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Age-related Differences in Beta-range Electroencephalography Activity and Its Correlation with Postural Sway during Prolonged Quiet Stance

Stephanie L. Kirk
University of Vermont

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Abstract

Falls are a multi-factorial, expensive and recurring issue in the older population. This study's objective was to determine whether age affects the contribution of the cortex and the relationship between the cortical activity and postural sway during postural balance. This quantitative, experimental study had a research sample of eleven healthy, old (mean age = 71 yrs) and ten healthy, young (mean age = 23 yrs) volunteers. Electroencephalography (EEG) and force plates recorded the brain activity and postural sway under two task conditions: narrow stance on firm surface (NEC) and narrow stance on foam surface (FEC) both with eyes closed. The maximum magnitude of the power spectral density (PSD) in the beta frequency range (i.e. 13-30Hz) and the peak-to-peak range, velocity and total displacement of the center of pressure (COP) in both the anterior-posterior (AP) and medial-lateral (ML) directions were extracted from the EEG and force plate data. The correlation between the EEG PSD and range of COP displacement (using the Pearson correlation) and beta corticokinetic coherence between EEG and contralateral COP were computed. The percent change of EEG PSD from the NEC to FEC condition and the EEG-COP correlation were compared between groups using one-tailed t-tests. No significant group difference ($p > 0.06$) was found in EEG PSD change. However, there were significant group differences in EEG-COP correlations in both the ML ($p < 0.000$) and AP ($p < 0.000$) directions. The correlation coefficients were positive for the young group (mean = 0.29 ± 0.27) and negative for the old group (mean = -0.40 ± 0.23). Furthermore, significant corticokinetic coherence was found for all subjects under both conditions. These results demonstrate a direct connection between cortical activity and postural sway in both young and older adults. Yet, the role of cortical involvement is significantly altered in old adults, suggesting an age-related difference in the modes of postural control that may be an important indicator for assessing fall risk.

Introduction

About one in three older adults, over 65 years of age, will experience a fall each year (World Health Organization, 2008). These falls are the leading cause of injuries to the older adult population, resulting in 2.5 hospital visits per year due to traumatic brain injuries, fractures and lower and upper limb injuries (Stevens, Corso, Finkelstein & Miller, 2006; World Health Organization, 2008). Not only are falls detrimental to the older adults' health, but also to the US public health system, as the average direct medical cost is $34,294 per fall (Rizzo et al., 1998). The expense of these falls have led to intervention programs being implemented to try to lower the risk of falls by altering the environment, physical capacity and mental attitudes of the older individuals (Karlsson, Vonschewelov, Karlsson, Cöster & Rosengen, 2013). Yet, to best care for the older adults and create effective preventative programs, an understanding of the underlying mechanisms that cause these falls is needed.

Falls are a multifactorial problem, arising from a variety of sources. These sources include poor cardiovascular health (i.e., heart tremors and attacks), deteriorating or abnormal nervous system structure and function, hindered neuromuscular communication (Lópex-Otín, Blasco & Kroemer, 2013), limited skeletal muscle strength (Johnson, Robinson & Nair, 2013), slow reaction and reflex times (Shaffer & Harrison, 2007), and decreased cortical functioning (Jagust, 2013; Jellinger & Attems, 2013; Mora, 2013). Most sources of falls have been widely-studied; the roles of cardiovascular (Ferrari, Radaelli & Centola, 2003; Minaker, 2011), skeletal, muscular (Johnson et al., 2013), and peripheral nervous (Shaffer & Harrison, 2007) systems in maintaining postural balance have been well demonstrated. The abnormal functioning of these systems has also been associated with higher fall risks (Papegaaij, Taube, Baudry, Otten &

Hortobágyi, 2014). However, the role that the cortex plays in maintaining postural control has only recently been studied.

Researchers used to think that postural balance was only maintained through subcortical activity (Varghese, Beyer, Williams, Miyasike-daSilva & McIlroy, 2015), however, more recent studies have found that the cortex and the central nervous system are also engaged during postural balance tasks (Horak, 2006; Jacobs & Horak, 2007). Tse et al. (2013) found that the level of cortical activity increases as the difficulty of the balance task increases, showing the level of involvement that the cortex actually has in postural control. However, the correlation between cortical activity and postural stability has yet to be studied. A correlation between cortical activity and postural sway, a measure of postural stability, would help to quantify and further confirm the cortex's role in postural control.

Also, whether there is an age-related difference in the amount of cortical activity during postural control tasks has yet to be determined. Whether there is an age-related difference in the correlation between cortical activity and postural sway is also unknown. Since the body experiences natural deterioration associated with aging, the older adults are at a higher risk of falling. It is known that aging has deteriorating effects on the muscles, bones and nerves (Johnson et al., 2013; Lopez-Otin, Blasco, Partridge, Serrano, & Kroemer, 2013; Mora, 2013), yet how aging affects the extent of cortical involvement in postural control is still unknown.

The objective of this study was to fill a gap in literature by focusing on the age-related differences in cortical activity and its relationship to postural sway during postural control tasks. To do so, this study aimed to answer the following research questions. Are there age-related differences in brain activity during postural control tasks? Does age have an effect on the relationship between brain activity and postural sway during postural control tasks? Is there a

synchrony between brain activity and postural sway, termed as corticokinetic coherence (which is discussed later in this introduction)? Through answering these questions, this study hoped to increase the understanding of the body's postural control system, the role of the cortex during postural control and the correlation between cortical activity and postural sway. From a clinical view, age-related differences in cortical activity would help justify the incorporation of brain and mental exercise into fall-prevention programs.

To address the above research questions, this study looked into the cortical activity of both young and old adults while on balancing on a foam surface with their eyes closed (FEC) and compared this to balancing with a narrow stance on a firm surface with the eyes closed (NEC). This stance condition was chosen to control the number of peripheral sensory inputs that were being received and utilized by the brain during the stance. The closing of the eyes inhibited the input of visual sensory information. The foam surface altered the stimulation of somatosensory receptors and their inputs to the brain. From NEC to FEC, only the input of the somatosensory system is changed, therefore, the percent change observed in the brain activity between the conditions likely resulted from the increased difficulty of the balance task due to the lack of the somatosensory input.

It has been demonstrated that postural tasks are more challenging to older adults than to young adults (Papegaaij et al., 2014). Aging causes structural and functional declines in the somatosensory system and cortical structures, which contribute to the decrease in postural stability of older adults (Pagegaaij et al., 2014; Shaffer, 2007). Furthermore, Tse et al. (2013) found that the cortical involvement in standing balance tasks increased with the difficulty of the tasks. Also, Baudry, Penzer & Duchateau (2014) found that older adults had greater corticospinal excitability than the younger populations. Additionally, Pichierri, Wolf, Murer & de Bruin

(2011) have found that balance tasks have a greater cognitive demand for older adults, which may result in increased cortical excitability, primarily the prefrontal cortex. This may be because the older adults had to give more attention and focus to completing the otherwise autonomic balance tasks. Thus, it was hypothesized that older adults would exhibit a much greater increase in the amount of cortical activity during more challenging balance tasks than younger adults. However, the older adults may only exhibit this greater increase of cortical activity due to the greater attention demand and focus required by them. Thus, the amount of cortical activity that they exhibit that actually is directly related to postural control may actually be quite small. On the other hand, the cortical activity in the younger adults may be more directly related to the maintenance of postural control. Therefore, it was hypothesized that the younger adults would show a greater relationship between the cortical activity and postural sway than the older adults.

This study not only looked at the age-related differences in the amount of cortical activity, but also at the age-related differences in its relationships to postural sway. This study examined the relationship (i.e. correlation) between the magnitude of the power spectral density (PSD) of the electroencephalography (EEG) of the cortical activity and the magnitude of the displacement of the center of pressure (COP) of the postural sway in the time domain. This study also examined the synchrony (i.e. coherence) between the oscillatory activities in the beta-frequency range (i.e. 13-30 Hz) in the cortex and in the postural sway in frequency domain (i.e. beta corticokinetic coherence). The coherence in the beta-frequency range between cortical and muscular activities (i.e. beta corticomuscular coherence) has been shown to associate with the brain's modulation of voluntary movement and muscular control (Kilner et al., 1999; Witham et al. 2011). To date, no studies have examined the corticokinetic coherence during stance. In an earlier study, Jacobs, Wu and Kelley (2015) and Isaacson et al. (2015) focused on

corticomuscular coherence (CMC) in the beta-frequency range during stance and deemed coherence to be a direct functional connection between the cortical and muscular activity. Since postural sway represents an integral effect of the postural control system, it was hypothesized that a beta corticokinetic coherence exists during a prolonged stance and is a measure of the brain's modulation of postural control.

Hypotheses

This study was designed to test the following research hypotheses:

1. It was hypothesized that the older subjects would experience a greater change in the level of activation of the sensorimotor cortex than the younger participants as the postural balance task changed from a narrow stance on a firm surface with eyes closed (NEC) to a foam surface with eyes closed (FEC). Thus, it was predicted that the percent change of the maximum magnitude of the electroencephalography (EEG) power spectral density (PSD) in the beta range between the NEC and FEC condition would be greater in the older group compared to the young group.
2. It was hypothesized that the younger subjects would have a greater correlation between the percent change of the level of activation of the sensorimotor cortex and the magnitude of postural sway than the older subjects when the stance condition changes from NEC to FEC. Thus, it was predicted that the correlation between the percent change of maximum magnitude of the EEG PSD in the beta range between the NEC and FEC condition and the maximum range of the COP displacement would be higher in the young group compared to the older group.
3. It was hypothesized that there would be a significant corticokinetic coherence in the beta range between cortical activity and body sway during the postural tasks for each age group under both stance conditions. Therefore, it was predicted that greater than fifty percent of the subjects in each group would have a peak corticokinetic coherence area above the significant threshold.

Key Terms

Beta coherence – the strength of similarity between the cortical activity and postural sway waves in the beta frequency range (13-30Hz) (Teplan, 2002)

Center of Pressure (COP) – the point at which the sum of the forces (i.e. gravity and ground reaction forces) act upon a body (Wang, Skubic, Abbot & Keller, 2010)

Cortical activity – the excitatory or inhibitory activation of neurons in various regions of the cortex

Corticokinetic coherence - synchrony between the oscillatory activities in the beta-frequency range (i.e., 13-30 Hz) in the cortex and in postural sway in frequency domain

Electroencephalography (EEG) – the measure of the electrical field generated from the summation of the cortical neurons' action potentials (Teplan, 2002)

Older adults – refers to men and women 65 years of age or older

Postural balance – "the ability to maintain the of the center of gravity within a bas of support in a quiet upright position during standing" (Jeter, Nkodo, Moonaz & Dagnelie, 2014)

Postural control – the body's integration of the central and peripheral nervous systems in order to maintain upright posture (Horak, 2006)

Postural sway –the deviation of the center of pressure (COP) as a measure of postural balance (Horak, 2006)

Power spectral density (PSD) – a method of analyzing EEG signals that reflects the distribution of signal power over a certain frequency (Tse et al., 2013)

Sensorimotor area – the pre-central and post-central gyri of the cortex involved in the processing of sensory information and movement control

Sensorimotor cortex activation – the excitatory or inhibitory activation of neurons in the sensorimotor cortex of the brain

Sub-cortical control – postural control maintained by structures below the level of the cortex (i.e. spinal cord, muscular reflexes, cerebellum and basal ganglia) (Papegaaij et al., 2014)

Review of the Literature

Search Strategy

Research articles were found using Ovid MEDLINE® Complete (1946 - present) through the University of Vermont Dana Medical Library server. Various combinations of the following terms were searched: postural control system, balance, elderly, fall, costs, aging. In addition, article titles were found by searching relative topics in Google Scholar (scholar.google.com), such as, cardiovascular system aging and cortex role postural control. Then full-text files for relevant articles from the Google Scholar searches were obtained by searching for their titles in Ovid MEDLINE®. Additional articles were selected by reviewing the articles' reference sections. Furthermore, supplementary articles were provided from faculty advisors.

Falls

Health concern. Falls are a major public health concern, as about one third of the US population over 65 years of age experiences a fall each year (World Health Organization, 2008). Falls are defined as "inadvertently coming to rest on the ground, floor or other lower level, excluding intentional change in position to rest in furniture, wall or other objects" (World Health Organization, 2008, p. 1). Falls are currently the leading cause of fatal and nonfatal injuries in the older adults in the United States (Centers of Disease Control and Prevention [CDC], 2013). Elderly falls resulted in 2.5 million emergency department visits, 734,000 hospitalizations and 25,464 deaths in 2013 (CDC, 2013).

Common injuries related to falls include hip fractures, traumatic brain injuries and upper limb injuries (World Health Organization, 2008). Depending on the individuals' support situation, mental attitude, and severity of their injury, a fall can be life changing and devastating. The resulting injuries may make it hard for the individual to return to their daily life activities or

live independently and a large percentage of these elderly remain in the hospital long-term (World Health Organization, 2008).

Assessment of fall risk. Being able to identify older individuals who are at an increased risk of falling is an important tool to provide necessary care and treatment. Various means of assessment have been used to determine fall risk, including the Timed Up and Go Test (TUG) and the Activities-specific and Balance Confidence (ABC) Scale. During the TUG, the individual rises from a sitting position, walks three meters, turns around and returns to sitting in their chair as quickly as they can. The TUG has been found to be a sensitive and specific means of differentiating those individuals with heightened risk of falling; the time to complete the test has strong correlations to the individual's functional mobility. Those who take longer than 14 seconds are more likely to be dependent on others during their daily activities and be more at risk of falling (Shumway-Cook, Brauer & Woollacott, 2000). The ABC Scale is a questionnaire that measures the level of psychological impact of falls based off an individual's self-efficacy in balance during daily activities. The questionnaire asks the individual to rate their confidence in performing 16 daily activities, where a score of 0% corresponds to no confidence and 100% corresponding to complete confidence. The ABC Scale has been found to have a sensitive and specific cut-off for classifying fallers as those who score lower than 67% (Hill, 2005). These forms of assessment are relatively simple and feasible means of identifying those individuals who are at increased risk of falling.

Fall costs. As a country, caring for these individuals and their fall injuries is a priority, especially since 1965 when Medicare went into effect and the government began to pay for their care. The average direct hospitalization cost for one of these fall injuries is $34,294 (Rizzo et al., 1998). This does not include the indirect costs of loss of productivity from both the individual

and family caregivers (World Health Organization, 2008). The direct medicals costs due to elderly falls equates to $30 billion, adjusting for inflation (Stevens et al., 2006). This is a large amount to pay for these unintentional falls. Therefore, preventing these falls from occurring has been an important concern of the public health community. A few programs have been implemented to fix the external environment, add physical training and focus on more individualized care for the elderly population (World Health Organization, 2008). Yet to best care for the elderly population and create the most effective fall-prevention program, we need to understand the physiology of how falls occur.

Postural Control

Overview. Postural control is the maintenance of the body's position in space to balance and stay properly oriented (Woollacott & Shumway-Cook, 2002), or in other words, the maintenance of upright standing (Papegaaij et al., 2014). Postural control has two main goals: postural orientation and postural equilibrium. Postural orientation refers to the orientation of the body to a reference frame, which may be gravity, the standing surface, or visual cues based off sensory information and internal sensors. Postural equilibrium refers to the maintenance of posture through the use of various movement strategies when stability is disturbed by voluntary movement or external perturbations. Posture is controlled in both a feedback and feedforward (i.e. anticipatory) fashion. Postural equilibrium is maintained in a feedback mechanism through automatic postural responses (APR) that integrate internal and external signals received by peripheral sensors after self-initiated or externally caused disturbances of posture. In addition, the body uses anticipatory postural adjustments (APA) prior to the onset of an anticipated disturbance to maintain postural equilibrium in a feedforward manner (Horak, 2006; Jacobs & Horak, 2007).

The system of postural control. Though researchers once believed that postural control involved solely subcortical reflex responses (Varghese et al., 2015), there has been significant amount of evidence found to show that postural control involves much more than just these subcortical measures (Horak, 2007; Jacobs & Horak, 2007). Postural control is a very complex system; it is a dynamic and context-dependent control of posture by the interactions between the spinal cord, brainstem and cortex. When the muscular response times to perturbations of postural stability are looked at, a variety of response latencies (ranging from 30 ms to 150 ms) are found. The initial muscular responses are in the range of 30-40 ms and are called short latency responses. Short latency responses are caused by the sub-cortical system and provide the initial response to perturbations. However, medium (approximately 80 ms) and long (approximately 130 ms) latency responses correspond to APRs and APAs and are thought to involve higher centers such as the cortex, cerebellum and basal ganglia. These signals provide a more complex, adaptable response to perturbations to bring the body back into equilibrium (Jacobs & Horak, 2007; Scholz, Noth, Friedemann, Dichgans & Bacher, 1987).

Jacobs and Horak (2007) stated that the cortex creates postural response synergies, which are motor plans sent to various muscle groups to maintain posture. The cortex has been found to modulate posture directly through the corticospinal tract. Additionally, the cortex indirectly modulates posture by communicating with the propriospinal neurons (Massion, 1992), the basal ganglia, the cerebellum and the brainstem nuclei that control other descending tracts, such as the pontine and medullary reticulospinal tracts (Massion, 1992; Stapley & Drew, 2009), the lateral and medial vestibulospinal tract (Markham, 1987), and the rubrospinal tract (Zelenin, Beloozerova, Sirota, Orlovsky & Deliagina, 2010).

The basal ganglia has been found to play a role in allowing flexibility of balance-correcting responses, assigning priority to postural tasks, and processing multimodal sensory information (Visser & Bloem, 2005). Various lesion studies have found that impairments to the substantia nigra pars compacta, putamen, globus pallidus internal, and subthalamic nucleus all have negative effects on balance control (Cummings et al., 1994). The thalamus, peduculopontine nucleus and substantia nigra pars reticulata have also been found to influence postural response signals (Takakusaki, Saitoh, Harada & Kashiwayanagi, 2004). In addition to these, the cerebellum, particularly the vestibulocerebellum and medial zone, has been found to be important in the maintenance of the body's orientation to vertical, anti-gravity senses and balance (Morton & Bastian, 2004).

The peripheral sensory systems also play a prominent role in postural control. The somatosensory system provides proprioceptive information from the cutaneous receptors in the skin, as well as, from the muscle spindles and golgi tendon organs, which regulate muscle length and tension (Pasma et al., 2014). These help provide feedback about the relative position of body segments in space and their contact with the surrounding environment. In addition to somatosensation, the visual system is also highly relied on to provide context and visual cues as to where the body is in space. Furthermore, the vestibular system provides information on the head's linear and angular acceleration in space, which helps to orient the body to vertical. All three sensory systems (somatosensory, visual and vestibular) are used for postural control, however, the amount to which an individual relies on the various systems differs depending on the context and the person. Typically, an individual relies more heavily on their somatosensory information (70%) compared to their visual (10%) or vestibular (20%) when maintaining balance in a well-lit, stable environment (Horak, 2006). However, on unstable surfaces, such as balancing

on foam or walking on sand, an individual's somatosensory information is less reliable, thus, they must rely more heavily on their visual and vestibular information. The ability to switch the amount of which one relies on each of the three sensory systems is called sensory re-weighting. As individuals age, their nervous system begins to deteriorate, nervous system disorders appear, and their ability to re-weight sensory information and maintain balance in various atypical environments is often impaired (Horak, 2006; Pasma et al., 2014).

Effect of aging. As the body ages, many physiological changes occur that decrease the effectiveness of postural control and thus lead to increased risk of falls. López-Otín, Blasco and Kroemer (2013) proposed nine age-related changes that occur on the cellular and molecular levels. These include (1) genomic instability, such as DNA damage and mutations, (2) weakening telomeres, (3) epigenetic alterations, (4) poor protein homeostasis, (5) accelerated anabolic signaling and (6) cellular senescence. In addition, aging decreases (7) mitochondria function, (8) stem cell regeneration and (9) intercellular communication.

Zooming out from the microscopic scale, aging has also been found to have effects on various organs including the kidneys (Epstein, 1996), lungs (Sharma & Goodwin, 2006; Rossi, Ganassini, Tantucci & Grassi, 1996), and heart (Ferrari et al., 2003; Minaker, 2011). Aging affects the kidney's structure and function reducing the kidney's response to stresses and increasing the risk of disease (Epstein, 1996). Changes in the lung structure create difficulty breathing, coughing, and responding to drugs. Lung changes include deformities in structure, decreases in muscle strength and airway receptor capabilities, and increases in alveolar dead space (Sharma & Goodwin, 2006). The heart's cells degenerate with age resulting in stiffer valves and abnormal heart rhythms (Minaker, 2011).

Furthermore, many of the body's systems are also altered due to the natural aging process. The cardiovascular system is altered due to the decreased function of the heart combined with age-related changes in the blood vessels (Ferrari, Radaelli & Centola, 2003; Minaker, 2011). The renal system (Epstein, 1996) and respiratory system (Sharma & Goodwin, 2006; Rossi et al., 1996) are altered due to the age-related changes in the kidneys and lungs. In addition to these, the immune system becomes exhausted, leading to a decrease in normal immune function and increasing the likelihood of diseases in the older adult population (Simpson et al., 2012). Moreover, the structure and function of somatosensory system is altered throughout aging (Shaffer & Harrison, 2007; Jagust, 2013).

The musculoskeletal system is also altered as sarcopenia, i.e., the decrease in skeletal muscle mass and strength, occurs with aging (Johnson et al., 2013) and mitochondria function is reduced (Johnson et al., 2013; Lopez-Otin et al., 2013). Also, the somatosensory system declines, largely resulting from the loss of distal large myelinated sensory fibers and receptors, and resulting in impaired distal lower-extremity proprioception, cutaneous reception and balance (Shaffer & Harrison, 2007).

Finally, aging alters the central nervous system and brain. Sensory, motor and cognitive declines have been associated with the aging of the brain (Mora, 2013). Decreases in brain volume, synaptic density, and gray and white matter volume begin in the middle age individual (Jagust, 2013). Brain atrophy, network dysfunction and an increase in cognitive activation have also been linked to the normal aging process (Jagust, 2013; Mora, 2013). The connectivity between the cortex and basal ganglia is weakened due to the compilation of years of activity. These changes lead to compensation during cognitive tasks, such as an increase in dopamine synthesis and increase in hippocampus activity in the older adults (Jagust, 2013). However, the

most likely cause for cognitive decline in older adults is not the neuronal loss or white matter changes, but rather synapse dysfunction, which may lead to slower conduction velocities and progression of signals (Jellinger & Attems, 2013; Mora, 2013). The nervous system's neurogenesis and neuroplasticity are hindered due to a decrease in the number of new maturing neuronal stem cells (Jellinger & Attems, 2013). These changes of the body's systems during aging all play a role in the health of older adults and make them more susceptible to various diseases and accidents, such as falling.

Measurement of postural control. Due to the complexity of the postural control system, accurately quantifying the effectiveness or ability of a person's postural control system through a single assessment technique is highly impractical. Therefore, the measurement of body sway is often used to evaluate the instability of a person when maintaining standing balance. Body sway refers to the slight movements of the body in the horizontal plane during quiet stance. Body sway is otherwise known as the amount of deviation of the center of gravity (COG) or center of pressure (COP) from the center reference point (Wang, Skubic, Abbot & Keller, 2010).

A common method of measuring body sway is the use of a force plate, which records the COP under the supporting feet of a person standing on the force plate. The COP displacement in both the anterior-posterior (AP) and the medial-lateral (ML) directions, referred to as AP and ML sway, during quiet stance has been found to have rather random patterns. However, several quantities of COP, such as the maximum sway range, average sway velocity, and total sway distance, have been found to be significantly different across various age groups, various health conditions and various stance conditions that alter the degree of challenge to the postural control system (Isaacson et al., 2015; Matijacic, Jakovljevic & Cikajlo, 2013; Tse, 2013). Other methods of measuring postural stability have been used, such as motion capture and analysis systems;

however, these systems are relatively expensive and much more complex, as they involve body sensors and multiple cameras (Wang et al., 2010).

No matter the means of measurement, body sway is still only a mechanical measure, giving researchers a quantified amount of the instability of a person when performing a postural control task. Though body sway can be used as an inference point to deduce potential postural control system problems, it does not give an insight into the body's inner complex postural control system nor tell which part or parts of the system are lacking (Horak, 1987; Wang et al., 2010).

Current Studies on Cortical Contribution in Postural Control

Jacobs (2014) emphasized the need for more research to be done in the arena of the role of the cortex in postural control as it is an emerging topic and much is still unknown. He highlighted how important the cortical neurophysiology is for maintaining balance particularly for individuals with advanced aging, chronic pain or neurodegeneration. Jacobs (2014) called for more research to be done to further explore and explain the unique neurophysiology systems of postural control. Varghese et al. (2015) delved deeper into the topic of cortical involvement during the maintenance of standing balance. They found increased peak amplitudes and spectral powers of EEG signal recordings as the difficulty of the standing balance task increased.

Tse et al. (2013) looked at postural sway in addition to cortical activity during standing balance task of increasing difficulty to provide evidence of the cortical involvement. They found that power of the beta and sigma bands of the EEG signals from the parietal and central areas of the brain were higher when eyes were open and either the base of support or surface compliance was altered. As task difficulty increased, by the alteration of vision and somatosensory information, postural sway also increased and the EEG band power decreased. This suggested

that the postural control was shifted to more subcortical structures in these cases. However, in the most challenging tasks the band power of beta and sigma increased significantly, suggesting the cortex is greatly needed in the more challenging tasks.

Both studies by Varghese et al. (2015) and Tse et al. (2013) provided much insight into the cortical involvement during postural tasks. However, both focused on healthy young subjects; 12 healthy volunteers with an age range of 19-37 years (Varghese et al., 2015) and 20 healthy volunteers, age range 24-32 (Tse et al., 2013). Tse et al. (2013) in their discussion recommended that studies on older adults also be performed. To date, no study has looked at both the young and old populations and attempted to determine if there is an age-related difference in the cortical activity during postural balance tests.

Papegaaij et al. (2014) expounded on the reorganization of postural control that accompanies aging and explained how so many elements of aging affect the postural control system (see Effects of Aging section). Papegaaij et al. (2014) detailed recent research in the area of aging and postural control, claiming that various imagination tests, external perturbation tests, and dual-task tests have been performed to show how aging affects cognitive capacity. However, aging also has been shown to have an effect on motor control and Papegaaij et al. stated the need for studies that look at the age-related changes of neural control mechanisms.

Jacobs, Wu and Kelly (2015) looked at the corticomuscular coherence (CMC) during standing balance tests of young subjects during various stance conditions. Additionally, Isaacson et al. (2015) looked at beta corticomuscular coherence in older subjects and older subjects with fall-risk. Both Jacobs et al. (2015) and Isaacson et al. (2015) found evidence of a beta corticomuscular coherence and additionally, Isaacson et al. (2015) found the CMC to be lower in the fall-risk group. To date, no study focused on the relationship between the cortical activity and

the postural sway to determine whether there is an age-related difference in these values or whether a beta corticokinetic coherence between cortical activity and postural sway exists.

As Pasma et al. (2014) also pointed out, there is a great need for new techniques that assess standing balance and detect the underlying cause of impaired standing balance at an early stage. There is a need for studies that add to the existing knowledge of the underlying mechanisms of postural control and highlight differences in the postural control system caused by aging, particularly by examining the relationship between cortical activity and postural sway through correlation and coherence. If a strong relationship between cortical activity and postural sway does exists, an understanding of this relationship could potentially lead to a simpler way of assessing standing balance and managing cortical degeneration.

Methods

The purpose of this study was to determine whether age affects the contribution of the cortex and the relationship between the cortical activity and postural sway during challenging postural balance tasks. This study was designed to test the following hypotheses:

1. Older subjects exhibit a greater change in brain activity compared to the young subjects as the difficulty of the postural balance tasks increases
2. Younger subjects exhibit a greater correlation between brain activity and body sway compared to the older subjects as the difficulty of postural balance tasks increases
3. Significant corticokinetic coherence exists for both younger and older subjects during both balance tasks

Research Design

This study used data from a previous research project and the methodology has also been described elsewhere (Jacobs et al., 2015). This study was a quantitative, experimental study with two independent age groups (young and older) that underwent balance tests under two stance conditions (NEC and FEC). The level of activation of the sensorimotor area and the amount of postural sway in the NEC and FEC postural task conditions were measured. Comparisons were made between the two age groups for the percent change in the cortical activity from the NEC to the FEC condition and for the correlation between cortical activity and postural sway. Also, a secondary analysis examined the existence of significant coherence between the cortical activity and body sway in each age condition and surface condition.

Subjects

The target population of this study was old adults and young adults. The sample population was old adults (aged 65 years or older) and young adults (aged 20-30 years) in the

greater Burlington, Vermont area. Inclusion criteria were that the subjects had to be non-smokers without history of neurological disorders, such as Parkinson's disease, multiple sclerosis, cerebral vascular disruptions, peripheral neuropathy, or vertigo. Subjects also had to be free of active cancer and cancer treatment, low back pain, rheumatoid arthritis, and centrally active medications. The older subjects had to have Activities-Specific Balance Confidence Scale (ABC) (Powell & Myers, 1995) scores of greater than 80 out of 100 and Timed Up and Go (TUG) (Podisadlo & Richardson, 1991) scores of less than 12 seconds, as well as not having experienced a fall in the last year. If any of these criteria were not met, subjects were excluded from the study.

The subjects were recruited by postings on bulletin boards, see Appendix A, in senior centers throughout Burlington, Shelburne, Charlotte, Winooski, Essex Junction and Williston, as well as in Retirement housing facilities such as the 3 Cathedral Square, the Pines and Pillsbury Manor. Postings were also placed in the Fletcher library, the YMCA in Winooski, the Community Health Center of Burlington and on the University of Vermont (UVM) campus. In addition to these, postings were also made on online sights, see Appendix A, including UVM News You Should Know, CHNS News, Front Porch Forum in Burlington and Craigslist. The Committee on Human Research in the Medical Sciences (CHRMS) at the University of Vermont approved the study and each subject signed a written informed consent form (see Appendix B), which detailed the procedures and potential risks of the study, prior to starting the experiment.

Instruments

Electroencephalogram. Electroencephalogram (EEG) data were gathered using an Advanced Neuro Technology (ANT, Enschede, the Netherlands) high-density ASA system with Waveguard 128-channel EEG caps (sintered Ag/AgCl electrodes). The cap was aligned

according to the 10-20 system, with the addition of electrodes F1, F2, FFC1h, FFC2h, FC1, FCz, FC2, FCC1h, FCC2h, C1, C2, CCP1h, CP1, CPz, CP2, CPP1h, CPP2h, P1, and P2 according to the 10-10 and 10-5 systems (Jasper, 1958), see Figure 1.

Each of the electrode sites was filled with conductive gel (Electro-Gel, Electro-Cap International, Inc., Eaton, OH). Impedances were adjusted to 10 kilo-Ohms or less before data collection began. Data from each channel were originally referenced to AFFz during data collection and were sampled with a 22-bit resolution at 1024 Hz. The EEG signals were collected through a DC amplifier and initial processing was done using ASA software version 4.7.3. (Advanced Neuro Technology, Enschede, the Netherlands). The EEG signals were synchronized with the EMG and force-plate data through the use of an external trigger signal.

Force plate. Body sway was quantified by the total body center of pressure (COP) under both feet during stance, which was computed through a summation of the COP under each foot. To do such, two OR6-6 force plates (AMTI, Inc., Watertown, MA, USA), one under each foot, were used to record the three-dimensional ground reaction forces (see Figure 2).

The force plates were lined with paper, so that the foot placements could be traced and the subjects' stances remain consistent throughout each trial of conditions. The force plate signals were collected at 2000 Hz and synchronized through Vicon recording software (VICON, Centennial, CO, USA). The force plate signals were also digitized with a 12-bit resolution by an analogue-to-digital converter at 2 kHz.

The EEG and force plate data were synchronized by an external trigger signal. This signal was generated from a separate, personal compute using a specialized Matlab program (The Mathworks Inc., Natick, MA). This external trigger signal also announced the start of data collection through a beeping sound from a micro speaker.

Procedures

Prior to their arrival at the University of Vermont Human Motion Analysis Laboratory, subjects were emailed an ABC scale questionnaire to fill out and an informed consent form to review on their own time, as well as instructions on how to get to the lab. When the subject arrived at testing, the informed consent was discussed between the primary investigator (PI) and the subject. All questions or concerns that the subject had were addressed. Then, if the subject agreed to participate in the study, the informed consent form was signed. After this the ABC scale questionnaire was collected. If the subject was part of the older group, a Timed Up and Go (TUG) test was then performed and their scores were recorded.

Then the subject was prepared for testing. First, the subject removed all hair accessories and changed into shorts that they brought with them, if not already wearing shorts. Then the subject was prepared for EMG (however data from the EMG was not used in the analyses for the particular research questions of this study). After this, their head measurements were taken. Marks were placed at 10% and 50% of the distance between the nasion to the inion, at 50% of the distance from the left to the right pre-auricular points, and at the point where the two 50% marks intersected. The EEG cap was placed by aligning the electrodes to the proper landmarks, as the 10-20 system details (Jasper, 1958). The Cz electrode was positioned on the 50% intersection mark, the Fpz electrode on the 10% mark on the forehead and the Iz on the inion. Caution was taken during this process to precisely align the cap to the correct landmarks for each subject, to keep consistency throughout the study. Conductive gel was inserted into the cap's electrode sites until the electrodes' impedances were below 10.

Then self-reported general characteristics about the subjects were recorded (Table 1), such as their height, weight, and limb dominance. The subject also put on a gait belt to wear as a safety precaution for the remainder of the study.

The subject then stood on the two force plates, each covered with a sheet of paper, with their bare feet as close together as possible without any contact and toes aligned straight ahead. The subject's feet were traced onto the paper to mark their foot placement. When they stepped off, the length of the foot and width across the metatarsal heads were measured and the distance between the acromions was marked.

Prior to the start of the experiment a random number generator was used to randomize a trial order between the six stance conditions: narrow stance on firm surface with eyes open (NEO) and eyes closed (NEC), wide stance on firm surface with eyes open (WEO) and eyes closed (WEC), and narrow stance on foam surface with eyes open (FEO) and eyes closed (FEC). Though 3 trials of 60 seconds were performed for each of these 6 conditions, for a total of 18 trials, only data from the narrow stance on firm surface with eyes closed (NEC) and the narrow stance on foam surface with eyes closed (FEC) conditions were used in this particular study.

Prior to each trial, the subjects were instructed to stand with their arms relaxed at their sides, relax their face, and close their eyes on the count-down "3, 2, 1, Go!" For the narrow stance on firm surface (NEC), the subjects' feet were positioned on the previously drawn outlines of both feet on the force plates. For the narrow stance on the foam surface (FEC), a foam mat (4-inches, medium-density, T-Foam, Alimed Inc., MA, USA) was placed on top of each of the force plates and the subjects were asked to stand with their feet as close together as possible without any contact occurring between them (see Figures 3-4).

During all trials, one to three assistants, depending on the subject's size and steadiness, guarded the subject. Aid was provided by assistants only when the subject's center of mass appeared to sway far enough outside the subject's base of support that the subject would fall without aid. All trials, including the trials where the aid of assistants was needed, were recorded on the subjects' trial sheets. The subjects self-reported fatigue rate and resting breaks were provided between trials to prevent fatigue.

Ethical Considerations

The balance tasks were designed to be no more difficult than functional tasks that are found in everyday activities and well within the capability of normal individuals. Nevertheless, the study involved 18 trials throughout a two-hour test session, which may have caused fatigue. Therefore, the subjects were provided with as much rest and recovery as they felt they needed. The study personnel regularly asked the subjects about their levels of fatigue, discomfort and safety concerns. Questions such as "are you tired?", "do you want to rest?", "are you comfortable?" and "do you feel unsafe?" were addressed and actions were taken to make the subject the most comfortable.

During the trials, the subject wore a gait belt, which was easy for the study personnel to grab ahold of and provide support to the subject. Up to three study personnel stood around the subject to provide assistance if the subject were to lose their balance or appear to under-go a fall. If the subject's center of mass moved outside their base of support, the study personnel would grab the gait belt and provide assistance.

Self-adhesive electrodes and medical tape were placed on the skin to measure muscle activities. These adhesives may have produced some mild irritation or redness of the skin. However this went away fairly quickly on its own. If the subject had a very sensitive scalp, they

may have experience slight discomfort when the hair was moved using a syringe in order to insert the salt gel into each of the electrodes of the EEG cap. In addition to this, the subject's hair was slightly soiled and un-styled when the cap was removed.

A very remote and unlikely risk existed that a minor electric shock from the electrodes could occur due to malfunction of the equipment. However, the design of the equipment was made to minimize the risk and potential amount of shock. In addition to this, the University of Vermont Technical Services Program provided annual inspections of the equipment used in this study to ensure its proper functioning.

There only existed very minor risks to the individuals in this study. However, had a serious adverse event occurred in which the subject needed medical attention, they were given access to the emergency department located in Fletcher Allen Health Care. The adverse event case would have been reported to the UVM IRB by principal investigator within 24 hours of the event using the University of Vermont Committee for Human Subject Research adverse event reporting document.

Finally, there was also a slight risk that the personal data that the subjects supplied could be disclosed to someone outside of the essential study personnel. To minimize confidentiality breaches, each subject was assigned a coded identification number, which was used in all study databases rather than the subject's name. The master list, which matched the subjects' names to their identification code, was kept in a locked cabinet in locked room, where only the principal investigator (PI) had access to the cabinet.

Data Processing

EEG processing. After collection of all data, processing of the EEG began. First, two examples of eye blink artifacts were selected and removed using the artifact correction parameter

with a maximum amplitude of 75 microvolts. After this, event markers were identified by setting the trigger extraction parameters to a threshold of 500 microvolts and a minimal trigger distance of 30 seconds. Next, epochs of 70 seconds were created, with the event durations beginning at 5 seconds before the external trigger signal and ending at 5 seconds after the 60-second trial. Finally, the signals were band-pass filtered from 1 to 60Hz. The power spectral densities (PSD) of the EEG signals at each node were computed in MatLab© by a customized program. The maximum magnitude in the beta range and the frequency at which this maximum magnitude occurred was also extracted.

The percent change in EEG PSD from the NEC to the FEC condition at each EEG node was used for group comparison. The percent change from the NEC to the FEC was calculated using the following equation:

% Change = (1- (FEC/NEC))*-100

to normalize the data, so that the COP and EEG values could be compared across persons and age groups.

Force plate processing. The force plate data (i.e. forces and moments) were processed in MatLab©. The data was first resampled to 1024Hz in order to be aligned with the EEG data, then low-pass filtered by a 4^{th}-order Butterworth filter with a cutoff frequency of 100Hz. The COP under each foot was computed from the ground reaction forces and moments of the corresponding force plate according to the following equations:

$COP_{AP} = (My/1000 + Fx*Zo)/Fz$

$COP_{ML} = (Mx/1000 - Fy*Zo)/Fz$

where COP_{AP} is the COP in AP direction, COP_{ML} is in ML direction, Fx, Fy and Fz are ground reaction forces from the force plate, and Mx and My are ground reaction moments from the force plate (see Figure 2).

The peak-to-peak range, velocity and total displacement of the COP in AP and ML directions were obtained, and were normalized by the corresponding foot length and width, respectively. The peak-to-peak range of the COP displacement for both feet in both the anterior-posterior (AP) and medial-lateral (ML) directions were correlated with the EEG power spectral density (PSD) magnitude at each of the nodes using Pearson correlation.

Coherence computation. First to improve the signal-to-noise ratio of coherence measures, the EEG signals were digitally re-referenced to a common average reference (Mima & Hallett, 199). Then the MatLab© coherence function 'mschoere' was used to compute the coherence between the reference-adjusted EEG signals of each node and COP of the contralateral foot in both the anterior-posterior (AP) and medial-lateral (ML) directions, respectively. The coherence between the central node and total COP (from both feet) was also computed. A forward time shift in foot COP was introduced from 0 to -200ms, at an increment of 25ms, to account for the time delay of the beta signal traveling from the cortex to the feet. The peak area of the coherence spectral above a significance threshold in the beta frequency band was extracted from each EEG-COP coherence at each COP time shift. The significant threshold of the coherence spectral was computed based on the method described by Androulidakis et al. (2007). The maximum value of the peak area among all time shifts was computed for each subject. The maximum value of the peak area of the coherence spectrum from all EEG electrodes in each hemisphere was selected for reporting. The percentage of subjects in each group with the maximum peak area above the significant threshold was computed.

Data Analysis

The normality of data was checked using the Shapiro–Wilks test. If data was found to be non-normal, the non-parametric Mann-Whitney test was used to determine group difference instead of a t-test. An average value of each outcome variable of the three trials of each condition was used as a single data point for each subject in the analyses. An unpaired, one-tailed t-test was used to determine if there was a significant difference between groups in the percent change in EEG PSD. The peak-to-peak range of the COP displacement under both feet in both the AP and ML directions were correlated with the EEG PSD in the beta range at each of the EEG nodes using the Pearson correlation. A paired, one-tailed t-test was used to determine group difference in the correlation coefficients of the EEG PSD and peak-to-peak range of the COP displacement under both feet in both the AP and ML directions. Finally, the percentage of subjects in each group with a maximum corticokinetic coherence area above the significant threshold was computed. All statistical tests were performed with a significance threshold of alpha value equal to 0.05.

Results

Subjects

The research sample of this study was eleven healthy, older (mean age = 71 years) and ten healthy, young (mean age = 23 years) volunteers. Subject characteristics can be seen in Table 1. There was no significant difference between groups in any variable except for age ($p < .01$).

Hypothesis 1: EEG Power Spectral Density

The maximum magnitudes of the power spectral densities (PSD) of the younger subjects had percent changes from the NEC to the FEC conditions ranging from -75% to 941%. The older subjects experienced PSD percent changes ranging between -46% and 225% from NEC to FEC (see Figure 4). The mean and standard deviation (SD) for the PSD percent changes from the NEC to the FEC condition for all the EEG nodes was 16% ± 59% for the young group and 6% ± 21% for the older group. The highest values of the EEG PSD occurred at the F7, T7, P7, F8, T8 and P8 nodes, all of which are on the periphery of the brain (see Figure 1). The periphery of the brain controls the upper extremities, which are not key muscles for postural control; therefore, these nodes were deemed as outliers and removed from the chart (see Figure 5). The t-test (or Mann-Whitney test) between the young group and the older group did not reveal any statistically significant differences at any of the EEG nodes ($p > 0.06$), see Table 2. However there appeared to be a trend that the older group had smaller PSD percent changes than the young group in most nodes except for T7, P1/2, P3/4 and P7/8 where the older group had greater percent changes in PSD.

Hypothesis 2: EEG PSD and COP Correlation

The correlations between EEG PSD percent changes and the COP range in ML and AP direction of the young group were mostly all positive, with correlation coefficients ranging from

-0.26 to 0.78 and a mean and standard deviation of 0.29 ± 0.27. The older group had mostly all negative correlations, ranging from -0.85 to 0.23 (see Figures 6-9) with a mean and standard deviation of -0.40 ± 0.23. The statistical test (i.e. Mann-Whitney) showed statistically significant group differences in both the ML ($p < 0.000$) and AP ($p < 0.000$) directions (see Figures 10-11).

Hypothesis 3: Beta Coherence

The maximum value of the peak area of the coherence spectrum between the EEG in each hemisphere and the contralateral COP, as well as between the central EEG and total COP, in both AP and ML directions, under both NEC and FEC conditions was found to be above zero (i.e. exceeding the significant threshold) for all subjects (i.e. 100%) (see Figure 12). The beta coherences for the young group in the NEC condition ranged from 0.02 to 0.13 with a mean and standard deviation of 0.07 ± 0.02. The beta coherences for the older group in the NEC condition ranged from 0.03 to 0.33 with a mean and standard deviation of 0.08 ± 0.04. The peak area of beta coherences of the young in for the FEC ranged from 0.02 to 0.13 with a mean and standard deviation of 0.06 ± 0.02 for the young subjects. The beta coherences for the older group in the FEC condition ranged from 0.25 to 1.11 with a mean and standard deviation of 0.13 ± 0.20.

The time shifts that created these maximum beta coherences between the EEG in each hemisphere and the contralateral COP recordings under both NEC and FEC conditions ranged from $1.0x10^{-14}$ sec to 0.19 sec, with a mean and standard deviation of 0.08 sec ± 0.04 sec for the young group in the NEC condition. The time shift for the older group for the NEC ranged from 0.002 sec to 0.19 sec, with a mean and standard deviation of 0.10 sec ± 0.05 sec. The time shift for the young group in the FEC condition ranged from 0.013 sec to 0.09 sec, with a mean and standard deviation of 0.11 sec ± 0.04 sec. The time shift for the older group for the FEC ranged from 0.00 sec to 0.20 sec, with a mean and standard deviation of 0.10 sec ± 0.05 sec.

Discussion

The objective of this study was to determine whether age affects the contribution of the cortex and the relationship between the cortical activity and postural sway during challenging postural balance tasks. This study was designed to test the following hypotheses. First it was hypothesized that the older group would have a greater increase in the percent change of the level of activation of the sensorimotor cortex (i.e. the maximum magnitude of the PSD in the beta range) as the postural control task changed from balancing with a narrow stance on a firm surface with eyes closed (NEC) to balancing on a foam surface with eyes closed (FEC). Secondly, it was hypothesized that the young group would have a greater correlation between the percent change of the level of activation of the sensorimotor area and the amount of postural sway when the stance changed from the NEC to the FEC condition. Thirdly, it was hypothesized that a significant beta coherence between the cortical activity of the sensorimotor area and the postural sway would exist for both the young and older groups during the FEC and NEC postural control tasks.

Hypothesis 1: Possible age-related differences in brain activity

The results from the EEG power spectral density did not support the first hypothesis. The percent change of the maximum magnitudes of the power spectral density from the NEC to the FEC conditions for the young and the older group showed no significant group differences. However, there appeared to be a trend that older group exhibited lower (or even negative) percent changes of PSD, in general, which suggested that the level of activation of the sensorimotor area changed less than the young group when switching from a firm to foam surface.

The results of the percent change in the PSD seem to be consistent with other studies, as the mean percent changes were all positive for both young (mean = 16% ± 59%) and old (mean = 6% ± 21%), suggesting that there was greater activation of the sensorimotor area when changing from the easier NEC to the harder FEC condition. Tse et al. (2013) also found a positive percent change in PSD when subjects changed from the easier condition, in their case the wide stance with eyes open condition, to each of the more challenging conditions. Additionally, Varghese et al. (2015) found an increase in cortical activity as their subjects' stance was changed from a standard Romberg stance (i.e. two feet placed together) to a tandem Romberg stance (i.e. feet heel-to-toe). However, Varghese et al. (2015) focused primarily on the Cz electrode and found significant differences in the theta, delta and gamma ranges.

Hypothesis 2: Significant age-related differences in brain-sway relationship

The EEG PSD and COP correlation results supported the second hypothesis. There were statistically significant group differences in the correlation between the percent PSD and COP in both the ML ($p < 0.000$) and AP ($p < 0.000$) directions. This difference was striking, as nearly all of the correlations between PSD and COP for the young group were positive and most all of the correlations for the older group were negative.

The results of the COP displacement and velocity are consistent with other studies, as well. The COP velocity and displacement tended to increase for both groups as the eyes closed and the support surface was changed from firm to foam (Amiridis et al., 2003; Tse et al., 2014). Furthermore the COP velocity and displacement tended to be greater in the older population compared to the young population (DuPasquier et al., 2013; Nagy et al., 2007; Teasdale et al., 1991). For example, Teasdale et al. (1991) found that the older group had an increase in sway range compared to the young, that the sway range increased for both groups when eyes were

closed, that sway increased in altered surface conditions for both groups but greater in the older group, and that a combination of altering vision and support surface elicited the greatest sway range for both groups, with the older group experiencing a much greater sway range. Furthermore, Nagy et al. (2007) found that the older subjects had greater COP sway paths in both directions and greater frequency of COP dispersion than the younger groups, particularly in the ML direction. Another study also found that the average instantaneous speed of the COP displacement and the total COP displacement were highly correlated with age (DuPasquier et al., 2003).

Additionally, Amiridis et al. (2003) found that in a more challenging balance task condition, in their case a narrow stance, that all groups swayed more, however the older group had a greater increase in sway. Our results are in agreement with these previous studies, as both groups experienced an increase in sway under the more challenging stance condition and when their eyes were closed. Furthermore the sway of the older group was greater than the sway of the young group in both the NEC and FEC conditions.

Hypothesis 3: Significant brain-sway synchrony

The beta coherence results supported the third hypothesis. The maximum values of the corticokinetic coherence area under both NEC and FEC conditions for both the young and older subjects were found to exceed the significant threshold. Significant beta coherence between the EEG and the contralateral COP and between the central node and the total COP in both the ML and AP directions was found.

The results on corticokinetic coherence cannot be compared with other studies because, to date, there has not been a study that examined the corticokinetic coherence. However, there have been several studies examining corticomuscular coherence (CMC) during standing balance

(Jacobs et al., 2015; Johnson & Shinohara, 2012; Kamp, Krause, Butz, Schnietzler & Pollok, 2013; Ushiyama et al., 2012). For example, Johnson & Shinohara (2012) looked at both the alpha and beta CMC and found significant differences in alpha CMC. Kamp et al. (2013) found that the CMC amplitude, CMC frequency and M1 power amplitude in the beta frequency range was significantly correlated with age. Ushiyama et al. (2012) looked into the change from the beta CMC to delta CMC and found that the central nervous system may regulate the frequency of the CMC to elicit various amounts of force in the muscles, and that this regulation coupling differs between muscles. Lastly, Jacobs et al. (2015) focused primarily on the beta CMC and found that the younger participants had greater beta CMC on their non-dominant side than older participants.

Overall, these studies found evidence of coherence between EEG and electromyography (EMG) of leg muscles during standing balance, suggesting a direct communication between the sensorimotor cortex and leg muscles. Since leg muscles play an important role in maintaining standing balance, it is likely that the postural sway is modulated by the sensorimotor cortical activities. Indeed, our finding of the significant beta coherence between the EEG and contralateral foot COP (i.e. corticokinetic coherence) suggests a direct communication between the cortical activity and postural sway. This gives support that the postural sway is directly modulated by the cortical activity.

Greater subcortical control in the older population

A compilation of the above results, seem to suggest that the older group may be using more subcortical or reflexive means of control, rather than higher cortical levels of control, to maintain balance under challenging stance conditions. Even though there was no significant difference between groups in the percent change in PSD, the younger group did have a slightly

higher trend of percent changes with a mean of 16% compared to the older group's 6% average increase. This trend of the older group having smaller percent change in PSD, suggests that they rely less on their sensory motor cortex when balancing under more difficult situations than the young group. This could be because the older group compensates by using sub-cortical modalities for postural control, or they may not have the capacity to increase their cortical activity to modulate their postural control during the more challenging task, due to the degenerative effects of aging.

The EEG PSD and COP correlation results also provide insight into the underlying differences that exist between groups in the role of cortical activity in postural control. In particular, the EEG PSD and COP correlations for the young group were nearly all positive and the older groups' were nearly all negative, with significant group differences in both the ML and AP directions. With the younger group a greater COP sway corresponds to a greater level of brain activity, yet with the older group a greater COP corresponds to a lower level of brain activity. These findings further suggest that the older population may depend more on the sub-cortical and/or spinal level of control to maintain balance during more challenging postural control tasks compared to the younger population.

Additional support of these postulations was found in the correlations between electromyography (EMG) data of leg muscles and postural sway that was generated from the data of the studies of Isaacson et al. (2015) and Jacobs et al. (2015) (see Figures 13 and 14). The correlation between the EMG from the gastrocnemius and tibialis anterior muscles and the magnitude of the AP and ML COP was nearly opposite compared to the relationship between the EEG PSD and COP correlations. In particular, the EMG and COP correlation for the young group was nearly all negative in both the AP and ML directions for both muscles, and the EMG

and COP correlation for the older group was nearly all positive (see Figures 13-14). This agrees with the idea that Nagy et al. (2007) suggested that the older group depended more on these leg muscle activities and subcortical response circuits than the younger group as the postural sway increased during more challenging postural balance tasks. Previous studies have shown that these lower leg activities, controlled at spinal or sub-cortical levels, are the first to be initiated during postural responses (Horak, 1987; Jacobs & Horak, 2007).

Nagy et al. (2007) suggested that the greater muscle activation found in the older population was actually due to a stiffer joint about the ankle. This stiffness was associated with a biphasic, ballistic-like pattern of torque at the ankle used to maintain balance through a closed loop as opposed to an open-loop mechanism (Nagy et al., 2007). Stiffer ankles in the older population would lead to a greater reliance on the hip strategy for maintaining balance; it has been shown that the older population does use the hip strategy to a greater degree than the young population (Amiridis et al., 2003). Furthermore, though Baudry et al. (2014) found an increase in corticospinal excitability in older adults, Baudry et al. (2014) mention that this may be caused by a general reorganization of the control of leg muscles as opposed a direct cortical control of postural balance. Additional response and regulation of posture would require an open-loop mechanism of control, which would require the use of higher cortical systems. However the older population may not be able to use these measures as readily as the younger population (Horak, Shupert & Mirka, 1989).

It is known that spinal or subcortical level of muscular control involves much faster response time (typically ranging from 30-40 ms for short latency muscular reflex responses of the leg muscles) than the cortical level control does (typically ranging from 80 ms for medium latency and 130 ms for long latency responses) (Jacobs & Horak, 2007). Therefore, if the older

group used more of the subcortical or spinal level of control than the cortical control as compared to the younger group, it is likely that there would have faster corrections in their postural sway. Consequently, we examined the mean COP velocity during the FEC conditions for each of the groups (See Table 3 and Figure 15) (Isaacson et al., 2015; Jacobs et al., 2015). Indeed, the COP velocities for the older population were found to be much higher, with means in the AP and ML COP of 19.32 %L-BOS/sec (i.e. percent of the length of the base of support per second) and 22.41 %W-BOS/sec (i.e. percent of the width of the base of support per second), compared to the younger population, means of 10.56 %L-BOS/sec and 13.01 %W-BOS/sec. This further supports the idea that the older population is relying more on their sub-cortical modes of postural control, compared to the younger population.

Based on the results of this study, the older group's reliance on subcortical measures of control could be due to the aging effects on the postural control systems (Horak et al., 1989). As adults age, they experience sensory, motor and cognitive declines (Mora, 2013) with decreases in brain volume, synaptic density, and gray and white matter volume (Jagust, 2013). Synapse dysfunction is also evident in older adults, which may lead to slower conduction velocities and progression of signals (Jellinger & Attems, 2013; Mora, 2013). The signals between the brain and muscles may also be inhibited due to these factors as Jacobs et al. (2015) found the beta CMC to be lower in older adults than in the young adults. Also, the older adults may not have the capacity to generate as high of a cortical response due to weakened connectivity in the brain (Jagust, 2013). This would result in delayed or diminished response from the cortex for controlling posture, due to slow central processing time or nerve conduction time in efferent pathways (Horak et al.,1989), which could be seen by the negative correlation between postural sway and brain activity in this study.

Clinical Implications

The results of our study suggest that the older adults are using more subcortical and reflexive measure of postural control during challenging balance tasks, rather than using higher cortical measures of control. This may suggest that balance training for the older population should involve a greater focus on the component of cortical involvement of postural balance, particularly under challenging conditions. Although this study did not look into particular exercises or interventions, a possibility exists that balance exercises or training programs could help older adults more readily use their cortex and increase their conduction velocity. Current balance exercises and training programs for the elderly tend to focus on strengthening muscles, increasing endurance, and increasing flexibility (Karlsson, Vonschewelov, Karlsson, Cöster & Rosengen, 2013). Recent studies have looked more into the cognitive side of things, finding positive effects of exergaming (Harris, Rantalainen, Muthalib, Johnson & Teo, 2015), video game training (Anguera et al., 2013) and mental imagery (Pichierri et al., 2011) on improving COP dispersion, cognitive capacity, and attention demands of tasks. These studies and our results give hope that the incorporation of balance exercises that require a greater amount of cortical activity, may prove to be beneficial for older adults. Exercises that require a greater amount cortical involvement may involve more slow, controlled movements, such as yoga or Tai Chi.

Future Studies

However, there currently have not been studies that particularly investigate whether balance training or exercise programs can increase the use of cortical involvement or increase the conduction velocity during postural tasks. Recent reviews of exergaming (Harris et al., 2015), video game training (Anguera et al., 2013) and mental imagery (Pichierri et al., 2011) looked into the effects on COP dispersion, cognitive capacity, and attention demands of tasks, but not

specifically at how training could increase the amount of cortical involvement in postural stability or increase conduction velocity. Therefore, future studies should look into ways to increase both cortical involvement and conduction velocity and potentially decrease the degenerative effect of aging on the brain in the older population to improve their postural control in challenging tasks. One potential family of exercises that should be looked into are those that use slow, controlled movements, which may require a higher level of cortical involvement and control to perform (e.g. yoga or Tai Chi).

Limitations

In this study, careful attentions were given to minimize instrumental and investigator biases. For example, the use of the electroencephalograph and force plates followed the similar methods of Slobounov, Sebastianelli & Hallett (2012), Tse et al. (2013) and Varghese et al. (2015) for proper recording of EEG and ground reaction forces. The EEG was set up according to the ten-twenty electrode system of the International Federation (Jasper, 1958). The set up and use of the force plate in this study was similar to the methods of many other studies, including Amiridis, Hatzitaki and Arabatzi (2003), DuPasquier, Blanc, Sinnreich, Landis, Burkhard and Vingerhoets (2003), Nagy et al. (2007) and Teasdale, Stelmach and Breuni (1991), though these previous studies used only one force plate and this particular study incorporated two.

Despite these careful attentions to testing procedures, certain limitations still existed. The small sample size most greatly limited the statistical power for the percent change in EEG PSD. For example, with a sample of 10 subjects per group, the power at the FCz node was 12.8%. It would be beneficial to repeat this study with a larger sample size to increase the power of the results. However to reach a power of 80%, a sample size of 264 would have to be used.

Increasing the sample size to 50 individuals per group (100 participants total) would increase the power to 18.7%.

Another limitation of this study was that it only focused on two stance conditions, the NEC and FEC conditions, and the change between those two particular conditions. Furthermore this study only looked at the beta range data from the EEG, excluding the other ranges. Due to these limitations of this study, caution must be taken when generalizing the results, as they cannot readily be applied across all postural task conditions or brain wave frequencies. Also, additional studies that address these limitations would be beneficial.

Conclusions

The results of this study did not support the first hypothesis that the older group would exhibit an increase in cortical involvement as the task difficulty increased. Even though no statistical group difference was found, there seemed to be a trend that the older people actually have less cortical involvement compared to the younger group as the balance condition becomes more difficult. The second hypothesis that the younger group would have a greater correlation between the brain activity and postural sway was supported by the results. Postural sway was positively correlated to cortical involvement for the young group and negatively correlated for the older group. The third hypothesis that significant beta corticokinetic coherence exists was also supported, as the results showed that all subjects under both stance conditions had peak coherence areas above the significant threshold.

In conclusion, the results of this study indicated a direct communication between the sensorimotor cortex and postural sway in both young and older adults. However, the role of cortical involvement during difficult balance tasks may be significantly altered in older adults compared to the younger adults. The results of this study suggest that there is an age-related difference in the modes of postural control when balancing under more challenging stance conditions. This group difference may be an important factor that could help to better assess the risk of falls associated with aging and create the most effective balance training programs for the older population.

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Table 1

Subject Characteristics

Measurement	Young Group (n=10)	Older Group (n=11)	P-value
Age (years)	22.5 +/- 2.9*	71.1 +/- 8.1*	< 0.01
Gender (# of males)	5	4	
Height (cm)	170.4 +/- 11.3*	169.3 +/- 7.7*	0.78
Weight (kg)	69.0 +/- 14.4 71.0*	71.0 +/- 15.1*	0.76
Foot Length (cm)	24.8 +/- 2.0*	24.5 +/- 1.4*	0.62
Foot Width (cm)	10.9 +/- 1.0*	10.5 +/- 1.9*	0.38
Hand Dominance (# in L:R:A)	3:7:0	0:10:1	
Foot Dominance (# in L:R:A)	1:9:0	0:10:1	
TUG Score (sec)	NA	7.4 +/- 1.5*	NA
ABCs Score (max = 100)	NA	95.3 +/- 6.1*	NA

*Numbers represent group mean +/- one standard deviation

Table 2

Group mean and standard deviation of the percent change in Power Spectral Density at each EEG node

	Younger Group		Older Group		T-Test
EEG node	Mean	STD	Mean	STD	p-value
Fz	31.75	88.61	8.23	17.60	0.63
FCz	9.19	19.84	5.48	13.94	0.32
Cz	8.56	50.97	-3.19	13.55	0.53
CPz	-2.04	23.40	-6.41	12.91	0.31
Pz	0.50	24.56	-4.20	12.67	0.68
F1	19.51	76.32	5.89	16.65	0.25
F3	21.43	76.89	9.61	27.31	0.48
F7	96.42	297.71	28.65	50.98	0.53
FFC1h	17.24	72.49	2.76	11.42	0.28
FC1	18.13	77.72	3.01	11.86	0.19
FCC1h	8.07	51.78	-2.57	13.52	0.48
C1	3.88	29.47	-2.24	18.25	0.80
C3	13.50	52.58	8.34	31.75	0.69
T7	48.80	56.24	81.56	81.41	0.43
CCP1h	1.44	26.01	-6.26	12.30	0.91
CP1	-2.01	25.03	-5.13	17.42	0.38
CPP1h	-0.34	25.57	-3.94	13.38	0.35
P1	-1.08	23.11	0.83	14.43	0.41
P3	0.56	21.61	6.23	17.93	0.27
P7	21.75	41.06	40.78	21.95	0.11
F2	19.19	69.63	-8.44	13.33	0.12
F4	13.95	61.54	-5.91	15.58	0.06
F8	70.67	226.50	16.92	30.09	0.68
FFC2h	7.26	67.87	-8.27	13.22	0.74
FC2	12.12	64.63	-10.04	11.96	0.35
FCC2h	8.67	53.18	-8.12	10.25	0.74
C2	7.72	50.11	-6.97	11.98	0.85
C4	5.79	52.69	-1.35	19.25	0.58
T8	79.53	82.26	48.57	53.43	0.68
CCP2h	8.41	47.88	-3.66	12.72	0.48
CP2	8.99	49.49	-6.59	11.35	0.17
CPP2h	-0.30	22.26	-5.99	12.98	0.63
P2	-1.31	22.22	1.25	23.57	0.74
P4	-0.51	21.67	8.86	27.05	0.85
P8	13.66	24.49	37.38	38.98	0.48

Table 3

Mean Value of the COP Velocities (in %Length of Base of Support(BOS)/sec for AP and %Width-BOS /sec for ML) in the FEC Condition

	Young Group	Older Group	p-value
AP Mean ± Std	10.56 ± 2.49	19.32 ± 10.11	0.012
ML Mean ± Std	13.01 ± 3.60	22.41 ± 13.14	0.027

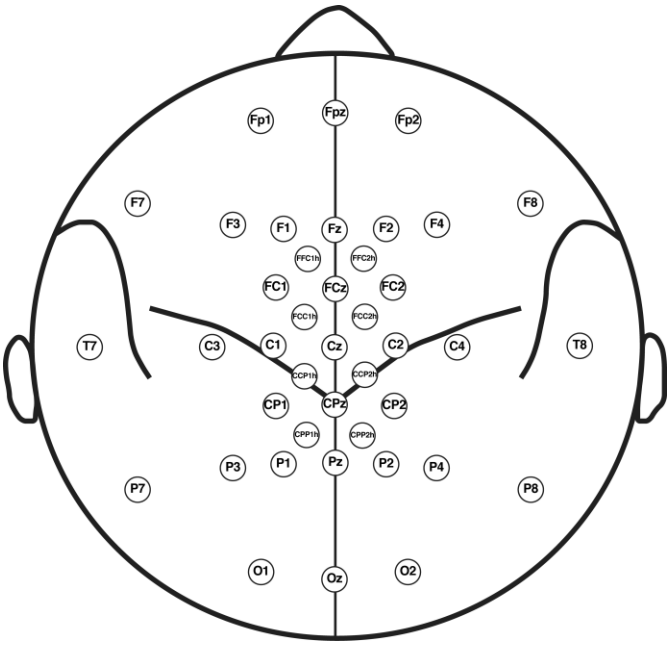

Figure 1. Electroencephalography electrode placement.

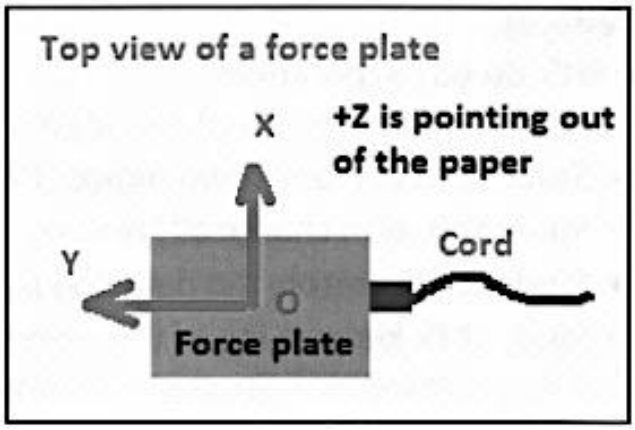

Figure 2. Set up of the force plates showing the directions of the ground reaction forces.

Figure 3. Experimental set up on foam surface, FEC condition.

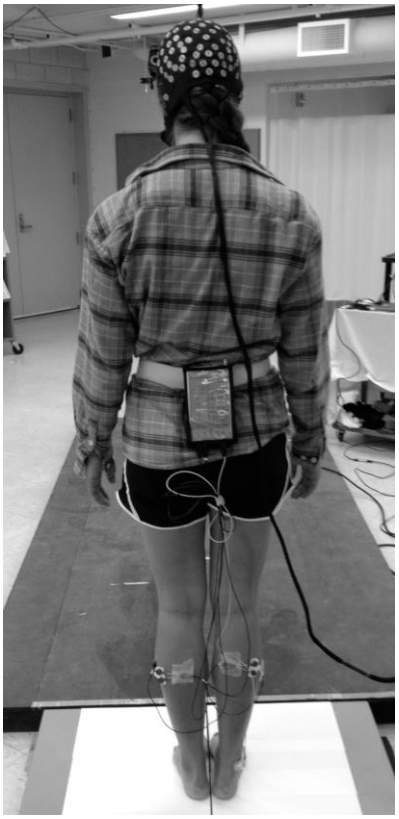

Figure 4. Experimental set up on normal/firm surface, NEC condition.

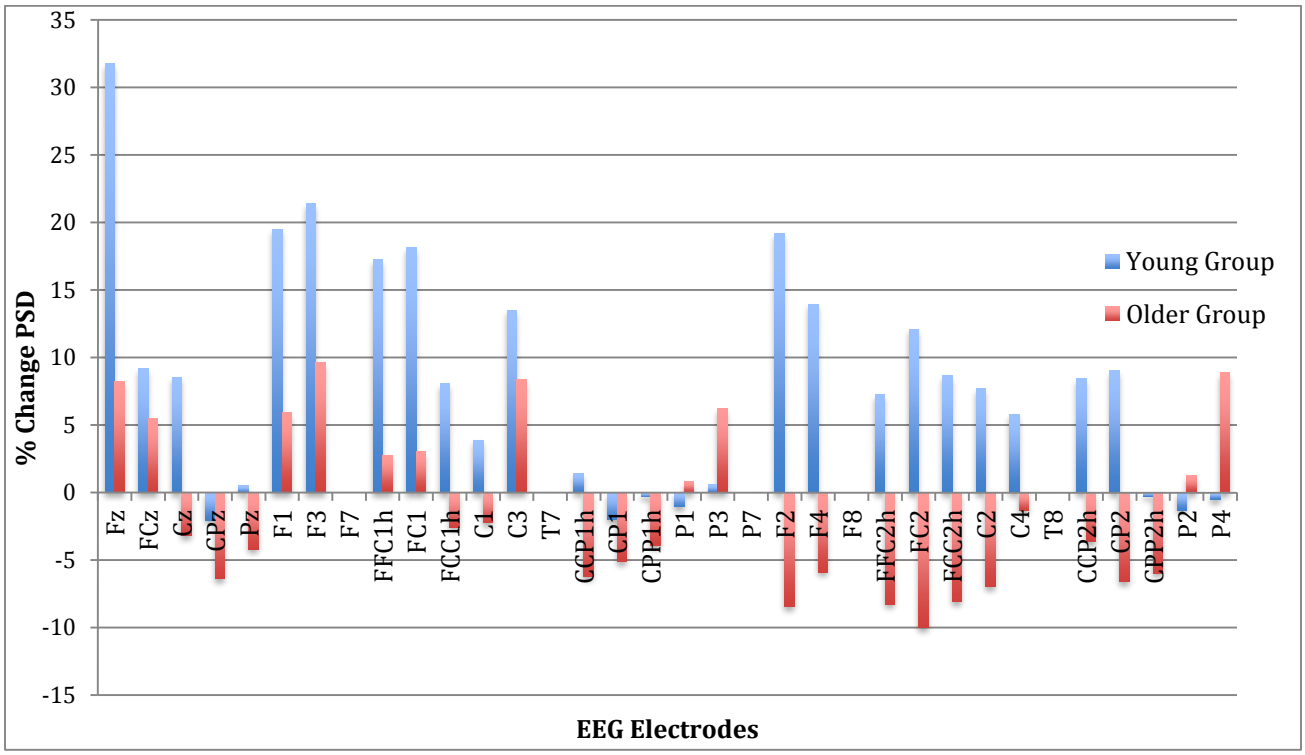

Figure 5. The group means of the percent change of the PSD from the NEC to the FEC condition in the younger and older subjects at the tested EEG nodes, disregarding the outermost nodes F7/8, T7/8 and P7/8.

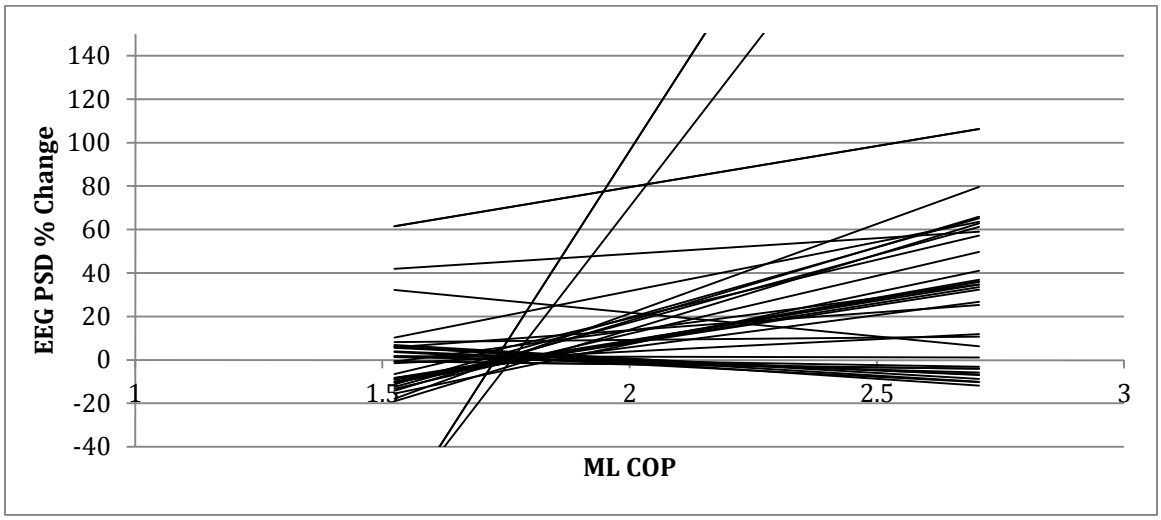

Figure 6. The regression lines between ML COP range and the percent change of the EEG PSD from the NEC to the FEC condition from each of the 35 EEG electrodes for subjects in the young group.

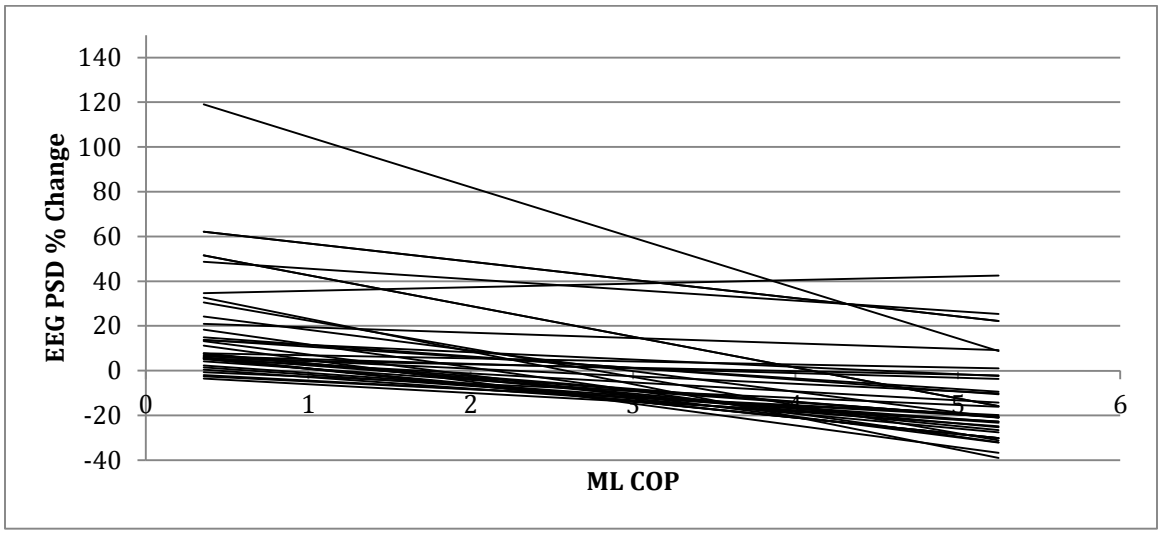

Figure 7. The regression lines between ML COP range and the percent change of the EEG PSD from the NEC to the FEC condition from each of the 35 EEG electrodes for subjects in the older group.

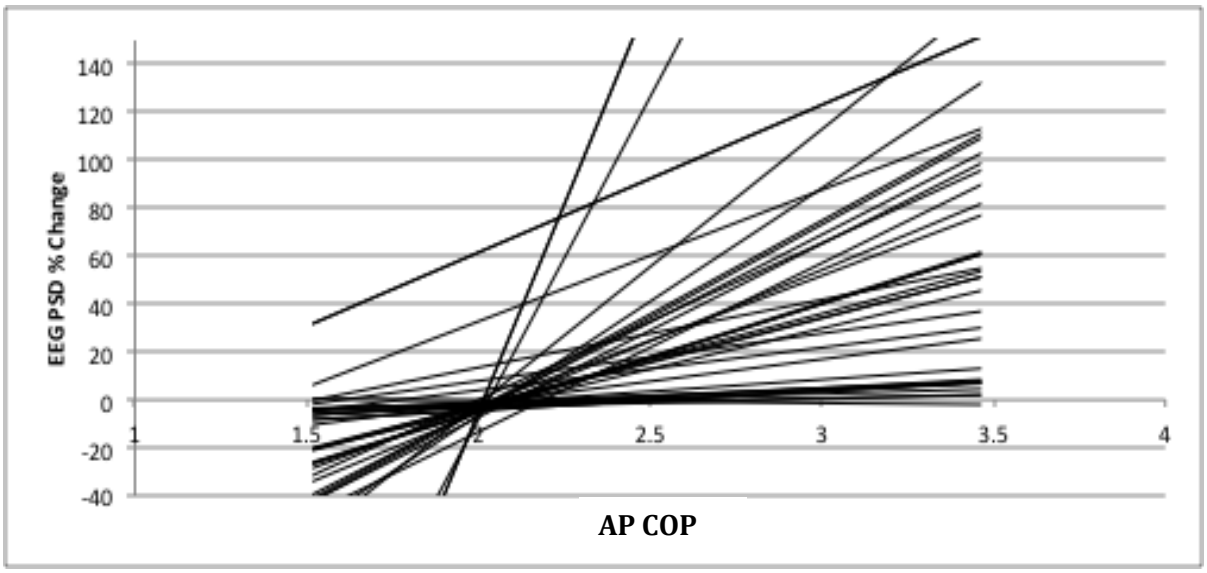

Figure 8. The regression lines between AP COP range and the percent change of the EEG PSD from the NEC to the FEC condition from each of the 35 EEG electrodes for subjects in the young group.

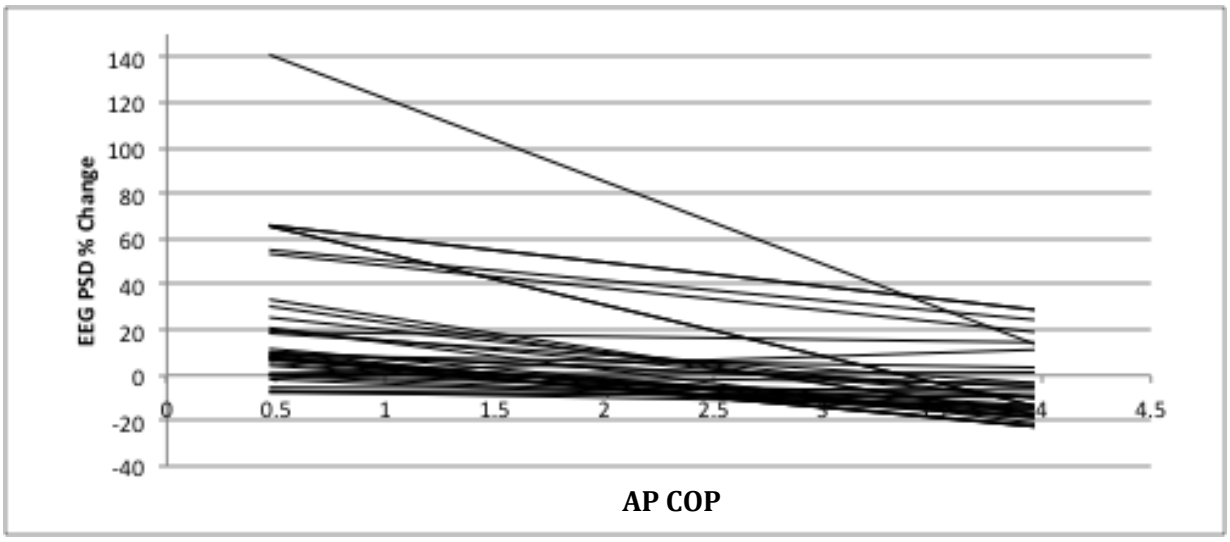

Figure 9. The regression lines between AP COP range and the percent change of the EEG PSD from the NEC to the FEC condition from each of the 35 EEG electrodes for subjects in the older group.

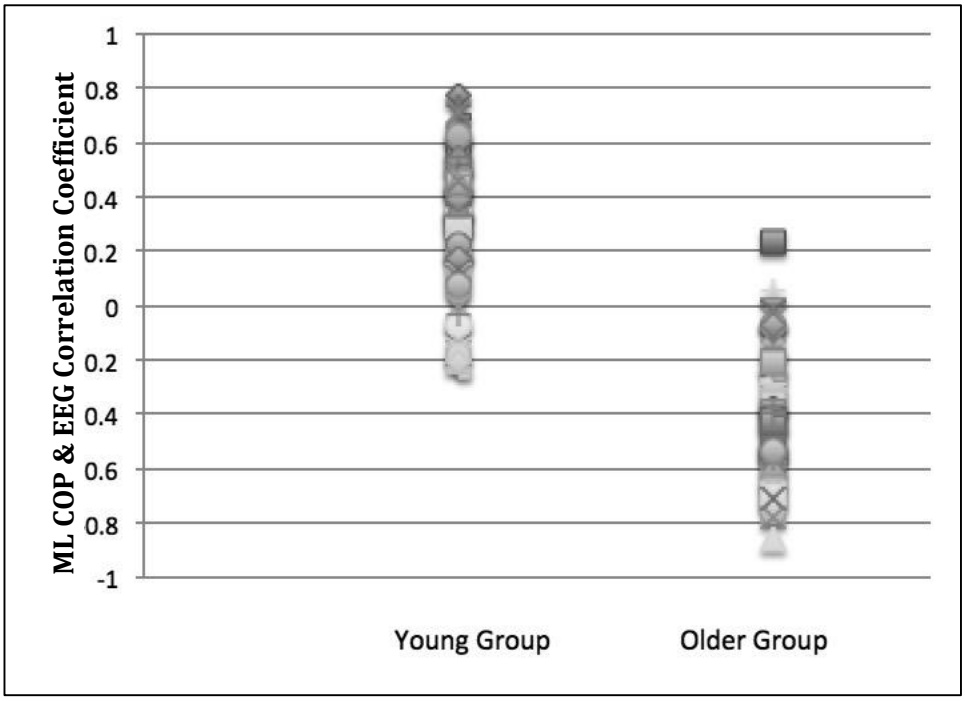

Figure 10. Mean values of the correlation coefficients between ML COP range and percent change of the PSD from each of the 35 EEG nodes in young and older groups.

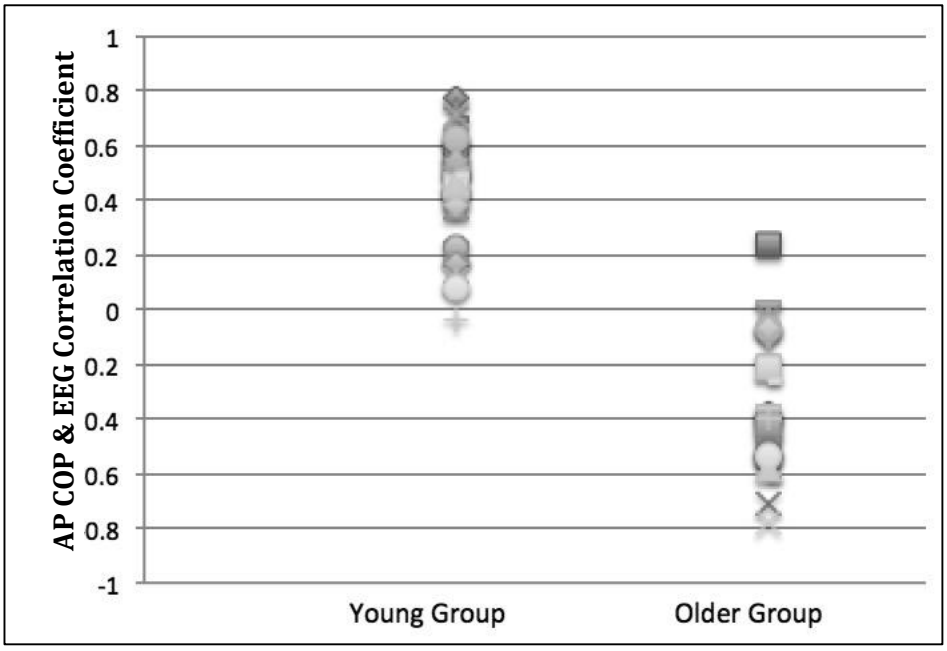

Figure 11. Mean values of the correlation coefficients between AP COP range and the percent change of the EEG PSD from each of the 35 EEG nodes in young and older groups.

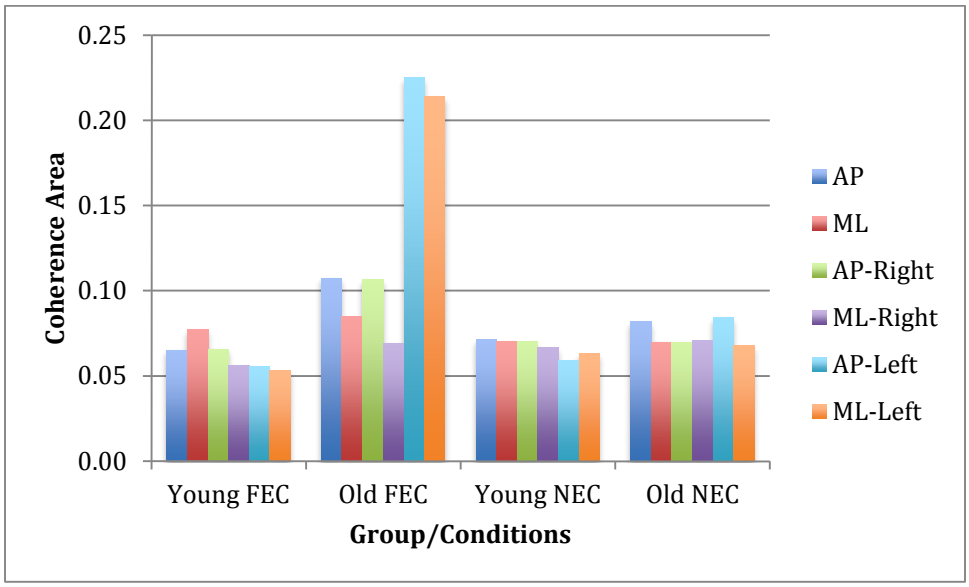

Figure 12. Group means of the maximum coherence area between EEG and COP range for the young and older groups in both conditions.

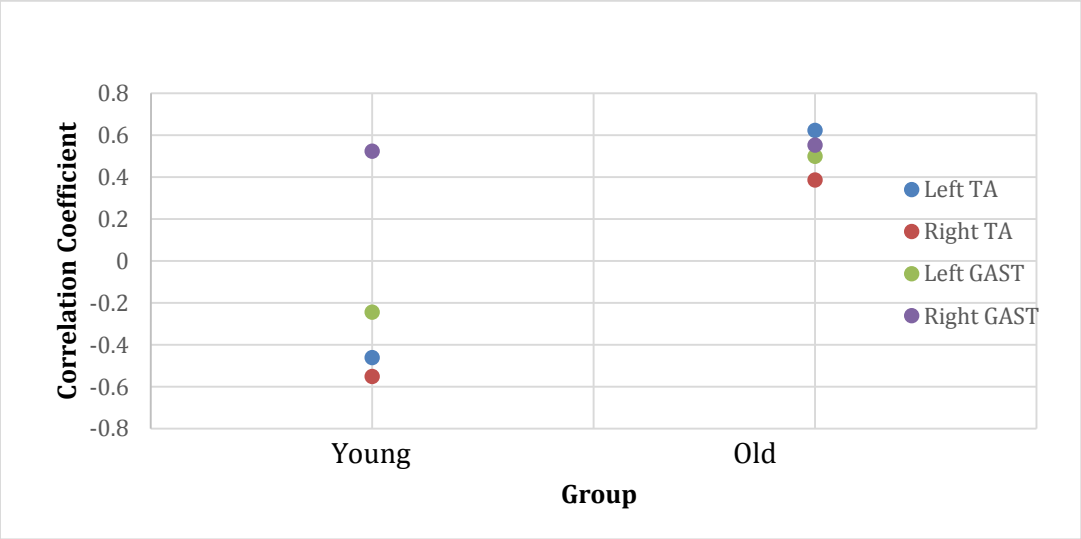

Figure 13. Correlation coefficients between AP COP range and leg EMG from both the left and right tibialis anterior and gastrocnemius muscles in the young and older groups.

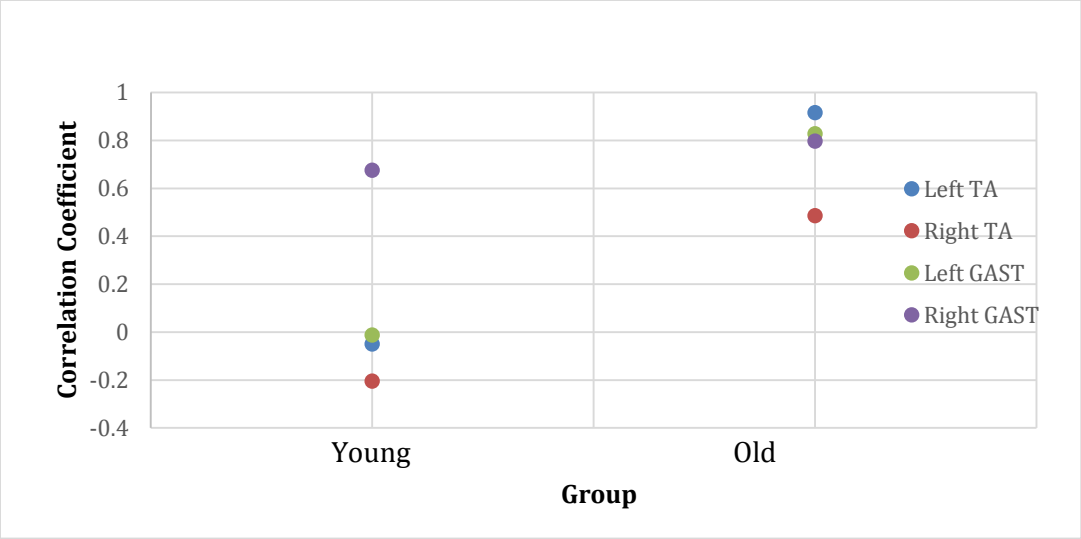

Figure 14. Correlation coefficients between ML COP range and leg EMG from both the left and right tibialis anterior and gastrocnemius muscles in the young and older groups.

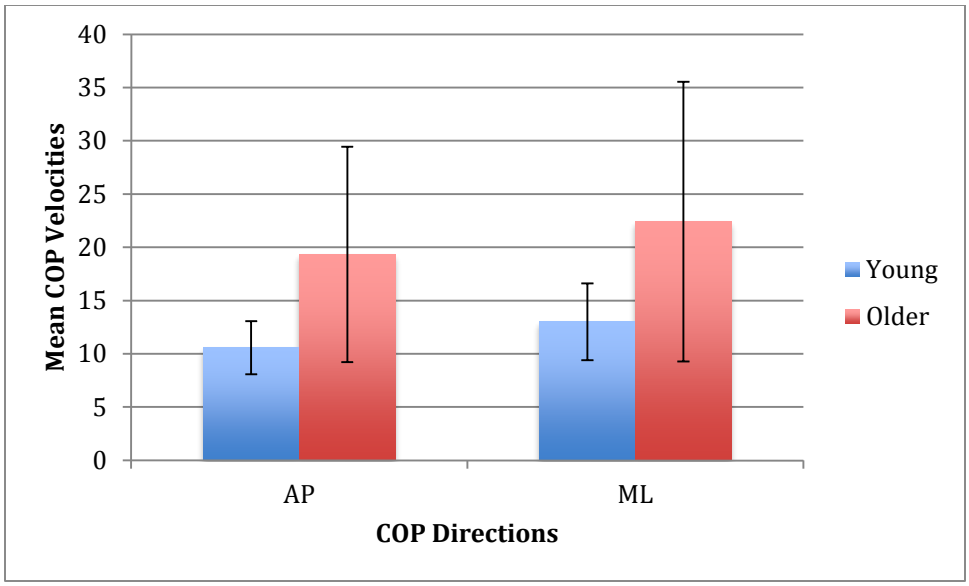

Figure 15. Mean values (± 1 standard deviation) of the COP velocities (in %BOS-L/sec for AP and %BOS-W/sec for ML) in the FEC condition for the young and older groups.

Appendix A

Appendix B

The UNIVERSITY of VERMONT
Committees on Human Subjects
Serving the University of Vermont
and Fletcher Allen Health Care

RESEARCH PROTECTIONS OFFICE
213 Waterman Building
85 South Prospect Street
Burlington, Vermont 05405
(802)656-5040 ph
www.uvm.edu/irb/

Memorandum
(Continuing Review)

TO: Ge Wu, Ph.D.
FROM: Melanie Locher, Research Review Administrator
DATE: 05-Dec-2013
SUBJECT: CHRMS: M10-110
Central and Peripheral Neuromuscular Control Regulations with Tai Chi Chuan Practice

Attached is a signed assurance form which certifies this application has been reviewed and approved.

If applicable, enclosed is a dated copy(ies) of your currently approved consent form(s). Please make sure that you are using the approved forms at all times. All previous versions (hard copy and Word) should be removed to avoid misuse and confusion with future submissions.

As the Principal Investigator of this approved protocol you have specific responsibilities. Please refer to the Research Manual, Section 9. Submission of Materials After Initial Approval is Obtained and Section 10. Investigator Responsibilities to review these responsibilities and obtain further guidance.

E-MAILED DEC - 5 2013

The UNIVERSITY of VERMONT
Committees on Human Subjects
Serving the University of Vermont
and Fletcher Allen Health Care

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Burlington, Vermont 05405
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www.uvm.edu/irb/

CHRMS: M10-110

Protection of Human Subjects Assurance
Continuing Review

Title: Central and Peripheral Neuromuscular Control Regulations with Tai Chi Chuan Practice
Principal Investigator: Ge Wu, Ph.D.
Institution: University of Vermont and State Agricultural College, Burlington, VT 05405

This institution has an approved assurance of compliance on file with the Department of Health and Human Services which covers this activity.

Assurance number for University of Vermont and State Agricultural College: FWA 00000723
IRB number IRB 00000485 Expiration Date: July 31, 2017
(Fletcher Allen Health Care Assurance number: FWA 00000727)

Certification of IRB Review

This activity has been reviewed and approved by an IRB in accordance with the requirements of 45 CFR 46, including its relevant Subparts; and, when applicable, with the requirements of 21 CFR 50 and 21 CFR 56.

Date of approval 12/5/13 Date of expiration 12/4/14

IRB Review Type: Expedited review

Institutional Signature/Date: 12/5/13
Name and Title of Official: David A. Kaminsky, M.D., Associate Chair,
Committee on Human Research in the Medical Sciences

Informed Consent

Title of the study: **Central and Peripheral Neuromuscular Control Regulations With Tai Chi Chuan Practice**

Principal Investigator: **Ge Wu, Ph.D.**

Sponsor: **The University of Vermont Department of Rehabilitation and Movement Science**

You are being invited to take part in this research study because you have practiced Tai Chi regularly for one or more years, or have not practiced Tai Chi at all. This study is being conducted by the University of Vermont in collaboration with the Harvard Medical School.

We encourage you to ask questions and take the opportunity to discuss the study with anybody you think can help you make this decision.

Why is This Research Study Being Conducted?
This study is among the first to investigate the underlying neural mechanisms of Tai Chi practice for improving balance and postural control. The results will allow us not only to gain an understanding of the potential of Tai Chi practice, but also to contribute to the understanding of the effect and mechanism of mind-body training in general.

How Many People Will Take Part In The Study?
A total of forty people will take part in the study.

What Is Involved In The Study?
You will be asked to participate in a two-hour test session at the Human Motion Analysis Laboratory at the University of Vermont, Burlington, VT. You will be first asked to provide information about your demographic profile such as your age, sex, height, weight, ethnicity, smoking and drinking habits, and exercise profile as well as information for an emergency contact person. If you are 65 years of age or older, you will first perform a Timed Up and Go test. This test consists of standing up from a chair, walking 3 meters, turning around, returning to the chair and sitting down again. You will be timed with a stopwatch. The TUG test will be performed 3 times and an average time will be found.

You will then have two electrodes placed on your lower leg for measuring muscle activity and you will have a cap placed on your head where a number of electrodes will be attached for measuring brain activity. You will be positioned on plates on the floor and asked to complete three sets of six standing balance tests. Rest will be provided after each set. Throughout the test, you will be supervised and monitored by the research team members for any signs of fatigue, discomfort, and safety concerns. You will be asked periodically about such questions as "are you tired", "do you want to rest", "are you comfortable", or "do you feel unsafe".

Each set of balance tests involve three double-leg stance tests. The first test will be performed with the feet separated in a wider base of support, standing on a flat surface. The second test will be performed with the feet touching, standing on a flat surface. The third test will be performed with the feet touching, standing on a foam pad. Each test will be performed with the eyes open and then with the eyes closed. A stopwatch will be used to record the time. Each stance will be held for 60 seconds. This set of tests will be repeated two additional times. Rest will be provided between sets, depending on the amount of fatigue you feel. The signals from the plates and the electrodes will be recorded by a personal computer.

What Are The Risks and Discomforts Of The Study?

There is no known risk for all the tests. All measures are non-invasive. The balance tests involve functional tasks that are common in daily activities. These tasks are well within the capability of normal individuals.

The electrodes for measuring muscle activities are placed on the skin of the tested muscles with a self-adhesive surface and medical tape which pose minimal discomfort. You may experience mild irritation or some redness which should go away fairly quickly.

The electrodes placed through the cap on your head for measuring brain activity require applying a salt gel to your scalp through small holes in the cap using a syringe. This syringe is used to move the hair from under the electrode within the cap, which may feel scratchy. Most people find this mildly uncomfortable, but some people may have a sensitive scalp and experience moderate pain during this motion with the syringe. In addition, your hair may be slightly soiled and unstyled upon removal of the cap.

There is a very remote and unlikely risk that a minor electric shock (tingling) from one of the electrodes could occur if the equipment malfunctions. The design of the equipment minimizes the risk and potential amount of shock, and the University of Vermont's Technical Services Program provides annual inspections of the equipment to ensure proper functioning.

The large number of repetitions of each task and the two hour test session, however, may cause fatigue. During the testing, you will be questioned about fatigue or discomfort by the PI. In the event of a serious adverse event that needed medical attention, you will have access to the emergency department located within Fletcher Allen Health Care. All serious adverse events will be reported to the University of Vermont Institutional Review Board by the PI within 24 hours of the event using the University of Vermont Committee for Human Subject Research adverse event reporting document.

There is the risk that personal data will be inadvertently disclosed to someone other than essential study personnel. This risk will be minimized by elimination your name and other identifying information from the study database. You will be assigned a coded identifier by the Principal Investigator. All collected data will be coded with that number. Only the Principle Investigator will have access to the master list matching your name to identifying code which is kept in a locked cabinet.

What Are The Benefits of Participating In The Study?

The benefits include an assessment of your balance, which may be helpful in increasing your awareness of your current balance condition. In addition, the results of this study will help us understand the effect of Tai Chi exercise on fall prevention and will benefit others in the future.

What Other Options Are There?
The only other option is not to participate in this study.

Are There Any Costs?
There is no charge for participation in the study. However, there is cost associated with travel to the University of Vermont.

What Is the Compensation?
You will be compensated $50 to participate in this study.

Can You Withdraw or Be Withdrawn From This Study?
You may discontinue your participation in this study at any time. You may be asked to withdraw from the study by the principle investigator if you are unable to complete the tests safely. All previously collected data will be stored but not used for analysis.

What About Confidentiality?
You will be assigned a coded identifier by the Principal Investigator. Your materials and collected data will be coded with that number. Only the PI will have access to the master list matching your name to identifying code. No case will be identified in subsequent reports, publications, or presentations resulting from the project. Hard copies of your information and other sources of named data will be stored in a locked cabinet in a locked office at the Department of Rehabilitation and Movement Science at UVM by the PI. Only the research team members will have access to the data. Representatives of the Institutional Review Board and regulatory authorities will be granted direct access to your research records for verification of procedures and/or data.

Your name, social security number, and address will be disclosed one time to the University of Vermont's Procurement Services Department for purposes of reimbursing you for participation in this study. Your information will be coded and this code and the information will be kept under lock and key with only authorized personnel accessing the data.

Contact Information
You may contact Dr. Wu, the Investigator in charge of this study, at 802-656-2556 for more information about this study. If you have any questions about your rights as a participant in a research project or for more information on how to proceed should you believe that you have been injured as a result of your participation in this study you should contact Nancy Stalnaker, the Director of the Research Protections Office, at the University of Vermont at 802-656-5040.

Statement of Consent
You have been given and have read or have had read to you a summary of this research study. Should you have any further questions about the research, you may contact the person conducting the study at the address and telephone number given below. Your participation is voluntary and you may refuse to participate or withdraw at any time without penalty or prejudice.

You agree to participate in this study and you understand that you will receive a signed copy of this form.

Signature of Subject Date

Name of Subject Printed

This form is valid only if the Committees on Human Research's current stamp of approval is shown below.

Signature of Principal Investigator or Designee Date

Name of Principal Investigator or Designee Printed

Ge Wu, PhD
Department of Rehabilitation and Movement Science
305 Rowell Building
802-656-2556

Committee on Human Research
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