DISSERTATION

NEUROMUSCULAR AGING AND FRAILTY

Submitted by

Megan Leigh Fritz

Department of Health and Exercise Science

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Doctoral Committee:

Advisor: Brian L. Tracy

Thorsten Rudroff
Raoul F. Reiser II
Deana Davalos

ABSTRACT

NEUROMUSCULAR AGING AND FRAILTY

The aging process is accompanied by gradual declines in physical and cognitive function. The majority of neuromuscular research has only approached the changes that occur from a chronological aging perspective. The way in which individuals age, however, is not necessarily accounted for in chronological years. Additional factors such as comorbidities, the development of disability, and frailty status play a role in determining successful vs. unsuccessful aging. It is the overall intention of this dissertation to assess aspects of neuromuscular aging within the context of physical frailty and explore potential interventions for improving age- or frailty-associated neuromuscular impairment.

The first chapter of this dissertation consists of a review of the proprioception literature. Proprioception is generally the perception of body movement. This afferent system is crucial for maintaining postural stability and reducing fall risk. The first experiment (Chapter II) was designed to assess proprioceptive perception at the ankle joint while comparing young adults, healthy older adults, frail older adults, and adults with comorbidities affecting the peripheral nervous system (peripheral neuropathy) and the central nervous system (stroke). The results indicate that healthy older adults have similar proprioceptive function at the ankle to that of young adults. Those aged with comorbidities such as peripheral neuropathy exhibited the greatest deficits in proprioceptive function.

Muscle spindles are considered the primary sensors of joint movement perception, a major component of the overall proprioceptive sense. Vibratory stimulus may alter the afferent signaling of muscle spindles. Robust vibration tends to impair or provide illusory sensations within muscle spindles, while low-level vibration has the potential to enhance muscle spindle sensation. The goal of the second experiment (Chapter III) was to determine if low-level sub-sensory vibration applied to the plantarflexor and dorsiflexor tendons could improve proprioception among healthy young adults. The study demonstrated that sub-sensory vibration did in fact improve ankle joint proprioception and those with the poorest proprioception experienced the greatest benefit from the vibration.

The third study (Chapter IV) was designed to assess the potential for the same sub-sensory vibration intervention among healthy and frail older adults. The results indicated that the sub-sensory vibration did not improve ankle joint movement perception in either the dorsiflexion or plantarflexion directions. Frail demonstrated impaired proprioception in both the plantarflexion and dorsiflexion directions compared with healthy older adults. Women exhibited greater (impaired) joint movement perception in the plantarflexion direction compared with the dorsiflexion direction, while men were similar across both directions. Frail women appeared to be driving the significant differences in joint movement perception and therefore may represent the most relevant target population for the proprioceptive interventions.

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CHAPTER I – LITERATURE REVIEW OF PROPRIOCEPTION

Proprioception is a general term used to describe the perception of body movement. The sense of movement has been divided into four subcategories based upon the sensations that are integrated within the central nervous system to formulate the overall awareness of body movement. These subcategories include the sense of position and change in position (kinesthetic sense), the sense of tension, the sense of balance, and the sense of effort (Proske, 2005). It is generally accepted that the muscle spindles provide a critical contribution to the kinesthetic sense, while the golgi tendon organs sense tension, the vestibular system contributes to the sense of balance, and the sense of effort is generated by central nervous system. This review is intended to focus on the role of the kinesthetic sense in proprioception.

The source of the kinesthetic sense was historically debated due to the complexity involved in both the integration of efferent and afferent signals within the central nervous system as well as the numerous potential peripheral sources of the kinesthetic sense, including the afferent signals generated though the alterations of the muscle, skin, joint capsule, and connective tissues including the fascia, tendons, and ligaments. Sherrington proposed that the kinesthetic sense was the result of peripheral receptors, and he favored the joints themselves as the likely source (Proske, 2005). This view was supported by the early research conducted through the mid 1950's (Boyd & Roberts, 1953). In the late 1950's, P.B.C. Matthews began to describe in detail the structure and function of the muscle spindle using animal models (Matthews & Rushworth, 1958), but it was not until 1972 that Goodwin, McCloskey, and Matthews

demonstrated that muscle spindles could give the illusion of kinesthesia across anesthetized joints in humans (Goodwin, McCloskey, & Matthews, 1972a). Other afferent sensors and central integration contribute to the perception of limb position and movement, yet the muscle spindles are still considered to be the primary source of the kinesthetic sense.

Sources of afferent sensation

The kinesthetic sense includes both the sense of limb position and the sense of limb movement. Studies assessing point to point movements have shown that when subjects are asked to repeatedly move their hand from point A to point B without visual feedback, the sense of movement (direction and trajectory) is preserved while the sense of limb position is not able to prevent a significant drift from the prescribed starting point (L. E. Brown, Rosenbaum, & Sainburg, 2003). Therefore, these two aspects of the kinesthetic sense can function independently of one another. Though these two components are closely related, they can be distinguished from one another using receptor-specific methods of proprioceptive assessment. The following section describes the potential sources of the kinesthetic sense from most to least influential.

Muscle spindles

A muscle spindle is made up of a small number of intrafusal muscle fibers surrounded by a capsular membrane. Intrafusal fibers do not have an abundance of actin and myosin filaments like their extrafusal counterparts, yet they contract in response to stimulation via the gamma motor neurons. There are two types of intrafusal muscle fiber, nuclear bag fibers whose nuclei congregate in the middle region of the fiber, and nuclear chain fibers whose nuclei are oriented in a linear fashion. There are

two main sensory receptors wrapped around the intrafusal fibers known as primary endings (or Ia afferents) and secondary endings. Primary endings are located around the mid-region of both the bag and chain fibers and convey both limb position sense and movement perception. Secondary endings are located only along the ends of the chain fibers and simply convey position sense (McCloskey, 1973). When muscle is lengthened, the primary endings send a fast and robust signal to the central nervous system. The firing rate of the muscle spindle modulates the central awareness of the extent to which the muscle has changed its length.

The functional sensitivity of proprioceptors may vary based upon location. Studies have shown that distal joints appear to have lower thresholds for joint movement perception, however, when comparing the change in fascicle length per degree of movement the differences in movement perception disappeared. This has been shown across both the upper (Hall & McCloskey, 1983) and lower extremities (Refshauge, Chan, Taylor, & McCloskey, 1995). The normal range of angular movement is different for each joint. For instance, the sagittal range for the hip is around 150 degrees, while the ankle is between 55-65 degrees. The movement detection as studied by Refshauge, et al. was at 0.04 deg for the hip (0.03% of the available range) and 0.16 deg for the ankle (0.3% of the available range). When accounting for the change in fascicle length, 1 deg of angular rotation produced 17.1 mm of linear displacement at the hip and 3.9 mm at the ankle. Therefore, at 0.04 deg the fascicle length at the hip changed by 0.684 mm and at 0.16 deg the ankle fascicle changed by 0.624 mm (Refshauge et al., 1995). Therefore, though the hip movement detection

occurred with only 0.04 deg of movement, as opposed to 0.16 deg at the ankle, the ankle movement occurred with the less change in actual fascicle length.

There is some evidence from experimental phantom limbs (temporary phantom limb sensations generated by experimentally induced anesthesia and paralysis), that the central nervous system not only derives information about limb position based upon the discharge of muscle spindles, but also the lack thereof. In studies using experimental phantom limbs, the position of the fingers prior to the nerve block influenced the perceived position of the hand after the anesthetic took effect. For example, if the fingers were extended prior to the nerve block, the subject perceived that the fingers began to flex after the nerve block, and vice versa for the fingers held in flexion prior to the nerve block. The interpretation of this data implies that when the hand is held in extension prior to the nerve block, the discharge of the muscle spindles from the lengthened finger flexor muscles signals the limb position. When the nerve block takes place, these signals are terminated and the central nervous system interprets that signal termination as movement in the opposite direction, in this case being finger flexion (Inui, Walsh, Taylor, & Gandevia, 2011). This effects both aspects of the kinesthetic sense due to a distortion of both the sense of limb position and a phantom sense of limb movement.

Cutaneous Receptors

Cutaneous skin receptors in the hand have been shown to elicit an illusion of joint movement through both electrical stimulation and skin stretch (D. F. Collins & Prochazka, 1996). Studies using microneurography show that both slow-adapting and fast-adapting cutaneous receptors discharge in response to skin stretch and thus

represent both static and dynamic joint positioning in the hand. However, the slow-adapting type II (Ruffini) endings likely play the most significant role in proprioception (B. B. Edin, 2004). A study comparing populations of muscle spindle and cutaneous skin afferents found that muscle spindles begin discharging around 50 ms sooner than skin receptors in response to joint movement in the hand (Grill, Hallett, & McShane, 1997), which implies that muscle spindles play the more dominant role in the kinesthetic sense. The majority of the kinesthetic studies related to the skin receptors have been performed in the hand; however, one study used skin stretch to provoke an illusion of joint movement at the index finger, elbow and knee. Their findings suggest that the cutaneous receptors may play a more significant role in kinesthesia at distal joints where many of the muscles are biarticular resulting in less specific feedback from the muscle spindles (D. F. Collins, Refshauge, Todd, & Gandevia, 2005); however, this study utilized active contralateral limb matching to assess proprioception. Another study assessed the use of skin stretch on joint movement perception at the ankles during passive standing and found that there was no change in proprioception with cutaneous alteration (Simoneau, Degner, Kramper, & Kittleson, 1997). Therefore, the method of proprioceptive assessment may play a significant role in the results and their interpretation, yet the evidence from multiple assessment sources places muscle spindles as the primary contributors to proprioceptive feedback.

Joint Receptors

Around 75% of joint receptors are slow adapting and increase their firing rate at the extreme ranges of joint motion. These receptors responding to alterations in the capsular structure are similar to the Ruffini endings found within the skin. There is some

activation through mid-range motions via Pascinian-like receptors, which are fast adapting and few in number (Burgess & Clark, 1969). Though these sensors play a role in the kinesthetic sense, it is not considered the primary source due to the fact that after joint replacement surgery, the kinesthetic sense is preserved even though the joint capsule and ligaments are removed (Grigg, Finerman, & Riley, 1973). A similar lack of kinesthetic disturbance has been demonstrated through anesthetizing the joint capsule (Ferrell, Gandevia, & McCloskey, 1987). Thus the preservation of the kinesthetic sense in the absence of afferent signals from the joint capsule removes the joint capsule receptors from the pool of possible primary afferent kinesthetic contributors.

The contribution of joint receptors and cutaneous receptors in the lower extremity can be evaluated independently of muscle spindles due to the difference in the anatomical location of their ascending pathways in the spinal cord. Sensory signals from the skin and joint receptors are relayed through the dorsal columns. In the lower extremity, the muscle receptors are relayed through the Clarke's column as the signal is transmitted superiorly through the thoracic and cervical regions of the spinal cord. Those with spinal cord injury to the dorsal columns in the thoracic region do not experience a significant loss of the kinesthetic sense in the lower extremity (Wall & Noordenbos, 1977), which further verifies that the muscle afferents are the primary contributors to joint position and movement perception rather than the joint or skin receptors.

There are few studies accessing joint receptor function in humans, and of those most of them were performed in the hand. At this time there are no known studies using artificial stimulation of joint receptor afferents to elicit responses relating to the

kinesthetic sense. Therefore, the current knowledge of the contribution of joint receptors to the kinesthetic sense is derived from studies that have used either anesthetic to silence various afferent signals or those that involve lesions to the joint afferents through either joint replacement surgery or central lesions within the afferent pathway. The current body of literature reflects the notion that the joint receptors provide kinesthetic input, but this signal is utilized secondarily in terms of the conscious perception of proprioception. Thus, joint receptors provide an important redundancy in the kinesthetic sense, especially at the extreme ranges of joint motion.

Central Contributions

During active movements, the central nervous system generates an efferent signal to initiate movement, while the peripheral receptors provide afferent feedback describing the motion that occurred. The central nervous system also relays the efferent signal to the central sensory areas. The copy of the efferent signal from the neuron that excites the alpha motor neuron is termed the corollary discharge. This signal is presumed to convey the sense of effort associated with muscle contraction, though this is admittedly an oversimplification of the sense of effort. The copy of the efferent signal from the motor neuron that excites the gamma motor neuron is termed the efference copy (Figure 1.1). The efference copy is used to compare the difference between the efferent signal and the expected afferent signal. This is commonly referred to as “reafference”. If there is a greater than expected afferent signal, or “exafference”, then it produces an independent sensation that contributes to the overall perception of movement (McCloskey, Gandevia, Potter, & Colebatch, 1983).

In its simplest form, reafference is the way in which the nervous system accounts for the activation of the gamma motor neurons which innervate the intrafusal muscle fibers associated with muscle spindles. This is illustrated by the fact that isometric contractions involve the activation of both alpha and gamma motor neurons, yet there is no perception of kinesthesia, therefore, the gamma motor activation along with the increase in muscle spindle firing rate must be accounted for by the central nervous system (McCloskey et al., 1983). Thus the central integration of the efferent and afferent signals is crucial for accurate conscious perception of limb position and movement.

Studies have shown that low-velocity joint movement perception is diminished in cases where the skin and joint receptors have been anesthetized in the hand (Gandevia, Hall, McCloskey, & Potter, 1983). Though muscle spindles are the primary afferents responsible for joint movement perception, the central nervous system integrates information from multiple afferent receptors in order improve sensitivity and perhaps maintain a mild form of redundancy within the system. Studies have also shown that stimulation of single afferents from either muscle spindles or slow-adapting type II cutaneous sensors do not provide any sense of joint movement or position (G. Macefield, Gandevia, & Burke, 1990), therefore the central nervous system requires stimulation from multiple populations of specific afferents in order to interpret their signals in a meaningful way. Though one muscle spindle may not be enough to trigger the kinesthetic sense, as little as ten activated muscle spindles in the hind limb of a cat can provide an accurate sense of limb position (Stein et al., 2004). Therefore, very small populations of muscle spindles are able to maintain joint position sensitivity.

Assessing muscle spindles in vivo

There are few studies assessing individual muscle spindle discharges in humans (V. G. Macefield, Sverrisdottir, & Wallin, 2003). This is likely due to the relatively difficult and invasive nature of the recording methods. For example, a study assessing muscle spindle discharge rates in the lower extremity used electrical stimulation to locate the common peroneal nerve followed by the insertion of a microelectrode into the muscle fascicle. The location of the microelectrode within the muscle fascicle was confirmed via electrical stimulation producing twitch contractions less than 0.02 mA, muscle afferent discharges with percussion or stretch, and no elicited response from cutaneous sensors. Individual muscle spindles were then isolated and the primary and secondary ending responses were characterized based on their responses to dynamic stretch. It is typical for studies such as this to have relatively low subject numbers; in this case there were only 10 subjects (Knellwolf, Hammam, & Macefield, 2016). Typically muscle spindle function is assessed in a more indirect way using either joint movement perception or position-matching tasks. As mentioned previously, the primary endings of muscle spindles signal both movement and position, while the secondary endings simply convey position sense(McCloskey, 1973). A recent study utilized microneurographic recordings of muscle spindles and cutaneous receptors that were responsive to movement in the dorsiflexor muscles during a movement detection task with and without the application of different levels of vibration. The subjects were oriented in a seated position and the ankle joint was rotated in either the plantarflexion or dorsiflexion position at 0.04 deg/s with only 0.5 deg range. Movement perception was determined based upon the correct identification of the movement direction or the

absence of movement. As expected, there was an increase in the muscle spindle discharges with movement in the plantarflexion direction while the cutaneous sensors remained silent. The range and velocity of the task were designed to optimize their psychophysical assessment of movement detection, and they concluded that this speed and range were likely to be too slow and too small to adequately evaluate the afferent changes associated with vibration (Ribot-Ciscar, Hospod, & Aimonetti, 2013). Though movement perception requires the transmission of the signal from the muscle spindle to the central nervous system and the central integration of that signal, it is much less invasive, easier to test, and generally accepted as a targeted assessment of primary afferent signals. The following chapters of this dissertation describe joint movement perception at the ankle using a similar passively rotating platform. The speed of the rotation was faster than the previously mentioned study (0.25 deg/s rather than 0.04 deg/s) and did not limit the range of rotation, but rather used the change in degrees as an indication of joint movement perception threshold. This method was developed and optimized for detection of movement perception impairment among those with peripheral neuropathy (Simoneau, Derr, Ulbrecht, Becker, & Cavanagh, 1996), and it is agreement with the recommendation of the microneural study implying that a faster and greater range of motion is needed for muscle spindle investigations (Ribot-Ciscar et al., 2013).

Manipulation of proprioception

Vibration

Studies performed in the 1970's lead to the adoption of the belief that muscle spindles are the primary sensors of limb position and movement by using tendon

vibration to create and illusion of joint movement. Vibration over joints did not produce the same illusion of position change. Microneuography has been used to confirm that muscle spindles are responsible for the vibration illusion (Roll, Vedel, & Ribot, 1989), and the primary endings of muscle spindles are specifically sensitive to vibration (Burke, Hagbarth, Lofstedt, & Wallin, 1976).

The effects of the vibratory stimulus are frequency-dependent. Vibration at around 80 Hz is ideal for stimulating the primary endings of muscle spindles (Roll et al., 1989), while vibration at low frequencies, around 20 Hz, stimulates only the secondary endings. Therefore, the lower frequency of vibration gives the illusion of displacement only due to the stimulation of the secondary endings rather than the primary endings (McCloskey, 1973).

The effects of the vibration stimulus can be altered based upon a variety of circumstances. For instance, vibration of agonists and antagonists at the same time with the same frequency will not produce a sense of change in position (Ribot-Ciscar & Roll, 1998). When muscles are vibrated while also actively contracting at fifty percent of their maximal voluntary contraction (MVC), the vibration illusion no longer has an effect (Ansems, Allen, & Proske, 2006). High-frequency, low-amplitude vibration can also worsen the joint movement sense by stimulating the rapidly-adapting Pacinian endings (Weerakkody, Mahns, Taylor, & Gandevia, 2007), while sub-sensory low-frequency, low-amplitude vibration may enhance the joint movement sense based upon studies that have used this form of vibration to improve postural stability (Priplata, Patritti, Rosengarten, et al., 2006).

Generally, the illusion of joint movement elicited by vibration has been used to confirm that muscle spindles are the primary source of the kinesthetic sense, yet the perceptions that result from robust vibration are very different from the perceptions that result from low-amplitude vibration. For example, robust vibration at 80Hz can elicit illusions of limb positions that are anatomically impossible (Craske, 1977). Some forms of vibration stimulus, however, can enhance the kinesthetic sense. Studies have shown improvement in balance performance among older adults (Priplata, Niemi, Harry, Lipsitz, & Collins, 2003), diabetic, and stroke populations (Priplata, Patritti, Niemi, et al., 2006) using sub-sensory vibration applied through the soles of the feet. Another study demonstrated that in combination with skin stretch via adhesive tape, vibration enhances the sense of joint movement perception specifically, to a greater degree than either vibration or skin stretch alone (D. F. Collins et al., 2005).

Exercise

Exercise-induced fatigue is known to influence kinesthetic proprioception. Anecdotally it is noticeable that after intense exercise of the lower extremity the legs may feel unsteady while walking. This proprioceptive decline may be especially true immediately after eccentric exercise, which can produce greater muscle damage compared with other forms of exercise (Brockett, Warren, Gregory, Morgan, & Proske, 1997). Brockett, et al. assessed the effect of both concentric and eccentric exercise of the elbow flexor muscles. They proposed that position matching impairments immediately after exercise would be most representative of fatigue and exercise-induced metabolic disturbances in the muscle, while more long-term position matching errors (4 days post-exercise) would be more indicative of muscle damage, particularly

with eccentric exercise. The results from this study demonstrated significant upper extremity position matching impairment following eccentric exercise only. Further research performed in this lab, however, found that eccentric exercise does not alter the muscle spindle discharge rates with the anesthetized cat (Gregory, Morgan, & Proske, 2004). This was presumably due to the fact that the intrafusal muscle fibers are very compliant, and therefore unlikely to be susceptible to damage during eccentric contractions within the muscle's normal physiologic range. Other studies that assessed position matching tasks about the elbow found that some errors in position matching persisted for up to four days following eccentric exercise; however, the position matching errors were also significant with concentric exercise indicating that the position matching impairment is the result of the decline in force production capability rather than muscle damage specifically (Walsh, Hesse, Morgan, & Proske, 2004). It is likely that the post-exercise position matching errors within the elbow flexor muscles were due to the subjects matching the reference arm based upon the sense of effort, rather than the sense of muscle length.

Another study used the change in the vibration illusion before and after "stretch-shortening cycles" to assess the influence of exercise on muscle spindle activity. After two days of recovery, there was an impaired vibration illusion at 80-100Hz, but an improved illusion at 40Hz. If the alterations in proprioceptive function were due to damage of the intrafusal muscle fiber, then one would expect impairment at all frequency levels, rather than improvement at 40Hz. They concluded that the exercise specifically impaired the dynamic sensitivity of the primary endings of the muscle spindle due to the localized impairment at the 80 and 100Hz vibration, which is

considered to be specific the primary endings (Regueme, Barthelemy, Gauthier, & Nicol, 2007).

Exercise-related position matching studies have found that there are significant differences in matching errors based upon whether or not the reference arm was supported. This implies that the effect of gravity and the perceived effort of maintaining a position has a greater effect on limb position sense than influence of exercise. This line of research implies that perhaps muscle spindles are the primary afferents responsible for joint movement perception, but the corollary discharge contributing to the sense of effort may be heavily relied upon for the static limb position sense (Allen, Leung, & Proske, 2010; Walsh et al., 2004). This concept is reiterated through studies showing that concentric exercise impairs the limb position sense, but does not impair passive joint movement detection (Allen & Proske, 2006). Another study concluded that joint movement detection was actually improved at the shoulder joint following fatiguing concentric exercise (Carpenter, Blasier, & Pellizzon, 1998).

A more recent study found that concentric exercise impaired limb position sense to a greater degree than isometric or eccentric exercise even though there was a greater reduction in strength with the eccentric exercise. They suggested that the concentric contraction results in a greater degree of impairment in position matching due to an insufficiency in the gamma motor neurons. During concentric contractions, the muscle is shortened and the muscle spindles are potentially less sensitive due to the relative slack in the intrafusal muscle fibers (Fortier, Basset, Billaut, Behm, & Teasdale, 2010), which may explain their conclusion that concentric contractions result in less sensitive limb position perception. The conflicting conclusions as to the influence of

exercise on proprioception could be due to the differences in methodology; however, it is clear that there is no defined consensus on the direct influence of exercise on the kinesthetic sense.

Metabolic Fatigue

Though exercise-induced proprioceptive impairment may not be the direct result of muscle damage, it may be affected by central fatigue. Central fatigue is more evident at the spinal level following eccentric contractions, even though concentric contractions have greater metabolic demand (Loscher & Nordlund, 2002). Group III and group IV afferent nerve fibers may be influenced by inflammatory mediators such as interleukin 6, kinins, or prostaglandins, which are prevalent following eccentric exercise. These afferent fibers may modulate the efferent signals at the spinal level through either pre-synaptic inhibition of the primary afferents of muscle spindles or the inhibition of alpha motor neurons, and perhaps contribute to supraspinal inhibition. This increased activation of group III and IV afferents has been confirmed following eccentric exercise (Martin et al., 2009), and may contribute to a desensitization of the primary endings of muscle spindles following fatiguing exercise.

The impaired joint position sense associated with acute muscle fatigue is thought to arise from either an accumulation of metabolites or it may be the result of the reduced force generating capacity of the muscle. Exercise-induced metabolites include H^+, lactate, and CO_2, which accumulate in the cytoplasm of muscle fibers. Animal models have been used to assess the influence of pH on muscle spindle discharge rates, and found that muscle spindle discharge rates are reduced in an acidic environment similar to that of fatiguing muscle contractions (Fischer & Schafer, 2005) To determine the

contribution of metabolites, researchers used eccentric exercise that was significant enough to reduce the muscle force by 50-60%. After a 24 hour period following the exercise, the metabolite effects were assumed to be absent and joint position was re-tested. They found that the joint position sense errors persisted, and therefore, the result of changes other than the acute metabolic alterations associated with exercise (Tsay, Allen, Leung, & Proske, 2012). Another study measured blood lactate levels before and after concentric, eccentric and isometric exercise and found that the metabolic stress was similar between the different forms of exercise, yet the concentric exercise produced the greatest impairment in position sense. Therefore they also concluded that the proprioceptive impairment related to exercise is independent of the metabolic attributes of exercise (Fortier et al., 2010).

Muscle Contraction

The joint movement perception threshold has been shown to be much lower (more sensitive) when the muscle is actively contracted compared with a relaxed muscle that is passively moved (Taylor & McCloskey, 1992; Wise, Gregory, & Proske, 1998). Other studies have shown the same trend across the finger joint when skin and joint sensations have been anesthetized (Gandevia & McCloskey, 1976). This is presumably due to the co-activation of the alpha and gamma motor neurons with active muscle contractions, which should make the muscle spindles more sensitive to stretch.

Animal experiments, however, have shown that passive movements generate greater activation levels of the primary muscle spindles during small movements compared to movements involving gamma motor neuron stimulation (Wise, Gregory, & Proske, 1999). In fact, this study found that if a conditioning contraction was performed

immediately prior to the passive movement, the muscle spindles were more sensitive to stretch than they were with static, dynamic, or both forms of gamma motor stimulation. Therefore, it is possible that the enhanced kinesthetic sense during active contractions is due to the presence of the efference copy within the central nervous system, which is absent during passive movements. During the first second of active movements there is a consistent overestimation of limb position. Researchers performed identical position matching tasks using active and passive movements about the elbow joint. They found that the passive movement produced larger position matching errors than the active movements, which implies that the efference copy associated with active movements may help to improve the sensitivity of the limb position perception to a significant degree (Gritsenko, Krouchev, & Kalaska, 2007).

Aging

Sarcopenia is associated with impaired proprioception (Butler, Lord, Rogers, & Fitzpatrick, 2008). Sarcopenia is generally used to describe the age-related loss of muscle mass. Studies have shown that impaired position sense at the knee is associated with increased fall risk along with diminished cutaneous vibration sensation, poor muscle strength, slower reaction times, and visual impairment (Lord, Ward, Williams, & Anstey, 1994). Therefore, understanding age-related changes to the kinesthetic sense is important for risk assessment and fall prevention.

Cadaver studies have shown that aged muscle has fewer extrafusal and intrafusal fibers (Swash & Fox, 1972). Most of the current knowledge of age-related changes to muscle spindles comes from animal studies. Their findings show that among those that maintain their muscle spindle innervation, there are significant morphological

changes to the primary endings. The secondary endings, however, seem to be preserved (Kim, Suzuki, & Kanda, 2007). Murine studies measuring muscle spindle size and function, found that the primary endings of aged mice have slower conduction velocities and smaller axons, thus resembling the secondary endings (Kim et al., 2007). As mentioned previously, the secondary endings are sensitive to static limb position, while the primary endings sense both limb position and movement. Therefore, the kinesthetic sense of older adults is likely to exhibit a greater impairment in joint movement perception in addition to limb position sense impairment.

Age-related changes in the kinesthetic sense have focused on the static position sense, although impairments in dynamic position sense have also been documented (Madhavan & Shields, 2005), joint movement sense is comparatively understudied. In a study assessing metacarpophalangeal and metatarsophalangeal joint movement sense they found that there was in fact no difference between young and older adults (Kokmen, Bossemeyer, & Williams, 1978). It is important to note that proprioceptive investigations have yet to consider the influence of aging quality, such as frailty or other comorbidities that may be important among the general population of older adults.

Studies have found a correlation between muscle weakness and impaired static position matching at the knee joint among sedentary older adults (Petrella, Lattanzio, & Nelson, 1997). This study found that active older adults exhibited diminished proprioception compared to younger adults, while also performing significantly better than sedentary older adults. Therefore, exercise or physical activity may be able to improve proprioception while also improving muscle strength. Additional studies aimed at reducing fall risk have found that exercise should include balance training in addition

to strength training, which may be able to improve some of the age-related decrements in the kinesthetic sense (Sherrington et al., 2008).

Sex Differences

The majority of proprioception studies using joint movement detection and position-matching tasks do not report any differences between men and women. Recently, a study conducted to determine sex difference in proprioception tested the ankle muscles in the seated position. Three aspects of muscle spindle function were used to assess age-related and sex-related differences, including joint movement perception (at 0.3 deg/s of passive rotation), static position-matching, and dynamic position-matching. They were unable to detect any consistent sex-related differences (Ko, Simonsick, Deshpande, & Ferrucci, 2015). Additional studies that have assessed muscle spindle function via the spinal stretch reflex have also found no significant differences between men and women in both the upper (Pisano, Miscio, Colombo, & Pinelli, 1996) and lower extremities (Blackburn, Padua, & Guskiewicz, 2008) despite greater musculotendinous stiffness among men. While the limited studies examining sex differences suggest that there may not be differences in muscle spindle function between men and women, it remains important to consider sex as a dependent factor as men and women have been shown to differ in some aspect of musculoskeletal aging (Tay et al., 2015).

Conclusion

The perception of limb position and joint movement are primarily provided through the afferent feedback of the muscle spindles. Research has unequivocally

shown that the muscle spindles are exquisitely sensitive to limb position and movement. Additional information is provided through cutaneous skin receptors and joint receptors which provide accessory information. This additional information may be of greater importance at distal joints utilizing primarily biarticular muscles. The sensitivity of the kinesthetic sense may be enhanced during active movements through the central activation of the efference copy. There are structural and functional changes to the muscle spindles associated with aging, which has consistently produced impairments in the kinesthetic sense among older adults. Both vibration and exercise are able to augment proprioceptive function, however, the way in which each of these interventions is applied is significant as both may be used to either enhance or diminish the kinesthetic sense. Additional research is needed to explore strategies for improving proprioception or at least mitigating the age-related losses in proprioception due to its impact on balance and fall risk.

FIGURES

Figure 1.1: Central Contribution to Kinesthetic Sense and Sense of Effort

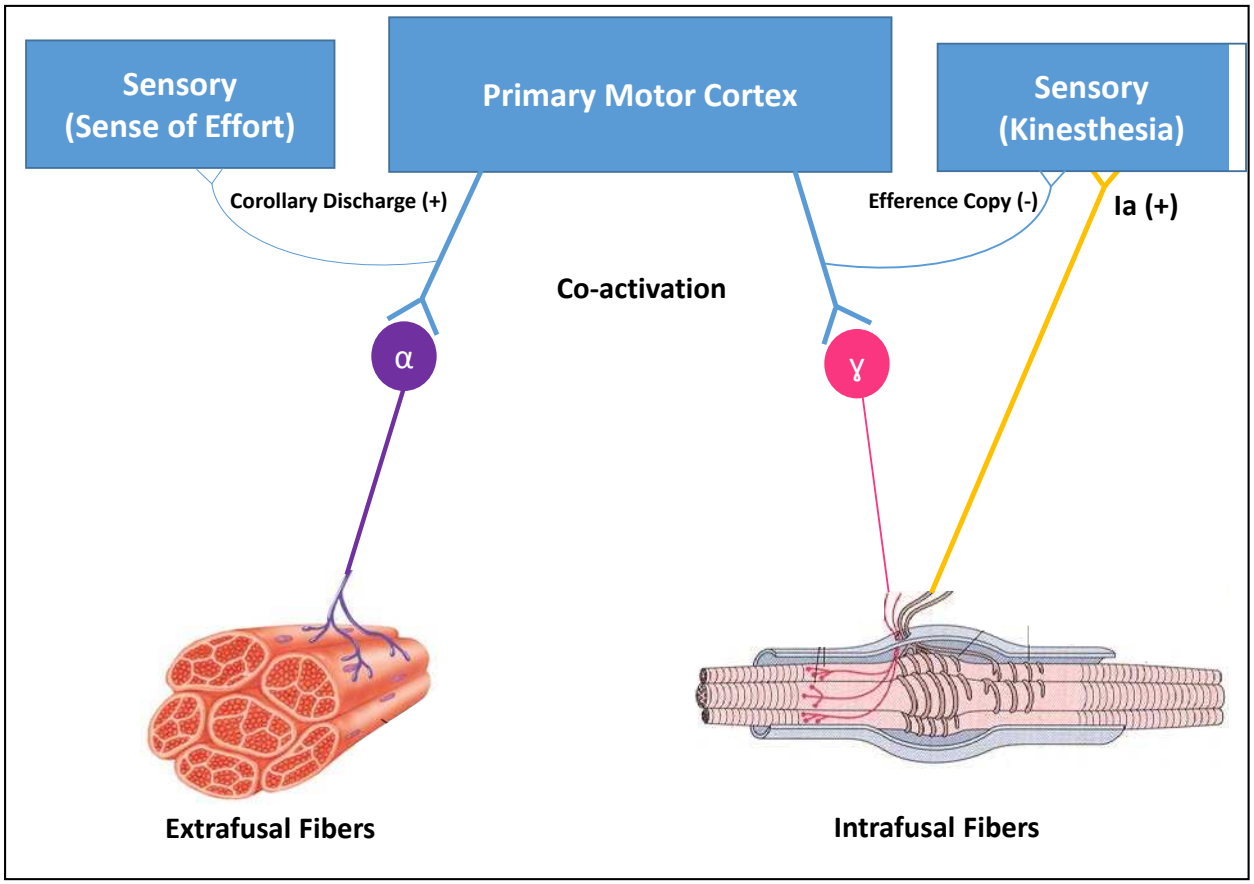

Figure 1.1 The motor neuron that excites the gamma motor neuron generates a signal known as the efference copy. The efference copy is used to compare efferent signal to the expected afferent signal, a process called reafference. If there is a greater than expected afferent signal, or “exafference”, then it produces an independent sensation that contributes to the overall perception of movement. (Adapted from (McCloskey et al., 1983) via (Proske, 2005))

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CHAPTER II – MANUSCRIPT I

Ankle proprioception in aging and neuromuscular dysfunction

Summary

Joint movement perception is an important component of the proprioceptive sense which is used to maintain postural stability and reduce fall risk. Aging is associated with declines in postural control and increased fall risk, yet the assessment of proprioception within the context of aging has only considered the role of chronological aging as opposed quality of aging, or frail vs. healthy aging. Though the definition of frailty is debated within the literature, it is generally accepted that some individuals age successfully while others age unsuccessfully with either comorbidity, disability, or frailty. The purpose of this study was to assess joint movement perception at the ankle joint in young adults, healthy older adults, frail older adults, and those aging with a peripheral comorbidity (peripheral neuropathy) or a central comorbidity (stroke) in order to better understand the changes in proprioceptive function within the context of biological aging as opposed to chronological aging alone.

Young adults (Young, n = 42, 21.6 ± 2.2yrs), healthy older adults (Healthy Older, n = 21, 74.6 ± 4.8yrs), frail older adults (Frail Older, n = 25, 82.0 ± 6.9yrs), adults with peripheral neuropathy (Neuropathy, n = 39, 64.7 ± 12.7yrs), and adults with previous unilateral stroke (Stroke, n = 6, 75.7 ± 8.6yrs) underwent assessment of ankle joint movement perception threshold (JMPT) in the dorsiflexion (DF) and plantarflexion (PF) directions. The ankle joint was passively rotated at 0.25 deg/s and the subjects pressed

a stop button when they perceived joint movement. The change in degrees was recorded as the JMPT value.

Age was correlated with JMPT in both the PF ($r = 0.277$, $P = 0.001$) and DF ($r = 0.348$, $P < 0.001$) directions. JMPT was similar between Young and Healthy Older adults in both the PF and DF directions ($P > 0.50$). Neuropathy subjects demonstrated greater JMPT in both the PF (4.60 ± 3.91deg vs. 1.94 ± 1.29deg, $P = 0.003$) and DF (2.74 ± 1.79deg vs. 1.65 ± 1.05deg, $P = 0.041$) directions compared with Healthy subjects despite being 10 years younger. Plantarflexion JMPT was negatively correlated with PF strength ($r = -0.463$, $P = 0.026$) among Frail Older subjects.

Proprioceptive function at the ankle joint is similar between Young and Healthy Older adults. Those with peripheral neuropathy and stroke tended to have the greatest impairment in neuromuscular function. Therefore, chronological aging may not be related to proprioceptive declines, but rather aging with comorbidities may present the greatest challenge to proprioceptive function.

Introduction

The sense of body movement and position is the result of integration of afferent information from sensory receptors including the vestibular apparatus, muscle spindles, and cutaneous receptors (Proske, 2005). Impaired proprioception reduces postural stability and increases fall risk, especially among older adults (Gravelle et al., 2002; Laughton et al., 2003; Priplata, Patritti, Niemi, et al., 2006; van Deursen & Simoneau, 1999). Aging may progress healthfully, with frailty, or with comorbidities such as peripheral neuropathy or stroke, which are often accompanied by proprioceptive deficits (Priplata, Patritti, Niemi, et al., 2006; Simoneau et al., 1996). Understanding the

influence of biological aging (healthy vs. frail) and neuromuscular comorbidity (i.e. stroke or peripheral neuropathy) on proprioception can improve our understanding and help to identify sub-groups of older adults that may benefit from targeted interventions.

Muscle spindles are primarily responsible for the sense of limb position and movement within the overall proprioceptive system. Joint receptors contribute afferent feedback related to limb position at the extreme ends of the range of motion, and cutaneous sensor provide a secondary system for limb position sense (D. F. Collins et al., 2005); however, the sense of limb position and movement is intact in cases where the joint receptors and cutaneous sensors are inhibited or removed (Burgess & Clark, 1969; Grigg et al., 1973; Wall & Noordenbos, 1977). Muscle spindles have been shown to begin discharging sooner than cutaneous receptors in response to limb movement (Grill et al., 1997). Thus, muscle spindles represent a key source of proprioceptive feedback during movement.

Aging is associated with a loss in both extrafusal and intrafusal muscle fibers in humans (Swash & Fox, 1972). Animal models have shown that muscle spindles exhibit a selective degradation of the primary endings associated with both denervation and a change in morphology of the primary endings while the secondary endings are relatively preserved (Kim et al., 2007). The primary endings convey both limb position sense and joint movement perception, while secondary endings relay static limb position. Therefore, if there is an age-associated loss in spindle-mediated proprioception it would likely be manifested in the assessment of joint movement perception.

Functional declines with aging have been associated with the presence of frailty including increased fall risk (Fried et al., 2001). Previous studies have found

proprioceptive impairment at the ankle joint for older (66-74yrs) versus young (20-24yrs) adults (Thelen, Brockmiller, Ashton-Miller, Schultz, & Alexander, 1998), but these studies have not taken into account the potential influence of frail versus healthy aging. Other studies assessing dorsiflexor muscle spindle function in older adults have found that proprioceptive function is maintained at the level of the short-latency stretch reflex and H-reflex (Klass, Baudry, & Duchateau, 2011). The H-reflex bypasses the muscle spindle via direct electrical stimulation of the Ia afferent neuron; however, the short-latency stretch reflex involves both the muscle spindle and the stretch reflex circuitry at the spinal level, thus proprioceptive impairment may be the result of central processing decrements as opposed to peripheral denervation (Klass et al., 2011).

The purpose here is to assess proprioceptive change with chronological aging (young vs. old), biological aging (healthy vs. frail), and aging accompanied by either peripheral or central neural comorbidities (peripheral neuropathy patients, stroke survivors). Joint movement perception threshold is a quantitative measure of proprioceptive function conveyed by the muscle spindle primary afferents. By assessing isolated joint movement perception in these populations we can gain a greater understanding of proprioceptive deficits and how to improve postural stability and reduce fall risk. We also chose to incorporate measures of ankle force production in the sagittal plane. Ankle muscle weakness is associated with increased postural sway, especially among those with recent falls (Cattagni, Scaglioni, Laroche, Gremeaux, & Martin, 2016). If the subject groups demonstrate both proprioceptive and strength impairment it may be an indication of a more global neuromuscular dysfunction.

Methods

Subjects

The subjects were sourced from separate studies which all utilize the same testing apparatus and experimental protocol for data collection and analysis. Healthy young adults (Young) 18-27 yrs (21.6 ± 2.2 yrs, 22 males, 20 females) were screened for previous ankle sprains requiring medical treatment, muscle soreness, or unusual leg exercises in the prior 24 hr period. See Table 2.1 for detailed subject characteristics. Older adults 67-94 yrs (78.6 ± 7.1 yrs, 23 males, 23 females) were screened for cardiovascular or neurological conditions which would affect the dependent variables and then divided into two groups based upon frailty status (Healthy Older and Frail Older) using a frailty index that we developed according to a standard method (Searle, Mitnitski, Gahbauer, Gill, & Rockwood, 2008). A list of the frailty index components and the scoring cut-points can be found in Appendix A. Subjects with physician-diagnosed peripheral neuropathy (Neuropathy) in the lower extremity were between 38-92 yrs (64.7 ± 12.7 yrs), and subjects who had experienced a hemiparetic stroke (67-90 yrs, 75.7 ± 8.6 yrs) were assessed bilaterally and the stroke-paretic (SP) and relatively unaffected stroke-non-paretic (SNP) legs were treated separately for the analysis. All subjects were oriented to the testing protocol and provided written informed consent prior to testing. The procedures were approved by the Human Subjects Committee at Colorado State University.

Testing Apparatus

A custom, testing apparatus was used in order to allow controlled passive movement of the ankle in the sagittal plane with continuous monitoring of ankle angle

(Figure 2.1). The same device has been used previously in assessing proprioception at the ankle (Simoneau et al., 1996). The speed of the ankle rotation was set at 0.25 degrees per second. Previous studies assessing JMPT at the ankle using several different speeds found that the 0.25 deg/s speed was optimal for discriminating sensory impairment (Simoneau et al., 1996), and is faster than the 0.16 deg/s sway speed that occurs at the ankle in the sagittal plane during normal quiet standing among young adults (Winter, Patla, Prince, Ishac, & Gielo-Perczak, 1998). The lateral malleolus of the subject was aligned with the axis of rotation of the testing device and the angular position of the platform (ankle angle) was measured with digital inclinometers as it rotated in either the plantarflexion or dorsiflexion directions. Platform rotation was initiated by the investigator and interrupted by the subject via a stop button. Rigid restraints with nylon/velcro straps were used to stabilize the lower leg during testing and reduce the influence of postural sway on the proprioceptive perception. A sturdy railing surrounded the subject in front and on the sides, and the subjects were instructed to hold on to the railing during testing with their thumb resting on the stop button. For stroke subjects the button push was performed by the unaffected hand if relevant.

Experimental Tasks

Preparation

Tape was used to mark the foot position for accurate replacement in case of movement between trials. The lower leg was strapped into the rigid restraints so that the muscles of the ankle could be as relaxed as possible during the trials. Headphones that played white noise were placed over the ears to prevent subjects from hearing the actuator or investigator communication during test trials. Subjects were instructed to

look straight ahead at the wall during trials. All subjects were oriented to the protocol with a standardized set of instructions.

Protocol

The subjects were told which ankle would be rotating during the trials. Platform rotation was initiated by the investigator at varying times so that the subject would be unaware of when the rotation began. Subjects were instructed to push the stop button the moment they perceived ankle rotation and they could determine which direction their ankle had rotated. The direction (PF or DF) of rotation for each trial was randomized among the subjects. The difference in ankle angle between the start position and the position at which the subject pressed the stop button was taken as the joint movement perception threshold (JMPT, deg). Two trials were performed in each direction and the average value was calculated. Only the trials where the subject accurately identified the direction of rotation (PF or DF) were used for the statistical analysis.

Force Measurements

Isometric maximal voluntary contraction (MVC) data was available for the plantarflexor and dorsiflexor muscles for all of the subject groups, except for the Young group. Briefly, the subjects were seated in a custom apparatus with the foot secured to an adjustable footplate. The load cell was positioned under the ball of the foot aligned with the first metatarsophalangeal joint. The subjects were given visual feedback as they performed maximal contractions with either the plantarflexor or dorsiflexor muscles. Three to five trials were performed, in order to obtain two trials where the maximal force was within five percent of each other. At least 30 seconds of rest between trials. The

greatest force from the maximal force trial was used for data analysis (Tracy & Enoka, 2002).

Statistical Analysis

A one-way analysis of variance (ANOVA) was used to assess the differences between each of the six groups. Given the difference in sample size between groups, the Games-Howell post-hoc test was used to remedy heterogeneity of variance in dataset as determined by the Levene Statistic ($P<0.05$). Bivariate correlations were used to assess relations between dependent variables within groups. Alpha was set at $P<0.01$ for the correlational analyses to minimize the likelihood of a type I error. A paired-samples t-test was used to analyze the differences between the paretic and non-paretic legs of the Stroke subjects. The subjects included in the other groups were tested unilaterally based upon a non-significant difference between limbs as described in previous research (Simoneau et al., 1996) The analyses were performed using SPSS (IBM, SPSS Statistics ver.22).

Results

Age Effects

The age was similar between the Healthy Older (74.6 ± 4.8yrs) and Stroke subjects (75.7 ± 8.6yrs, $P = 0.999$). Healthy Older adults were significantly younger than Frail Older adults (82.0 ± 6.9yrs, $P = 0.001$) and significantly older than those with peripheral neuropathy (64.7 ± 12.7yrs, $P = 0.001$). Frail Older adults were also significantly older than the Neuropathy subjects ($P < 0.0001$).

Age was significantly correlated with PF ($r = 0.277$, $P = 0.001$) and DF JMPT ($r = 0.348$, $P < 0.001$, Figure 2.2) across all groups. Age, however, was not correlated with

JMPT among Frail and Healthy subjects (P > 0.11). Among young and older adults, without neuropathy or stroke, the regression equation for the PF direction (y = 0.01x + 1.34) indicated a 0.01 degree increase in JMPT per year. Similarly, the regression equation for the DF direction (y = 0.01x + 0.86) demonstrated a 0.01 degree increase in JMPT for each year.

Group Differences by Direction

The JMPT was similar between the Young and the Healthy Older in the PF (P = 0.972, Figure 2.3a) and DF directions (P = 0.504, Figure 2.3b), while the difference between Young and Frail Older neared significance (P = 0.056). The PF JMPT was significantly greater among the Neuropathy compared with Young, Healthy Older, and Frail Older subjects (Figure 2.3a). Neuropathy JMPT was also significantly greater than Young and Healthy Older subjects in the DF (Figure 2.3b) direction even though the Neuropathy subjects were significantly younger than the Healthy Older subjects (P = 0.001). When comparing JMPT among the older adult groups, the Neuropathy group demonstrated greater PF JMPT than the Frail Older group (P = 0.04). There were no significant differences in JMPT between the Stroke-Paretic (SP) or Stroke-Non-Paretic (SNP) legs (P = 0.46) and the other subject groups.

Pooled across groups, PF JMPT is correlated with DF JMPT (r = 0.634, P < 0.0001, Figure 2.4) and when split by group this correlation is persistent among Young (r = 0.755, P < 0.0001), Frail Older (r = 0.579, P = 0.007), and Neuropathy subjects (r = 0.568, P < 0.0001).

Proprioception and Strength

There are no MVC values for the young adults in this compiled sample. Pooled across groups, PF MVC was correlated with DF MVC ($r = 0.614$, $P < 0.0001$, Figure 2.5) and when split by group this correlation was persistent among the Neuropathy subjects ($r = 0.839$, $P < 0.0001$). PF MVC was significantly different between Healthy Older vs. Frail Older subjects (493 ± 215N vs. 274 ± 116N $P = 0.033$). DF MVC was significantly different between Healthy Older vs. Neuropathy (263 ± 63.0N vs. 205 ± 85.4N, $P = 0.049$), Healthy Older vs. SP (263 ± 63.0N vs. 109 ± 60.4N, $P = 0.003$), Frail Older vs. SP (217 ± 75.4N vs. 109 ± 60.4N, $P = 0.028$), and Neuropathy vs. SP (205 ± 85.4N vs. 109 ± 60.4N, $P = 0.054$). There were no differences between the SP and SNP groups for both JMPT and MVC (all $P > 0.05$). PF JMPT was negatively correlated with PF strength ($r = -0.463$, $P = 0.026$) among Frail Older subjects.

Discussion

The main findings were 1) proprioception was similar between Young adults and Healthy Older adults in both the PF and DF directions, 2) movement perception threshold for Neuropathy subjects was significantly greater (impaired) for the DF and PF directions compared with the Healthy Older subjects despite being 10 years younger than the Healthy Older subjects, 3) movement perception threshold was correlated between the DF and PF directions.

Aging

The positive correlation of JMPT with age across the 20-94 yr age range suggests an incremental impairment when the comparison includes young adults. However, for the older group (healthy and frail older adults pooled), JMPT was not

correlated (did not rise significantly) with chronological age. In fact, the lack of difference in JMPT between Young adults and Healthy Older adults indicates that healthy aging is not necessarily accompanied by proprioceptive impairment. Although the proprioception values were not significantly lower for the Frail Older adults than the Healthy Older adults, the mean values for proprioception and strength consistently trended in the direction of impairment for Frail Older adults. The Frail Older group JMPT was greater (impaired) compared with the Young adult group in the DF direction. Therefore, the frailty phenotype may be accompanied by changes in the somatosensory system that are greater than those observed for purely chronological age.

There is a loss of intrafusal muscle fibers in humans associated with aging (Swash & Fox, 1972) and a selective denervation of primary endings within rodent models of aging (Kim et al., 2007), yet other studies have demonstrated that muscle spindle reflex arc function (from the H-reflex) is preserved with age in the DF muscles (Klass et al., 2011). It is possible that age-related alterations in muscle spindle number and morphology may vary between muscles. For example, researchers found an age-related reduction in the diameter and number of muscle spindles in the deltoid muscle, but not in the quadriceps femoris (Kararizou, Manta, Kalfakis, & Vassilopoulos, 2005). Therefore, although the generalized pattern in which human muscle spindles age is not clearly defined, perhaps comorbidities are an important driver of the relationship between age and proprioceptive impairment either by affecting the peripheral muscle receptors, as in peripheral neuropathy (Muller, Ryals, Feldman, & Wright, 2008), or central processing, as with stroke (Ben-Shabat, Matyas, Pell, Brodtmann, & Carey, 2015). Although it is common to differentiate older adults versus those with peripheral

neuropathy or stroke, it is less common for studies to differentiate between frail and healthy aging. This may strengthen the rationale to integrate a battery of frailty indicators in future aging research.

Peripheral Neuropathy

Peripheral neuropathy significantly impacted both strength and proprioception. Neuropathy subjects exhibited greater JMPT values in both the PF and DF directions when compared with Healthy Older adults, and in the PF direction when compared with Frail Older adults. Previous studies found impairments in JMPT among those with diabetic peripheral neuropathy in both PF and DF directions, though the subjects were around 10 years younger than our subject group (Simoneau et al., 1996). Studies in murine models of diabetes demonstrated altered muscle spindle morphology and innervation, yet there is still no clearly defined mechanism related specifically to the neuropathy that often accompanies diabetes (Muller et al., 2008).

Dorsiflexor strength was significantly less for Neuropathy subjects than Healthy Older adults. Muscle strength was also correlated between the PF and DF directions, indicating that those who exhibited motor weakness were relatively consistent across both movement directions. Motor weakness at the ankle corresponds to the severity of neuropathy for subjects in the 44-69 year range compared with age-matched controls (Andersen, Nielsen, Mogensen, & Jakobsen, 2004); however the reduction in strength associated with peripheral neuropathy appears to be independent of diabetes. Andersen et al. compared diabetic patients with and without peripheral neuropathy and found that the subjects with neuropathy exhibited a 41% reduction in ankle strength and a 65% reduction in distal muscle mass compared with diabetics that did not have

neuropathy (Andersen, Gadeberg, Brock, & Jakobsen, 1997). Animal models of diabetes have been utilized to determine the cause for reduced strength, including slowed motor conduction velocity and denervation, however the findings are still unclear (Wilson & Wright, 2014). Therefore, those with a peripheral comorbidity such as neuropathy are likely to have impaired proprioceptive function and muscle strength as a result of the disease process apart from aging.

Stroke

The stroke subjects were very similar in age to the Healthy Older adults, yet they had poorer proprioception in the PF direction (Figure 2.3a) along with significantly reduced strength in the PF and DF muscles. Although the Stroke-Paretic limb tended to have more severe impairment, the differences in proprioception and strength between Stroke-Paretic and Stroke-Non-Paretic failed to reach statistical significance, owing presumably to the relatively small number of subjects in that group.

The stroke subjects most likely experience proprioceptive impairment at the cortical level (Ben-Shabat et al., 2015; Perennou et al., 2000). A recent study found that vibration of muscle tendon at 70Hz was able to improve limb stability in hemiparetic stroke survivors, presumably by activating muscle spindles and enhancing the quality of sensorimotor information processing within the cortex (Conrad, Gadhoke, Scheidt, & Schmit, 2015; Smith & Brouwer, 2005). This implies that although hemiparetic stroke is a comorbidity that impairs proprioception compared with healthy aging, the fact that the central lesion spares peripheral proprioceptive (spindle) afferents suggests a potential for some level of stability recovery via enhanced activation of the sensorimotor system. The aforementioned study assessed the upper extremity, thus further investigation is

needed to explore the potential for proprioceptive enhancement at the ankle joint with the aim of reducing fall risk.

Limitations

This study is limited in that the results may only be generalizable to passive movements of the ankle. Other measures of proprioception, such as joint position perception, could contribute to a more complete understanding of the complex integration of sensory information needed to perform active functional movements.

The proprioception and strength measurements in this study are unable to determine the source of neuromuscular dysfunction. It is presumed that deficits among those with peripheral neuropathy are representative of peripheral denervation and that the deficits among the stroke subjects are the result of cortical impairment, yet here there were no direct measurements of neural transmission performed that would allow the exact source of impairment to be determined.

The sample sizes for the older adult groups were highly variable, and thus the relationships between the subject populations such as the stroke and frailty groups may have been statistically underpowered.

Conclusion

This study measured ankle joint movement perception across a large age range in a controlled manner while in a passive standing position. The results suggest that normal healthy older adults exhibit proprioceptive sensation that is similar to younger adults, yet frail older adults demonstrate impaired proprioception compared with young adults. Those with peripheral neuropathy and stroke exhibit proprioceptive and strength impairment compared with healthy older adults. Therefore, healthy aging without

comorbidities such as stroke, peripheral neuropathy, or frailty may not necessarily be accompanied by significant deficits in ankle joint movement sense.

TABLE

Table 2.1: Subject Characteristics

Group	n	Age Range (yrs)	Age (Mean, SD)	BMI (kg/m^2)
Young	42	18-27	21.6, 2.2	23.3
Healthy	21	67-83	74.6, 4.8	25.5
Frail	25	67-94	82.0, 6.9	27.1
Neuropathy	43	38-92	64.7, 12.7	31.8
Stroke	6	67-90	75.7, 8.6	25.2

FIGURES

Figure 2.1: Proprioceptive Testing Apparatus

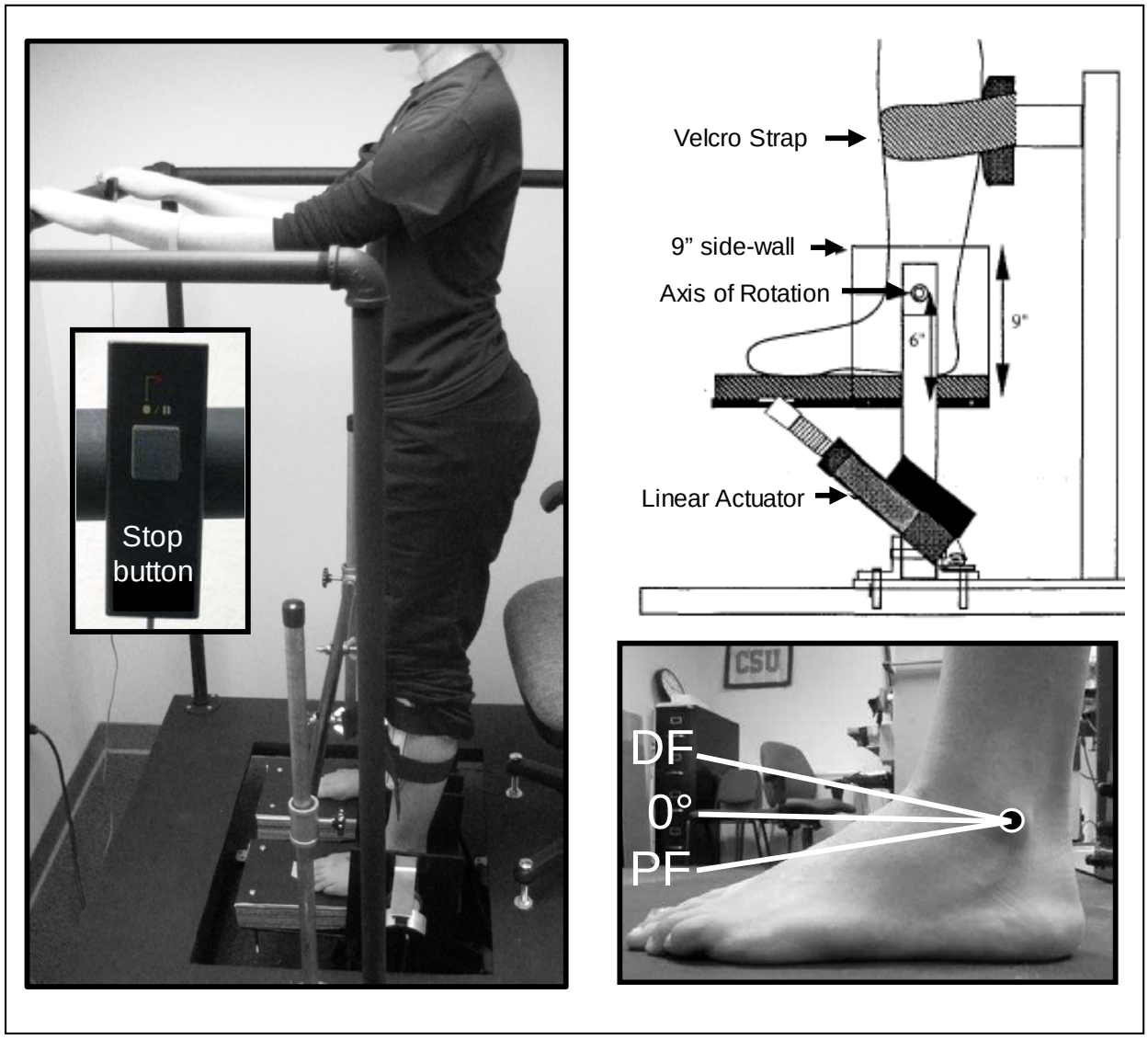

Figure 2.1. Depiction of experimental setup. Foot platforms are slowly rotated by an actuator located below the platform. Inclinometers register the angular movement of the platform. Lower legs are strapped to rigid restraints. The subject is standing erect with hands on railing, looking straight ahead, thumb on a stop button, and listening to white noise via headphones.

Figure 2.2: Age and JMPT Performance

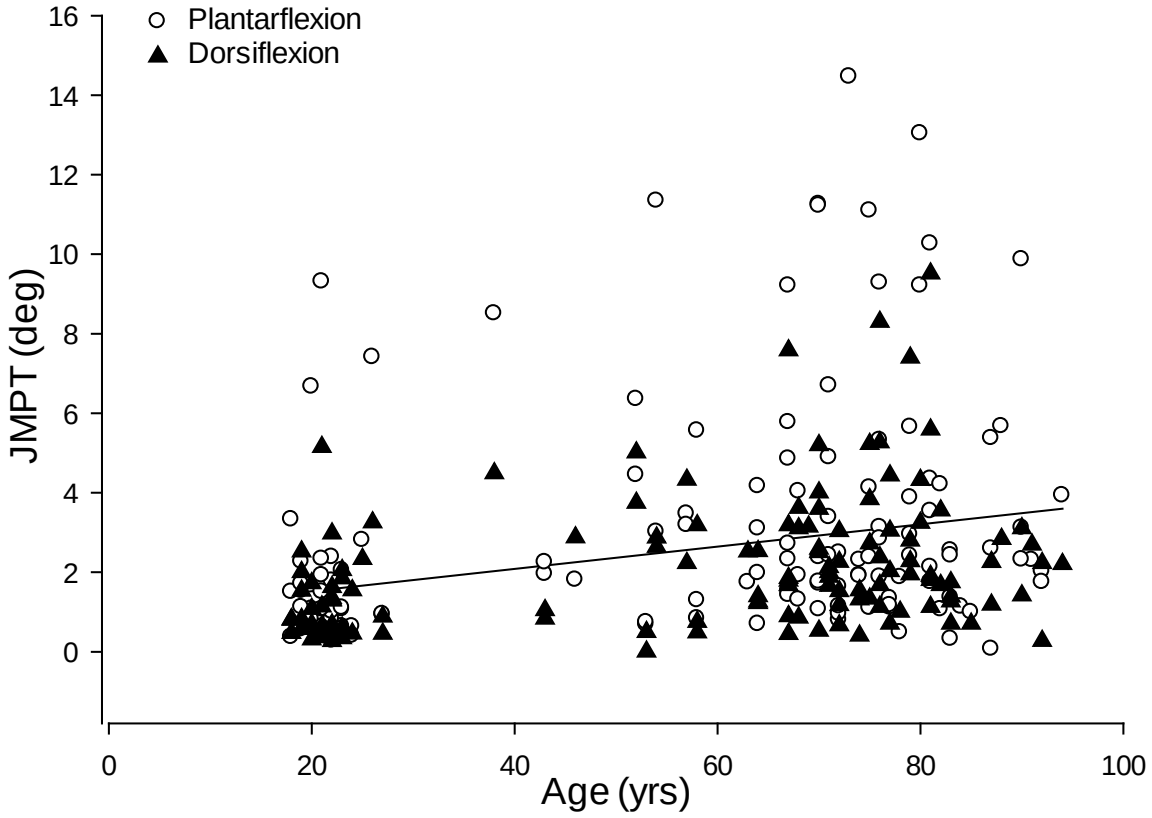

Figure 2.2. Pooled across group, age was significantly correlated with PF ($r = 0.277$, $P = 0.001$) and DF JMPT ($r = 0.348$, $P < 0.001$) joint movement perception threshold (JMPT, deg).

Figure 2.3: Group JMPT Performance in the Plantarflexion and Dorsiflexion Directions

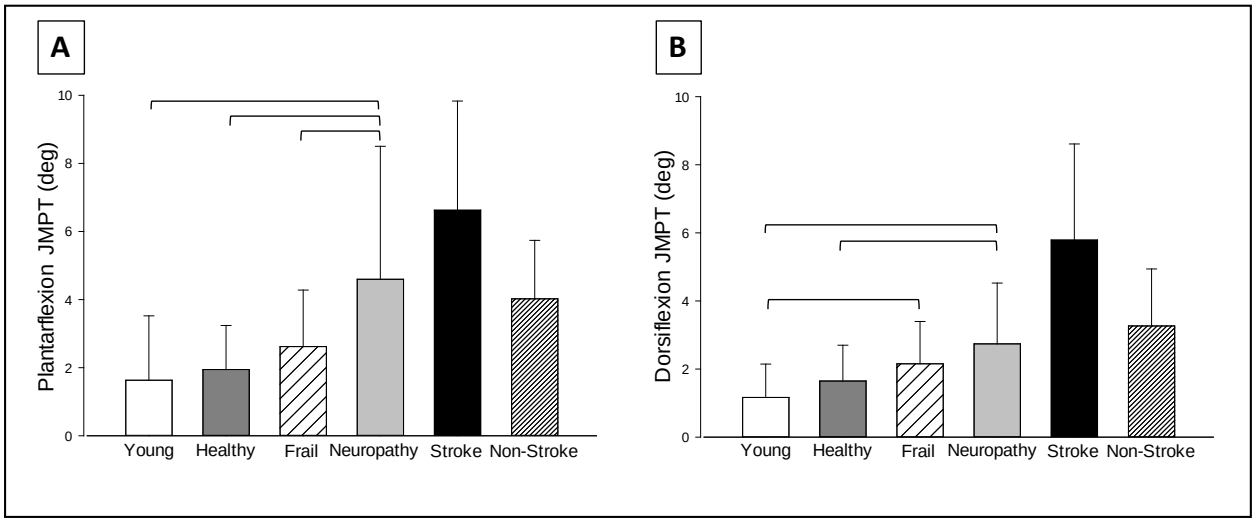

Figure 2.3. A) Average JMPT performance for each group in the plantarflexion direction. Neuropathy subjects had significantly poorer joint movement perception compared with Young (P = 0.001), Healthy (P = 0.003), and Frail (P = 0.04) subjects. B) Average JMPT performance for each group in the dorsiflexion direction. Neuropathy subjects had significantly poorer joint movement perception compared with Young (P < 0.001), Healthy (P = 0.041) and Frail (P = 0.028) subjects. Young adults were significantly different than Frail Older adults (P = 0.056) subjects in the DF direction.

Figure 2.4: JMPT Directional Correlation

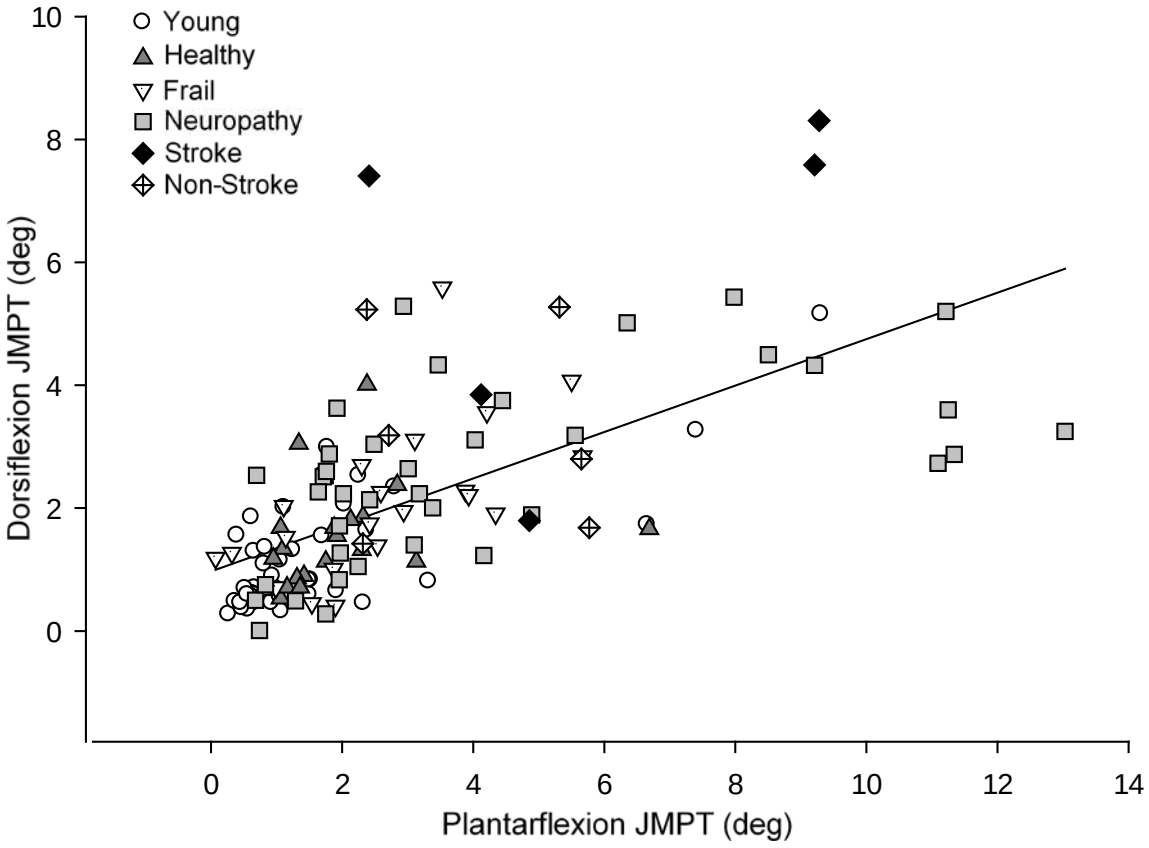

Figure 2.4. Pooled across groups, plantarflexion joint movement perception is correlated with dorsiflexion joint movement perception ($r = 0.634$, $P < 0.0001$), and when split by group this correlation is persistent among Young ($r = 0.755$, $P < 0.0001$), Frail ($r = 0.579$, $P = 0.007$), and Neuropathy subjects ($r = 0.568$, $P < 0.0001$).

Figure 2.5: Strength Correlations

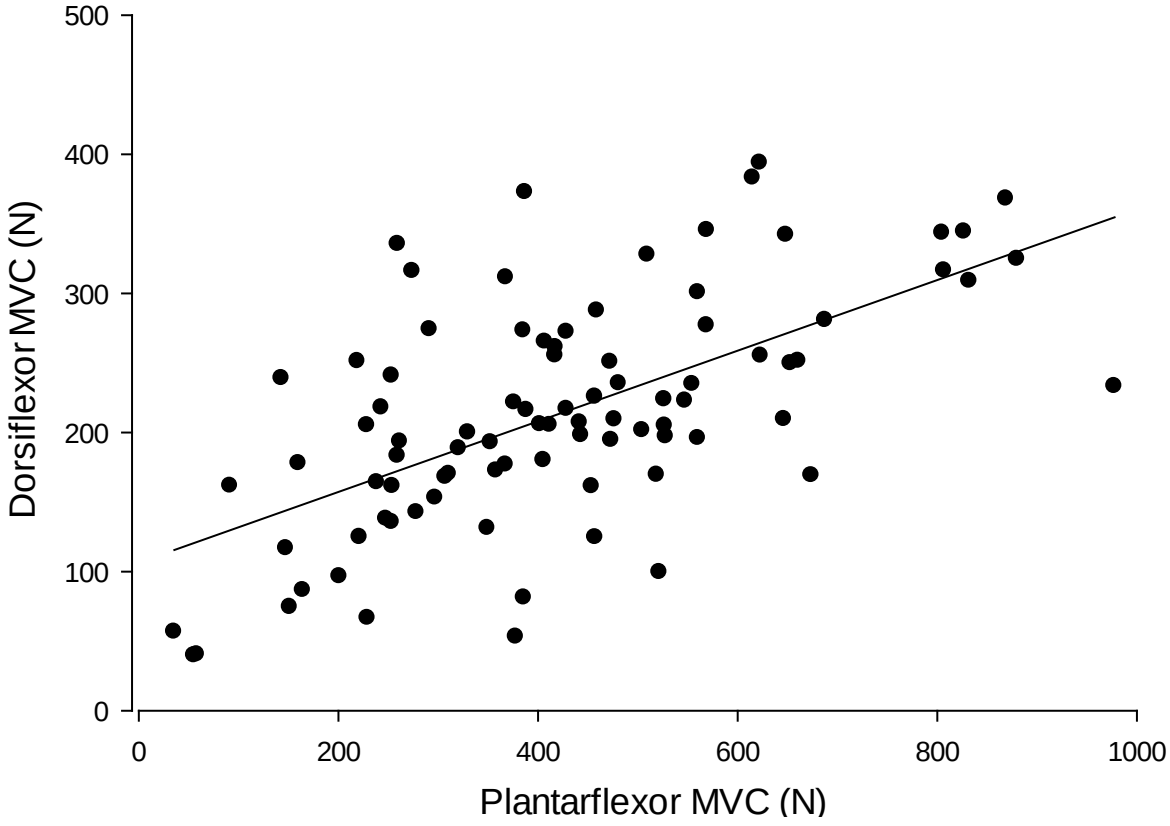

Figure 2.5. A) Pooled across groups, plantarflexor strength was correlated with dorsiflexor strength ($r = 0.614$, $P < 0.0001$).

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CHAPTER III – MANUSCRIPT II

Sub-sensory mechanical noise input to ankle tendons improves movement detection

Summary

Joint position sense is conveyed in part by muscle spindles. Low amplitude mechanical noise input to tendons, in-vivo, can alter both muscle spindle afferent discharge. The purpose of this study was to determine whether sub-sensory vibration applied to the plantarflexor and dorsiflexor tendons would improve ankle movement detection in the sagittal plane.

Healthy 18-27 yr-old adults (21.3 ± 2.34 yrs) underwent assessment of joint movement perception threshold (JMPT). The ankle rotation that produced perception of movement was recorded during slow (0.25 deg/s), passive, unilateral ankle dorsiflexion (DF) and plantarflexion (PF) on a motorized platform. Trials were performed in DF and PF directions, with (VIB) or without (NOVIB) tendon vibration. VIB was applied to the Achilles and tibialis anterior tendons at just below the subject-reported cutaneous sensory threshold via strap-mounted vibrating discs.

Pooled across movement directions, JMPT was less for VIB than NOVIB (1.11 ± 1.35 deg vs.1.40 ± 1.52 deg, P=0.002). The effect of VIB was similar for DF (0.94 ± 0.58 deg vs. 1.17 ± 0.98 deg) and PF (1.29 ± 1.82 deg vs. 1.63 ± 1.89 deg). Pooled across VIB conditions, JMPT was less for the DF than PF direction (1.05 ± 0.81 deg vs. 1.46 ± 1.85 deg, P=0.03). JMPT was correlated between DF and PF directions for both the VIB

(r=0.66, P<0.0001) and NOVIB (r=0.76, P<0.0001) conditions. The change in JMPT between VIB and NOVIB was correlated with JMPT for the DF (r=-0.82, P<0.0001) and PF (r=-0.32, P=0.04) directions.

Sub-sensory mechanical noise to ankle tendons improved detection of ankle joint movement. The improvement was greater for those with worse movement detection. The data suggest that sub-sensory mechanical input to tendons can improve proprioception, perhaps by increasing the sensitivity of muscle spindles to changes in muscle length.

Introduction

The critical role of proprioception in neuromuscular control, as well as the functional consequences of degraded proprioception, as with older adults or peripheral neuropathy patients, have been clearly established (Butler et al., 2008; Priplata et al., 2003; Priplata, Patritti, Niemi, et al., 2006). Multiple receptors are involved in the messaging of joint position and movement. Removal of cutaneous feedback in the hand was revealed to greatly impair movement detection (Gandevia & McCloskey, 1976; Provins, 1958; Refshauge, Kilbreath, & Gandevia, 1998). Joint receptors are thought to signal the extremes of joint motion (Burgess & Clark, 1969), but interestingly, degraded joint receptor feedback does not produce substantial proprioceptive deficits (Barrack, Skinner, Cook, & Haddad, 1983; Ferrell, 1987; McNair, Marshall, Maguire, & Brown, 1995). Due to their sensitivity to changes in muscle length, muscle spindles provide an important contribution to the proprioceptive message (Cordo et al., 1996; Roll & Vedel, 1982; Smetacek & Mechsner, 2004).

Due to tensioning of intrafusal muscle fibers, the discharge of spindle afferents is most robust during muscle lengthening (Inglis, Frank, & Inglis, 1991). Muscle spindle

primary afferents are also frequency- and amplitude-responsive to vibratory stimuli (Burke et al., 1976). Robust tendon vibration dramatically increases the discharge rate of spindle afferents, resulting in a perceptual illusion of muscle lengthening, substantial proprioceptive error, and functional effects such as postural instability (Eklund, 1972; Goodwin, McCloskey, & Matthews, 1972b; Roll & Vedel, 1982).

Much smaller amplitude mechanical noise has been shown to alter the responsiveness of sensory systems. For example, very low amplitude vibration applied to tendon or skin can enhance the sensitivity of proprioceptors and cutaneous receptors (J. J. Collins, Imhoff, & Grigg, 1996; Cordo et al., 1996). Many studies have reported increased detection of small stimuli with sub-sensory noise, thus enhancing tactile sensation in diabetics, stroke survivors, and healthy subjects (J. J. Collins et al., 1996; W. Liu et al., 2002). Furthermore, an unpublished report documented reduced postural sway in young and elderly adults during application of sub-sensory mechanical noise to ankle tendons (Priplata, Patritti, Niemi, et al., 2006), and Magalhães et al (Magalhaes & Kohn, 2012) demonstrated that sub-sensory mechanical noise applied to the triceps surae decreased plantaflexor force fluctuations and improved postural sway.

Given 1) the exquisite sensitivity of muscle spindles, 2) the importance of muscle spindle discharge in the detection of joint movement, and 3) the evidence that small amplitude noise applied to intact human muscle-tendon units can increase the responsiveness of spindle afferents during extremely small joint movements (Cordo et al., 1996), the purpose of this study is to determine the effects of mechanical noise applied to tendons on movement perception at the ankle. We hypothesize that mechanical noise will reduce the threshold of movement detection (Cordo et al., 1996;

Inglis et al., 1991). These results have been presented in abstract form previously (Paxton et al., 2011).

Methods

Experimental Procedures

Subject Characteristics

Healthy 18-27 yr-old adults (21.3 ± 2.34 yrs, 22 men, 20 women) provided informed consent and were oriented to the protocol. Subjects were screened for sprains in the dominant (test) ankle severe enough to require medical treatment. Subjects reported no caffeine intake in the previous four hours, no lower leg muscle soreness, and no unusual sleep patterns or unusual leg exercise within 24 hours that could affect testing. Two subjects reported significant ankle sprains and thus the non-dominant ankle was tested. The height, body mass, and body mass index (BMI) of the subject sample was 1.74m ± 0.089 m, 71.04kg ± 10.24 kg, and 23.3 ± 2.62 kg/m^2, respectively. The sensory threshold was 1.68 ± 0.424 (range 0.5-2.3) arbitrary gain units on the tactor amplifier. Subjects were oriented and provided signed informed consent. The procedures were approved by the Human Subjects Committee at Colorado State University.

Testing Apparatus

A custom-designed, instrumented testing rig was used to provide continuous measurement of ankle angle during controlled, passive, isovelocity rotation of the ankle in the sagittal plane (Figure 3.1A). The device was used previously to assess ankle

proprioception (Simoneau et al., 1996). Platform rotation was controlled by mechanical actuators, monitored with digital inclinometers (Lucas Sensing Systems, Inc.), and could be initiated randomly by the investigator and stopped by the subject via a stop button. The ankle was aligned with the platform axle to match the rotation of the device and the ankle. The front of the lower leg was strapped to a rigid restraint. A railing surrounded the subject.

Mechanical noise was delivered to the dorsiflexor (DF) and plantarflexor (PF) tendons via two vibrating discs (C-2 tactors, Engineering Acoustics, Inc.) attached to the inside of an elastic/velcro ankle strap (Figure 3.1D). The tactors are discs 28 mm in diameter, 8 mm thick, with a 9 mm diameter round vibrating surface in the center of one side of the disc. The position of the tactor on the inside of the strap was adjustable. The strap was wrapped around the distal shank and carefully adjusted so that the vibrating element of the tactors was placed directly on the DF (tibialis anterior) and PF (Achilles) tendons just above the ankle. The tactors were excited with amplitude-adjustable, Gaussian noise played through an amplifier. The noise contained significant power in frequencies between 10 and 100 Hz with a broad peak in the power spectrum from 15-40 Hz (Figure 3.1F).

Experimental Tasks

Preparation

The apparatus was adjusted for each subject. Foot position was marked to ensure accurate repositioning between trials when necessary. The tractor strap remained in place for all vibration and no-vibration trials. The lower leg was strapped in

place immediately before testing. During trials white noise was played through headphones to mask the sound of the actuator. Subjects were standing and gazed straight ahead at a blank wall (1m), and handrails were lightly grasped. Subjects were oriented with standardized instructions.

Vibration sensory threshold

Prior to testing, the sensory threshold was measured by slowly increasing the gain of the noise until the subject confirmed feeling the vibration. After several seconds, the vibration was applied well above threshold and slowly decreased until the subject reported an absence of vibration. The smaller of the threshold amplitude values from the increasing and decreasing trials was taken as the sensory threshold value. During the vibration (VIB) test trials, the vibratory stimulus was delivered at an amplitude just below the cutaneous sensory threshold for vibration (W. Liu et al., 2002) so that the subject would not be aware of which condition was being tested (VIB vs. NOVIB). The sensory threshold (1.68 ± 0.42 arbitrary gain units) was not different between men and women ($P = 0.22$). Subjects were queried between trials to ensure they could not perceive the vibration via cutaneous sensation.

JMPT Testing Trials

For a test trial, subjects were told that the movement would start sometime in the next several seconds. White noise was then played into the headphones. Platform rotation was initiated by the investigator at varying times so that the subject was unaware of when the rotation began. Subjects were instructed to push the stop button the moment they perceived ankle rotation.

Prior to the test trials one NOVIB practice trial was given in each movement direction. Two test trials were performed in each movement direction (DF, PF) and vibration condition (VIB, NOVIB), for a total of eight trials. The order of presentatifon of NOVIB and VIB conditions was counterbalanced so that half of the subjects either did all VIB trials first followed by NOVIB, or vice versa. Within each vibration condition, the DF and PF movement directions were randomly presented. Ten seconds rest was given between trials and three minutes of seated rest was given between vibration conditions. The tactors were excited only for the duration of each VIB trial. The difference in ankle angle between the start position and the position at which the subject pressed the stop button was taken from the inclinometer and recorded as joint movement perception threshold (JMPT, degrees).

Statistical Analysis

The statistical analysis included a between-subjects comparison between men and women as previous studies have explored sex-related difference in ankle JMPT in the seated position, but not in the standing position (Ko et al., 2015). Repeated-measures analysis of variance (RMANOVA) was used to assess sex differences, the effect of vibration, and the effect of movement direction on JMPT. The between-subjects variable was sex (men, women) and the within-subjects variables were vibration condition (VIB, NOVIB) and movement direction (DF, PF). A repeated-measures analysis of the practice trials versus the experimental trials within each movement direction showed no systematic change in JMPT, thus the mean of two test trials within vibration condition and movement direction were taken as the JMPT outcome.

Results

Vibration and Direction Effects

Pooled across movement directions, JMPT was less for the VIB compared with NOVIB conditions (1.11 ± 1.35 vs. 1.40 ± 1.52 deg, P = 0.002, Figure 3.2A). There were no differences (vibe x direction interaction, P = 0.52, Figure 3.2B) in the vibration effect (VIB vs. NOVIB) between the DF direction (0.94 ± 0.58 vs. 1.17 ± 0.98 deg) and PF direction (1.29 ± 1.82 vs. 1.63 ± 1.89 deg). Pooled across vibration conditions, JMPT was less for DF than PF (1.05 ± .0.81 vs. 1.46 ± 1.85 deg, P = 0.03).

Sex Effect

Pooled across movement directions and vibration conditions, there were no significant differences in JMPT between men and women (0.94 ± 0.65 vs. 1.54 ± 1.94 deg, P = 0.15). Additionally, there were no differences (vibe x direction interaction, P = 0.44) in the vibration effect (VIB vs. NOVIB) for men (0.88 ± 0.53 vs. 1.10 ± 0.74 deg) compared with women (1.36 ± 1.86 vs. 1.72 ± 2.02 deg). However, there was a larger difference (sex x direction interaction, P = 0.03) in JMPT between DF and PF directions for women (DF: 1.11 ± 0.94 vs. PF: 1.97 ± 2.52 deg) compared with men (DF: 1.00 ± 0.67 vs. PF: 0.99 ± 0.63 deg). Thus it appears that the differences observed for the women account for the differences in JMPT found between the DF and PF directions.

Correlations Between Movement Directions

Within subjects, JMPT values were positively correlated between DF and PF for the VIB (r = 0.66, P < 0.0001) and NOVIB (r = 0.76, P < 0.0001) conditions (Figure

3.3A). The change in JMPT from NOVIB to VIB condition was negatively correlated with JMPT in the NOVIB condition for both the DF ($r = -0.82$, $P < 0.0001$) and PF ($r = - 0.32$, $P = 0.04$) directions (Figure 3.3B), such that subjects with greater NOVIB JMPT values experienced the greatest change with the VIB condition.

Discussion

The main findings were 1) very low amplitude (sub-sensory) mechanical noise applied to the dorsiflexor and plantarflexor tendons significantly decreased the threshold for perception of joint movement in both the dorsiflexion and plantarflexion directions, 2) movement perception threshold was lower in the dorsiflexion than plantarflexion direction, 3) movement perception threshold was correlated between the dorsiflexion and plantarflexion direction, and 4) the reduction in movement perception threshold with vibration was larger for subjects with relatively greater movement perception thresholds.

The vibration used was similar in amplitude and application to previous studies that attempted to alter the sensitivity of foot sole sensory receptors (Priplata et al., 2003) and the sensitivity of leg muscle spindles via tendon vibration (Priplata, Patritti, Rosengarten, et al., 2006). Intraneural recordings of cutaneous afferents during vibration of the tibialis anterior tendon demonstrated the relative silence of the cutaneous sensors during this form of stimulation (Vedel & Roll, 1982), which supports the importance of the muscle spindle in joint movement perception. Importantly, the purpose of this vibration was not to produce robust discharge of spindle afferents as can be readily accomplished with larger amplitude (1-3mm), ~100 Hz vibratory tendon

stimuli (Matthews, 1966). Rather, we sought to bring spindle afferents closer to discharge threshold and thereby increase the likelihood of afferent discharge in response to joint movement and change in muscle length. Other studies have argued that an external vibratory stimulus (80-120 Hz) applied to tendon may produce spindle afferent firing that is more robust than during lower frequency natural movements, and thus overestimate the contribution of muscle spindle activity to the joint movement perception (B. Edin, 2001). The utilization of very low amplitude, 15-40 Hz noise serves to minimize this confounding feature of more robust vibration stimulation.

Stochastic noise, applied to cutaneous foot sole receptors via custom footbeds, has been shown to reduce the amplitude of postural sway in older adults and sensory-impaired neuropathy patients, ostensibly due to enhanced sensory information about changes in foot sole pressure during standing (Priplata et al., 2003; Priplata, Patritti, Niemi, et al., 2006). Also, an unpublished report suggested that similar sub-sensory noise input to the dorsiflexor and plantarflexor tendons was sufficient to improve some parameters of postural sway in young and older adults (Priplata, Patritti, Rosengarten, et al., 2006). The present data suggest that a very small amplitude noise input to tendons can reduce the threshold for movement detection in healthy young adults with normal sensory function. A likely explanation for this result is that some of the mechanical noise input to the tendon was successfully transferred to some of the muscle spindles, bringing them closer to discharge threshold. During the vibration condition, the small amount of muscle lengthening produced by the passive joint rotation may have elicited action potentials in the primary spindle afferents slightly

sooner and more robustly, providing a proprioceptive message that was more robustly perceived in cognitive centers compared with the no-vibration condition.

The notion that this small mechanical input to tendons could affect muscle spindle activity aligns with several observations in basic and applied neurophysiology. First, the muscle spindle is exquisitely sensitive to very small mechanical perturbations. For example, Matthew's seminal work demonstrated that spindle afferents will discharge action potentials in response to sinusoidal length changes of the muscle-tendon unit of less than 5 μm (Matthews & Stein, 1969). A large subsequent literature described the extreme sensitivity of muscle spindles (M. C. Brown, Engberg, & Matthews, 1967). Also, small amplitude, mechanical noise-induced alteration of spindle sensitivity has been demonstrated in human muscle/tendon units *in vivo*. Cordo et al showed that small amplitude stochastic vibrations, applied to wrist muscle tendons, increased spindle afferent discharge in response to extremely small changes in wrist joint position (Cordo et al., 1996). Thus, the intact human proprioceptive system appears to possess a sensitivity sufficient to explain our observed effects of subliminal vibration on joint movement perception. We believe this to be the first report of sub-sensory vibration-induced improvements in joint movement detection. That the vibration-induced improvement in perception threshold was greater for those with higher thresholds is at least suggestive of 1) an effect of stochastic noise on the threshold for discharge in spindle afferents and 2) enhancement of proprioceptive function in those with relatively worse detection of joint movement. Furthermore, the finding that movement perception threshold was correlated between movement directions suggests that those with relatively poor or relatively good movement perception in one direction also tended to

exhibit the same quality in the other direction. This may indicate that the sensitivity to movement is similar in different muscles and directions for a particular individual, at least across a range of movement perception thresholds observed in our healthy young sample.

These data also suggest a lower threshold for ankle joint movement perception in the dorsiflexor direction compared to the plantarflexion direction, when the ankle is at a right angle and the knee is fully extended. This could be explained by the fact that in the tested ankle/knee position the plantarflexor muscle-tendon unit is relatively longer and more tensioned than the dorsiflexors and therefore the plantarflexor muscle spindles were more pre-tensioned during the test trials. The muscle spindles of the gastrocnemius and soleus are active when these muscles are lengthened and contribute to the proprioceptive message as the ankle rotates in the dorsiflexion direction. Also, although we positioned the subject and conducted the trials so that the plantarflexors would be as relaxed as possible, slight tonic activation of the plantarflexors could have altered the sensitivity of spindles that were lengthened during rotation into dorsiflexion. Other studies have argued that the compliance in the plantarflexor muscle-tendon unit minimizes changes in muscle length during normal standing compared with other muscles (Di Giulio, Maganaris, Baltzopoulos, & Loram, 2009). This would suggest that the dorsiflexors would provide significant proprioceptive feedback at the ankle joint, and we would expect to see greater movement perception sensitivity in the plantarflexion direction as the dorsiflexors lengthen. Our results, however, demonstrate that though the relative change in muscle length may be small in

the plantarflexor muscles, the muscle spindles are capable of detecting the length changes and conveying this information supraspinally to cognitive areas.

The enhancement of movement detection via small amplitude mechanical stimulus could potentially be applied to the degraded proprioception observed in aging or disease. It is well known that age-related neurodegeneration is associated with impaired postural control and increased fall risk (Rubenstein, 2006; Vandervoort, 2002). Previous studies have found that number of nuclear bag fibers responsible for dynamic position sense are not diminished with age (J. X. Liu, Eriksson, Thornell, & Pedrosa-Domellof, 2005). In fact, some studies suggest that older adults rely more heavily on muscle spindle function for dynamic position sense as other afferent sensors decay (Verschueren, Brumagne, Swinnen, & Cordo, 2002). Mechanical stimuli may be a means by which muscle spindle-based proprioceptive function could be enhanced in light of the central processing decrements that seem to be a significant source of proprioceptive decline among older adults (Klass et al., 2011). While sub-sensory vibration is unlikely to fully restore functional losses, it could perhaps be enough to improve proprioception and reduce fall risk. In this study we have illustrated that among normal healthy young adults, those with the poorest baseline proprioceptive function exhibited the greatest gain with the vibration application. Further work is needed to determine the efficacy of mechanical vibration in proprioception-impaired clinical and aging populations.

Though significant improvements were made in proprioceptive function, the degree of improvement may be enhanced with an optimized vibration protocol. Here, the vibration setting was set to just below the self-reported perceived sensory threshold,

but other frequency and amplitude combinations should be explored to improve joint movement perception. The stimulus was delivered continuously, but it is possible that a customized, intermittent pattern of vibration would be better suited for more functional movements. Instead of continual vibration, integration with mobile sensing technology could provide the capability to activate a vibratory stimulus during a postural perturbation or challenging task instead of vibrating the tendons continually.

The functional relevance of this improvement in joint movement perception with the application of sub-sensory vibration is unclear in this young adult population. Unpublished results from a prior study demonstrated that this application of sub-sensory vibration to the ankle tendons is sufficient to reduce postural sway among older adults (Priplata, Patritti, Rosengarten, et al., 2006). While the significant, yet relatively small degree of improvement in JMPT with vibration may not be functionally relevant for young adults, it could be important for older adult populations where earlier detection of ankle joint movement may be critical for perturbation recovery. Additional neuromuscular investigation would help better understand the influence of sub-sensory vibration on afferent signals and processing. For example, electromyography should be used during experiments to assess the degree to which sub-sensory vibration influences efferent signals to the plantarflexor and dorsiflexor muscles. Intraneural measures of spindle afferent discharge, as in Cordo et al (Cordo et al., 1996) would allow for more concrete conclusions about the ability of different amplitudes of subliminal vibration to enhance afferent signals from spindles, as compared with the effect on cutaneous receptors demonstrated in other studies (D. F. Collins et al., 2005). Further investigation of brain responses via electroencephalography or functional MRI

could increase the understanding of sub-sensory stimulation on higher sensory processing centers and to some extent minimize the subjectivity in the perceptual reporting by subjects. Thus, basic and applied research should be directed at expanding knowledge of the mechanisms and functional importance of these findings and the associated literature, especially for those with impaired function and proprioception.

We utilized passive movements here and thus the findings should be interpreted in that context. Movement detection was the main outcome, thus these data can't provide information on other features of proprioception such as absolute joint position perception. Without measures of muscle activation during the ankle rotation task, we cannot be sure that the plantarflexors were completely inactive. That said, the ability to detect very low levels of muscle activation via surface electromyography is limited.

It is also possible that the enhancement of joint movement detection was specific to the task being performed. Other studies have found that muscle spindle discharge can be altered by simply asking an individual to focus on the experimental task (Ribot-Ciscar, Hospod, Roll, & Aimonetti, 2009), presumably owing to altered fusimotor outflow. This observation does not diminish our observed effects of sub-sensory vibration, but might limit the extrapolation to a more active ambulatory setting.

Conclusions

This study measured joint movement perception during slow, controlled passive ankle rotation. The results suggest that young healthy adults may experience enhanced proprioception at the ankle joint with the application of sub-sensory mechanical vibration applied to tendons, presumably by bringing the muscle spindles closer to threshold and

reducing the change in joint angle necessary to elicit muscle spindle discharge in both plantarflexion and dorsiflexion directions. Those with the poorest proprioceptive function exhibited the greatest improvement with the application of the vibration stimulus. Sub-sensory vibration stimulus may therefore be a viable therapeutic intervention for those with impaired proprioception at the ankle joint.

FIGURES

Figure 3.1: Proprioception Testing Apparatus and Vibration Setup

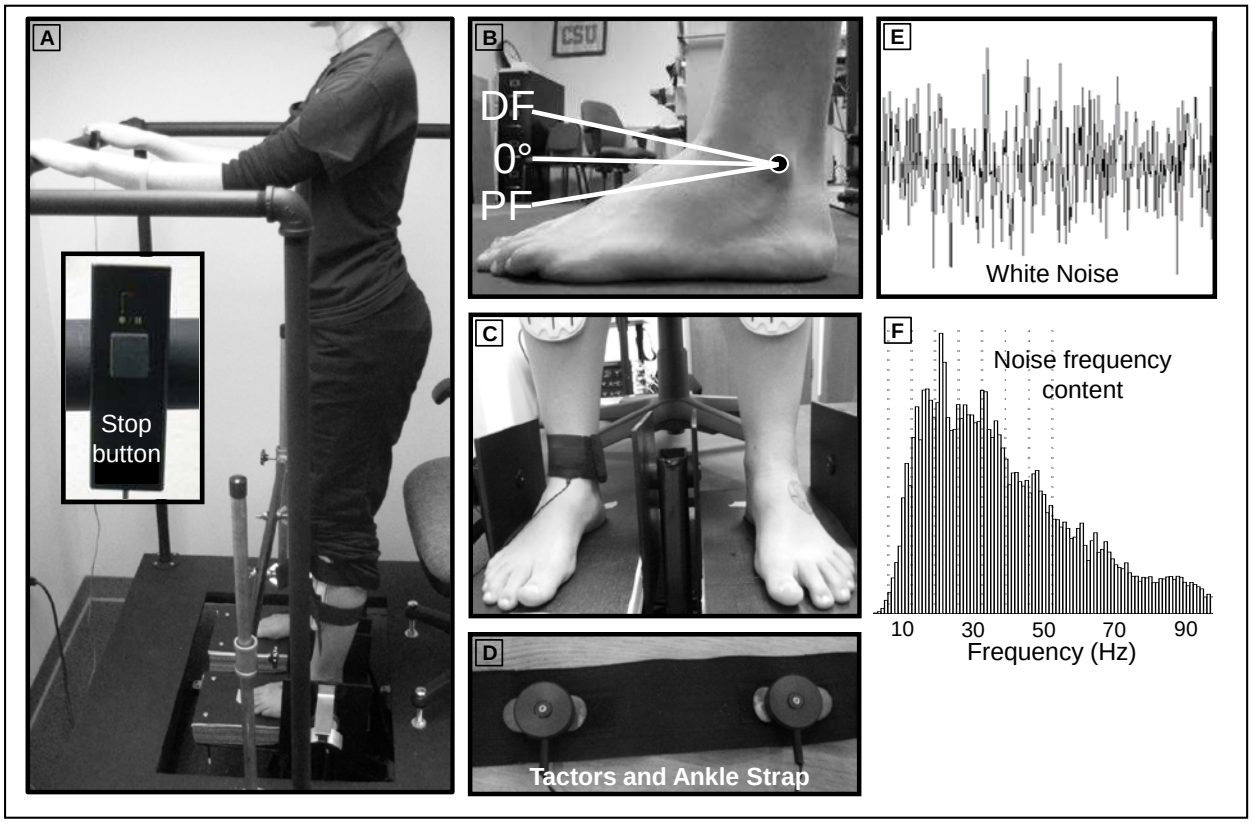

Figure 3.1. Depiction of experimental setup. Foot platforms are slowly rotated by an actuator located below the platform. Inclinometers register the angular movement of the platform. Lower legs are strapped to rigid restraints. Subject is standing erect with hands on railing, looking straight ahead, thumb on a stop button, and listening to white noise via headphones.

Figure 3.2: Joint Movement Perception Threshold with and without Vibration

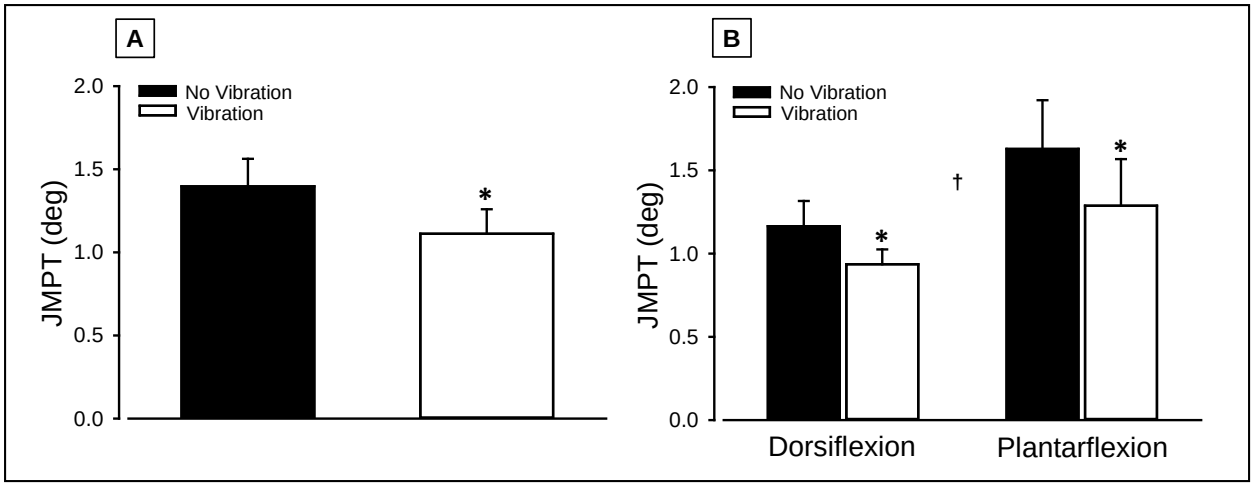

Figure 3.2. A) Joint movement perception threshold (JMPT, deg) for the No Vibration (black bar) and Vibration (white bar) conditions, pooled across movement directions. * JMPT was significantly (P = 0.002) reduced in the Vibration condition. B) JMPT during No Vibration (black bar) and Vibration (white bar) for the plantarflexion and dorsiflexion movement directions. * JMPT was significantly reduced in the Vibration condition to a similar extent for both movement directions. † JMPT was significantly lower (P = 0.03) for dorsiflexion compared with plantarflexion.

Figure 3.3: Joint Movement Perception Threshold Correlations

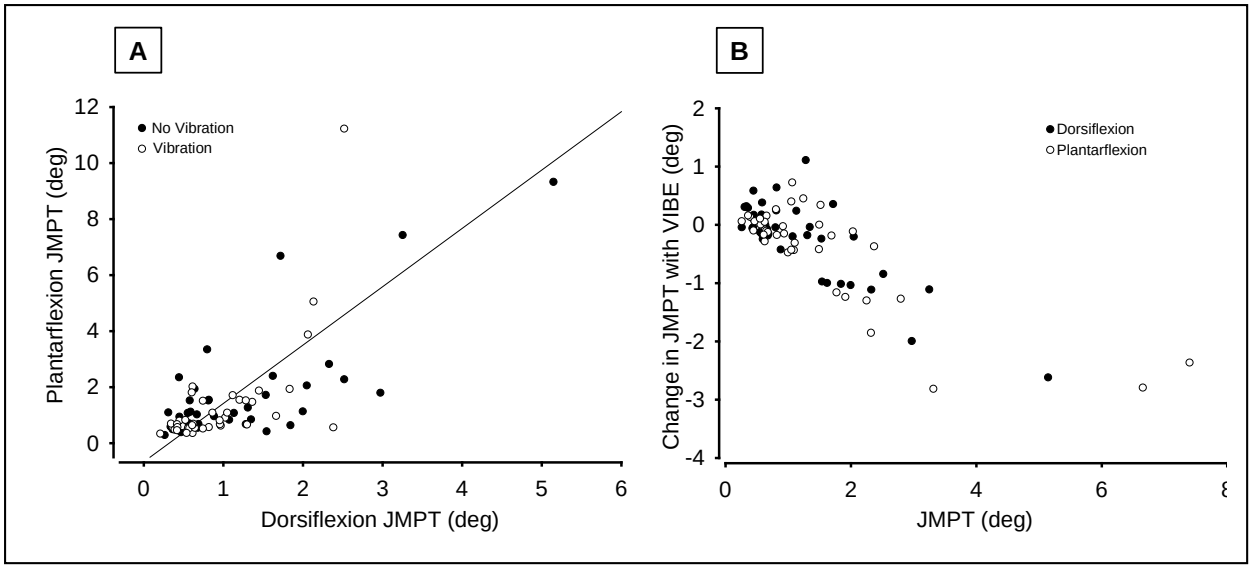

Figure 3.3. A) Joint movement perception threshold (JMPT) was correlated between the dorsiflexion (DF) and plantarflexion (PF) movement directions. Vibration (open circles, r = 0.66, P < 0.0001) and No Vibration (black circles, r = 0.76, P < 0.0001) conditions are plotted for each subject. B) The vibration-induced change in JMPT (Vib – NoVib) was negatively correlated with No Vibration JMPT for the DF (r= -0.82, P < 0.0001) and PF (r = -0.32, P = 0.04) movement directions.

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CHAPTER IV – MANUSCRIPT III

Sub-sensory ankle vibration in frail vs. healthy older adults

Summary

Aging is associated with impaired postural stability and balance which relies heavily on ankle joint proprioception. Low-level mechanical stimulus (vibration) applied to the soles of the feet or ankle tendons have been shown to improve postural stability among older adults. The purpose of this study was to assess proprioceptive function among healthy vs. frail older adults and attempt to improve ankle proprioception with the application of sub-sensory vibration to the ankle tendons.

Forty-six older adults (78.6 ± 7.1yrs, range: 67-94yrs) were assigned to either the Healthy (n = 21, 74.6 ± 4.8yrs) or Frail (n = 25, 82.0 ± 6.9yrs) groups based upon their frailty index score. A motorized platform slowly rotated (0.25 deg/s) the non-dominant ankle in either the plantarflexion (PF) or dorsiflexion (DF) directions. Subjects were instructed to press the stop button as soon as they perceived ankle motion and they could determine the direction of rotation (PF or DF). The change in degrees was recorded as the joint movement perception threshold (JMPT). Sub-sensory vibration was applied using strap-mounted vibrating discs applied to the Achilles and tibialis anterior tendons below the cutaneous sensory threshold. Trials were performed both with vibration (VIB) and without vibration (NOVIB).

Frailty index score was correlated with PF JMPT performance ($r = 0.326$, $P = 0.035$), while age was not a significant predictor of JMPT (PF: $r = 0.196$, $P = 0.214$). Frail older adults demonstrated impaired JMPT compared with healthy older adults

(2.21 ± 0.91 vs. 1.59 ± 1.14 deg, P = 0.018). Baseline (NVIB) PF and DF JMPT values were correlated (r = 0.56, P < 0.0001). The significant frailty group by sex interaction (P = 0.003) suggests that frail women are driving the difference in JMPT between frail and healthy older adults.

The difference in JMPT between the PF direction and DF direction is greater for women (2.54 ± 1.43 vs. 1.76 ± 0.96 deg) than for men (1.62 ± 0.86 vs. 1.68 ± 0.86 deg) (Direction by sex interaction, P = 0.009). There was no improvement in JMPT with VIB (P = 0.473). There were no significant vibration effects within movement directions, frailty groups, or sex groups (all P > 0.05).

Frailty is predictive of joint movement perception at the ankle more so than chronological age. Sub-sensory tendon vibration did not improve joint movement perception in the PF or DF directions. Frail women appear to be driving the significant differences in proprioceptive function among older adults, and therefore may represent an important target population for proprioceptive rehabilitation.

Introduction

The kinesthetic sense of limb position and joint movement is derived primarily from afferent information provided from muscle spindles. These sensors are capable of detecting mechanical stimuli that produce as little as 5μm of disturbance (Brown, Engberg, & Matthews, 1967). Cutaneous skin receptors aid in the kinesthetic sense (Collins & Prochazka, 1996), yet studies have shown that the muscle spindles are activated approximately 50ms sooner than cutaneous afferents (Grill, Hallett, & McShane, 1997), and therefore are more sensitive to joint movement perception than cutaneous receptors. Joint capsule receptors also contribute to the kinesthetic sense,

especially at the ends of the range of motion (Burgess & Clark, 1969), yet joint position sense is not impaired when the joint capsule is removed following hip or knee replacement surgery (Barrack, Skinner, Cook, & Haddad, 1983; Grigg, Finerman, & Riley, 1973). Thus, joint receptors may not be functionally relevant for proprioception in mid-range of motion. Additionally, in cases of spinal cord injury to the dorsal columns that result in loss of cutaneous and joint capsular afferents with preservation of the spindle afferents, the kinesthetic sense is preserved in the lower extremity (Wall & Noordenbos, 1977). Thus the muscle spindles represent a very important source of kinesthetic sensation.

The extraordinary sensitivity of cutaneous (Priplata, Patritti, Niemi, et al., 2006) and muscle mechanoreceptors has been exploited in studies where electrical or mechanical noise is applied in order to enhance the quality of sensory feedback. For example, cutaneous sensors in the foot sole are responsive to electrical and mechanical input (Priplata, Niemi, Harry, Lipsitz, & Collins, 2003). Mechanical noise delivered to the ankle tendons has been shown to improve balance in older adults (Priplata et al., 2003; Priplata, Patritti, Rosengarten, et al., 2006) and in sensory impaired adults (Priplata, Patritti, Niemi, et al., 2006), presumably by enhancing the sensitivity of mechanoreceptors and improving sensory feedback to higher centers. Microneurographic recordings in spindle afferents have demonstrated that extremely low amplitude mechanical noise delivered to intact human tendon can potentiate the spindle afferent response during very small wrist movements and changes in muscle length (Cordo et al., 1996). This may explain Priplata's unpublished finding of improved balance in older adults when the ankle tendons were vibrated with small amplitude

noise (Priplata, Patritti, Rosengarten, et al., 2006). The noise presumably brings mechanoreceptors closer to threshold and increases their response to sensory inputs such as changes in muscle length.

Older adults have impaired proprioception at the ankle compared with young adults (Thelen, Brockmiller, Ashton-Miller, Schultz, & Alexander, 1998; Toledo & Barela, 2014), which contributes to poor balance (Lord & Ward, 1994) and increased fall risk. Accordingly, ankle joint proprioception has been used to predict falls in peripheral neuropathy subjects (Richardson, Demott, Allet, Kim, & Ashton-Miller, 2014). The aging process is complex and is often accompanied by comorbidities that lead some individuals to develop physical frailty while others age more healthfully. It is therefore important to describe age-related changes in the context of both chronological and biological (i.e. frail vs. healthy) aging.

The widely ranging definition of frailty in the literature has resulted in multiple models that describe and identify physical frailty (Cesari et al., 2015; Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013). The two dominant models are the frailty phenotype (Fried et al., 2001) and the deficit accumulation model (Rockwood et al., 2005). The phenotype model is comprised of five simple measures that can roughly categorize individuals as healthy, pre-frail, or frail, while the deficit accumulation model utilizes multiple components to form a frailty index that scores every individual on a 0-1 continuous scale. Previous studies have found that frailty is more prevalent among women (Fried et al., 2001), and the gait speed component of the frailty phenotype model to be the most informative component of the identification criteria (Hoogendijk, van Kan, Guyonnet, Vellas, & Cesari, 2015a). For the purpose of this study, we

employed a battery of measures and adopted the deficit accumulation model with a modified frailty index, due to its enhanced discriminatory ability for severity of frailty and fall prediction (Ritt et al., 2015).

The purpose was to determine the effect of sub-sensory mechanical vibration of plantarflexor (PF) and dorsiflexor (DF) tendons on the threshold for detecting ankle movement in older adults. This study was also designed to explore the differences between an index of biological aging (healthy vs. frail) and chronological aging in the context of ankle joint movement perception.

Methods

Subjects

Forty-six (78.6 ± 7.1yrs, range: 67-94yrs) older adults volunteered for the study, and were assigned to either the Healthy (n = 21, 74.6 ± 4.8yrs) or Frail (n = 25, 82.0 ± 6.9yrs) groups based upon their frailty index score. Subjects were screened for significant diseases, injuries, neurological conditions, or medications that would influence the dependent measures prior to participation. Participants were oriented to the study procedures and provided written informed consent with the approval of the Institutional Review Board at Colorado State University.

Experimental Design

The participants underwent a ~2 h experimental session that consisted of a physical function test, questionnaires, and an assessment of joint movement perception threshold (JMPT) about the ankle joint both with and without sub-sensory vibration in the non-dominant limb. Vibration (VIB) and no vibration (NVIB) conditions were tested separately in random order. A rest break was given between each testing condition to

ensure that there were no residual vibratory effects between conditions. The direction of testing in either PF or DF was randomized within the VIB or NVIB condition. The dominant limb remained stationary during testing of the non-dominant limb.

Experimental Protocol

Frailty Assessment

The subjects completed questionnaires assessing Activities of Daily Living (ADLs) (Katz, Ford, Moskowitz, Jackson, & Jaffe, 1963), Instrumental Activities of Daily Living (IADLs) (Lawton & Brody, 1969), exhaustion (Fried et al., 2001), balance confidence (ABC Scale) (Powell & Myers, 1995), physical activity (CHAMPS) (Stewart et al., 2001). Physical assessments included the Timed Up and Go (TUG) (Rolfson, Majumdar, Tsuyuki, Tahir, & Rockwood, 2006), stair climb, single leg standing balance, Short Physical Performance Battery (SPPB) (Sayers, Guralnik, Newman, Brach, & Fielding, 2006), five meter gait speed (Fried et al., 2001), functional reach (Weiner, Duncan, Chandler, & Studenski, 1992), four square step test (Dite & Temple, 2002), rapid stepping (Medell & Alexander, 2000), and grip strength. The Brief Test of Adult Cognition by Phone (BTACT) was used to assess multiple dimensions of cognitive processing (Lachman, Agrigoroaei, Tun, & Weaver, 2014). Each of these measures were used to calculate frailty index score, which was computed according to a standard procedure (Searle, Mitnitski, Gahbauer, Gill, & Rockwood, 2008) in which the items were individually scored, summed, and divided by the number of items in the index to produce a single frailty index score ranging from 0 (extremely healthy) to 1 (extremely frail). A complete list of the items and individual scoring schemes can be found in Appendix A.

JMPT

The subjects were placed in a custom apparatus (Simoneau, Derr, Ulbrecht, Becker, & Cavanagh, 1996) in a neutral standing position. The lateral malleoli were aligned along the rotational axis of the device in the sagittal plane. Shin guards with nylon and velcro straps were positioned between the knee and ankle to secure the leg to the device. Subjects were instructed to lightly grasp the front railing for support and postural stability. Leg dominance was determined by asking which leg they would use to kick a ball. The platform was set to slowly rotate the non-dominant leg only in either plantarflexion or dorsiflexion at 0.25 deg/s from anatomical position. The subjects were instructed to rest their thumb on the stop button that was secured to the railing (Figure 1) and press the stop button as soon as they perceived ankle motion and could determine in which direction (PF or DF) the motion occurred. The degrees of movement were recorded and used as the JMPT value. Only the trials where the subjects reported the direction of rotation accurately were used during data analysis. During the trials the subjects wore headphones that played white noise so that they could not hear the motor driving the rotating platform. They were also instructed to look straight ahead at a blank wall during the trials. The subjects underwent two trials in each direction with each VIB or NVIB condition for a total of eight trials.

Vibrating tactors (driven by a white noise, 10-100Hz, Figure 1) were secured to nylon straps and were positioned over the tibialis anterior and Achilles tendons. The cutaneous vibration sensory threshold was determined prior to the initiation of the JMPT trials and was set at an immediately sub-sensory level during VIB trials. The subject

was thus unaware of which type of trial (VIB or NVIB) was being administered. The order was counterbalanced between subjects.

Data analysis

The frailty index scores were calculated according to either published cut-points or based upon the standard procedure for establishing frailty index cut-points (Searle et al., 2008). The subjects were divided into two equal groups (“frail” vs. “healthy”) based upon the median frailty index score of the overall sample.

The JMPT values were averaged over two trials for a direction of movement (PF vs. DF) and vibration condition (VIB vs. NVIB).

Statistical analysis

A multiple regression analysis was used to assess the ability of chronological aging (age) or a maker of biological aging (frailty index) to predict JMPT with and without vibration. Both repeated measures and one-way analysis of variance (ANOVA) were used to assess the differences between frail and healthy, men and women, vibration effect, movement direction, and aging on JMPT. Correlations were used to assess the distribution of the JMPT variables across the aging or frailty index spectrum.

Results

Movement Perception, Aging, and Frailty

In the multiple regression the frailty index score emerged as the significant predictor of JMPT performance in the PF direction ($P = 0.035$). Frailty index score was correlated with PF JMPT performance ($r = 0.326$, $P = 0.035$), while age was not a significant predictor of JMPT (PF: $r = 0.196$, $P = 0.214$). Neither frailty index nor

chronological age predicted JMPT in the DF direction ($r = 0.216$, $P = 0.176$ and $r = 0.236$, $P = 0.137$). Frailty index and age were correlated ($r = 0.569$, $P < 0.0001$). Pooled across sex, direction (PF and DF), and vibration condition (NVIB and VIB), frail older adults demonstrated impaired JMPT compared with healthy older adults (2.21 ± 0.91 vs. 1.59 ± 1.14 deg, $P = 0.018$) (Figure 2a). Baseline (NVIB) PF and DF JMPT values were correlated ($r = 0.56$, $P < 0.0001$) (Figure 2b).

Sex Effects

Pooled across movement direction, vibration condition, and frailty group, women tended to have greater JMPT values compared with men (2.15 ± 1.19 vs. 1.65 ± 0.86 deg, $P = 0.055$, Figure 3a). Pooled across direction and vibration condition, the significant frailty group by sex interaction ($P = 0.003$) suggests that frail women are driving the difference in JMPT between frail and healthy older adults. There was a significant difference between frail and healthy women with no difference between frail and healthy men (Figure 3b).

Across condition and groups, JMPT in the PF direction was greater than JMPT in the DF direction (2.08 ± 1.24 vs. 1.72 ± 0.90 deg, $P = 0.025$). Pooled across vibration condition and frailty group, the difference in JMPT between the PF direction and DF direction is greater for women (2.54 ± 1.43 vs. 1.76 ± 0.96 deg) than for men (1.62 ± 0.86 vs. 1.68 ± 0.86 deg) (Direction by sex interaction, $P = 0.009$, Figure 4a). Frail women appear to be driving this directional difference as healthy women have similar PF vs. DF to that of both frail and healthy men ($P = 0.069$, Figure 4b).

Vibration Effect

Pooled across movement direction, sex, and frailty group, there was no improvement in JMPT with VIB ($P = 0.473$). There were no significant vibration effects within movement directions, frailty groups, or sex groups (all $P > 0.05$). The sensory threshold (2.35 ± 0.50 arbitrary gain units) was not different between men and women ($P = 0.285$).

Discussion

The main findings were 1) the frailty index (biological aging) was correlated with proprioceptive function while chronological aging was not, 2) older adults with greater frailty index scores display impaired JMPT compared with those with lower scores, 3) the differences in JMPT between frail and healthy groups appear to be driven by frail women, and 4) plantarflexion and dorsiflexion movement perception thresholds were correlated. There was no improvement in JMPT with the application of sub-sensory tendon vibration.

Aging

There is currently a lack of consensus as to the most effective assessments to quantify biological aging (Cesari et al., 2015; Clegg et al., 2013). Approaches to assessing biological age include numerous frailty models (Clegg et al., 2013; Hoogendijk, van Kan, Guyonnet, Vellas, & Cesari, 2015b) along with metabolic predictors, such as the metabolic age score (Hertel et al., 2015). The goal of these studies is to describe changes in adverse health risks and poor health outcomes independent of chronological age. Over half of the components of the frailty index used in this study were similar to previous studies (Searle et al., 2008) with the addition of

cognitive and physical function tests that are commonly used in aging research (Appendix A). Although the frailty index used here was only able to predict joint movement perception in the plantarflexion direction, no measures of proprioception were related to chronological aging. Therefore, proprioceptive decline may be independent of chronological age.

In aged animals there is a selective denervation and change in morphology of the primary endings of muscle spindle while the secondary endings are preserved (Kim, Suzuki, & Kanda, 2007). The primary endings convey both position and movement sense, while the secondary endings contribute to position sense. Therefore, age-related declines in proprioception should be most evident in joint movement perception. A recent ankle proprioception study assessed seated joint movement perception and position matching. They found an increase in joint movement perception with age and did not find a significant correlation between ankle position matching and age, which affirms the notion that joint movement perception is the most appropriate assessment of proprioception in aging. This study also found no proprioceptive differences between males and females. The age range for their study was more broad (51-95 yrs), subjects were excluded only for severe pain or range or motion limitations, and they did not differentiate between frail and healthy older adults (Ko, Simonsick, Deshpande, & Ferrucci, 2015). In this study we did not find a decline in joint movement perception with chronological age. This implies that the differences in biological aging (operationalized here as frail aging vs. healthy aging) may play a role in the loss or preservation of proprioceptive function. Further investigation of the frailty index components may improve prediction of proprioceptive function in the dorsiflexion direction.

Movement Direction

Joint movement perception was assessed in the plantarflexion and dorsiflexion directions among groups (healthy vs. frail), conditions (NVIB vs. VIB), and sexes (males vs. females). The only significant movement direction findings were among the female group. Women demonstrated greater JMPT values (less sensitivity) in the plantarflexion direction while men exhibited similar JMPT values between directions. This result is similar to our findings elsewhere among young adults (Fritz, et al. *Submitted Manuscript*). Further investigation revealed that this finding was driven by the significant differences between directions for frail women, with no differences between directions with healthy women and all men. The plantarflexor muscles (gastrocnemius and soleus) lengthen as the ankle rotates in the dorsiflexion direction, and are therefore the muscles primarily signaling ankle proprioception in the dorsiflexion direction. In the standing position, the gastrocnemius muscle is relatively longer. Therefore, the resting length of the gastrocnemius muscle in the standing position may partially explain the less-impaired proprioceptive sensitivity in the dorsiflexion direction among frail women; however, there is no clear explanation in the current literature as to why joint movement perception impairment and directional differences are only present in frail women.

Sub-sensory Vibration

Previous studies have found that sub-sensory mechanical noise applied to the soles of the feet can improve postural sway performance among older adults (68-78 yrs), stroke subjects (31-90 yrs) and those with diabetic peripheral neuropathy (38-81 yrs) (Priplata et al., 2003; Priplata, Patritti, Niemi, et al., 2006). Also an unpublished report similarly demonstrated improved in postural sway among older adults (70-77 yrs)

when sub-sensory noise was applied with vibrating ankle wraps similar to those used in the present study (Priplata, Patritti, Rosengarten, et al., 2006). These studies used the same type of vibrating disks (tactors) and the same methods for determining the vibration amplitude as those used in this study. The same equipment and protocol were used to assess the vibration effects on JMPT in young adults and found an improvement in both the PF and DF directions with the application of sub-sensory vibration (Fritz, et al. *Submitted Manuscript*). Each of these studies reported an improvement with the use of sub-sensory vibration and did not find significant differences between males and females. Though the average age of the subjects presented here (78 yrs) was greater than those in previously mentioned studies, it is unclear as to why there were no improvements in JMPT with VIB. Though the sub-sensory vibration intervention explored in this study failed to improve impaired proprioception, further exploration is needed to determine if targeted proprioceptive improvement is possible among frail females. It is possible that changes in muscle spindle characteristics and function with age explain the lack of effect of vibration on our older adults (Kim et al., 2007; Rosant, Nagel, & Perot, 2007).

Limitations

This study is limited based upon the relatively small sample size for the comparisons across directions, vibration conditions, frailty groups, and sex. It is thus possible these findings could be limited to this sample and therefore be less representative of the larger older adult population.

Although the frailty index was formulated based upon a standardized method (Searle et al., 2008), the particular set of measures that comprised our index has not been validated with health outcomes in a large group of older adults.

It is unclear if this method of passively assessing proprioceptive function and applying sub-sensory vibration to ankle tendons in the research setting would translate to improvements in the active muscle contractions during functional movements. Further research is needed to assess the effectiveness of this strategy in a more real-world setting.

Conclusion

Frailty among women is associated with poor joint movement perception at the ankle. Sub-sensory tendon vibration did not improve joint movement perception in the dorsiflexion or plantarflexion directions. In many studies using a variety of frailty identification methods, frailty is statistically more prevalent among women than men (Clegg et al., 2013). Therefore frail women may reflect an important and prevalent portion of the aging community that should be targeted for therapeutic interventions.

FIGURES

Figure 4.1: Proprioception Testing Apparatus and Vibration Setup

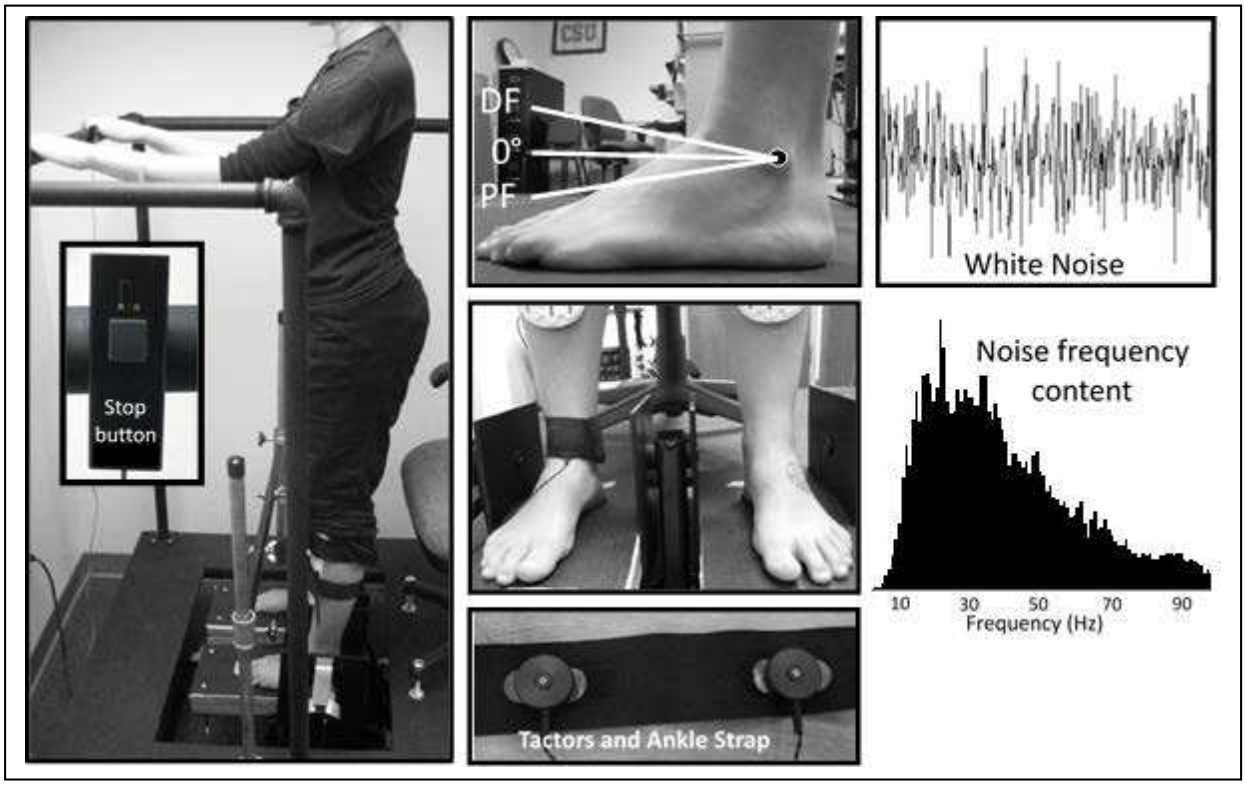

Figure 4.1. Experimental setup. The foot platform is slowly rotated by an actuator below the platform. Inclinometers register the rotation of the platform. The lower leg is strapped to rigid restraints. Subject is standing with hands on railing, looking straight ahead, thumb on a stop button, and listening to white noise via headphones.

Figure 4.2: Joint Movement Perception Threshold and Directional Correlation

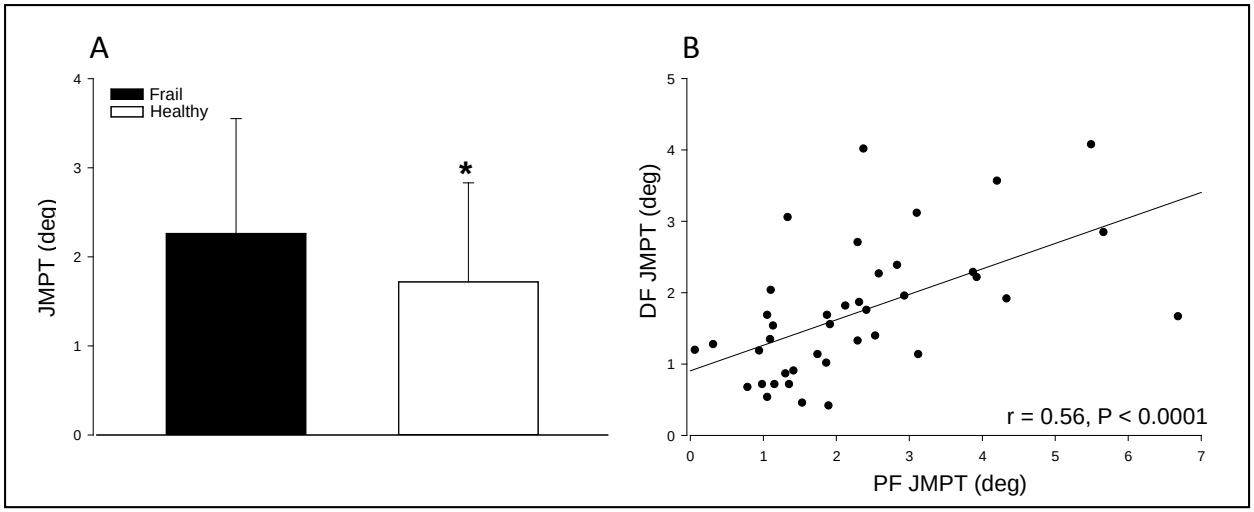

Figure 4.2. A: Pooled across sex, direction, and vibration condition, JMPT was impaired among frail older adults (2.21 ± 0.91 vs. 1.59 ± 1.14 deg, * P = 0.018). B: Baseline (NVIB) PF and DF JMPT values were correlated (r = 0.56, P < 0.0001).

Figure 4.3: Movement Perception by Sex and Frailty Group

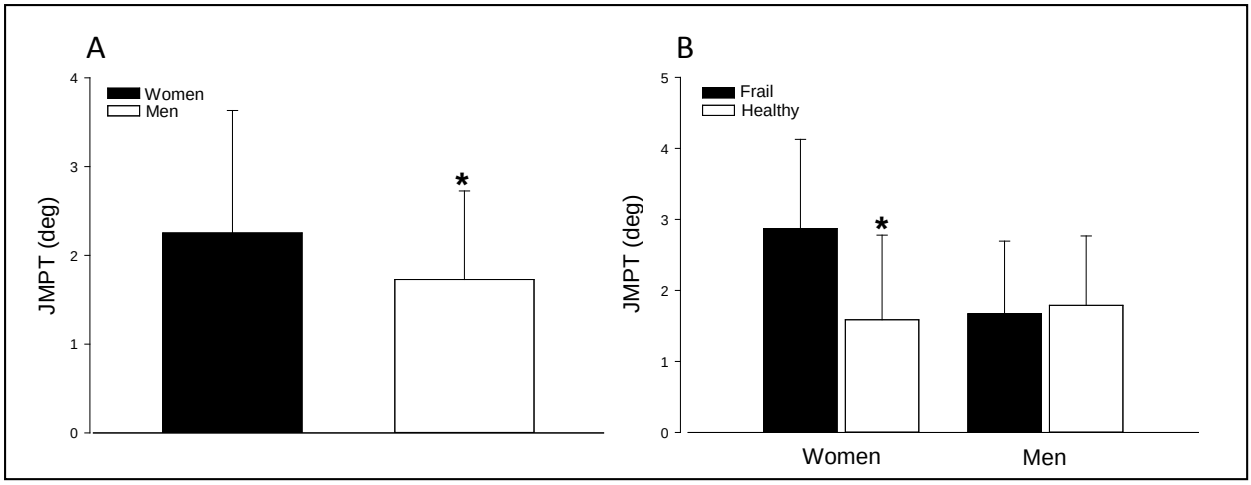

Figure 4.3. A: Pooled across movement direction, vibration condition, and frailty group, women tended to have greater JMPT values compared with men (2.15 ± 1.19 vs. 1.65 ± 0.86 deg, * P = 0.055. B: The difference between frail and healthy women (2.86 vs. 1.43 deg) was greater than for men (1.56 vs. 1.75 deg) (frailty group by sex interaction P = 0.003).

Figure 4.4: Movement Direction by Sex and Frailty Group

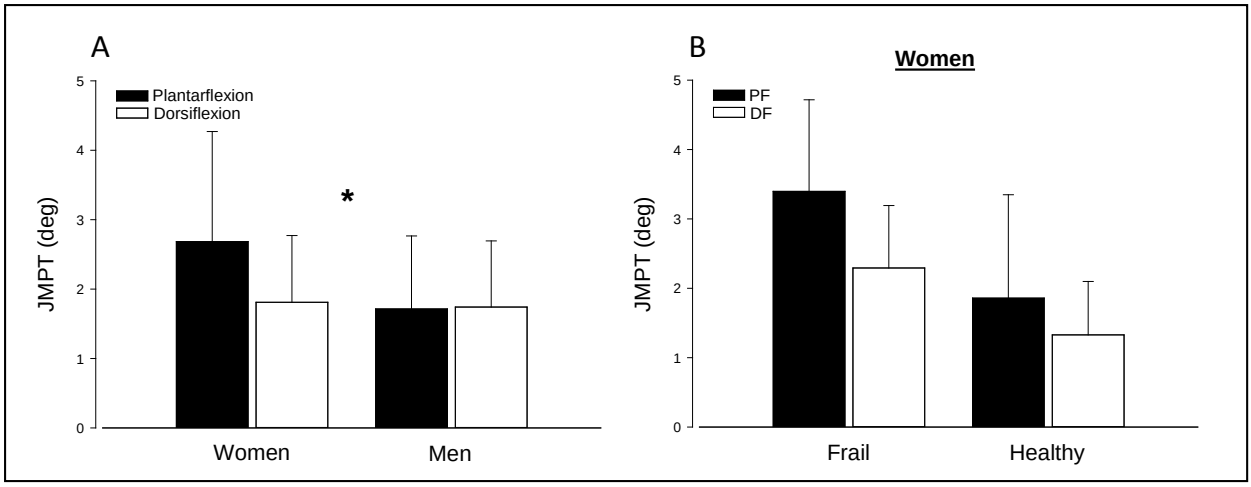

Figure 4.4. A: Pooled across vibration condition and frailty group, the difference in JMPT between the PF direction and DF direction is greater for women (2.54 ± 1.43 vs. 1.76 ± 0.96 deg) than for men (1.62 ± 0.86 vs. 1.68 ± 0.86 deg) (direction x sex interaction, * P = 0.009). B: Frail women appear to drive this directional difference as healthy women have similar PF vs. DF (1.59 vs. 1.27deg) to that of both frail (1.47 vs. 1.64 deg) and healthy (1.77 vs. 1.73 deg) men (P = 0.069).

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CHAPTER VI – OVERALL CONCLUSIONS

The use of frailty identification as a descriptor of biological aging is important to the understanding of neuromuscular function as it is more predictive of proprioception and neuromuscular function than chronological aging alone. This is particularly relevant to the neuromuscular control of the ankle joint as it pertains to postural stability and fall risk.

The proprioceptive sense of joint movement perception is governed by the afferent signals arising from the muscle spindles located on the intrafusal fibers. Impairment from this afferent system may be the result of age-associated changes in the peripheral receptors or the central integration of the afferent responses. Joint movement perception thresholds were assessed in both the plantarflexor and dorsiflexor directions among young adults, healthy older adults, frail older adults, adults with peripheral neuropathy, and adults with prior hemiparetic stroke. Proprioceptive function among healthy older adults was not different than that of the younger adults, indicating a preservation of muscle spindle afferent system with healthful aging. Those with comorbidities, such as peripheral neuropathy or frailty, exhibited the impairment in proprioceptive function.

Sub-sensory vibration applied to the ankle muscle tendons has been shown to improve postural stability. This proprioceptive sensitization strategy successfully improved joint movement perception thresholds in young adults, demonstrating that those with the most impaired proprioception experienced the greatest benefit from the vibration application. Subsequently, the same intervention was not successful in improving proprioception among older adults. Further exploration of therapeutic

interventions is needed to improve proprioceptive function, particularly among frail older women.

Incorporating frailty identification into our understanding of neuromuscular aging is important not only in terms of the physiological relevance, but also the treatment strategies that are used to either improve balance and proprioception or reduce fall risk. The findings here represent the first steps toward the incorporation of frailty identification in neuromuscular aging with the hope of improving our understanding of aging and more successfully improving quality of life for both healthy and frail older adults.

APPENDIX A

Frailty Index Variables and Cut-Points

Item	Cut-point	Reference
Using the phone	Without help = 0, With some help = 0.5, Unable = 1	Lawton, 1969
Getting to places out of walking distance	Without help = 0, With some help = 0.5, Unable without special arrangements = 1	Lawton, 1969
Shopping for groceries	Without help = 0, With some help = 0.5, Unable = 1	Lawton, 1969
Preparing meals	Without help = 0, With some help = 0.5, Unable = 1	Lawton, 1969
Doing housework	Without help = 0, With some help = 0.5, Unable = 1	Lawton, 1969
Doing handyman work	Without help = 0, With some help = 0.5, Unable = 1	Lawton, 1969
Doing laundry	Without help = 0, With some help = 0.5, Unable = 1	Lawton, 1969
Taking medications	Without help = 0, With some help = 0.5, Unable = 1	Lawton, 1969
Managing money	Without help = 0, With some help = 0.5, Unable = 1	Lawton, 1969
Bathing	Without help = 0, With some help = 0.5, Unable without help = 1	Katz, 1963
Continence	Complete control = 0, occasional “accidents” = 0.5, incontinent = 1	Katz, 1963
Dressing	Without assistance = 0, assistance tying shoes = 0.5, unable without assistance = 1	Katz, 1963
Feeding	Without assistance = 0, assistance cutting meat or buttering bread = 0.5, unable without assistance = 1	Katz, 1963
Toileting	Without assistance = 0, some assistance = 0.5, unable without assistance = 1	Katz, 1963
Transferring	Without assistance = 0, some assistance = 0.5, unable to get our of bed = 1	Katz, 1963
How often in the last week did you feel that everything was an effort?	0 days = 0, 1-2 days = 1, 3 or more days = 2	Fried, 2001
How often in the last week did you feel you could not get going?	0 days = 0, 1-2 days = 1, 3 or more days = 2	Fried, 2001
BMI	18.6-24.9 = 0, 25-30 = 0.5, ≤18.5 or >30 = 1	Searle, 2008
Number of Medications	0-4 = 0, 5-7 = 1, 8-10 = 2, 11-13 = 3	Rockwood, 2011
Fallen in the last year	0 = no, 1 = yes	

Frailty Index Variables and Cut-Points (Continued)

Item	Cut-point	Reference
SPPB: Tandem standing	≥ 10 seconds = 0, < 10 seconds = 1	Sayer, 2006
SPPB: 5x chair rise	≤11.19s = 0, 11.20-13.69s = 0.25, 13.70-16.69s = 0.5, 16.7-29.99s = 0.75, >60s or unable = 1	Sayer, 2006
BTACT: Word List Recall	6-12 words = 0, 4-5 words = 0.5, 0-3 words = 1	Tertiled
BTACT: Backward Digit Span	5-8 digits = 0, 4 digits = 0.5, 0-3 digits = 1	Tertiled
BTACT: Category Fluency	>26 correct responses = 0, 19-25 correct responses = 0.5, 0-18 correct responses = 1	Tertiled
BTACT: Number Series	4-5 = 0, 2-3 = 0.5, 0-1 = 1	Tertiled
BTACT: Backward Counting Number Reached	0-60 = 0, 61-67 = 0.5, 68-100 = 1	Tertiled
BTACT: Backward Counting Errors	0 errors = 0, 1 error = 0.5, 2 or more = 1	Tertiled
BTACT: Short-delay Word Recall	4-10 words = 0, 2-3 words = 0.5, 0-1 word s= 1	Tertiled
TUG	0-10s = 0, 11-20s = 0.5, >20s, patient is unwilling or requires assistance = 1	Rolfson, 2006
ABC Scale	>86.94 = 0, <86.94 = 1	Scaled
Physical Activity: CHAMPS	Caloric expenditure in 1 week for all exercise-related activities, >3698kcals = 0, <3698kcals = 1	Scaled
Single Leg Standing Balance	Right leg eyes open, right leg eyes closed, left leg eyes open, left leg eyes closed (30s max per trial). Sum >34.81s = 0, < 34.80s = 1	Scaled
Functional Reach	>32.51cm = 0, <31.51cm = 1	Scaled
Four Square Time	<8.82 = 0, > 8.82 = 1	Scaled
Rapid Stepping Time	Dominant leg stepping to the front, side, and back. Time sum stepping six times in each direction. <38.27s = 0, > 38.27s = 1	Scaled
Stair Climb	Time to walk up and down a standard flight of stairs. < 14.64s = 0, > 14.64s = 1	Scaled
5m Gait Speed	> 1.21 m/s = 0, < 1.21 m/s = 1	Scaled
Grip Strength	Normalized by arm lean mass, Men: > 9.09 = 0, < 9.09 = 1, Women: > 8.27 = 0, < 8.27 = 1	Scaled

APPENDIX B

Consent to Participate in a Research Study
Colorado State University

TITLE OF STUDY: *Ankle Steadiness, Postural Control, and Physical Frailty*

PRINCIPAL INVESTIGATOR: *Brian L. Tracy, Ph.D. 491-2640*

CO-INVESTIGATOR: *Raoul Reiser II, Ph.D. 491-6958*

WHY AM I BEING INVITED TO TAKE PART IN THIS RESEARCH? *You are a man or woman between the ages of 18-30 or 65-95 years. You either 1) do not report major health problems, or 2) report problems with falling and/or frailty. Our research is looking at the effect of healthy and frail aging, and contributions to the control of muscle force.*

WHO IS DOING THE STUDY? *This research is being performed by Brian Tracy, Ph.D., and Raoul Reiser II, PhD of the Health and Exercise Science Department. Trained graduate students, undergraduate students, research associates, or research assistants are assisting with the research. These studies are paid for by the National Institutes of Health, a part of the US Government.*

WHAT IS THE PURPOSE OF THIS STUDY? *The way in which muscles are controlled by the brain and nerves may change in older people. The effect of vision, mental distraction, and/or vibratory stimuli feedback may be different in young, healthy elderly, and frail elderly, and may be different between muscles. The purpose of the research is to examine these changes and differences in hand, arm, and leg muscles.*

WHERE IS THE STUDY GOING TO TAKE PLACE AND HOW LONG WILL IT LAST? *This whole research project will take place over a period of approximately two years. Your part in this study will take place over five to seven visits over a period of eight weeks.*

WHAT WILL I BE ASKED TO DO? *This consent form applies to a large research project. You are only being asked to participate in parts of the total project. Depending on the part of the research project that you are involved in, you will be asked to participate in some of the following procedures. Many potential procedures are described in the section below. However, the procedures that you will be asked to do for this part of the study have a check mark next to them. The check marks were put there by one of the researchers. A member of the research team will fully explain each checked procedure that applies to your participation.*

_____ *You will be asked to answer some questions about your health and exercise to determine if you can participate in the study. (~ 30 minutes)*

_____ *(your initials)*

_____ *If you are in the 65-95 yr-old age group, you will be asked to undergo a brief physical exam by a physician. This test will occur in the Human Performance Clinical/Research Laboratory in the Department of Health and Exercise on the CSU campus. (~ 15 minutes)* _____ *(your initials)*

_____ *The fat, muscle, and bone in your body will be measured using an x-ray device (dual-energy x ray absorptiometer) that will scan you from head to toe while you lie quietly on a special table for approximately 10 minutes. The amount of x-ray radiation you will receive is extremely low.*

_____ *(your initials)*

_____ *You will be asked to lightly warm-up your arms and legs with light stretching, simple footwork and slow walking at a comfortable level. (~ 5 minutes)*

_____ *(your initials)*

_____ *You will be asked to complete brief mental tests of your ability to remember words and numbers on two separate occasions. (~ 20 minutes)*

_____ *(your initials)*

_____ *You will perform a short physical performance test comprised of simple one-legged and two-legged balance tests with your eyes open or closed, rising from a chair five times, and walking a short distance. (~ 20 minutes)*

_____ *(your initials)*

_____ You will be asked to ascend and descend a staircase at a pace comfortable to you. A handrail and research assistant will be within close reach at all times for assistance. (~ 2 minutes)

_____ *(your initials)*

_____ You will undergo clinical examination of the sensory capacity using fine filaments and probes on the skin surface to measure sensory capacity.

_____ (your initials)

_____ *While standing, you will complete two different stepping tests. You will be asked to step as rapidly as possible to the front, side, and rear. (~20 minutes)*

_____ *(your initials)*

_____ *You will perform three reaction time tests with a computer and keyboard. You will respond to either a symbol on the computer screen or a brief sound.(~15 minutes)*

_____ *(your initials)*

_____ *You will perform a mobility test. This will involve rising from a chair, walking 10 feet, turning around, walking back to the chair, and sitting down. This will be repeated three times. (~5 minutes)*

_____ *(your initials)*

_____ *You will stand next to a wall and reach your arm out as far as you can without moving your feet. This task will be attempted and measured three times. (~2 minutes)*

_____ *(your initials)*

_____ *You will sit in a special chair and perform light and heavy muscle contractions with your hand, arm, thigh and/or ankle muscles while your leg, hips, and shoulders are comfortably secured. (1 – 2.5 hours)*

_____ *(your initials)*

_____ *You will stand as still as possible for 15-60 seconds with your feet together and arms by your side. This will be performed several times in a row with several minutes rest between each trial. During some of the trials you will look forward at a point on a wall in front of you. During some of the trials you will have your eyes closed. During this test you will be standing on a device called a force plate that measures the forces that your feet apply on the surface. (~20 minutes)*

_____ *(your initials)*

_____ *You will stand on the force plates and gently sway or lean forwards and backwards without falling while keeping your feet flat for 60-90 seconds. You will be spotted by a research assistant. (~20 minutes)*

_____ *(your initials)*

_____ *You will stand in place while keeping your feet flat for approximately a minute on the force plates while a small weight disrupts your stance gently. (~20 minutes)*

_____ *(your initials)*

_____ *While performing light and heavy muscle contractions or standing tasks, you may be asked to perform a slightly challenging counting drill out loud during the task. (1-2.5 hours)* _____ *(your initials)*

_____ *Sticky electrodes will be placed on the skin over the muscles involved for some of the visits and will remain in place until the end of that visit. Natural oil in the skin will be removed with rubbing alcohol, and the skin will be gently roughened with a fine abrasive paste or cloth.*

_____ *(your initials)*

_____ *An electrode made of hair-sized fine wires will be inserted into your hand, arm, thigh and/or ankle muscle using a small needle. The skin will be thoroughly disinfected, similar to when you get your blood drawn. The needle is sterilized and is the same as the ones used for blood drawing. Either the fine hair size wires or the needle will remain in your muscle for the duration of the visit and then will be removed. Usually there will only be one electrode insertion. However, it is possible that electrodes may need to be inserted 1-5 times in different locations in the muscle. (1-2.5 hours)*

_____ *(your initials)*

_____ *A vibrating device will be placed against leg muscle/tendon for a time period of several seconds up to several minutes, causing a brief muscle contraction.*

_____ *(your initials)*

_____ *An electrical stimulus will be delivered to a nerve or muscle in your leg or arm using a standard stimulator. This may cause a brief muscle contraction.*

_____ *(your initials)*

ARE THERE REASONS WHY I SHOULD NOT TAKE PART IN THIS STUDY? *If you are not 18-30 or 65-95 years of age, are pregnant, are a regular smoker, or have any diseases that would affect our measurements, we will not be able to include you in the research.*

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS? *(The procedures that apply to your proposed participation are checked)*

- _____ *Health questionnaires – There are no known risks associated with answering health questions. All information is kept strictly confidential.*

  _____ *(your initials)*

- _____ *Physical examination – There are no known risks associated with a physician-administered physical examination.*

  _____ *(your initials)*

- _____ *Warm-up – There are no known risks associated with completing this preventative task. It will be completed at a level comfortable to the subject.*

  _____ *(your initials)*

- _____ *Stair climb task – There is a slight risk of falling on the stairs during this test. There will be a research investigator near you for assistance and a handrail within reach at all times. Rest will be given to prevent tiredness.*

  _____ *(your initials)*

- _____ *Brief mental Tests – There are no known risks associated with completing these tests. The information is confidential.*

  _____ *(your initials)*

- _____ *Short physical performance test – There is a slight risk of falling and potential muscle strain during these tests. A research investigator will be spotting nearby at all times to prevent falls and rest will be given to prevent tiredness.*

  _____ *(your initials)*

- _____ *Sensory acuity exam – There is no risk associated with this task.*

  _____ *(your initials)*

- _____ *Rapid stepping test – There is a slight risk of soreness or muscle strain with these procedures. A researcher will be nearby for safety. Rest will be given to prevent tiredness.*

  _____ *(your initials)*

- _____ *Reaction time – There are no known risks associated with the computer reaction time tests.*

  _____ *(your initials)*

- _____ *Mobility test – There is a slight risk of falling and injury as a result of rising from a chair and walking a short distance. A research investigator will be nearby to help. Rest will be given to prevent tiredness.*

  _____ *(your initials)*

- _____ *Standing reach test – There is a slight risk of falling or muscle strain from this test. You will be next to a wall to help keep balance. A research investigator will be next to you for safety.*

  _____ *(your initials)*

- _____ *Muscle contractions – There is a slight risk of muscle strain and muscle soreness resulting from brief, light and strong muscle contractions with the hand, arm, thigh and/or ankle. Soreness should not last more than two days or affect your normal function.* _____ *(your initials)*

- _____ *Postural Standing – The risks associated with this balance test include loss of balance with the potential for falling. This risk is extremely low because you will have both feet on the ground and be closely surrounded by a padded handrail and a research assistant.* _____ *(your initials)*

- _____ *Postural Sway – The risks associated with this balance test include loss of balance with the potential for falling. This risk is extremely low because you will have both feet on the ground and be closely surrounded by a padded handrail and a research assistant.* _____ *(your initials)*

- _____ *Perturbed Standing – The risks associated with this balance test include loss of balance with the potential for falling. This risk is extremely low because you will have both feet on the ground and you will have a security rail, a research assistant near and a cord attached to the ceiling to prevent you from falling if you lose your balance.* _____ *(your initials)*

- _____ *Counting drill - There is a minimal risk of feeling anxious while counting and performing muscle contractions or standing. Although, trials will be less than 30 seconds at a time and are not meant to be strenuous. The task will be terminated if you feel uncomfortable.* _____ *(your initials)*

- _____ *<u>Sticky electrodes</u> – There is no known risk with the preparation or use of sticky electrodes on the surface of the skin.*

  _____ *(your initials)*

- _____ *<u>Fine-wire electrodes</u> – There is a risk of discomfort from the needle, temporary soreness in that muscle, and a remote risk of infection. The equipment we use is sterile and only used once and then thrown away. We use special procedures to kill the germs on the skin. In cases where we keep the needle in the muscle during the test, it may cause slightly more discomfort.*

  _____ *(your initials)*

- _____ *<u>Vibration of muscle or tendon</u> – There is no known risk associated with vibration of your tendon or muscle. The sensation you will feel is similar to what you would feel from a home massage device. The muscle that is vibrated may experience a small involuntary contraction.*

  _____ *(your initials)*

- _____ *<u>Electrical stimulus of nerve or muscle</u> – There is no known risk associated with electrical stimulation of nerves or muscle. The device is isolated from dangerous electrical voltages. You will experience a mild sensation of electrical shock in your arm or leg when we stimulate with low levels. When we stimulate with higher levels, you will likely experience a brief but uncomfortable sensation of electrical shock. The electrical stimuli will likely cause an involuntary muscle contraction.* _____ *(your initials)*

- _____ *<u>Body composition (DEXA) scan</u> – the risks associated with the DEXA are very low. The radiation you will receive is less than 1/3000th of the Food and Drug Administration (FDA) limit for annual exposure. The FDA is a government organization responsible for medical safety. In other words, you could receive 3000 DEXA scans in a single year and still not meet the FDA limit for radiation exposure. In this study you will receive one scan. The more radiation you receive over the course of your life, the greater the risk of having cancerous tumors or of inducing changes in genes. The radiation in this study is not expected to greatly increase these risks, but the exact increase in such risks is not known. Women who are pregnant or could be pregnant should receive no unnecessary radiation and should not participate in this study.* _____ *(your initials)*

- It is not possible to identify all potential risks in research procedures, but the researcher(s) have taken reasonable safeguards to minimize any known and potential, but unknown, risks.

ARE THERE ANY BENEFITS FROM TAKING PART IN THIS STUDY? *There are no direct benefits to you for participating in this study except the health information from the body composition assessment.*

DO I HAVE TO TAKE PART IN THE STUDY? *Your participation in this research is voluntary. If you decide to participate in the study, you may withdraw your consent and stop participating at any time without penalty or loss of benefits to which you are otherwise entitled.*

WHAT WILL IT COST ME TO PARTICIPATE? *There is no cost to you for participating except that associated with your transportation to our facilities.*

WHO WILL SEE THE INFORMATION THAT I GIVE? *We will keep private all research records that identify you, to the extent allowed by law. Your information will be combined with information from other people taking part in the study. When we write about the study to share it with other researchers, we will write about the combined information we have gathered. You will not be identified in these written materials. We may publish the results of this study; however, we will keep your name and other identifying information private. We will make every effort to prevent anyone who is not on the research team from knowing that you gave us information, or what that information is. For example, your name will be kept separate from your research records and these two things will be stored in different places under lock and key. You should know, however, that there are some circumstances in which we may have to show your information to other people. For example, the law may require us to show your information to a court, the National Institutes of Health, or to the Human Research Committee at CSU.*

CAN MY TAKING PART IN THE STUDY END EARLY? *Your participation in the study could end in the rare event of muscle strain, if you become pregnant, or if you miss an excessive number of appointments.*

WILL I RECEIVE ANY COMPENSATION FOR TAKING PART IN THIS STUDY? For experiments that involve fine wire electrodes, you will be paid $8/hr.

WHAT HAPPENS IF I AM INJURED BECAUSE OF THE RESEARCH? *Please be aware that for this study the University has made special arrangements to provide initial medical coverage for any injuries that are directly related to your participation in this research project. The research project will provide for the coverage of reasonable expenses for emergency medical care related to the treatment of research-related injuries, if necessary.*

LIABILITY:
Because Colorado State University is a publicly-funded, state institution, it may have only limited legal responsibility for injuries incurred as a result of participation in this study under a Colorado law known as the Colorado Governmental Immunity Act (Colorado Revised Statutes, Section 24-10-101, et seq.). In addition, under Colorado law, you must file any claims against the University within 180 days after the date of the injury. In light of these laws, you are encouraged to evaluate your own health and disability insurance to determine whether you are covered for any physical injuries or emotional distresses you might sustain by participating in this research, since it may be

necessary for you to rely on your individual coverage for any such injuries. Some health care coverages will not cover research-related expenses. If you sustain injuries, which you believe was caused by Colorado State University or its employees, we advise you to consult an attorney. Questions concerning treatment of subjects' rights may be directed to Janell Barker, Human Research Administrator at 970-491-1655.

WHAT IF I HAVE QUESTIONS? *Before you decide whether to accept this invitation to take part in the study, please ask any questions that might come to mind now. Later, if you have questions about the study, you can contact the investigator, Brian Tracy, Ph.D., at (970)491-2640, or via email at tracybl@cahs.colostate.edu. If you would like to ask a medical doctor about your participation in the study, you may contact Russell Risma, M.D. at (970) 491-7121, or page Wyatt Voyles M.D. at (970) 202-4020. If you have any questions about your rights as a volunteer in this research, contact Janell Barker, Human Research Administrator at (970) 491-1655. We will give you a copy of this consent form to take with you.* Your signature acknowledges that you have read the information stated and willingly sign this consent form. Your signature also acknowledges that you have received, on the date signed, a copy of this document containing 6 pages.

_____ _____

Signature of person agreeing to take part in the study Date

_____

Printed name of person agreeing to take part in the study

_____ _____

Name of person providing information to participant Date

_____

Signature of Research Staff