the 25% MVC to task failure ( $23.6 \pm 5.1$  vs  $24.8 \pm 5.9$ ,  $P = 0.003$ , Cohen's  $d = 0.21$ ). Anxiety before and after the first pain assessment in each session was not different ( $P > 0.05$ ), indicating that the pain test itself did not induce changes in state anxiety. Additionally, no main effect for sex ( $P = 0.17$ ) was found nor was there a sex and time interaction ( $P = 0.49$ ).

## MAP, Heart Rate and RPE

MAP, heart rate and RPE were analyzed at quartiles (start of contraction, 25%, 50%, 75% and end contraction) for each of the submaximal tasks. All three increased over time during the 25% MVC x 2 min task ( $P < 0.001$ ) and 25% MVC to task failure ( $P < 0.001$ ) sessions. There was no difference between the men and women for either MAP or heart rate at onset of exercise, and no main effect of sex or interaction between sex and time for any of the three variables ( $P > 0.05$ ). No significant correlations were

identified between change in MAP, heart rate or RPE with change in pain reports in either submaximal session.

## **DISCUSSION**

We examined EIH following isometric exercise of elbow flexor muscles at various durations and intensities in healthy older adults. The main findings of the study were: 1) Older adults experienced EIH, which was similar across all three tasks (3 MVCs, 25% MVC held for 2 min, and 25% MVC held to task failure); and 2) Both older men and women experienced increases in pain threshold, but only older women experienced reductions in pain ratings. To assess whether reductions in pain were a manifestation of repeated pain testing (Padawer & Levine, 1992), we examined pain sensitivity before and after 30 minutes of quiet rest. There was no change in pain reports, thus the pain testing itself did not induce the reduction of pain following isometric exercise. Furthermore, the absence of a visit order effect when comparing baseline pain reports indicates that pain sensitivity was not affected by exposure to the pain device.

Several studies have shown pain relief following training programs of aerobic or dynamic resistive exercise in older adults with a variety of chronic pain conditions, including lower back pain, osteoarthritis, myofascial pain and osteoporosis (reviewed by Koltyn, 2002b). The present study adds to the literature by showing an acute change in pain sensitivity following a single session of isometric exercise in healthy older adults. While previous studies have shown a reduction in pain following isometric contractions, they have examined either young (Hoeger Bement et al., 2008; Hoeger Bement et al., 2009; Koltyn et al., 2001; Kosek & Ekholm, 1995; Umeda et al., 2010) or middle-aged

(Ge et al., 2012; Kadetoff & Kosek, 2007; Kosek et al., 1996; Staud et al., 2005) healthy adults. To our knowledge, this is the first study to examine this response in adults over 60 years of age.

In young adults, EIH is dependent on the type of isometric contraction. Both high and low intensity isometric contractions decrease pain, however the greatest decrease in pain occurs following contractions of lower intensity (25% - 50% MVC) held to task failure (Hoeger Bement et al., 2008; Naugle et al., 2012). Previously we hypothesized that the task specificity in young adults was due to activation of high-threshold motor units (Hoeger Bement et al., 2008). Specifically, pain decreased with maximal intensity contractions and submaximal contraction held to task failure, tasks when high-threshold motor units are activated. No reduction in pain was seen with submaximal contractions held for short duration (22% - 37% of time to task failure) when few high-threshold motor units are recruited. The lack of task specificity in older adults may be due to the age-related atrophy of Type II fibers. However, a reduction in pain following the 2 minute exercise task suggests that fiber type recruitment does not fully explain EIH following isometric contractions. There are likely several mechanisms responsible for EIH (Cook & Koltyn, 2000; Koltyn, 2000), and high-threshold motor unit recruitment may act as an additive factor in young, but not older adults.

Few studies have examined sex differences in EIH following isometric exercise. Our data indicates that only older women reported a reduction in pain ratings following exercise and a trend for women to have greater increases in pain threshold was also found. These findings are similar to those of Koltyn et al (2001) in young adults following an isometric handgrip contraction at 40%-50% MVC where young women but

not men experienced increased pain thresholds and decreased pain ratings. In contrast Umeda et al (2010) found EIH magnitude to be similar between young men and women. Women however reported greater pre-exercise pain sensitivity than men both in this study and by Koltyn et al (2001), whereas no sex difference in pre-exercise pain sensitivity was identified by Umeda and colleagues (2010). Thus, higher pre-exercise pain sensitivity may be associated with greater EIH. To assess this possibility, we conducted hierarchical regression analyses controlling for sex. The failure of pre-exercise pain to make a unique contribution to the prediction of relative change in pain threshold when controlling for sex, along with the lack of an association between pre-exercise and relative change in pain ratings, indicates that pre-exercise pain sensitivity alone does not explain the sex difference in EIH magnitude.

Alterations in anxiety and interactions between the cardiovascular and pain regulatory systems have the potential to impact the EIH response. Higher levels of state or trait anxiety (Okawa et al., 2005) for example, have been shown to be associated with heightened pain sensitivity, and it has been suggested that there is an interaction between the cardiovascular and pain regulatory systems (Koltyn & Umeda, 2006; Ring et al., 2008). In order to address the possible influence of anxiety and the cardiovascular exercise response on our findings, we examined state anxiety before and after exercise as well as MAP, heart rate and RPE during exercise. Our findings showed average state anxiety to be somewhat less during the MVC session than the 25% MVC to task failure in part due to a small increase in state anxiety following the fatiguing submaximal contraction. These differences were slight, separated by only 1-2 units with small effect sizes (Cohen's  $d$  0.22 and 0.39, respectively), and do not appear to have influenced the

EIH response as reductions in pain were similar across all three tasks. No associations were found between change in pain reports with change in heart rate, MAP or RPE; a finding consistent with prior reports in young adults (Hoeger Bement et al., 2008; Umeda et al., 2010). Despite having comparable levels of state anxiety and similar cardiovascular responses to exercise, older women experienced greater reductions in pain ratings following exercise than older men. Collectively, these results indicate that neither state anxiety nor cardiovascular reactivity mediate the EIH response.

While the underlying mechanisms for EIH are not clear, the finding of a reduction in pain at a site distant to the exercising muscles suggests central or systemic mechanisms are involved. One such mechanism is activation of endogenous inhibitory pathways via conditioned pain modulation (CPM) (Cook & Koltyn, 2000). CPM involves attenuation of pain sensitivity in one body area in the presence of a conditioning painful stimulus elsewhere (i.e., “pain inhibits pain”). Older adults have been found to have reduced efficiency of the CPM response (Lariviere et al., 2007; Riley et al., 2010; Washington et al., 2000). If CPM is responsible for EIH, older adults would therefore be expected to experience a lower magnitude of EIH than young adults. An examination of relative change in pain in young adults following a low intensity isometric contraction held to task failure, exercise likely to be perceived as painful and thus act as a conditioning stimulus, revealed the young adults reported a 48% increase in pain threshold (Cohen’s  $d = 0.60$ ) and 24% decrease in pain ratings (Cohen’s  $d = 0.50$ ) (Hoeger Bement et al., 2008). In contrast our older subjects reported a 20% increase in pain threshold (Cohen’s  $d = 0.26$ ) and 20% decrease in pain ratings (Cohen’s  $d = 0.26$ ) using the same exercise protocol and pain induction method. Although speculative at this time as muscle pain



induced *during* exercise was not assessed in either study, it is plausible that age-related changes in CPM may account for these differences in EIH effect size. Future studies are clearly needed to examine the possible role of CPM in EIH and its relation to changes in the exercise response with aging.

The finding that older adults can obtain equivalent pain relief from several different isometric contraction dosages has important implications for exercise prescription in the management of pain in adults, especially for older women. Practitioners and their older clients may have more flexibility in choice of isometric exercise parameters and greater ability to individualize and vary a home exercise program to best meet the client's current needs, abilities and preferences. Young adults on the other hand may require greater specificity of exercise prescription in order to achieve maximal clinically important reductions in acute pain. Reductions in pain ratings of 15% are considered to be minimally clinically significant (i.e., the smallest magnitude of change correlating with patient perception of an overall improvement in pain) in patients with chronic musculoskeletal pain (Salaffi et al., 2004). Older adults in this study reported reductions in pain in both pain ratings and pain thresholds of ~19%, and greater reductions have been found in young adults with the same exercise protocol (Hoeger Bement et al., 2008). Thus isometric exercise has the potential to induce clinically relevant pain relief for adults of all ages. Importantly, because men did not demonstrate a change in pain ratings after exercise, these data suggest that older men may have less pain relief than older women following isometric exercise.

The present study is the first to examine the dose-response relationship of isometric exercise and pain reduction in older men and women. It does have some

limitations. We examined the EIH response in healthy older adults without pain. As musculoskeletal pain complaints increase with age, our subjects may not be representative of older adults with persistent ongoing or chronic pain conditions. Future studies are needed to determine if the acute pain response following exercise in adults over age 60 is altered by the presence of such a condition. We also did not examine the duration of the hypoalgesic response after exercise cessation. It is not known if EIH duration after exercise is similar for older adults as for younger adults. Finally, differences in strength cannot be ruled out as having an impact on pain relief following isometric exercise. It is well established that men are usually stronger than women (Hunter & Enoka, 2001) and these strength differences persist with aging (Hunter et al., 2004; Peiffer et al., 2010). Despite exercising at different absolute forces, our protocols were designed so that men and women reached the same physiological end-point with 25% MVC to task failure contractions; hence the reduction in MVC was similar. Additionally, while both men and women experienced increases in pain thresholds and a relation between strength and relative change in pain threshold was found, no relation was found with change in pain ratings despite a robust sex difference in magnitude of EIH. Future studies are needed to clarify the potential influence of strength on EIH.

## **Conclusion**

In contrast to young adults who receive the greatest pain relief with isometric contractions of low-moderate intensity held for long duration (Hoeger Bement et al., 2008; Naugle et al., 2012), we have shown that isometric contractions of varying intensities and durations induce similar reductions in pain in healthy older adults.

Although both older men and women experienced increases in pain threshold, only older women experienced decreases in pain ratings. These age and sex differences demonstrate that older healthy men and women have different exercise requirements than young adults for the reduction of pain.

## CHAPTER FOUR

### RELATION BETWEEN CONDITIONED PAIN MODULATION AND EXERCISE-INDUCED HYPOALGESIA IN YOUNG AND OLDER ADULTS

This is a non-final version of an article published in final form in *Medicine & Science in Sports & Exercise*. <http://journals.lww.com/acsm-msse/pages/default.aspx>

Lemley, K. J., Hunter, S. K., & Hoeger Bement, M. K. (in press). Conditioned Pain Modulation Predicts Exercise-Induced Hypoalgesia in Healthy Adults. *Med Sci Sports Exerc.*

## INTRODUCTION

Pain is the primary reason people seek healthcare and more than 100 million Americans suffer from chronic pain (Institute of Medicine: Committee on Advancing Pain Research, 2011). Additionally, the frequency of pain reports increases with age, with up to 80% of community dwelling older adults experiencing some type of pain (Mobily et al., 1994). The effectiveness of exercise as a non-pharmacological means of pain management is well established (Hoeger Bement, 2009). Most types of exercise have been found to reduce pain sensitivity; a phenomenon known as exercise-induced hypoalgesia (EIH) (Hoeger Bement, 2009).

Previous research has demonstrated a reduction in pain at both the exercising limb (Koltyn et al., 2001; Kosek & Lundberg, 2003; Umeda et al., 2010) and distant sites, such as the non-exercising limb (Hoeger Bement et al., 2008; Koltyn & Umeda, 2007; Kosek & Lundberg, 2003; Lemley et al., 2014). Attenuation of pain outside of the exercising muscles suggests central or systemic mechanisms are involved in EIH. Both opioid and non-opioid mechanisms have been implicated (Cook & Koltyn, 2000; Hoeger Bement,

2009; Koltyn, 2000) and include the following: increase in beta endorphins, altered psychological states, interaction between the cardiovascular and pain processing systems, recruitment of high threshold motor units, and activation of the primary motor cortex (Hoeger Bement, 2009; Hoeger Bement et al., 2008; Koltyn & Umeda, 2006; Okawa et al., 2005).

Conditioned pain modulation (CPM) is another potential factor that could influence EIH, especially given that exercise is sometimes perceived to be painful. With CPM, pain from a noxious stimulus (conditioning stimulus) results in the inhibition of pain during the application of a second noxious stimulus (test stimulus) applied elsewhere (i.e., “pain inhibits pain”). The difference in pain experienced with the test stimulus applied with and without the conditioning stimulus is a measure of CPM. The noxious conditioning stimulus activates descending inhibitory pathways resulting in inhibition of extra-segmental spinal and trigeminal wide dynamic range (WDR) neurons (Le Bars & Willer, 2009) thereby decreasing pain associated with the test stimulus. It has been postulated that pain experienced during exercise may act as a conditioning stimulus resulting in EIH (Cook & Koltyn, 2000).

CPM protocols are used to indirectly measure the efficiency of descending inhibitory pathways (van Wijk & Veldhuijzen, 2010). Despite the frequent use of CPM protocols to assess endogenous pain modulation, intervention studies using CPM are limited. Two such studies have reported an association of CPM with pain reduction using transcutaneous electrical nerve stimulation in individuals with fibromyalgia (Dailey et al., 2013) and pulsed radiofrequency current in individuals with cluster headaches (Chua et al., 2011). Specific to exercise, there are likely multiple mechanisms responsible for EIH

(Cook & Koltyn, 2000; Hoeger Bement, 2009; Koltyn, 2000), and CPM could provide an additive effect as the exercise becomes painful. For example, pain is seen to increase steadily during prolonged submaximal isometric contractions (Frey Law et al., 2010). Because greater CPM is produced by a stronger conditioning stimulus (Willer et al., 1989), CPM may explain why in young adults the greatest pain relief with isometric exercise occurred following contractions held for long duration compared with shorter durations (Hoeger Bement et al., 2008; Naugle et al., 2012). Few EIH studies have assessed muscle pain during exercise, and to the best of our knowledge no study has directly examined the predictive relation of CPM to EIH in young or older adults.

Older adults typically have an attenuated CPM response compared with young adults when using a thermal (Edwards, Fillingim, et al., 2003; Riley et al., 2010; Washington et al., 2000) or electrical (Washington et al., 2000) test stimulus. Age-related differences in pain perception (independent of CPM) appear to be dependent upon the noxious stimulus utilized (Edwards & Fillingim, 2001; Lautenbacher, 2012). Whether the attenuation in CPM that occurs with aging is modality specific and occurs with a pressure test stimulus is not known. A generalized reduction in CPM in older adults may help to explain the absence of task differences in EIH following isometric contractions of varying durations (Lemley et al., 2014).

The purpose of this study was to determine if there are age-related differences in CPM using a noxious pressure test stimulus and if there was a predictive relation between CPM and EIH using an exercise protocol that is typically perceived as painful. We hypothesized that 1) older adults would exhibit an attenuated CPM response compared

with young adults using a noxious pressure test stimulus and 2) CPM would predict EIH so that those with less CPM would have less EIH.

## **MATERIALS AND METHODS**

### **Participants**

Fifty men and women were recruited for this study. Exclusion criteria included presence of acute or chronic pain, current use of analgesics or psychotropic medications, a score of less than 25/30 on the Mini Mental Status Examination (MMSE), any risk factors that would preclude participation in the exercise session or immersion in an ice water bath, and inability to tolerate the ice water bath. Eleven participants were unable to complete testing for the following reasons: history of cardiovascular disease ( $n = 5$ ), musculoskeletal injury ( $n = 1$ ), symptoms associated with a neurological condition ( $n = 2$ ), and inability to tolerate the ice water bath (3). Thirty-nine participants [10 young men ( $22.6 \pm 3.8$  years), 10 young women ( $21.3 \pm 2.9$  years), 10 older men ( $71.4 \pm 4.7$  years) and 9 older women ( $72.7 \pm 4.6$  years)] completed the protocol and were included in the final analysis.

### **Experimental Protocol**

Participants completed three sessions: one familiarization and two experimental. All sessions were separated by approximately one week and experimental sessions were counterbalanced across sex and age. The protocol was approved by the Institutional Review Boards at Marquette University and Concordia University Wisconsin.

Pressure pain perception was measured in all three sessions with a custom-made pressure pain device (Romus Inc., Milwaukee, WI) used previously in the assessment of EIH in young and older adults (Hoeger Bement et al., 2008; Hoeger Bement et al., 2009; Hoeger Bement et al., 2011; Lemley et al., 2014). This device consisted of a weighted Lucite edge (8 x 1.5 mm) equivalent to a 1.5 kg mass placed on the dorsum of the right index finger midway between the proximal and distal interphalangeal joints for one minute. During the one minute test the subject was asked to say the word “pain” when the pressure changed to pain (i.e., pain threshold measured in seconds) and to rate the intensity of pain every 10 s using the 0 - 10 NRS (McCaffery & Pasero, 1999). The average of the six time points during the 1 min pressure pain test was used to identify potential relations between variables and group differences. Participants were informed they could stop at any time if they reached pain tolerance.

During the familiarization session, participants signed informed consent and were familiarized to the experimental procedures (e.g., pressure pain device and ice water bath). Pressure pain perception was measured twice with a 30 min quiet rest between the two tests. Previous pilot data in our laboratory indicated that 30 minutes was necessary between the two pressure pain tests because 15 minutes was not adequate recovery for the pilot subjects (Hoeger Bement et al., 2008). Participants also completed several questionnaires including the Spielberger State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983), Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995), Fear of Pain Questionnaire (McNeil & Vowles, 2004), Modified Pain Attitude Questionnaire – Revised (Yong et al., 2003), and a self-report measure of Physical Activity (Kriska & Bennett, 1992). The state portion of the STAI was administered three times, prior to the

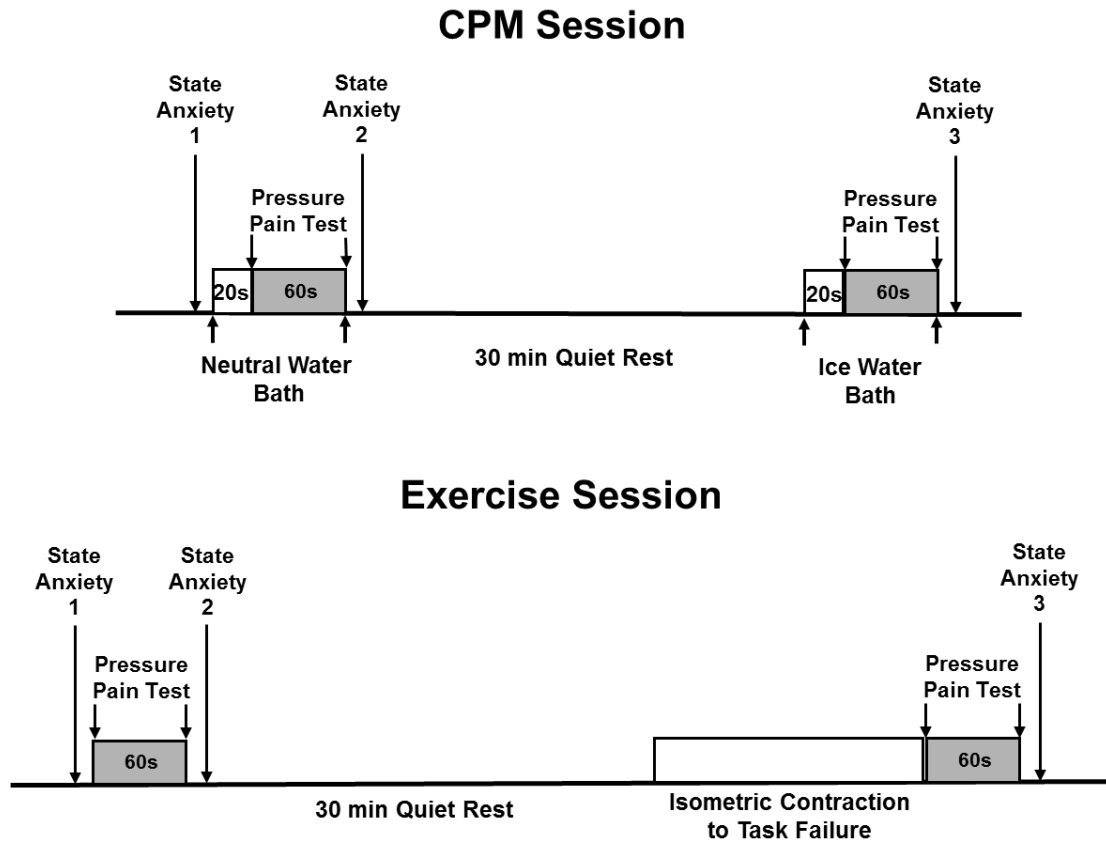


initial pain test and again immediately after each of the two pressure pain tests. Because performance of maximal voluntary contractions (MVCs) has been found to influence pain reports in young (Hoeger Bement et al., 2008; Koltyn et al., 2001) and older (Lemley et al., 2014) adults, determination of left elbow flexor MVC force was performed during the familiarization session following completion of the two pressure pain tests. A series of three MVC's were performed with a one-minute rest between contractions. Participants were verbally encouraged to achieve maximal force on each attempt. The highest value of the three maximal efforts was used for calculation of the submaximal target force in the exercise session.

## **Experimental Sessions**

### **EIH Session**

Pressure pain perception (i.e., pain threshold and pain ratings) was assessed before and after painful isometric contraction of the left elbow flexor muscles. Pressure pain perception was assessed within 60 s following the termination of the isometric contraction. A 30 minute quiet rest period separated the completion of the first pain test and initiation of isometric exercise. The state portion of the STAI was administered prior to the initial pain test and again immediately after each of the two pressure pain tests (Figure 4.1).



**Figure 4.1 – Study Design.** Sessions were counterbalanced across age and sex and were separated by approximately 1 week. Note that figure is not time to scale.

The isometric contraction was submaximal (25% MVC) and sustained until task failure. Measurement of force was performed using established procedures (Hoeger Bement et al., 2008; Lemley et al., 2014). Participants were seated upright in an adjustable chair with a padded nylon strap placed vertically over each shoulder to stabilize the subject and minimize shoulder-region substitution. The left shoulder was placed in a position of slight abduction with the elbow flexed to 90 degrees and resting on a padded support. The forearm was parallel to the floor in a neutral position midway between pronation and supination. The forearm, wrist and hand were placed in a modified wrist-hand-thumb orthosis (Orthomerica, Newport Beach, CA) which was held

in place by Velcro straps and rigidly attached to a force transducer (JR-3 Force-Moment Sensor; JR-3 Inc., Woodland, CA) mounted on a custom-designed adjustable support. The transducer measured the vertically directed force at the level of the wrist which was recorded on-line using a Power 1402 A-D converter and Spike2 software (Cambridge Electronics Design, Cambridge, UK). The force signal was digitized at 500 samples per second.

During performance of the submaximal exercise task participants were required to match the target force as displayed on a monitor. Participants were asked to rate the intensity of pain in the exercising elbow flexor muscles every 30 s throughout the duration of the exercise task. Participants were verbally encouraged to sustain the force for as long as possible. Task failure was determined using a computer based software program that signaled when force output reached pre-established criteria of a decline of greater than 10% of the target value for three out of five consecutive seconds (Hoeger Bement et al., 2008; Lemley et al., 2014).

### **CPM Session**

Pressure pain perception at the finger (test stimulus) was measured initially while the foot was immersed in a neutral ( $25^{\circ}\text{C} \pm 1$ ) water bath and then 30 min later while the foot was immersed in a noxious ice ( $2^{\circ}\text{C} \pm 1$ ) water bath (conditioning stimulus) (Dailey et al., 2013). The neutral water bath was used to control for potential distraction associated with water immersion. The difference in pressure pain ratings between the neutral bath and noxious water bath was used as a measure of CPM. Twenty seconds after foot immersion participants reported pain intensity of the water bath using an 11

point (0-10) numerical rating scale (NRS) and the 1 min pressure pain test was initiated (total duration of water bath immersion was ~80 s). The NRS anchors were 0 = No pain, 5 = Moderate Pain, and 10 = Worst Pain (McCaffery & Pasero, 1999). At completion of the pressure pain test and immediately prior to removing the foot from the water, participants again reported pain intensity for the water bath. The state portion of the STAI was administered prior to the initial pain test and again immediately after each of the two pressure pain tests (Figure 4.1).

### **Psychosocial Questionnaires**

#### *Spielberger State-Trait Anxiety Inventory (STAI)*

The STAI (Spielberger et al., 1983) is an assessment of transient (state) and enduring (trait) levels of anxiety. Each subscale consists of 20 questions. Higher values are associated with greater levels of anxiety.

#### *Pain Catastrophizing Scale (PCS)*

The PCS (Sullivan et al., 1995) is a 13 statement questionnaire that measures the degree to which an individual experiences exaggerated negative pain-related thoughts when anticipating or experiencing pain. Higher PCS total scores are indicative of greater catastrophizing. Participants were instructed to respond to the statements relative to their thoughts and feelings in general when in pain (i.e., dispositional) and were given the same set of instructions with each administration.

### *Fear of Pain Questionnaire – Nine (FPQ-9)*

This nine question version of the FPQ has a scoring range of 9 – 45. Higher scores indicate greater fear of pain associated with specific situations (McNeil & Vowles, 2004).

### *Modified Pain Attitude Questionnaire – Revised (PAQ-R)*

The modified version of the PAQ-R is a 23 item scale used for the assessment of stoicism and cautiousness about pain with each dimension further subdivided into two subcategories (Yong et al., 2003). Scale items are rated from 1 (strongly disagree) to 5 (strongly agree). Higher scores are associated with greater stoicism or cautiousness regarding pain.

### **Physical Activity**

Participants self-reported physical activities in which they regularly participated (i.e., at least 10 times) over the past 12 months with a modified physical activity questionnaire (Kriska & Bennett, 1992) and reported as kilocalorie expenditure of energy per week.

### **Statistical Analysis**

Data was analyzed using Statistical Package for the Social Sciences (SPSS, version 20, IBM, Chicago, IL) and was screened for outliers ( $> 3$  SD from the mean) and missing data points. Outliers were altered to one unit greater than the next extreme score

(Tabachnick & Fidell, 2001). Missing pain ratings due to participants asking to stop the pressure pain test prior to the 60 second duration were imputed with a rating of 10.

There were some missing data points for pain threshold, with the greatest number of missing values in the CPM session. Failure to report pain threshold occurred 1.5 times more frequently during the ice water bath than the neutral water bath (15 vs. 9). More than one-half of the older adults (10/19), including 7 of 9 older women, did not say “pain” during the ice water bath, whereas one-quarter of the young adults (5/20) failed to do so. Due to the number of missing data points, pain threshold was excluded from further analysis.

Separate mixed-design multivariate repeated-measures ANOVAs with age group and sex as between subject factors were used to assess for change in pressure pain ratings for each session [trial (pre vs. post) x time (pressure pain rating every 10 s during the 60 s pressure pain test)]. The two levels of trial varied by session: pain ratings during the familiarization were assessed before and after quiet rest; CPM pain ratings were assessed with foot immersion during neutral water and ice water; and EIH pain ratings were assessed before and after exercise.

To determine if anxiety was altered with the pain testing or intervention procedures, change in state anxiety was assessed for each session with separate mixed-design repeated measures ANOVAs (time: baseline, post pressure pain test 1, post pressure pain test 2). Age group and sex were between subject factors. When a significant effect was found, simple contrasts followed by Bonferroni corrected t-tests for post hoc multiple comparisons were used to identify differences.

Multivariate repeated measures ANOVA was used to assess for learning or order effects with the pressure pain device across sessions. The first pain assessment of each session (baseline measures) were compared for differences in pain ratings. Factors were session number (1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>) and time (pain ratings every 10 s during the 60s pressure pain test). Paired t-test assessed for differences in baseline state anxiety between the two experimental sessions. Independent t-tests assessed for age and sex differences in dependent variables.

Pain ratings were averaged over the 60 s pressure pain test to determine change in pain with exercise (EIH) and ice water immersion (CPM). Change in pain ratings due to exercise or CPM was calculated by subtracting the average pain rating of the second pressure pain test from the average pain rating of the first pressure pain test (i.e., pre-exercise average – post-exercise average or neutral water average – ice water average, respectively). To avoid the possible confounding effect of baseline pain, associations between variables were assessed using partial Pearson correlations with session baseline pain as a covariate. Session baseline pain is defined as the average pain rating of the initial pressure pain test for that session. Hierarchical regression analysis assessed for a predictive relation between CPM and EIH. Because baseline pain and age have been found to influence EIH (Hoeger Bement et al., 2011; Lemley et al., 2014) these potential confounders were controlled for in our regression analysis. Age group and pre-exercise average pressure pain ratings (i.e., EIH baseline pain) were entered (step one) prior to the inclusion of CPM (step two) in the prediction of EIH. A p-value of < 0.05 was used for statistical significance. Data are reported as mean  $\pm$  SD within the text and mean  $\pm$  SEM in the figures.

## RESULTS

Five outliers were identified and altered: one pain catastrophizing score, one baseline state anxiety score in each of the three sessions (total of 3), and one physical activity score. No pain scores were  $> 3$  SD from the mean. Six participants (four older women, one older man, and one young woman) asked to stop at least once over the six pressure pain trials (two trials per session). Thus, a total of 28 missing pain ratings (2%) for the three sessions were imputed with a rating of 10.

### Familiarization Session

A summary of participant characteristics (e.g., pain catastrophizing, physical activity) is found in Table 4.1. Pain ratings during the 1-minute pressure pain test were similar before and after the 30 minute quiet interval (trial:  $P > 0.05$ ). Additionally, there was no effect of session number on baseline pain ( $P > 0.05$ ). Pain ratings increased during the 1-minute pain test (time:  $P < 0.001$ ,  $\eta_p^2 = 0.85$ ) with no difference between trials (trial x time:  $P > 0.05$ ). No age-related main or interaction effects were identified. Women reported higher pain ratings ( $P = 0.008$ ,  $\eta_p^2 = 0.19$ ) and a greater increase in pressure pain ratings than men during the 1 min pressure pain test (time x sex:  $P = 0.017$ ,  $\eta_p^2 = 0.35$ ). State anxiety was higher prior to the first pain test ( $27.6 \pm 6.9$ ) than at the two post-pain test administrations ( $25.6 \pm 5.3$  and  $24.8 \pm 4.6$ , respectively), with no difference between the latter two (time:  $P = 0.01$ ,  $\eta_p^2 = 0.24$ ). There were no main or interaction effects for either age or sex in state anxiety.



**Table 4.1 Participant Characteristics**

	All Participants	Young Adults	Older Adults	Women	Men
Pain Catastrophizing	10.8 ± 8.0	12.3 ± 8.3	9.2 ± 7.5	8.9 ± 7.3	12.6 ± 8.3
Fear of Pain	12.8 ± 5.2	12.7 ± 4.7	13.1 ± 5.7	13.4 ± 6.0	12.4 ± 4.3
Pain Attitude – Stoicism Reticence	3.4 ± 0.5	3.3 ± 0.6	3.4 ± 0.4	3.2 ± 0.5	3.5 ± 0.6
Pain Attitude – Stoicism Superiority	3.3 ± 0.7	3.3 ± 0.8	3.4 ± 0.5	3.3 ± 0.7	3.3 ± 0.7
Pain Attitude – Cautiousness Self-Doubt	2.7 ± 0.8	2.8 ± 0.8	2.6 ± 0.8	2.6 ± 0.8	2.8 ± 0.8
Pain Attitude – Cautiousness Reluctance	3.6 ± 0.6	3.6 ± 0.7	3.6 ± 0.5	3.5 ± 0.6	3.6 ± 0.7
Trait Anxiety	30.8 ± 7.9	33.6 ± 8.0	28.0 ± 6.8	31.6 ± 7.4	30.2 ± 8.4
Physical Activity	42.8 ± 32.5	49.5 ± 34.9	35.8 ± 28.9	39.6 ± 40.9	45.8 ± 22.3
Exercise Session					
State Anxiety Time 1	26.7 ± 7.6	28.1 ± 7.7	25.2 ± 7.3	26.2 ± 7.4	27.1 ± 7.9
Time 2	26.7 ± 7.3	28.6 ± 7.6	24.7 ± 6.6	26.2 ± 7.1	27.2 ± 7.7
Time 3	29.2 ± 7.9	32.6 ± 8.2	25.7 ± 5.8	29.5 ± 8.1	29.0 ± 7.8
Peak Arm Pain	6.97 ± 3.25	6.63 ± 3.20	7.34 ± 3.35	7.00 ± 3.32	6.95 ± 3.27
Pre-Exercise Average PPR	3.42 ± 2.41	2.88 ± 2.09	4.00 ± 2.64	4.57 ± 2.68	2.33 ± 1.50
Post-Exercise Average PPR	2.94 ± 2.32	2.15 ± 1.95	3.77 ± 2.42	4.06 ± 2.35	1.87 ± 1.74
EIH	0.48 ± 1.36	0.73 ± 1.38	0.23 ± 1.33	0.51 ± 1.43	0.46 ± 1.34
CPM Session					
State Anxiety Time 1	27.6 ± 7.2	29.7 ± 7.5	25.4 ± 6.3	26.5 ± 6.5	28.6 ± 7.8
Time 2	28.1 ± 7.8	30.9 ± 7.4	25.2 ± 7.2	27.1 ± 7.4	29.0 ± 8.2
Time 3	27.6 ± 7.0	29.8 ± 7.0	25.4 ± 6.3	26.6 ± 6.0	28.6 ± 7.8
Foot Pain Ice Water (20s)	4.23 ± 2.50	4.45 ± 2.01	4.00 ± 2.96	4.63 ± 2.61	3.85 ± 2.39
Foot Pain Ice Water (80s)	5.69 ± 2.59	5.85 ± 2.08	5.53 ± 3.08	6.47 ± 2.20	4.95 ± 2.76
Neutral Water Average PPR	3.58 ± 2.24	3.15 ± 1.62	4.03 ± 2.73	4.68 ± 2.25	2.54 ± 1.72
Ice Water Average PPR	2.67 ± 2.52	1.52 ± 1.40	3.88 ± 2.89	3.61 ± 2.67	1.77 ± 2.05
CPM	0.91 ± 1.40	1.63 ± 0.91	0.15 ± 1.45	1.06 ± 1.54	0.77 ± 1.28

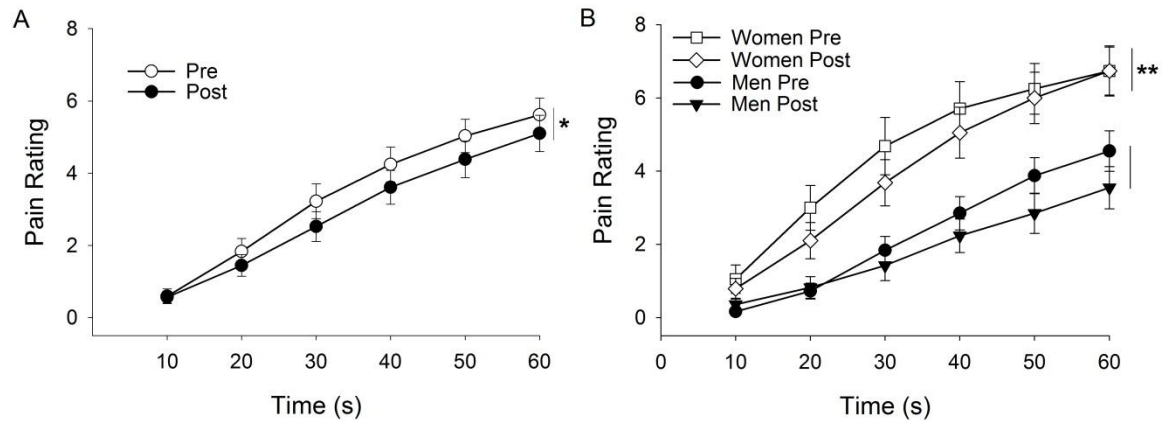
Note: PPR = Pressure Pain Rating (Finger), EIH = Exercise-Induced Hypoalgesia, CPM = Conditioned Pain Modulation, Time 1 = Before Pressure Pain Testing, Time 2 = After Pressure Pain Test 1, Time 3 = After Pressure Pain Test 2

**EIH Session: Pain Ratings**

Average pressure pain ratings decreased approximately 14% following exercise ( $P = 0.03$ ,  $\eta_p^2 = 0.12$ ; Table 4.1 and Figure 4.2A). There was a significant main effect for age ( $P = 0.02$ ,  $\eta_p^2 = 0.15$ ); older adults reported higher pressure pain ratings than young adults. No significant interaction effects for age were identified; young and older adults had similar decreases in pressure pain reports following exercise (trial x age:  $P > 0.05$ ).

A significant main effect for sex was also identified. Women reported higher pressure pain ratings than men ( $P = 0.001$ ,  $\eta_p^2 = 0.30$ ). Women also reported a steeper increase in pressure pain ratings than men during the 1 min pressure pain test (time x sex:  $P = 0.024$ ,  $\eta_p^2 = 0.33$ ). Both men and women experienced a similar magnitude of EIH (trial x sex:  $P > 0.05$ ; Figure 4.2B).

No group differences were identified for the perception of exercise-induced arm pain. Young and older adults perceived exercise as equally painful as did men and women ( $P > 0.05$ ; Table 4.1). Peak arm pain during exercise was not associated with EIH ( $P > 0.05$ ).



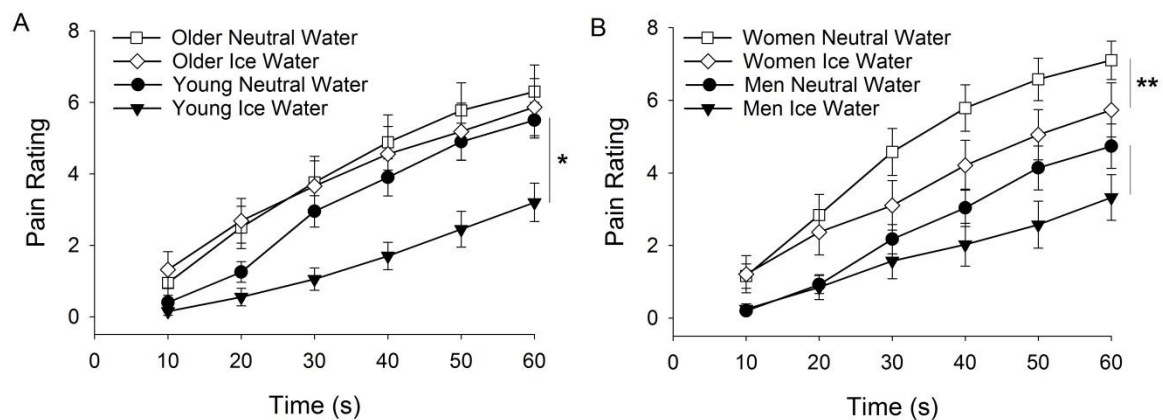
**Figure 4.2 Exercise Session Pain Ratings.** Pressure pain ratings before (pre) and after (post) isometric exercise. Pressure pain ratings decreased following exercise (A). Women reported higher pain ratings than men during the 1 min pressure pain test, but men and women reported a similar decrease in pressure pain ratings following exercise (B). Data are represented as mean  $\pm$  SEM. \*Trial:  $P < 0.05$ , \*\*Sex:  $P < 0.05$ .

### CPM Session: Pain Ratings

Pressure pain ratings (measured at the finger) decreased approximately 25% while the foot was immersed in the ice water bath compared with the neutral water bath ( $P < 0.001$ ,  $\eta_p^2 = 0.38$ ; Table 4.1). The rise in pressure pain ratings during the 1 min pressure pain test was also less when the foot was immersed in the ice water bath (trial  $\times$  time:  $P < 0.001$ ,  $\eta_p^2 = 0.55$ ). There was a significant main effect for age ( $P = 0.006$ ,  $\eta_p^2 = 0.20$ ) as well as a trial and age interaction ( $P = 0.001$ ,  $\eta_p^2 = 0.29$ ). Post hoc analysis revealed a reduction of pressure pain with the foot immersed in the ice water bath compared with the neutral water bath only for the young adults and not the older adults (young:  $P < 0.001$ , Cohen's  $d = 1.08$  and older:  $P > 0.05$ , Cohen's  $d = 0.05$ ; Figure 4.3A).

Women reported higher pressure pain ratings at the finger than men ( $P = 0.001$ ,  $\eta_p^2 = 0.26$ ) with a greater increase in pain ratings during the 1 min pressure pain test (time  $\times$  sex:  $P = 0.028$ ,  $\eta_p^2 = 0.32$ ; Figure 4.3B). Men and women, however reported similar pressure pain reductions with foot immersion in the ice water bath compared to

foot immersion in the neutral water bath (trial x sex:  $P > 0.05$ ). An age and sex interaction ( $P = 0.039$ ,  $\eta_p^2 = 0.12$ ) was identified with older women reporting higher pressure pain ratings than younger women in both water baths (Neutral Water:  $5.91 \pm 2.21$  vs.  $3.57 \pm 1.69$ ,  $P = 0.018$ , Cohen's  $d = 1.19$ ; Ice Water:  $5.50 \pm 2.44$  vs.  $1.92 \pm 1.50$ ,  $P = 0.001$ , Cohen's  $d = 1.77$ ). No age-related difference in pressure pain ratings was found for men ( $P > 0.05$ ).



**Figure 4.3 CPM Session Pain Ratings.** Age and sex differences in pressure pain ratings with the foot immersed in the neutral water bath compared with the ice water bath. Only the young adults reported a decrease in pressure pain ratings while their foot was immersed in the ice water bath compared with the neutral water bath (A). Women reported higher pressure pain ratings than men for both the neutral and ice water baths, but both men and women experienced similar reductions in pressure pain with the foot immersed in the ice water bath compared with the neutral water bath (B). Data are represented as mean  $\pm$  SEM. \*Trial:  $P < 0.001$ , \*\*Sex:  $P = 0.001$ .

Average foot pain intensity during immersion in the ice water bath was  $4.2 \pm 2.5$  at 20 s immersion (immediately prior to the onset of the test stimulus) and  $5.7 \pm 2.6$  immediately prior to removing the foot from the ice water bath (Table 4.1). There were no age or sex differences in the perception of pain for the water baths at either time point ( $P > 0.05$ ). Perception of pain intensity for the ice water bath was not associated with magnitude of CPM ( $P > 0.05$ ).

### ***Strength and Time to Task Failure***

Strength (MVC force) did not differ between young and older adults ( $225 \pm 78$  N vs.  $210 \pm 82$  N,  $P > 0.05$ , Cohen's  $d = 0.19$ ). Time to task failure for the submaximal isometric contraction was also similar for young and older adults ( $587 \pm 235$  s vs.  $739 \pm 379$  s,  $P > 0.05$ , Cohen's  $d = 0.48$ ). Time to task failure did not differ between men and women ( $601 \pm 337$  s vs.  $725 \pm 294$  s,  $P > 0.05$ , Cohen's  $d = 0.66$ ). Men however were stronger than women ( $282 \pm 48$  N vs.  $150 \pm 38$  N,  $P < 0.001$ , Cohen's  $d = 3.0$ ), and MVC force was negatively associated with time to task failure ( $r = -0.47$ ,  $P = 0.003$ ) such that stronger individuals had a briefer time to failure. Strength was also negatively associated with average pain ratings before ( $r = -0.52$ ,  $P = 0.001$ ) and after ( $r = -0.53$ ,  $P = 0.001$ ) the submaximal isometric fatiguing contraction, but neither strength nor time to task failure were associated with change in pain following exercise ( $P > 0.05$ ).

### **Psychosocial Variables**

#### ***Anxiety***

Initial state anxiety was similar between experimental sessions ( $P > 0.05$ ). There was no change in anxiety over time in the CPM session ( $P > 0.05$ ). During the exercise session, state anxiety was similar before and after the first pressure pain test but increased following exercise (time:  $P = 0.005$ ,  $\eta_p^2 = 0.27$ ). Older adults were less anxious than young adults in both sessions (exercise age:  $P = 0.047$ ,  $\eta_p^2 = 0.11$ ; CPM age:  $P = 0.030$ ,  $\eta_p^2 = 0.13$ ; Table 4.1). There were no significant main or interaction effects for sex in either session.

As state anxiety was stable over time in the CPM session, the 3 scores were averaged and the average score was used for correlational analyses. State anxiety was positively associated with change in pain ratings for the CPM session ( $r = 0.423$ ,  $P = 0.008$ ); those participants with higher state anxiety experienced greater reductions in pain with the ice water bath. No association of state anxiety with EIH was found nor was trait anxiety related to change in pain in either session ( $P > 0.05$ ).

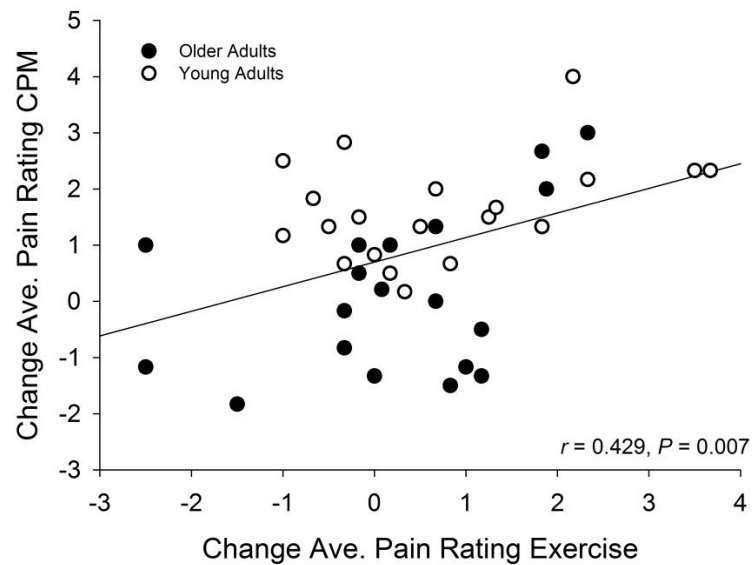
### ***Pain Catastrophizing, Fear of Pain, Pain Attitude, Physical Activity***

No age or sex differences were identified for pain catastrophizing, fear of pain, physical activity or pain attitude. Additionally, no relations were identified for pain catastrophizing, fear of pain or pain attitude with change in pain in either the CPM or EIH session. Physical activity was moderately related to change in pain ratings with CPM ( $r = 0.368$ ,  $P = 0.023$ ), but not following exercise ( $P > 0.05$ ). More physically active participants experienced greater CPM.

### **Hierarchical Regression Analysis**

Baseline pain in the CPM session (i.e., average pressure pain ratings with the foot immersed in the neutral water bath) showed a strong positive relation with baseline pain in the EIH session (i.e., pre-exercise average pressure pain ratings;  $r = 0.79$ ,  $P < 0.001$ ). After controlling for age group and EIH session baseline pain, the change in pain with CPM uniquely explained 8.8% of the variance in change in pain ratings following exercise. Individuals with greater reductions in pressure pain in the ice water bath also experienced greater reductions in pain following exercise (Figure 4.4). Of the three

predictor variables, only CPM and baseline pain uniquely predicted EIH. As a whole, the final model explained 23% of the variance in EIH,  $F(3, 35) = 4.71$ ,  $P = 0.007$  (Table 4.2).



**Figure 4.4 CPM - EIH Relation.** Conditioned pain modulation efficiency is significantly correlated with the change in pressure pain ratings following exercise. Note positive numbers represent a hypoalgesic response, and negative numbers represent a hyperalgesic response.

**Table 4.2 Hierarchical Regression Analysis**

DV	IV	Model 1			Model 2		
		<i>B</i>	<i>SE B</i>	$\beta$	<i>B</i>	<i>SE B</i>	$\beta$
EIH	Age Group	-0.767	0.413	-0.285	-0.198	0.480	-0.073
	Pre-Exercise Pain	0.236	0.087	0.417**	0.193	0.085	0.342*
	CPM				0.352	0.169	0.362*
$R^2$ /Adjusted $R^2$		0.199/0.155			0.288/0.227		
$F$ for change in $R^2$		4.485*			4.340*		
$F$ for model		4.485*			4.714***		

Note: DV = dependent variable; IV = independent variable

\* $P < .05$ , \*\* $P = 0.01$ , \*\*\* $P = 0.007$

## DISCUSSION

It has been theorized that painful exercise may activate CPM, thereby explaining the systemic reduction in pain sensitivity often seen following exercise. We examined the impact of age on CPM using a pressure pain test stimulus and the predictive relation of CPM for EIH following a low intensity prolonged isometric contraction. The main findings of this study were: 1) CPM was attenuated in older adults when using a noxious pressure test stimulus and 2) the reduction in pain ratings following isometric exercise was predicted by the CPM response. To our knowledge this is the first study to demonstrate that CPM is predictive of the pain response after exercise.

An attenuated CPM response in older adults using electrical and thermal test stimuli has been shown previously (Edwards, Fillingim, et al., 2003; Riley et al., 2010; Washington et al., 2000). The present study extends these results to a tonic pressure test stimulus. Only young adults experienced CPM whereas older adults experienced a broad range in their pain response between individuals: nine older adults reported no change in pain; five reported hyperalgesia; and five reported hypoalgesia. This finding has important clinical implications when utilizing interventions mediated by activation of descending inhibitory pathways. Older adults as a whole may have a lower response compared with younger adults to such interventions, but some older adults will likely find these interventions as equally effective as their younger counterparts in the management of pain. One limitation of this study was that the small sample size precluded identification of characteristics of those older adults experiencing hypoalgesia as opposed to hyperalgesia with CPM testing.



Our findings showed that CPM predicted the EIH response in young and older adults such that those individuals that demonstrated a greater ability to activate descending inhibitory pathways reported greater EIH. While this association is not causal, these results provide insight into the variability in the pain response that is often reported following exercise (Hoeger Bement et al., 2011; Naugle et al., 2012). For example, others have suggested that the attenuated pain relief or even pain exacerbation following exercise in some pain patients may be due to abnormal descending inhibition (Staud et al., 2005; Vierck et al., 2001). Assessment of CPM efficacy may be warranted to assist in clinical decision making to individualize pain management interventions and establish characteristics of those who will likely benefit most.

Pain relief occurs with non-painful as well as painful isometric contractions (e.g., short duration low intensity contractions or brief MVCs) (Hoeger Bement et al., 2008; Lemley et al., 2014). When exercise is painful however, CPM may work as an additive effect for pain relief. Other studies have demonstrated the additive effect of CPM with transcranial stimulation of the primary motor cortex in elevating pressure pain thresholds (Reidler et al., 2012). Specific to exercise, the ability to engage descending inhibitory pathways may augment another unknown mechanism to explain the impact of exercise duration on EIH in young adults (Hoeger Bement et al., 2008; Naugle et al., 2012). Isometric contractions of both short and longer duration produce EIH; however the greatest EIH response occurs with longer duration isometric contractions that typically induce more pain as the duration increases (Frey Law et al., 2010). Involvement of CPM in EIH may also help to explain the lower effect size for EIH in older adults compared with young adults using the same exercise protocol in an earlier study (Lemley et al.,

2014) because older adults have reduced CPM (Edwards, Fillingim, et al., 2003; Riley et al., 2010; Washington et al., 2000).

Despite CPM predicting EIH, the relation between CPM and EIH was not strong indicating that there are other factors involved in pain reduction following exercise. We investigated several potential contributors to the EIH response. Baseline pain perception during the exercise session partially explained the variance in EIH and had a similar beta value as CPM; individuals with higher pre-exercise pain ratings experienced greater reductions in pain after exercise. This is consistent with our previous finding in individuals with fibromyalgia, where participants with lower pre-exercise pain thresholds were more likely to experience reductions in pain after isometric exercise (Hoeger Bement et al., 2011). In the fibromyalgia study, we hypothesized that greater experimental pain sensitivity may also result in greater pain during the exercise task thereby producing greater EIH. Pain during exercise was not assessed in the fibromyalgia study to confirm this relation, however no relation was found between peak pain during exercise and either baseline pain sensitivity or EIH in the current study.

A variety of psychosocial factors have been shown to be associated with pain perception (Campbell et al., 2010; Okawa et al., 2005; Sullivan et al., 1995; Yong et al., 2003) and have the potential to moderate EIH. To assess for possible contributions of psychosocial factors to EIH, we examined anxiety, pain catastrophizing, fear of pain and pain attitude. Despite a small increase in state anxiety following exercise, neither trait nor state anxiety correlated with EIH which is consistent with our previous findings in both young and older adults (Hoeger Bement et al., 2008; Lemley et al., 2014). A positive association with state anxiety was found for CPM, although this may have been mediated

by age. Young adults had slightly higher anxiety scores than older adults, a finding previously reported in the literature (Stanley et al., 1996). We found neither pain catastrophizing, fear of pain or pain attitude to be related to either EIH or CPM.

Additionally, we examined the potential contribution of physical activity to the pain response to exercise and CPM. Interestingly, more physically active participants experienced greater CPM. This finding is consistent with the recent report of a predictive relation of total and vigorous physical activity and CPM (Naugle & Riley, 2014). Participation in regular physical activity may impact a person's ability to activate descending inhibitory pathways, or an alternative explanation is that individuals with more efficient activation of inhibitory pathways may find intense exercise to be less unpleasant and thus participate more in physical activity. The former has potential clinical implications for rehabilitation in that CPM may be modified with physical activity, while the latter has implications for health promotion and wellness. Whether physical activity can be manipulated to alter CPM or minimize its attenuation with aging is not known. Furthermore, all our participants were healthy, without pain, and most participated in regular physical activity, which may not be representative of the general or clinical pain populations.

Considering that CPM was a predictor of EIH and older adults experienced less CPM than young adults, an age-related difference in EIH magnitude might be anticipated. Our results did not show a statistical difference between age groups under the current experimental protocol. Previous work in our laboratory however, has shown moderate EIH effect size for young adults (Hoeger Bement et al., 2008) and small effect size for older adults (Lemley et al., 2014). In the current study, the effect size for both young and

older adults was substantially reduced compared to our earlier findings. The main difference between the earlier protocols and the current protocol are the parameters of the pressure pain device. Earlier studies utilized a 1.0 kg mass and two minute test duration; the current study used a 1.5 kg mass for one minute prompted by the need to limit the duration of the ice water bath. Comparison of pain reports for the two protocols showed that peak pain ratings and average pain ratings were similar. Thus, while participants perceived similar pain intensity with the two protocols, the rate of rise to peak pain was significantly more rapid with the heavier mass. The reduced effect size with change in stimulus parameters therefore suggests that magnitude of EIH may be dependent on the rate at which pain intensity increases during a noxious stimulus. Future experiments should be conducted utilizing a lighter weight to avoid pain saturation in order to more clearly identify whether older adults have attenuated EIH following painful isometric exercise.

## **Conclusion**

Older adults had an attenuated CPM response compared with young adults using a tonic pressure test stimulus, and this CPM response was predictive of EIH in both older and younger adults. Understanding the relation between CPM and EIH could help establish the principles necessary to create clinical practice paradigms for the use of exercise as an effective pain management tool, while also establishing profiles of people who will benefit most.

## CHAPTER 5

### DISCUSSION AND CONCLUSION

This dissertation is the first to examine the impact of age on EIH following isometric contractions and to examine the possible contribution of CPM to EIH in any age group. While EIH following isometric contractions in young adults has received attention in the literature, there is a paucity of information on older adults. Additionally, limited evidence is available on the impact of psychological factors on pain perception in older adults. Study one examined the repeatability of pain reports with a pressure pain device and the relations of state anxiety and pain attitudes of stoicism and cautiousness with pain perception in healthy older adults. Study two assessed EIH following isometric contractions of the elbow flexor muscles of various intensities and durations in older men and women. Lastly, the third study investigated the relation of CPM and EIH following low intensity isometric contractions typically perceived as painful in both young and older men and women.

*Study one* results demonstrated that the relation of state anxiety with pain perception using a noxious pressure stimulus continues beyond middle-age into later adulthood, whereas a relation of pain attitude with pain sensitivity was not found (*Study 1, Aim 1*). An association of pain and anxiety was expected as this relation has previously been shown in older adults with chronic (Casten et al., 1995; Smith & Zautra, 2008) and post-operative (Feeney, 2004; Saracoglu et al., 2012) pain. This finding extends those results to a noxious pressure stimulus and suggests that psychosocial factors have a significant impact on the perception of pain in healthy older adults. While more anxious older adults are likely to experience greater pain than their less anxious peers, our

findings in *study three* indicate that anxiety is not related to the magnitude of EIH experienced.

Importantly, *study one* showed that healthy older adults report pressure pain similarly before and after quiet rest. While previously shown in young adults and in women with fibromyalgia (Hoeger Bement et al., 2008; Hoeger Bement et al., 2009; Hoeger Bement et al., 2011), this is the first study to demonstrate similar reports before and after quiet rest in older adults. Furthermore, the variability in the pressure pain reports was similar in session two as in session one for those participants that were asked to repeat the pressure pain protocol. Compliance with reporting pain threshold however did improve with subsequent exposure to the pain device. These results indicate that a single exposure is sufficient to familiarize older adults to the testing procedure and to improve reporting of pain threshold during complex pain assessments.

In *study one*, men and women reported similar pressure pain thresholds and pressure pain ratings. In both *study two* and *study three*; however there were sex differences in pain perception with women reporting lower pain thresholds and/or higher pain ratings than men. Consistent with *studies two and three*, sex differences have been found in several studies. Two recent reviews of the literature concluded women typically experience lower pain thresholds and lower tolerance for noxious pressure stimuli than men (Fillingim et al., 2009; Riley et al., 1998); although pressure pain ratings tend to be similar (Racine et al., 2012). It is unclear why sex differences were not identified in the first study, particularly for pain threshold. A comparison of state anxiety and baseline pain found no statistically significant differences between studies for either men or women. Considering the large amount of variability that is seen in the reporting of pain

(Bishop et al., 2010; Racine et al., 2012) and the recommendation that a minimum of 41 subjects per group is needed to consistently identify sex differences in pain thresholds (Riley et al., 1998), the differing results in this dissertation reflects the equivocal results often reported in the literature (Bishop et al., 2010; Racine et al., 2012).

Similar to the potential for sex differences in pain perception, there is also evidence that aging impacts the reporting of pain as demonstrated by elevations in pain thresholds and reductions in pain tolerance (reviewed by Gibson & Farrell, 2004; Gibson & Helme, 2001; Lautenbacher, 2012). Additionally, older adults have been found to rate suprathreshold stimuli as more painful than young adults (Edwards & Fillingim, 2001; Harkins et al., 1986), while others have failed to confirm these findings (Chao et al., 2007; Kunz et al., 2009). Age-related differences in the perception of pain intensity were examined in *study three*. Whereas no difference was identified in the familiarization session, older adults reported greater pressure pain ratings than young adults in both experimental sessions. *Study one* suggests that psychosocial factors may have contributed to the variability in session findings. We found older adults to be less anxious than young adults in the experimental sessions. This is unlikely to explain our results however as lower state anxiety would be expected to result in lower pain ratings rather than higher for the older age group. While the factors influencing the age-related differences in pressure pain ratings are not clear, our results for the experimental sessions are in agreement with those of others (Edwards & Fillingim, 2001; Harkins et al., 1986).

Several research studies have shown that young adults experience EIH following isometric contractions (Hoeger Bement et al., 2008; Hoeger Bement et al., 2009; Koltyn et al., 2001; Koltyn & Umeda, 2007; Kosek & Ekholm, 1995; Kosek & Lundberg, 2003;

Umeda et al., 2010; Umeda et al., 2009) and this response persists into middle age (Ge et al., 2012; Hoffman et al., 2005; Kadetoff & Kosek, 2007; Kosek et al., 1996; Meeus et al., 2010; Staud et al., 2005). This dissertation is the first to show that older adults also experience EIH following isometric exercise (*Study 2, Aim 2*). Thus isometric exercise has excellent potential to be used as a pain management tool across the lifespan.

In young adults, the greatest reduction in pain occurs following contractions of low intensity held for long duration (Hoeger Bement et al., 2008; Racine et al., 2012). In contrast, older adults experience similar pain reductions across exercise tasks. Age is associated with sarcopenia and a greater proportional loss of cross-sectional area for high versus low threshold motor units (Hunter, 2009a; Hunter & Brown, 2010). If activation of high threshold motor units contributes to EIH as has been proposed (Hoeger Bement et al., 2008), a greater reduction in volume of high threshold motor units with aging may explain the lack of task specificity seen in older adults. Clinically, a lack of task specificity suggests that older adults can receive similar pain-relieving benefits from a wide range of isometric exercise doses, whereas young adults may require more specific exercise protocols for maximum pain relief.

Both the older men and women experienced elevations of pain thresholds following isometric exercise, and only the older women experienced reductions in pain ratings (*Study 2*). These results are similar to our previous research in young healthy adults. Following submaximal isometric exercise, there was a trend ( $p = 0.08$ ) for young women to report greater decreases in pain ratings (but not pain threshold) compared with young men (Hoeger Bement et al., 2008). The results of the current study show that EIH occurs for older men and women which is dependent on the type of pain assessment used.



Exercise may be helpful for older men to delay when they first feel pain, whereas for older women exercise can delay the onset of pain and the suprathreshold intensity of the pain. The reduction of pain ratings in addition to an increase in pain threshold suggests that older women may experience greater pain relief after isometric exercise than older men. A greater proportional reduction in volume of high threshold motor units may also help to explain why only the older women experienced reductions in pain ratings after exercise. Men have a greater proportional area of high threshold motor units than women (Hunter, 2009b). With aging a proportionately greater loss of high threshold motor units may therefore impact men to a greater extent than women.

A novel finding of this dissertation is the predictive relation of CPM and EIH (*Study 3, Aim 3*). Those individuals who had greater ability to activate descending inhibitory pathways also experienced greater EIH. While not causative, these results show that CPM is associated with pain relief following exercise. Exercise that is perceived as painful may enhance pain relief through CPM.

While both men and women experienced similar pressure pain reduction at the finger with the foot immersed in the ice water bath, only young adults were found to experience CPM (*Study 3*). An attenuation of CPM with aging has been consistently shown using thermal and electrical test stimuli (Edwards, Fillingim, et al., 2003; Lariviere et al., 2007; Riley et al., 2010; Washington et al., 2000). This is the first study to show that the attenuation of CPM occurs with a pressure test stimulus. Interestingly, the relation of CPM and EIH was not driven solely by the young adults. Older adults as a whole did not experience CPM, but there was a range of responses among the older adults in this study. Subgroups of older individuals experienced hypoalgesia,

hyperalgesia and no change in pressure pain with foot immersion in the ice water bath. Thus, some older adults demonstrate the ability to activate the CPM pathway, and these older adults experience greater pain relief following isometric exercise.

The effect size for EIH in older adults in *study two* was attenuated compared with young adults using the same EIH protocol (Hoeger Bement et al., 2008). Unexpectedly, the results in *study three* failed to support a similar age-related difference in EIH. This is particularly surprising given that CPM was a predictor of EIH and older adults had attenuated CPM. The EIH effect size for both age groups was substantially lower in *study three* than in our previous studies (Hoeger Bement et al., 2008; Lemley et al., 2014), and is likely related to a change in the pain testing protocol. In *study three*, a greater force was used to induce pain which resulted in a more rapid increase in pressure pain intensity ratings. One possible explanation is that the heavier weight induced greater strain on the periosteum of the middle phalanx. Deep tissue nociceptors are activated by and encode mechanical strain (Finocchietti et al., 2012); and higher strain has been associated with lower pressure pain thresholds (Finocchietti et al., 2012). Thus, EIH appears to be influenced by the magnitude of the experimental pain applied. Future studies of young and older adults using a lower magnitude of pressure pain may provide additional insight into the presence of age-related differences in EIH.

Pain threshold was not analyzed during *study three* due to lack of compliance with reporting of pain threshold. Almost 80% of the older women failed to report when they first felt pain (pain threshold) when their foot was immersed in the ice water bath. This is unlikely to be accounted for by learning as sessions were counterbalanced, and reporting of pain threshold was significantly better in the exercise session. There are

several potential reasons for the decrease in pain threshold reporting during the CPM sessions: With age, working memory is diminished (Salthouse, 1994) and may be more impaired in women than men under stressful conditions (Schoofs et al., 2013). The ice water bath may have acted as a stressor (Bentz et al., 2013) affecting older women the most. While state anxiety was similar before and after CPM testing, we did not assess stress or anxiety *during* the pain test to confirm this possibility. Furthermore, the adverse effects from stress on cognitive processing may have been exacerbated by the concurrent application of the test and conditioning stimuli creating a dual task situation, and older adults are more susceptible to dual task performance decrements than young adults (Hein & Schubert, 2004). This novel finding may have important implications for aging and dual task performance in the assessment of CPM.

## **Conclusion**

Together the result of this series of studies significantly adds to the body of knowledge on the influence of age on pain perception and EIH. Older adults experience pain similarly before and after quiet rest and variability in pain reports is unchanged with repeated exposure to the pain device. These results also verified that the influence of state anxiety and pain perception occurs across the lifespan. Thus, when working with adults of any age, minimizing anxiety may be an important factor in the management of pain.

Specific to exercise, anxiety does not appear to influence the reduction of pain following isometric contractions. Older adults experience EIH following isometric contractions of varying intensities and durations, and the magnitude of EIH is not task dependent. Both men and women report increases in pain thresholds, however only older

women report reductions in pain ratings after exercise. Therefore older women may find greater pain relief following isometric exercise than older men. The lack of task specificity further suggests that practitioners may have greater leeway in designing isometric exercise programs for older adults, whereas more specific protocols may be required for younger adults to maximize treatment efficacy.

The finding that CPM predicts EIH following isometric exercise perceived as painful has important clinical implications for pain management. The integration of CPM, beyond exercise prescription, may be an important rehabilitative approach to maximize pain relief. The prediction of EIH by CPM may also provide a means of assisting in clinical decision making when prescribing exercise programs for pain relief. Assessment of CPM efficacy may be used as a predictive tool to establish the characteristics of individuals who will initially benefit most from isometric exercise, thereby aiding in clinical decision making when designing exercise programs for the management of pain.

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