CORTICAL CONTROL OF HUMAN UPRIGHT STANCE

A Dissertation
Presented to the
Faculty of the Department of Health & Human Performance
University of Houston

In Partial Fulfillment
Of the Requirements for the Degree of
Doctor of Philosophy
in Kinesiology
&
Graduate Certificate in Cognitive Sciences

By
Recep Ali Ozdemir

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ABSTRACT

This dissertation examined, for the first time, differences between young and elderly volunteers in cortical representations of human posture control during (1) quiet stance with normal and altered sensory stimulation, (2) biomechanical perturbations, and (3) dual tasking. The primary focus of the first part was to monitor changes in cortical activity when unexpectedly altering the sensory conditions of upright stance, such as switching from stable (eyes open, fixed support surface) to less-stable (eyes closed, sway-referenced support surface) conditions (experiment 1). Our results demonstrate increased cortical activations in delta (0.2-4Hz) and gamma (30-50 Hz) oscillations, primarily over central-frontal, central and central parietal cortices during challenging postural conditions. While increased delta rhythms were observed in both groups during challenging sensory conditions, elderly individuals also showed increased gamma band activity over sensorimotor and parietal cortices, when compared to the younger group. Correlation analyses also suggest that increased cerebral activity became more relevant to the control of Center of Mass dynamics when upright stance was threatened, especially in the elderly group. The second part studied compensatory postural responses to unexpected perturbations while simultaneously recording Electroencephalography, Electromyography, and Center of Mass dynamics (experiment 2). Our results also suggest that, rather than motor system malfunctioning, impairments in perceptual processing of sensory afferences forms the basis of prolonged postural responses to perturbed stance conditions in non-faller older adults. In general, our results are not only consistent with previous reports suggesting involvement of cerebral cortices in human upright stance control, but also extend them by showing ageing related cortical activity modulations during challenging postural tasks.

The third part focused on performance changes in posture control-cognition dual tasking as well as cortical representations of these performance changes both in cognitive and posture control tasks (experiment 3). Postural and cognitive data analyses showed that elderly people had no performance deficits during single postural task conditions, but decreased cognitive performance even during challenging single cognitive tasks. Dual tasking analyses indicated that working memory impairments in the elderly group can be observed when a challenging cognitive task is performed in any postural condition, while postural control performance differences only became significant during dual tasking with challenging postural and cognitive task conditions. EEG analyses showed increased delta, theta and gamma oscillations, primarily over frontal, central-frontal, central and central-parietal cortices during challenging dual tasking conditions. While delta oscillations are more responsive to challenging postural conditions, theta rhythms are found to be changing as a function of cognitive task difficulty in both groups, with more pronounced increases in the young subjects. These results, in general, indicate that elderly subjects may adopt a non-automated conscious control strategy and prioritize postural performance over cognitive performance to maintain upright stance only when the cognitive load is low. High cognitive loads, on the other hand, dramatically increase postural sway, thus the risk of falling, in the elderly people. Regarding the cortical basis of age related performance differences during dual tasking conditions, EEG analyses suggest that while increased theta over frontal and central-frontal cortices may underlie the cortical correlates of high level cognitive computations including encoding and retrieval, delta oscillations, in general, maybe underlie cortical monitoring of changes in postural state of the body when sensory conditions of upright stance is compromised.

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CHAPTER I

1. Introduction

Most of us find bipedal standing to be a simple motor task we perform in everyday life that requires minimum energy with almost no mental effort. Development of the ability to maintain an efficient upright stance on various terrestrial conditions, however, can be considered as one of the most striking milestones in the history of human evolution. The evolution of our unique bipedal posture ability allows us to vertically orient our body to the gravitational field while engaging in a vast array of functional activities critical for human survival. Today, anthropologists and other social scientists have arrived at a consensus on the notion that 'bipedalism' has led the evolution of higher order cognitive/motor capabilities in human ancestors including object manipulation for various goal directed tasks, linguistic skills and functionally improved locomotion (Stanford, 2003; Gramsbergen, 2005: Mihara et al., 2008).

This essential human skill, unfortunately, is also subject to deteriorations and specific impairments, especially in the aging body, which in turn may cause a physically risky and sometimes fatal phenomenon: 'falling'. To emphasize the alarming health consequences of falls in the aging society, the recent report of the 'National Center for Injury Prevention and Control' (2013) states that the death rates from falls among elderly people has increased dramatically during the last decade. They reported that in 2010 about 21,700 elderly individuals died due to unintentional fall injuries and 2.3 million others were treated for non-fatal fall injuries, with the estimated health care cost of $30 billion. Thus, it is crucial to identify factors causing falls in the elderly. This, at the very first step, requires complete

comprehension of the complex neurophysiological mechanisms of optimally functioning human posture control system in a variety of settings.

A large body of research, therefore, has been devoted to examine sensory-motor aspects of upright stance both in healthy, such as children, young adults or elderly, and impaired populations, such as Parkinson's, vestibular and diabetic patients (Woollacott & Shumway-Cook, 1990; Alexander, 1994; Winter, 1995; Woollacott & Burtner, 1996; Hadders-Algra, Brogren, &Forssberg. 1997; Bonnet, Carello, Turvey; 2009; Horak, 2010; Kim et al. 2013). It is now well understood that optimally functioning human upright stance relies on intact sensory-motor functioning. While sensory functioning includes continuous processing and integration of visual, somatosensory and vestibular afferents to monitor the biomechanical state of the body, motor functioning refers to the ability to initiate anticipatory and corrective neuromuscular responses to retain the body's center of mass (COM) within the base of support (Shumway-Cook & Woollacott, 2000). Deficiencies in any posture control related sensory (e.g. vision loss, vestibular disorders, disrupted proprioception) or motor systems (e.g. lower body injuries) may increase postural instabilities and cause falling (Horlings et al., 2008; Ray et al. 2008). In a wide variety of research settings, specific contributions of these systems to upright stance have been examined (Paulus, Straube & Brandt, 1994; Bloem et al., 2002; Ducic, Short & Dellon, 2004; Ageberg et al. 2005; Michel-Pellegrino et al., 2006; Carpenter, Murnaghan & Inglis, 2010). However, cortical dynamics of human upright stance with the specific role of cerebral brain regions in monitoring the postural state of the body has yet to be understood.

Historical pioneers of neuromotor physiology (Sherrington, 1910; Sherrington, 1947; Magnus, 1926) mostly devoted their studies to understand reflexive control of movements. They mainly concluded that human upright standing is governed by brainstem and spinal networks (Liddell & Sherrington, 1924; Magnus, 1926, Schaltenbrand, 1928). The cerebral cortex was mostly assumed to be involved in higher order cognitive activities with no essential role on the control of upright stance (Marsden, Merton & Morton, 1981) since many animal studies showed that posture control related responses were still functioning, even when the cortex was transected (Bazett & Penfield, 1922; Bard & Macht, 1958; Wilson, 1961, Shik, Orlovskii & Severin, 1968). These early findings preceded the development of traditional posture control theories mostly focused on picturing sub-cortical sensory motor control of upright stance (Nashner, 1976; Nashner & Woollacott, 1979). Starting from the late 1980's, behavioral studies on human postural control, however, indirectly indicated the involvement of cortical networks to postural responses (Shumway-Cook & Woollacott, 2000). Evidence shows that changes in cognitive loads (i.e. dual tasking) (Brown & Marsden, 1991), focus of attention (i.e. directing attention to primary or secondary task) (Kerr, Condon & McDonald; 1985), and mood states (anxiety, fear of falling) (Balaban & Thayer, 2001) of the person can change behavioral response of the person to a postural task. Moreover, predictability of environment with respect to the upcoming posture events can also modulates postural responses both in healthy and impaired populations (Hansen, Woollacott & Debu, 1988; Sliper et al. 2002). People who expect or anticipate upcoming postural events (i.e. perturbations) can modify their neuromuscular responses accordingly (Shumway-Cook & Woollacott, 2000; Schmidt & Lee, 2005). All these mental functions, such as anticipation,

attention, cognition, memory, and mood state, are known to be controlled by the cortex, and thus supporting its interacting role on postural control (Dehaene et al., 2004; Kaiser & Lutzenberger, 2005; Naghavi & Nyberg, 2005; Jacobs & Horak, 2007). Although behavioral evidence from variety of studies suggests cortical involvement on postural tasks, neurophysiological evidence is still very limited.

Advancements in medical technologies, especially the development of non-invasive neurophysiological signal recording tools, now enable researchers to monitor higher order cortical activities during a variety of motor tasks (Thompson, Sebastianelli, & Slobounov, 2005; Neuper, Muller-Putz, Scherer, & Pfurtscheller, 2006; Morash, Bai, Furlani, Lin, & Hallett, 2008; McFarland, Sarnacki, & Wolpaw, 2010; Presacco, Goodman, Forrester, & Contreras-Vidal, 2011; Jain, Gourab, Schindler-Ivens, & Schmit, 2013). Indeed, recent research with electroencephalographic (EEG) recordings indicates increased and/or modulated activity in various cerebral regions including pre-motor, primary motor and somatosensory cortices during upright standing tasks (Slobounov, Hallett, Stanhope, & Shibasaki, 2005; Slobounov, Cao, Jaiswal, & Newell, 2009). Although these studies have shed some light on cortical dynamics of posture control, the role of cortex on postural responses to constantly changing environmental conditions is still unclear. For example, how the spontaneous COM sway or what features of COM dynamics (changes in position or velocity) are monitored by cortical regions are yet to be identified. Moreover how the assumed cortical control changes during aging is also unknown.

Apart from these basic physiological questions, we also know that, for any posture control system to secure stability, timely detection of body configuration with respect to gravito-inertial vector in constantly changing environment is essential to plan, coordinate and

perform corrective motor responses (Shumway-Cook & Woollacott. 2000). Thus, any prolonged sensory, perceptual or motor delays in the posture control loops will cause marginal deviations of the COM from functional stability limits and may lead to falls. Indeed, behavioral studies reported increased threshold for body movement detection (Skinner, Barack & Cook, 1984) and delayed postural responses to balance perturbations in older adults (Woollacott et al. 1986; Studenski et al; 1991). However, whether the cause of prolonged response delays is due to peripheral (increased threshold level at somatosensory receptors), perceptual (cortical processing of sensory afferents), or motor (muscle activation patterns) system malfunctioning is unknown. To date, no systematic research has been conducted, for example, to investigate sources of prolonged delays in corrective responses to perturbed balance in older adults.

Dual task paradigms have also been of particular interest in experimental posture control research (Dault, Frank & Allard, 2001; Woollacott& Shumway-Cook, 2002; Swan, Otani & Laubert, 2007; Bock, 2008; Boisgontier et al. 2013). We live in changing environmental conditions while performing multiple tasks concurrently. This requires efficient allocation of attentional resources to different tasks simultaneously or shifting the focus of attention from one task to another as a function of environment-task constraints. Optimal functioning in multi-tasking activities also requires considerable amount of perceptual processing (Della et al., 1995). To date, no systematic research investigating neurocognitive dynamics of performance changes in dual tasking has been reported. Most of the dual tasking research in posture control has focused on behavioral data, and the results have been conflicting. Directly monitoring cortical activity during dual tasking should provide new insights into perceptual processing differences between young and older adults.

Thus, considering the paucity of knowledge on the role of cortical activity in human posture control, this dissertation was conducted to examine, for the first time, differences between young and elderly volunteers in cortical representations of human posture control during (1) quiet stance with normal and altered sensory stimulation, (2) biomechanical perturbations, and (3) dual tasking.

1.2. Motivation

We in the US and Western Europe are living in an aging society, which brings up its own set of social challenges and health problems. Maintaining optimal mobility and postural functions will be one of the key health priorities for millions of senior citizens since falls are considered to be a leading cause of severe traumatic injuries (i.e. hip fractures, head traumas) and early death among elderly population (Speechley & Tinetti, 1991; Sattin, 1992; Siracuse et al., 2012). In this regard, understanding the underlying neurophysiological mechanisms of optimally functioning posture control system and age related impairments in the underlying neurophysiology of this control system would provide researchers valuable insights in developing preventive interventions for people who are at risk of falling.

Early research, conducted with limited technological resources, mainly postulated that muscles of the posture control system are controlled by sub-cortical neural circuits located at spinal and supra spinal levels (Magnus, 1926). This traditional perspective considers reflexive control, including monosynaptic stretch, tonic vibration and vestibulospinal reflexes, and mechanical stiffness properties of postural muscles, as the basis of postural control with minimum or almost no involvement of higher order cortical networks (Marsh & Geel, 2000; Lackner & DiZio, 2005). Within the scope of this understanding, it

was also assumed that the amount of positional COM deviation away from the center of the base of support indicates the degree of instability (Murray et al. 1975; Goldie et al. 1989). Recent studies, however, consider spatial-temporal dynamics of COM sway as a measure of instability and also attribute considerable role to cerebral regions on monitoring the state of human upright stance (Haibach et al., 2007a; 2007b; Slobounov, Slobounova, & Newell, 1997; Slobounov et al., 1998). In a recent series of research, for example, Slobounov et al showed increased and modulated cortical activity with respect to changing constraints of postural tasks in primary sensory-motor cortices (Slobounov et al., 2005; Slobounov et al., 2009) . Unlike the traditional perspective, they also suggest that the cortically driven posture control system takes not only the positional dynamics but also the temporal characteristics of COM sway into account with respect to the functional stability boundaries of the individual when monitoring the state of stability. By monitoring spatial-temporal characteristics of COM sway within the individual stability zone, this approach examines postural control with two time measures quantifying (1) the least stable moment (TTBminimum) and (2) the ratio of overall COM sway (integratedTTB - iTTB) under a specified time threshold with respect to the entire trial duration (Ozdemir, Pourmoghaddam & Paloski, 2013). Previous studies suggest TTB as a "perceptually controllable" variable that is represented in higher cortical regions including frontal-central and parietal-occipital cortices (Slobounov et al., 2009). However, experimental findings on the cortical correlates of TTB and whether brain regions associated with TTB modulate their activity as a function of the constantly changing environmental requirements remains to be examined (Slobounov et al., 2009). Moreover, how these cortical representations of TTB dynamics change by aging are also unknown. Therefore, one of the aims of this study is to monitor cortical activation patterns of young

and elderly individuals during various postural tasks to specifically investigate if changes in TTB dynamics of the COM are associated with cortical activity modulations in the sensory-motor cortices.

An optimally functioning posture control system should also be able to quickly detect sudden changes in environmental constraints, such as unexpected perturbations, to adjust compensatory neuromuscular responses in maintaining upright stance (Horak, Henry & Shumway-Cook, 1997). A considerable amount of behavioral research in this regard shows that older adults are less able to maintain their upright stance during perturbed balance conditions, when compared to young people (Nashner 1976; Stelmach, Teasdale, Di Fabio, & Phillips, 1989; Maki, Holliday, & Topper, 1994; Gu, Schultz, Shepard, & Alexander, 1996; Lin, Woollacott, & Jensen, 2004). In one of the first experimental studies, for example, Alexander et al. (1992) monitored kinematics of individual body segments via motion capture systems in response to various perturbed balance conditions. Older adults, compared to younger individuals, exhibited increased individual segment rotations and greater kinematic variability in all joints as a result of perturbations. Later studies also documented that older adults have prolonged response delays along with increased COM sway following postural perturbations which significantly increase their risk of falling (Allum et al., 2002; Mansfield & Maki, 2009).

A complete set of postural responses to unexpected balance perturbations can occur in several stages. Due to their mechanical properties (stiffness, damping), postural muscle fibers resist changes imposed by external forces and function as the first "filter" to postural a perturbation without having any time delay. Reflexive compensatory responses originating from spinal circuits result in short-latency responses observed around 30-50 ms following

sudden perturbations (Schmidt & Lee, 2005). A later set of pre-programmed muscular reactions originating in the brainstem circuits, such as vestibular nuclei, result in medium-latency responses observed around 80-110 ms post-perturbation (Schmidt & Lee, 2005). These responses are thought to assist in postural recovery. However, all these short and medium latency responses have limited contributions to functional recovery from perturbed posture. Cortically driven voluntary postural responses, on the other hand, are considered to have a key role in maintaining upright stance during perturbations (Horak, Henry, & Shumway-Cook, 1997). These voluntary responses are usually initiated around 180-250ms after the onset of perturbations in healthy young adults, and, compared to earlier responses, require considerable amount of perceptual processing and motor coordination for unexpected perturbations (Schmidt & Lee, 2005).

The perceptual component includes continuous integration of visual, vestibular and proprioceptive afferents to monitor postural stability. This perceptual integration is, then, used to plan, coordinate and initiate corrective motor responses (Redfern et al., 2001). Since older adults are reported to have decreased sensory, cognitive and motor systems performance, the resulting retardations in sensory functioning will prolong initiation of voluntary responses to unexpected postural perturbation and thus increase the risk of falling. Although behavioral studies showed prolonged response delays to unexpected perturbations in older adults, the underlying source of these delays –whether cognitive/perceptual or motor response– are unknown. To date, for example, no studies have simultaneously monitored both perceptual and motor system functioning during perturbed postural conditions to identify causes of prolonged delays in older adults. Given the absence of experimental data, we aimed to simultaneously monitor both postural muscle (measured with electromyography-

EMG) and cortical (EEG) activity along with changes in COM sway dynamics during unexpectedly perturbed balance conditions. We also aimed to examine how these different processing stages differed between young and old volunteers.

Another main theme of posture control research is to understand age related changes in attentional demands of controlling upright stance (Brown & Shumway-Cook, 1999; Brauer, Woollacott, & Shumway-Cook, 2002). Since most of our daily living activities require attending to multiple concurrent physical and cognitive tasks (i.e. standing in a moving bus and keeping a discussion), dual-task paradigms have been commonly used to study interaction between cognitive tasks and postural control performance, as well as the changing nature of this interaction in relation to aging (Boisgontier et al., 2013). For the cognitive performance side, it has generally been reported that concurrently performing a challenging secondary postural task detrimentally affects cognitive performance. This impaired cognitive performance during secondary postural tasks is more pronounced in older adults or people with postural disorders, indicating increased allocation of cognitive sources to postural control in this population, as compared to healthy young adults (Brauer, Woollcott & Shumway-Cook, 2001; Brown, Shumway-Cook & Woollacott, 1999; Rapp , Krampe & Baltes, 2006; Redfern et al. 2001; Shumway-Cook & Woollacott, 2000; Teasdale et al. 1993).

However, the extant results in the dual tasking literature have been conflicting and difficult to interpret for the effects of secondary cognitive tasks on postural performance, partly due to the wide variety of experimental practices and the versatile nature of task requirements that have been used. Several studies, for example, have reported increased postural sway during dual-tasking (Teasdale et al., 1993; Lajoie et al., 1996; Brown et al.,

1999; Marsh &Geel, 2000; Teasdale & Simoneau, 2001; Dault & Frank, 2004; Swan et al., 2004; Raymakers et al., 2005; Bernard-Demanze et al., 2009; Berger & Bernard-Demanze, 2011; Granacher et al., 2011). Still a number of studies have provided conflicting results by reporting either unchanged or decreased postural sway during dual-task conditions in older adults (Shumway-Cook et al., 1997; Melzer et al., 2001; Weeks et al., 2003; Prado et al., 2007; Dromey et al., 2010; Van Impe et al., 2013; Yogev-Seligmann et al., 2013). Different theoretical explanations, including "shared attention theory", "facilitatory control" and "task prioritization models" have been suggested to explain existent discrepancies in the dual tasking literature (Brauer et al, 2002; Fraizer & Mitra, 2008). Moreover, most of these interpretations have been heavily based on behavioral observations without having neurophysiological evidence regarding the conflicting nature of dual-tasking performance. It is therefore necessary to monitor cortical activity during posture control dual-tasking designs to understand central processing modulations as well as changes in invested attentional resources associated with observed performance differences in older adults. Therefore, the second main goal of this dissertation was to monitor changes in cortical activations during dual tasking both in young and older adults. By using the state of the art of EEG technology in posture-cognition dual tasking paradigms, we were able to provide valuable insights into the cognitive mechanisms employed in dual tasking posture control settings.

Taken together, it is clear that our current understanding of the neurocognitive mechanisms of posture control is still in its infancy, especially on the role of cortical activity in controlling upright stance. Changes in the cortical control of posture in older adults are also largely unknown. Thus, this dissertation was conducted in two parts with the main goal of understanding cortical representations of human posture control during varying

environment and task related constraints both in young and elderly people. The primary focus of the first part was to examine changes in cortical activity when unexpectedly switching from stable (eyes open fixed referenced platform) to less-stable (eyes closed sway referenced platform) postural conditions. The first part also focused on postural responses to unexpected perturbations while simultaneously recording EEG and EMG along with COM sway dynamics. This part helped us to study basic physiological question of whether or not the changes in postural state of the person is monitored by cortical centers, and if so, how this cortical monitoring of balance state differs between younger and older adults. Perturbation analyses provided insights into the sources of prolonged response delays to perturbations in elderly people. The main purpose of the second was to examine performance changes in dual tasking and cortical representations of these performance changes both in cognitive and posture control tasks.

1.3. Problem Statement

Although many previous behavioral studies have indirectly indicated relationships between various cognitive processes and postural control performance, experimental evidence for the cortical involvement in postural control is still very limited. To date, no systematic research has been conducted to identify the role of cerebral activity on postural control in a wide variety of settings. Cortical correlates of postural control in older adults are also largely unknown. The neurocognitive mechanisms of prolonged response delays to unexpectedly perturbed balance are yet to be understood in older adults. Finally, how cortical activity changes during dual tasking both in young and elderly people is not documented by any previous research. All these knowledge gaps in the field led to the principle questions that will be addressed in this dissertation.

Question #1: Does the posture control system use Time-to-Boundary (TTB) information as a perceptual variable to maintain stability?

Question #2: Does posture control related cortical activity change as a function of aging?

Question #3: How is the Center of Mass (COM) behavior temporally related to cortical activity and involuntary muscle responses during unexpected postural perturbations as a function of aging?

Question #4: How do secondary cognitive tasks interfere with postural control responses as a function of postural task difficulty and age?

Question #5: How does posture related cortical activity change during dual tasking as a function of aging**?**

1.4. Research Objectives

The overall research objective of this dissertation was to study the role cortical activity on human postural control. In this regard, two separate, but conceptually related, experiments have been designed to address the main research questions stated above. Ten healthy young adults (aged between 20-35 years) and 10 older adults (aged between 64-80 years) with no history of any neurological and musculoskeletal disorders participated in this study. Subjects were selected from among those reporting no regular exercise participation within in the preceding 6 months since physical fitness level differences among subjects might be a confounding factor for balance performance and, thus, may affect cognitive involvement levels. The purpose of each experiment is discussed in the following paragraphs.

Experiment #1: This experiment was designed to answer research questions #1, #2 and #3. Both young and elderly participants were asked to perform a series of bipedal stance postural tests. The level of postural task difficulty was progressively increased by manipulating the available, veridical sensory information by standard techniques (from eyes open fixed support surface to eyes closed sway-referenced support surface) to investigate if cortical activity is modulated as a function of changes in TTB dynamics (research Q1). Comparisons in EEG modulation (changes in the frequency content of the EEG signals) between young and older adults were performed to examine whether posture related cortical activity changes as a function of age (research Q2). Postural perturbations (forward/backward translations and toes up/down rotations) tests were also applied to examine underlying neurocognitive and neuromuscular mechanisms of prolonged response delays in older adults (research Q3). EEG activity, EMG activity and COM sway were monitored simultaneously throughout all testing, and the order of test trials was fully randomized.

Experiment #2: Research questions #4 and #5 were addressed by this experiment. A widely used N-back working memory test was used as a primary cognitive task to investigate changes in postural performance during dual tasking (research Q4). EEG activity was monitored along with COM sway dynamics to examine posture related cortical activity during dual tasking (research Q5). A 2x2 (Cognitive condition: 1 back vs 2 back memory test; Postural condition: fixed support vs sway-referenced support) experimental design was employed to specifically examine how cognitive tasks interfere with postural performance as a function of task difficulty. EEG monitoring also allowed us to study cortical correlates of performance changes in the volunteers. Performance comparisons were made between young and older adults (research Q5).

1.5. Research Hypotheses

For experiment #1, we expected to see increased cortical activity as a function of changes in TTB dynamics and we expected this increase to be more pronounced in the elderly group. For perturbation trials, older adults were expected to have prolonged response delays to perturbations, compared to younger participants, due to delays in cognitive perception of perturbations (as identified by the time difference between COM deviation and cortical response). Specific hypotheses for the experiment #1 are as follows.

Hypothesis #1.1: Compared to non-challenging balance tasks (eyes open fixed support), posture control related cortical activity–as measured by EEG signal power changes in frequency domain–will change in both young and elderly participants during challenging balance tasks (eyes closed sway support), but this change will be more pronounced in elderly people.

Hypothesis #1.2: Changes in frequency domain representations of EEG signals will reflect the postural state of the individual as quantified by TTB.

Hypothesis #1.3: The sudden increase in COM velocity/position, as a result of unexpected perturbations will evoke cortical activity (event related potentials –ERPs) which will then lead corrective muscular activation (involuntary EMG in posture control muscles).

Hypothesis #1.4: During perturbation trials, the latency between unexpected COM displacement and cortical response as quantified by ERPs, and also, between ERPs and involuntary EMG response will be longer in elderly participants, when compared with the time latencies in young participants.

For experiment#2, we expected to see changes in postural performance as a function of cognitive task difficulty. We also expect to see "Cognitive and Postural task" interactions for young and older adults, and we expected to see cortical activity be modulated during dual tasking. Specific hypotheses for the experiment #2 are as follows.

Hypothesis#2.1: Compared to single task performance (cognitive only), cognitive and postural performance will not change in either young or elderly participants during dual tasking with non-challenging cognitive (1-Back working memory) or non-challenging posture conditions (fixed support) conditions.

Hypothesis #2.2: Compared to single task performance (postural only), balance performance will not change in young participants but will degrade in elderly participants, as evidenced by increased TTBmin and decreased iTTB measures, during dual tasking with challenging cognitive (2-Back working memory) and non-challenging balance conditions (fixed support).

Hypothesis #2.3: Compared to single task performances, both cognitive and postural performance will decrease in all participants, but more in elderly participants than in young participants, during dual tasking with challenging cognitive (2-back working memory) and balance conditions (sway support).

Hypothesis #2.4: Compared to single cognitive tasks (eyes open fixed support), posture control related cortical activity–as measured by EEG signal power changes in frequency domain–will change both in young and elderly participants during dual tasking condition, and this change will be more pronounced in elderly people.

1.6. Dissertation Outline

Chapter 1, Introduction – introduces the reader to the main topic and the general ideas of this dissertation. This includes importance of research topic by emphasizing the current balance problems in the aging society and a summary of the current state of knowledge in the neurophysiology of human upright stand, gaps of knowledge in this field and limitations of previous research.

Chapter 2, Literature Review – this chapter, in general, provides a detailed overview of the current state of knowledge, existing gaps in knowledge, and potential problems in closing the identified gaps. Specific details were given on the sensory-motor systems involving in human posture control and identified age related impairments in these sensory-motor systems. Current state of the neurocognitive mechanisms of postural control was also provided. Finally, existing gaps on the role on cortical activity on postural control were also discussed.

Chapter 3, Manuscript I: *Cortical Involvement to Upright Stance Control: Age related changes during challenging quiet and perturbed stance conditions*-describes cortical representations of human upright stance control during (a) quiet stance with normal and altered sensory stimulation, and (b) biomechanical perturbations, in young and elderly human volunteers. Results demonstrate increased cortical activations in delta (0.2-4Hz) and gamma (30-50 Hz) oscillations, primarily over central-frontal, central and central-parietal cortices as a function of postural task difficulty. Correlation analyses also suggest that increased cerebral activity became more relevant to the control of Center of Mass (COM) dynamics when upright stance is threatened, especially in the elderly group. Finally results also suggest that, rather than motor system malfunctioning, impairments in perceptual processing of sensory

afferences forms the basis of prolonged postural responses to perturbed stance conditions in non-faller older adults.

Chapter 4, Manuscript II: *Cortical activity modulations underlying age related performance differences on posture control dual tasking conditions*- describes (1) age related changes in dual tasking postural control performance along with (2) task related cortical activity modulations. Dual tasking analyses mainly indicated that working memory impairments in the elderly group can be observed when a challenging cognitive task (N2) is performed in any postural condition, while postural control performance differences only became significant during dual tasking with challenging postural and cognitive task condition. EEG analyses mainly showed increased delta, theta and gamma oscillations, primarily over frontal, central-frontal, central and central-parietal cortices during challenging dual tasking conditions.

Chapter 5, *Summary, Future Directions and Limitations*- this chapter combines the results from the two manuscripts and discussed these findings in a common context regarding the role of cerebral regions on human postural control. In addition, methodological and experimental limitations of the conducted research projects are discussed in this chapter, and implications for future studies are presented.

Chapter 6, *References* – sources and references cited.

Chapter 7, *Appendices* – a list of supplementary materials and methods.

1.7. Potential Contributions

Cortical mechanisms involved in human postural control are incompletely understood. The outcomes of this study will provide us valuable information regarding the involvement of higher order brain regions in monitoring and controlling spatial-temporal characteristics of COM sway during single and dual tasking in challenging and non-challenging conditions. Moreover, as changes in cortical dynamics of posture control in older adults are largely unknown, our findings will not only expanded our knowledge on basic questions about the neurophysiology of human posture control, but also provided valuable insights into neurocognitive mechanism of postural control impairments in the elderly population. This will contribute to the development of effective cognitive and motor interventions to improve posture control in elderly population.

1.8. Definitions of Important Terms and Abbreviations

APAs- Anticipatory postural adjustments

BOS- Base of support

COP - Center of pressure

COM- Center-of-mass

COG-Center-of-gravity

CNS-Central Nervous System

EEG- Electroencephalography

EMG-Electromyography

PERs-Perturbation related potentials

SOT-Sensory organization Test

SOT-1-Eyes open fixed support-fixed surrounding postural test

SOT-2-Eyes closed fixed support-fixed surrounding postural test

SOT-4-Eyes open sway support-fixed surrounding postural test

SOT-5-Eyes closed sway support-fixed surrounding postural test

TTB-Time to boundary

TTBmin-Minimum time to boundary

iTTB-Integrated time to boundary

MMSE - Mini Mental State Examination

PAR-Q-Physical Activity Readiness Questionnaire.

WM-Working memory

CHAPTER II

2. Literature Review

This chapter covers the detailed literature regarding the biomechanical and neurophysiological mechanisms underlying human upright stance. While posture control related neural systems residing at spinal or brain stem regions have been relatively well identified, there is a little consensus on the role of cerebral circuits involving in upright stance control. Additionally, how the proposed posture related cortical activity is changing as a function of aging and task requirements has yet to be documented.

The literature review starts with the description of basic biomechanical requirements underlying upright stance. Sensory information provided by different modalities and their basic role on postural control is also discussed. Special emphasis is given to motor control of upright stance with the detailed literature describing functioning of posture related neural systems distributed at all levels of the central nervous system. The chapter then includes brief summary of recent studies non-invasively monitoring electrophysiological activity of the cerebral regions in a variety of postural tasks. Closing sections provides brief description of seminal papers regarding the changes in postural control in the elderly population.

2.1. Biomechanical Characteristics of Upright Stance.

Most daily human activities require vertical orientation of the body to the gravitational vector. Human upright stance in gravitational fields, however, is inherently unstable due to biomechanical design of the body and external forces acting on it. Modeled as an ‘inverted pendulum’, human upright stance is never in perfect vertical alignment with respect to the gravity vector (Winter, 1995). Slight dorsi-flexion of ankle joints, between 4-6

degrees, during natural upright standing leans the body forward and causes constant gravitational torques at the ankle joints (Figure 2.1a). Another stability problem arises from the biomechanical design of the body in which movements of many segments, linked by joints with various degrees of freedom, disturb the COM of the system and introduces instabilities. Thus, control and establishment of upright stance, although seemingly effortless, depends on complex dynamical interactions between musculoskeletal and several neural systems, collectively described as the "postural control system" (Bernstein, 1967; Shumway-Cook & Woollacott, 2000). The postural control system constantly monitors position and orientation of the body in space via multiple sensory channels, and initiates necessary motor actions to secure upright stability.

Mechanically, upright postural stability requires maintaining the balance of forces and moments acting on the system, which basically implies keeping the vertical projection of COM motions within the base of support area (BOS). Although the previous postural control research defines limits of BOS as the physical surface under the feet, and assumes mechanically fixed stability limits, more recent research has suggested that postural stability limits are not fixed biomechanical boundaries but changes as a function of the task (Forth et al., 2011), and individual characteristics (Slobounov et al., 1998). Earlier, Slobounov and colleagues (1998) reported that spatial characteristics of stability limits are independent from biomechanical boundaries and functional stability limits decrease as a function of advanced age in the elderly. In their recent work, Forth et al (2011) also introduces a novel approach to quantify functional stability limits within BOS and suggested an eclipse shaped region changing as a function of available sensory information (Figure 2.1b).

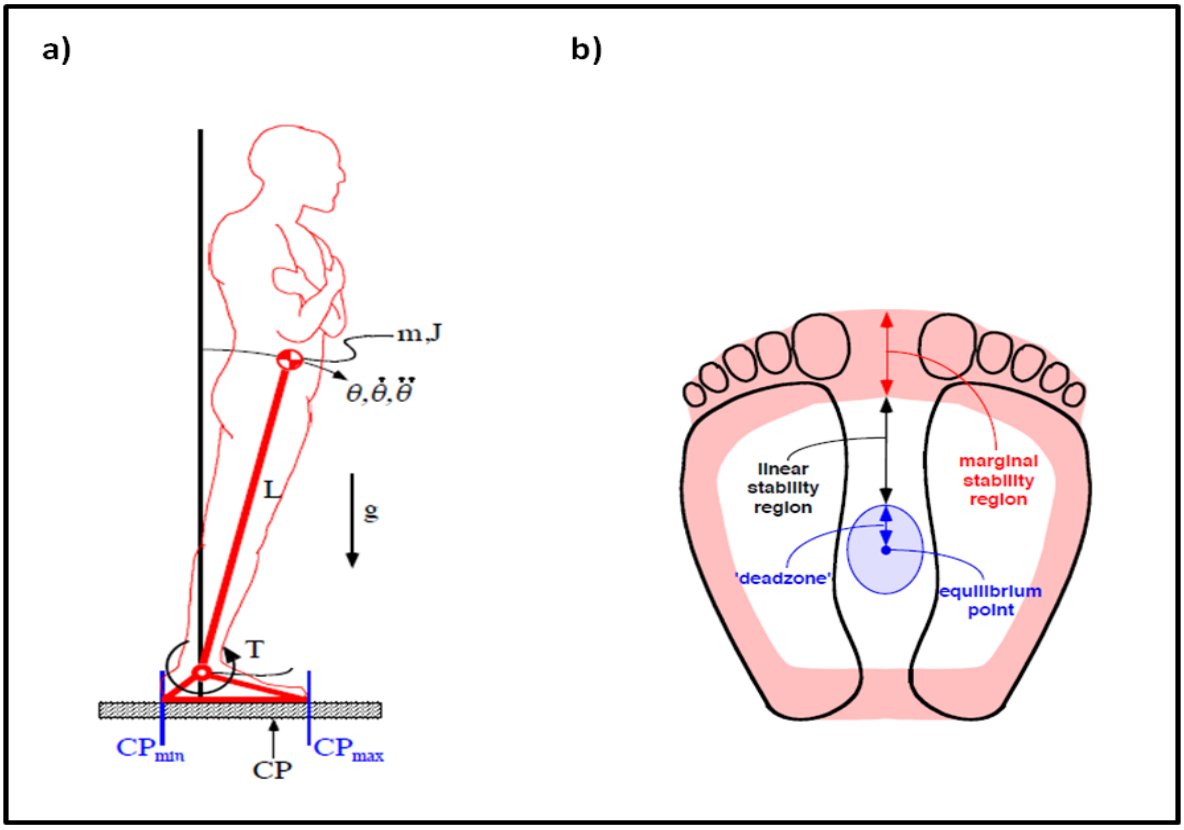


Figure 2.1. Inverted pendulum model of human upright stance (a) with the Base of Support characteristics (b). CP represents vertically projected position of the COG which can be controlled within the range of CPmin and CPmax representing physical borders of the BOS in antero-posterior direction. Gravitational torque (T) occurs primarily at ankle joints in inverted pendulum model. The system is considered to be stable when the projected COG is being maintained in the blue shaded region called 'dead zone' located at the center of the BOS (b). Depending on spatio-temporal characteristics of the COM ($^{\theta}$,$^{\theta i}$, $^{\theta ii}$), the system may become unstable as the COM moves towards the limits of the BOS in any direction. Adapted from Dr. William Paloski's Integrated Systems Physiology lecture notes (2013).

Early research on postural control has also mainly quantified postural performance by solely monitoring positional characteristics of the COM. In this understanding upright stance is assumed to be stable when the COM is positioned in the center of BOS (Figure 2.1b), and any deviations of the COM from this central point is considered to be correlated with the degree of postural instability (Murray et al. 1975; Goldie et al. 1989). Later research,

however, indicates that spatial characteristics of the COM alone are a poor indicator of postural control performance under various circumstances and do not enable researchers to capture underlying neurophysiological variables used by the postural control system on monitoring postural states of the body. In several lines of studies, Slobounov and colleagues (1997, 1998, 2005 and 2009) have suggested that the postural control system considers not only spatial but also temporal dynamics of the COM in relation to stability boundaries to monitor postural state of the body. This current understanding determines postural instability by "Time to Boundary- TTB" measures which quantify balance as how fast the COM is moving towards the functional stability boundary from any given spatial location at any time (Figure 2.1b).

The postural control system is hypothesized to utilize TTB as a perceptual variable when monitoring balance state of the system (stable vs unstable) and initiating motor corrections if necessary (Slobounov et al. 2009). Monitoring balance state of the system requires continual processing of sensory information from several modalities in a feed forward manner (Franklin & Wolpert, 2011; Maurer & Peterka, 2005; Wolpert, Ghahramani & Jordan, 1995) within a closed-loop system (Figure 2.2). Understanding the role of intact sensory modalities in an optimally functioning postural control system is necessary to better identify system responses during challenging postural conditions. Next section, therefore, describes the functional contributions of each relevant sensory channel to upright stance.

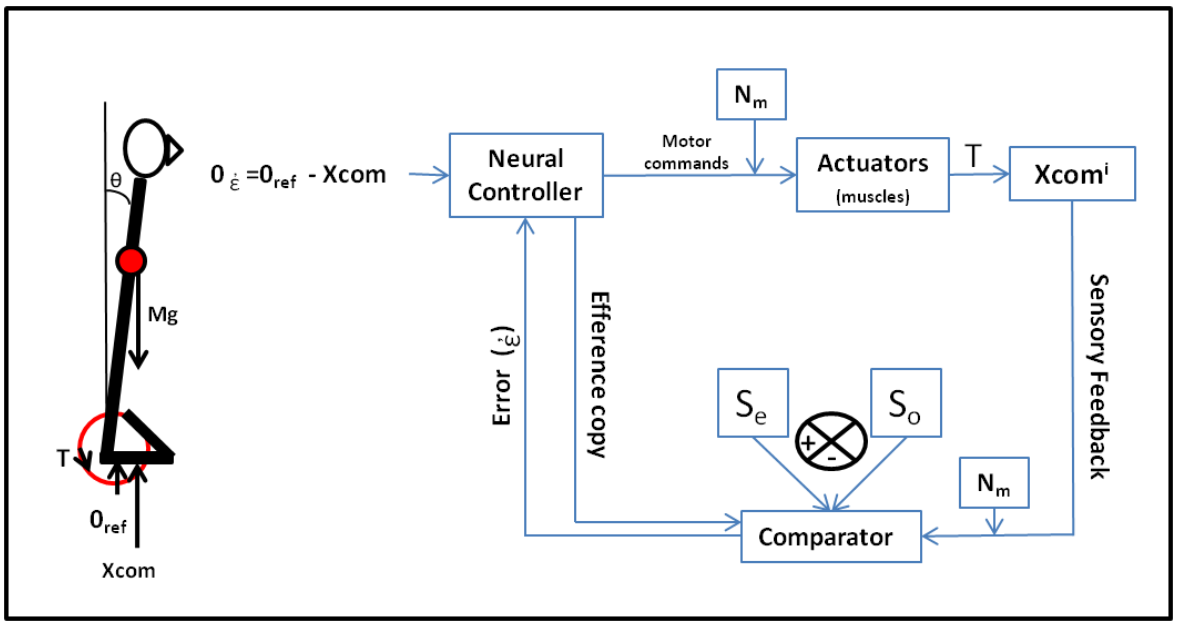


Figure 2.2 Closed-loop control of inverted pendulum model. The main input to the neural controller is the sensed body sway ($0_{\dot{\varepsilon}}$) representing error between the desired state (0_{ref}) and the current position of the COM 'Xcom'. The neural controller generates motor commands as well as the efference copy representing expected sensory consequences (S_e)of these motor commands. The input to the inverted pendulum is the torque (T) generated by postural muscles and exerted about an axis through ankle joints to correct disturbances due to gravitational torques. The corrective torque (T) updates the COM position ($Xcom^i$) and generates resultant affarences (S_o) representing the observed sensory states. The comparator unit continually monitors the difference between S_e and S_o and generates an error ($\dot{\varepsilon}$)signal to update neural controller about the current state of the body with respect to the desired state (0_{ref}). For details see Maurer & Peterka, 2005. N_m represents the noise present in neurophysiological signals and considered as one of the main reasons for the Error ($\dot{\varepsilon}$).For details see Wolpert, Ghahramani& Jordan, 1995.

2.2. Sensory Contributions to Postural Control

The postural control system must continually integrate sensory information from visual, vestibular and proprioceptive afferents to establish a functional neural map, an internal model, representing the vertical body schema in space. According to the prevailing understanding (Franklin & Wolpert, 2011) this internal model is used in a feed forward manner by the postural control system to evaluate accuracy of the expected sensory information and initiate required postural behaviors (Figure 2.2). Although each sensory

system contributes to a different aspect of the internal model, recent studies indicates that the postural system is quite adaptive and can either substitute the lack of information from one sensory channel with another (Horak, 2006) or re-weight the contribution of each channel to the overall internal model based on changes in environmental characteristics (Paloski et al. 2006, Peterka, 2002).

2.2.1. Proprioceptive system contributions to postural control

Proprioception is an umbrella term that refers to functioning of specialized somatosensory (tactile), kinesthetic (joint movements) and muscular perceptions derived from various sensory receptors distributed throughout the joints, muscles, tendons, and skin. Although, it is quite challenging to observe independent contributions of these individual sensory receptors to the overall proprioceptive functioning in vivo, animal studies or studies with impaired populations have revealed the importance of intact proprioceptive functioning on optimal postural control.

Proprioceptors, in general, provide information about position and direction of limb movements in relation to each other. In the context of postural control, we use proprioceptive information to identify the support surface characteristics. Large-diameter I-a afferents from muscle spindle fibers and I-b afferents from the Golgi tendon organ inform the postural control system rapidly with respect to changes in postural muscle mechanics (i.e., postural muscle length changes as body sway) and thus provide crucial cues about postural orientations by identifying limb dynamics through muscle activation. These muscle receptors are also responsible from triggering early automatic responses (i.e., stretch reflexes) to postural perturbations that will be discussed in later sections.

Joint receptors, such as paciniforms, ruffini type endings and ligament receptors, are located in the joint capsule and sensitive to angular changes of joints. Cutaneous receptors, especially mechanoreceptors, are also crucially important in postural control. They reflect changes both in support surface conditions and, more importantly, position of the COP under the feet, thus contribute estimating positional COM deviations within the BOS.

Impairments in these proprioceptive functioning, such as in peripheral neuropathy, may cause specific deficiencies in postural responses. Recent experimental studies also indicated that destruction of the group-I fibers throughout the body causes significantly delayed postural responses to support surface movements both in quadruped and biped animals (Stapley et al., 2002). These results basically suggest that proprioceptors may reflect acceleration dynamics of the COM movements and can be used in closed feedback loops of internal models to initiate the activation of postural muscles over time (Macpherson and Horak, 2013).

2.2.2. Vestibular system contributions to postural control

Vestibular system is primarily important for establishing gravitational reference in the context of upright stance control. Consisting of three semicircular canals positioned orthogonal to each other, and two otolith organs sensitive to the gravitational vector, vestibular system provides two main sensory references: (1) angular velocity of head rotations via semicircular canals, (2) the linear acceleration of the head in space or tilt of the head with respect to the gravitational vector via otolith organs. The vestibular system also has an essential role in motor aspect of the postural control system including the regulation of

postural muscle tones and initiating certain automatic postural reactions to biomechanical perturbations through the vestibulospinal tract which will be discussed in later sections.

The postural control system uses vestibular information to establish general orientation of the body by neurally mapping "which way is up" with respect to the gravitational vector. Velocity of the body sway information in three-dimensional space as well as how much the body is tilted from the support surface with respect to the gravitational vector can also be estimated via vestibular afferents. Having all this vestibular information, the postural control system can model the gravitational reference, and keep the position of the head aligned with the gravitational vector, even during various bodily positions oriented away from the gravitational vector, since the accuracy of gravity perception is highest in this head position.

Unlike patients with proprioceptive dysfunction, who display delayed postural reactions, patients with vestibular disorders exhibit either hypermetric or reversed postural reactions to postural perturbations depending on the perturbation condition. In experimental animals without vestibular afferents, surface platform tilts results in opposite or reversed postural reactions that instead of actively resisting perturbations by moving the body in the opposite direction to the perturbation, the postural control system activates muscles accelerating animals toward the direction of the perturbation. Similarly, human experiments also showed that vestibular patients fail to develop sensory reweighting in case of conflicting sensory conditions. In his seminal paper, for example, Peterka (2002) observed the postural behavior of blindfolded subjects (eyes closed) during continuous antero-posterior sway conditions. Results indicated that healthy subjects first oriented their bodies with respect to the support surface up to 2 degrees of continuous surface sway. However, when the surface

sway was larger than 2 degrees healthy subjects switched their body orientations from the surface reference to the gravity reference by moving in the opposite direction to sway, and thus exhibited functional sensory reweighting. Vestibular patients, on the other hand, failed to develop sensory reweighting by keeping the surface orientation as the only reference and consequently fell down around 4 degrees of surface sway. This suggests that vestibular patients cannot map the gravitational reference and thus have to rely solely on the surface reference in maintaining upright stance even when the surface orientation threatens upright stance stability.

When the support surface was, however, moved horizontally (forward or backward translations), vestibular patients were able to exhibit functional postural responses, although the postural responses were hypermetric and prolonged (increased response magnitude, frequency and duration). Since the orientation of support surface was aligned with gravitational vector during linear surface perturbations, subjects with vestibular deficits exhibited directionally correct but dysfunctional scaling of postural responses leading larger overbalancing behaviors and finally instabilities (Macpherson and Horak, 2013). Thus intact vestibular system is particularly essential for maintaining upright stance when vision is either reduced or removed and the support surface is not aligned with the gravitational vector, such as walking down through the handicap ramp in a dark theatre room or standing on a sailing boat at night.

2.2.3. Visual system contributions to postural control

Vision is the primary sensory modality in navigational tasks. The postural control system uses visual afferents to construct the physical environment and adjust orientation of

the body with respect to position of objects in our surrounding. Vision also contributes to our establishment of verticality in gravitational fields. Body sway or motion information can be extracted from visual afferents through the peripheral and focal processing pathways. This information, however, may sometimes lead self-motion illusions, known as vection, in moving visual fields since the postural control system interprets a swaying environment as the body tilt or motion due to egocentric visual processing (Paulus, Straube, & Brandt, 1984).

Research has provided extensive evidence that vision reduces body sway. Increased postural sway in quiet stance conditions has been reported in people with visual impairments. In experimental settings, closing eyes also increases body sway (Shumway-Cook and Woollacott, 2000). In dynamical balancing tasks, visual information also provides stabilizing cues. Athletes engage in extensive spinning activities, such as skaters or dancers, fixate their gaze to maintain upright stance while performing (Macpherson and Horak, 2013).

Postural task related visual information processing is too slow (180-200msec) compared to proprioceptive and vestibular processing (40-80msec) (Nashner & Woollacott, 1979). Thus, contribution of visual afference to postural responses during unexpected balance perturbations is limited. Instead, visual system informs the postural control system about upcoming postural events, such as placing the feet over the obstacles, and contributes to anticipatory postural adjustments.

As it can be seen from the provided literature, any single sensory modality is not sufficient for optimal postural control, thus multiple sensory modalities should be integrated to establish coherent body perception. Vestibular system, for example, cannot distinguish head movements from the whole body sway, through the ankle joints, without having

proprioceptive inputs from ankle and neck joints. Proprioceptive afferents are alone also not sufficient to establish gravitational reference which has great importance for postural control. By integrating multiple sensory modalities, the postural control system can plan, coordinate and execute optimal postural responses in constantly changing environmental conditions. The underlying neurophysiology of these postural responses is discussed in the next section.

2.3. Motor control of upright stance

The postural control system is able to generate a wide variety of motor responses ranging from short latency (SL) reflexive contractions around single joints to long latency (LL) complex whole body responses utilizing several joints and large number of muscle groups. These responses are initiated at different neural subsystems distributed at all levels of the nervous system depending on the nature of task and environmental condition.

Researchers generally disturb the balance either in a controlled or in an unexpected manner in order to examine the postural control system responses (Nashner 1976; 1977). Changes in ground reaction forces, displacement characteristics of the COM and kinematic analyses of limb movements are generally quantified to understand the postural control output at the behavioral level. The electrical activity (EMG) of postural muscles is also widely recorded during postural responses (Allum 1983). Temporal activation patterns of a single muscle group as well as the activation sequence of different muscle groups provides window into the active neural processes underlying particular postural response for upright stance control. This section is therefore dedicated to understand characteristics of postural responses and their underlying neural mechanisms distributed at different levels of the nervous system including, spinal, supra-spinal, sub-cortical and cortical sites. Specific emphasis is given to cortical networks underlying cognitive aspects of upright stance control.

2.3.1. Spinal neural circuits in upright stance control

To identify the role of specific neural circuits on postural responses early research has focused on neural structure of reflexive postural control mechanisms in animals (Mott & Sherrington, 1895). Complete transection of spinal cord, for example, eliminates neural inputs from higher centers and allows researchers to study spinal network contributions to postural control. It has been reported that spinalized adult cats can be able to stand up and show appropriate antigravity support with a fairly normal horizontal trunk and semi-flexed hind limb orientation after a specific training (Shumway-Cook & Woollacott, 2000). Ground reaction forces were also observed to remain in normal orientation suggesting that spinal circuits are able to control required muscle stiffness for antigravity support. However, maintenance of postural balance in response to perturbations was so greatly affected that these animals did not show functional postural responses to retain the COM within BOS when support surface is moved (Macpherson and Horak, 2013).

When human postural control system is challenged with an unexpected perturbation, a series of compensatory postural responses can be observed. Motor outputs of the postural control system were mainly studied by monitoring temporal characteristics of electromyography (EMG) in postural muscles in response to exposed external perturbations. One of the earliest studies concerning muscle responses to unexpected postural perturbations in human subjects is provided by Gurfinkel and colleagues in 1974. They reported that very small perturbations (0.2 degrees) to the upright stance are primarily corrected by viscoelastic properties of postural muscles around ankle joints (Gurfinkel et al., 1974). These initial corrections were reported to be purely mechanical, due to stiffness properties of skeletal muscles, with a negligible delay and not associated with any neural activity. For larger

displacements (40 deg/sec), the first EMG burst generally observed with 30 to 50ms delays after perturbations in postural muscles (Allum, 1983; Nasher, 1977). These SL but low amplitude contractions are originated from Ia afferent-alpha motor neuron loops at spinal circuits and appear to function like tonic stretch reflexes. However, the role of these SL reflexive responses on maintaining balance is debatable and many scientists (Jones & Watt, 1971; Latash, 1998) do not consider them as functional postural responses due to their very limited corrective effects on the COM dynamics. The first experimental evidence for the role of this monosynaptic reflex on unexpected ankle joint displacements was provided by Jones and Watt in 1971. They record the EMG activity of gastrocnemius muscle during either unexpected Achilles tendon tapping or dorsi-flexion perturbation. The first EMG response was recorded in about 37 ms after perturbation. However, these monosynaptic responses did not result in any noticeable force modulation (Jones & Watt, 1971). Thus, when surface rotation or translation velocity is large enough to initiate COM deviations from the center of the BOS, these spinally originated reflexes are not sufficient to result in any meaningful corrective changes in the COM dynamics in healthy subjects. Moreover, unlike spinalized cats, people with complete spinal cord injuries (SCI) cannot even exhibit any weight support to maintain their upright stance.

Taken together, it appears that spinal circuits have very limited role on posture control in humans. Although viscoelastic properties of muscles and spinally originated tonic stretch reflexes are considered as the first line of defense in response to unexpected perturbations, they have no functional role on correcting larger COM deviations in healthy subjects. These short latency reflexive responses, however, are still important in terms of reflecting optimal functioning of the sensorimotor systems.

2.3.2. Supra-spinal, cerebellar and sub-cortical circuits in upright stance control

Following SL responses, the postural control system continues to exhibit functionally stabilizing muscle activations in multiple muscle groups synergistically in response to unexpected postural perturbations. Such postural responses to sudden disturbances are not simple reflexes but complex set of activations with a typical sequence. These activations are considered as the basis of functional postural responses since goal oriented COM position corrections can be observed after the initiation of these responses. Organization of these synergistic muscle activations highly depend on the nature of the perturbation (small vs large), surface conditions (narrow vs wide) and physical status of the person (healthy young vs elderly). If the perturbation is not too strong, and support surface is fixed and wide enough to place feet in a natural upright stance position, young healthy subjects temporally initiate corrective muscle activation patterns from distal (ankle) to proximal (hip) joints called "ankle strategy". The time delay for the ankle joint muscle activation is about 90ms and observed in tibialis anterior or gastrocnemius muscles, followed by hamstring or quadriceps 20-30ms later, and eventually in para-spinal muscle groups after another 20-30ms of delay. However, if the perturbations are large in a narrow support surface or if the individuals have diminished muscle strength at ankle joints, such as in elderly people, temporal muscle activation patterns are usually observed from proximal to distal joints called "hip strategy" where the first EMG bursts can be observed in para-spinal groups and followed by hamstring and finally by ankle muscles (Horak & Nasher 1986, Nashner, 1976).

Although the complete set of neural circuits underlying these long latency postural responses has not been clearly identified yet, recent consensus on the underlying neurobiology of corrective responses suggested that initial phases of these responses are

originated from polysynaptic supra-spinal networks including brain stem regions such as reticular formation, medulla and vestibular nuclei (Figure 2.3). Vestibulo-cerebellar, vestibulo-spinal and spino-cerebellar neural pathways along with sub-cortical loops including basal ganglia are also indicated to play major roles in modification and scaling of LL postural responses due to changes in environment and task demands (Macpherson and Horak, 2013).

Located at the rostral medulla and caudal parts of the pons, the vestibular nuclei receive sensory inputs from semicircular canals and otolith organs specifying tilt and angular motions of the head with respect to the vertical reference. Two major lines of neural pathways originate from the vestibular nuclei, called medial and lateral vestibulo-spinal tracts, project to medial part of spinal centers and regulate initiation of compensatory responses at proximal and distal leg muscles during postural disturbances signaled by otolith organs and semicircular canals (Purves et al. 2001). The reticular formation is also a cluster of neural circuits located in center of the brain stem (Figure 2.3). Descending pathways from the reticular formation also terminate at local spinal circuits and are involved in compensatory as well as anticipatory postural responses. Lesions both in vestibulo-spinal and reticular tracts are reported to results in severe postural deficits (Macpherson and Horak, 2013).

The cerebellum can be considered as the primary supra-spinal region with number of critical functions in postural control and orientation including coordination, adaptation and monitoring of postural movements (Figure 2.3). Two main regions called vestibulo-cerebellum and spino-cerebellum are highly interconnected with vestibular nuclei, and reticular formation. These cerebellar circuits also both project direct connections to and receive inputs from primary somatosensory cortices. With respect to monitoring role of

ongoing postural movements, cerebellar networks are also considered to be the main neural sites of sensory integration and developing feed forward internal models for postural balance and orientation. The spino-cerebellum, for example, receives direct inputs from proprioceptive and cutaneous afferents.

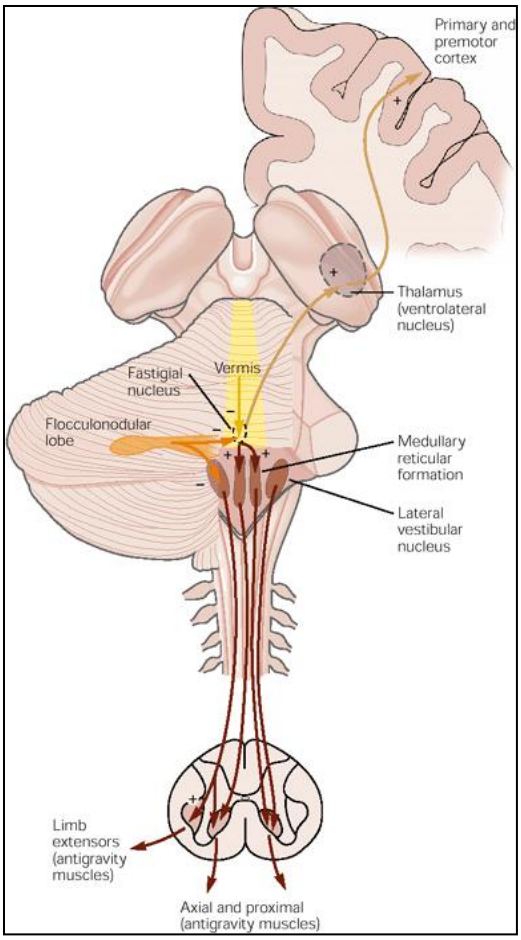


Figure 2.3. Vestibulospinal and reticulo-spinal projections to postural muscles. Red arrows indicated descending neuronal connections originated from brain stem networks. Both vestibilo-spinal and reticulo-spinal tracts terminate at the local spinal circuits and have important roles on initiating postural responses. Cerebellar regions including fastigial nucleus and the Vermis are also illustrated. These regions have reciprocal connections with higher cortical networks. Adapted from Lisberger and Thach 2013.

Given these complex and highly interconnected pathways with reciprocal connections, cerebellar lesions can cause profound disorders in upright stance control.

Lesions of brainstem and vestibulo-cerebellum connections, for example, lead orientation deficits in the control of head and trunk with tilted stance suggesting distortions in representations of body schema in space (Graves & Jen, 2013). Ability to scale or adjust the magnitude of postural responses in perturbed balance has also been reported to be deteriorated in anterior cerebellar lesions (Horak & Diener 1994, Horak et al., 1989). Patients with spino-cerebellum disorders exhibit hypermetric postural responses to sudden platform disturbances. In one of their studies, Horak and Diener (1994) asked subjects to maintain their balance in response to horizontal surface translations. Both healthy and vestibulo-cerebellar patients showed appropriately adjusted postural responses when perturbation velocity was increased at each trial, although vestibulo-cerebellar patients have larger and variable responses as compared to healthy controls. However, when perturbation amplitude changed after repeated perturbations vestibulo-cerebellar patients failed to adjust their responses accordingly. For example, although the temporal activation patterns were similar to healthy controls, they always over reacted to repeated blocks of perturbations reflected with high amplitude EMG responses as if they always expect large perturbations (Horak & Diener, 1994). These results suggest that vestibulo-cerebellar patients can use the velocity information directly projected from proprioceptive afferents of the feet but fail to use prior experience to adjust magnitude of postural responses in subsequent trials.

Basal ganglia are also essential sub-cortical networks in the context dependent modulation of movements. For example, when we change the environmental conditions, such as surface characteristics, or postural task requirements, such as switching from standing balance to sitting balance, the postural control system is able to quickly modify postural response patterns. Parkinson's patients, however, have apparent difficulties in modifying

their functional postural responses as a result of sudden change in initial task and environment conditions (Horak et al., 1992). When healthy subjects switch from standing to sitting position the same postural perturbation (backward surface translation) results in totally different postural responses. While backward surface translations activate posterior postural muscle groups including gastrocnemius, hamstrings and para-spinals during upright stance conditions, no lower leg musculature activation was observed for the same translation during seated conditions since sitting balance is secured with an enlarged BOS. Parkinson's patients, however, continue to exhibit similar muscular activation patterns in response to backward surface translations during both standing and seated conditions, indicating that Parkinson's patients have difficulty switching from one movement set to another. Similar results were also observed in changing surface conditions. While healthy subjects readily change their movement strategy from hip to ankle strategy when they immediately switch from standing on the beam to flat surface conditions, Parkinson's patients keep employing hip strategy for a number of trials after switching from the beam to flat surface conditions (Horak et al., 1992).

All these studies indicate the greater importance of supra-spinal, cerebellar and sub-cortical circuits on postural control and orientation that although the first line of responses to COM sways purely depend on mechanical and viscoelastic properties of postural muscles, these responses are not strong enough to restore postural stability. Therefore postural balance and orientation are primarily controlled by neural circuits of brain stem and cerebellar regions. There are, however, numerous set of complex postural responses which has not been mentioned so far. These complex postural responses, which will be discussed in the next section, cannot be explained solely by the functioning of supra-spinal, cerebellar and sub-cortical networks.

2.3.3. The cortex and upright stance control

Humans are multi-tasking organisms. We rarely maintain our upright stance for the sake of standing only. Upright stance is rather considered to be a baseline tool to accomplish a variety of other goal directed tasks (Haddad et al. 2013). Most of our daily activities require performing multiple motor tasks such as walking while talking on the phone, or searching for our car keys among other keys in the key ring concurrently. These multiple motor tasks sometimes accompanied with variety of other cognitively demanding activities including reading the signs, doing some mathematical calculations or using working memory components to remember the location of our car in a parking lot. How the nervous system organizes to plan, coordinate and control all of these tasks while concurrently securing stability of upright stance has remained unanswered for a long time and is still debatable.

Traditionally, it has been claimed that neural mechanisms underlying the control of upright stance are operating independently from voluntary motor-movements or cognitive functions, and located at distinct levels of nervous system in a hierarchical manner. In this understanding, upright stance control was assumed to be primarily controlled by spinal and brain stem networks with no involvement or interaction from cortical cortices. In 1926, Nobel Prize nominee Rudolph Magnus, one of the historical pioneers of neuromotor physiology, established the basis of traditional posture control theories when he wrote:

> *"In concluding, I wish to draw your attention to the fact that the whole righting apparatus is arranged sub-cortically in the brain-stem, and in this way made independent of direct voluntary influences. The attitudinal as well as the righting reactions are involuntary. If under the influence of cortical impulses the normal position of the body be disturbed, the brain-stem apparatus is ready to restore it, so that every new cortical action finds the body in a normal starting position without previous voluntary effort"* (Magnus, 1926).

Almost 90 years after this statement we now have ample empirical findings indicating involvement of the cortex in controlling human upright stance in a variety of ways, although the direct neurophysiological evidence is still limited. One of the first empirical findings regarding the involvement of higher cortical centers to upright stance control in a feed-forward manner was provided by Belen'kii and colleagues in 1967 when they asked subjects to raise up their arms rapidly while standing. EMG recordings from antigravity muscles and from primary movers of shoulders have revealed a unique postural control mechanism called "anticipatory postural adjustments- APAs" (Belen'kii et al. 1967). After the onset of movement instructions, first EMG activities were observed in the postural muscles, followed by the EMG activity in primary shoulder movers with 50-60 ms latency. Such findings were consistently produced and analyzed in great details by the followers (Nashner & Cordo, 1980; 1981) suggesting that the postural control system is not only able to employ compensatory responses to already experienced perturbations but also "predict" future postural instabilities based on the given task requirements and environmental context. Nasher and Cordo (1981), for example, showed how APAs can be regulated by the CNS regarding the changes in environmental context. In their design, subjects were asked to push or pull a handle in a reaction time task under two postural conditions; (1) up right stance and (2) leaning forward to horizontal bar during upright stance. Regular postural APA's were observed in the former condition while reduced or no APA's were reported in the latter condition indicating that this predictive postural control functioning is able to differentiate destabilizing features of the given task and thus can selectively activate or deactivate APA's as a function of current affordances.

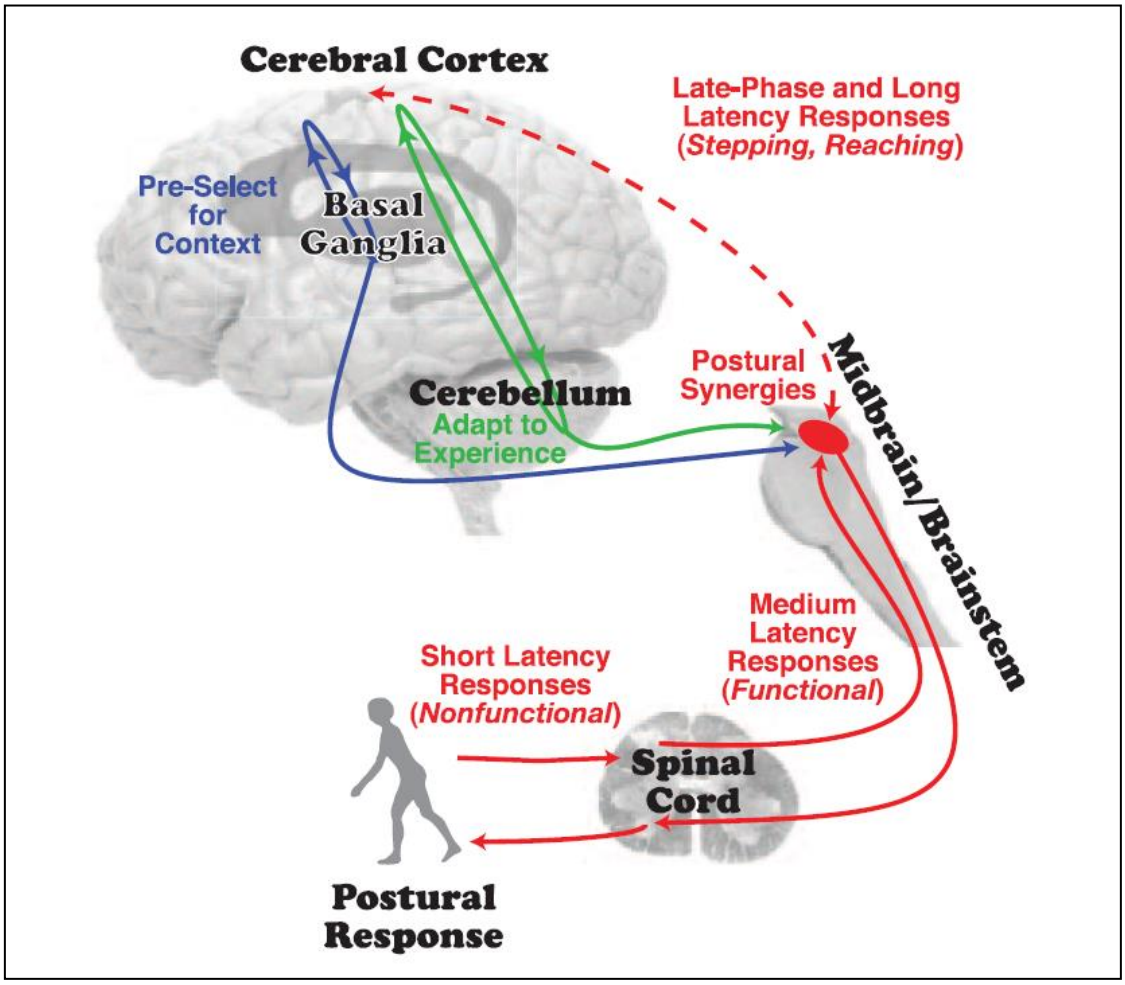


Figure 2.4.A simple model of neural pathways involved in cortical control of both APAs and Long latency (LL) postural responses. Motor cortices along with subcortical structure basal ganglia can select and activate APAs based on the postural context. Higher motor centers also have reciprocal projections to supra-spinal networks to modify LL postural responses. Adapted from Jacobs and Horak 2007.

Neural mechanisms underlying these APA's were initially attributed to higher centers of the CNS (Figure 2.4) (Cordo & Nashner 1982; Jacobs and Horak; 2007). Supporting evidence came from animal studies. For example, Massion and colleagues (1979) trained cats for a limb lifting task which requires employing APA's at other 3 legs. They also noticed that direct electrical stimulation of primary motor cortex controlling forelimb flexors can elicit the same limb lifting along with complete set of APA's in supporting limbs (Massion, 1979).

They hypothesized that pyramidal tracts originated from motor cortex can also activate postural pathways of the brain stem in a descending manner while sending commands to the prime mover.

Apart from the existence of APA's, a number of postural control studies also indicated involvement of the cortex in postural responses. When healthy subjects are informed about the nature and timing of upcoming postural perturbations they can adjust their responses accordingly. Moreover, initial instructions given to subjects can also alter postural responses to perturbations. For example, when subjects are instructed to take a step, as compared to staying stationary, compensatory short latency muscle activations were either reduced or disappeared in response to platform perturbations (Burleigh et al. 1994).Thus, it appears that the postural control system may select and employ different strategies depending on the nature of expected postural events. These postural adaptations and employment of different postural strategies requires learning and prior motor planning, all of which is considered to be controlled by the cortex.

Originally, upright stance control was also thought to require minimal attentional sources, and thus assumed to not interact with other voluntary motor or cognitive tasks (Magnus 1926). However, many behavioral studies have disproved this early assumption by showing upright stance performance to interact with a number of motor and cognitive tasks (Brown & Shumway-Cook, 1999; Brauer, Woollacott, & Shumway-Cook, 2002). Attention is generally described as the total information processing capacity of the cognitive system. Although various attention theories, such as "shared capacity theory" or "bottleneck theory"(Deutsch & Deutsch 1961; Kahneman, 1973; Pashner 1994; Wickens 1980; 1984), have been extensively studied in cognitive psychology, the general consensus is that (1) the

cognitive-perceptual system has limited attention capacity and (2) performing any kind of goal oriented task, either motor or cognitive, requires the use of certain portion of this capacity. Another main premise is that if two tasks are using similar attentional sources and require more than the total available attentional resources, the performance of either or both tasks will diminished when the two tasks are performed concurrently (Woollacott & Shumway-Cook, 2002).

The first experimental evidence regarding the attentional requirements of upright stance during dual tasking was provided by Kerr and colleagues in 1985. They asked subjects to perform a spatial visual working memory and non-spatial working memory tasks while either sitting (single cognitive task) or standing in a tandem Romberg position. Results showed that performing memory tasks concurrently with tandem Romberg stance postural task significantly increased number of errors in memory tasks, as compared to single cognitive task condition. There was no significant change in postural performance in either spatial or non-spatial working memory tasks suggesting that upright stance control is attentionally demanding in healthy subjects and may interfere with performance of other cognitive tasks (Kerr, Condon &McDonald; 1985). Following this seminal paper, numerous dual-tasking studies have been conducted with a variety of conditions in different populations (Brown & Shumway-Cook, 1999; Brauer, Woollacott, & Shumway-Cook, 2002). Although we have now reached a general consensus on attentional aspect of upright stance, underlying dynamics of posture control and cognitive tasks interference are still considerably ambiguous with inconsistent findings relying on various theoretical explanations. For example, in one of their studies Stoffregen and colleagues (2000) employ a visual fixation task with a cognitive component during upright stance. Contrary to previous dual tasking findings, results showed

that subjects swayed less when they were asked to fixate their gaze and count the frequency of target letters in the text as compared to balance task only condition. The authors interpret their findings on the basis of facilitatory control hypothesis (Frasier and Mitra 2008), which considers the postural control mechanisms as an integrated component of perception-action systems and thus can be modified in requirements of primary cognitive tasks to enhance performance. Regardless of these conflicting findings, the apparent fact we can take from dual-tasking literature is that the posture control system is not an independently functioning set of neural networks but continuously interacting with the neural pathways underlying other cognitive functions.

The postural control system has also been shown to be influenced by emotional state of a person (Adkin et al. 2008). People with major depressive disorders exhibited greater postural instabilities as compared to healthy controls during dual tasking conditions (Doumas et al. 2012). Moreover, the effects of postural confidence, anxiety and fear of falling on postural control have been extensively studied during the last decade (Carpenter, Frank & Silcher, 1999; Carpenter et al. 2001; Brown, Melody & Doan, 2006). Increasing the surface height at which the subjects stand is a commonly used paradigm in this line of research to examine how physically threatening conditions may affect postural behaviors. Findings generally indicate that subjects adopt a tighter postural control strategy as reflected by decreased amplitude but increased frequency of the COM sway during heighten surface conditions (Carpenter, Frank & Silcher, 1999; Carpenter et al. 2001; Brown, Melody & Doan, 2006).

Taking all these different line of research together, we have now enough behavioral evidence to believe that the cerebral cortex is involved in controlling human upright stance.

Concerning postural responses to unexpected perturbations, many researchers assume that initial phases of postural responses, up to 100ms, are coordinated by brain stem circuits while higher cortical networks are responsible for modifying later phases. In this regard, Burleigh and colleagues (1994), for example, found that although later phases of autonomic postural responses in the gastrocnemius muscle could be inhibited in the predicted conditions, early response phases (0-50ms) were present regardless of the postural condition (Burleigh, Horak & Malouin, 1994). This suggests that postural responses are generated as a result of context-dependent interactions among neural sub-systems distributed at all levels of the CNS, rather than the independent activity of spinal or brain-stem circuits.

Moreover, various mental functions, such as, working memory, visual spatial tasks, anticipation and mood states, utilized in postural control research are known to be regulated by the cortex (Dehaene et al. 2004; Kaiser & Lutzenberger, 2005; Naghavi & Nyberg, 2005; Jacobs & Horak, 2007). Despite these ample behavioral findings suggesting influence of cerebral regions on postural control, neurophysiological evidence is still very limited. Providing such information requires monitoring cortical activity during postural tasks. Next section, therefore, will highlight the content of some recent studies using electrophysiological monitoring tools to understand cortical correlates of upright stance.

2.4. Monitoring cortical activity during upright stance tasks.

Staring from the late 1980's, researchers have been able to monitor changes in cerebral potentials following a perturbed stance by using EEG systems. In one of the earliest studies, Dietz and colleagues (1984) have reported perturbation evoked cerebral potentials (PEPs) with an average latency of 42ms over the sensorimotor cortices in humans (Dietz, Quintern & Berger, 1984). Following studies (Ackerman, Diener & Dichgans, 1986; Adkin

et al. 2003; Dietz et al. 1985; Dimitrov, Gavrilenko & Gatey, 1996; Duckrow et al. 1999; Quant et al. 2004; Staines, McIlroy & Brookes, 2001) have also consistently identified PEPs with varying latencies (Figure 2.5).

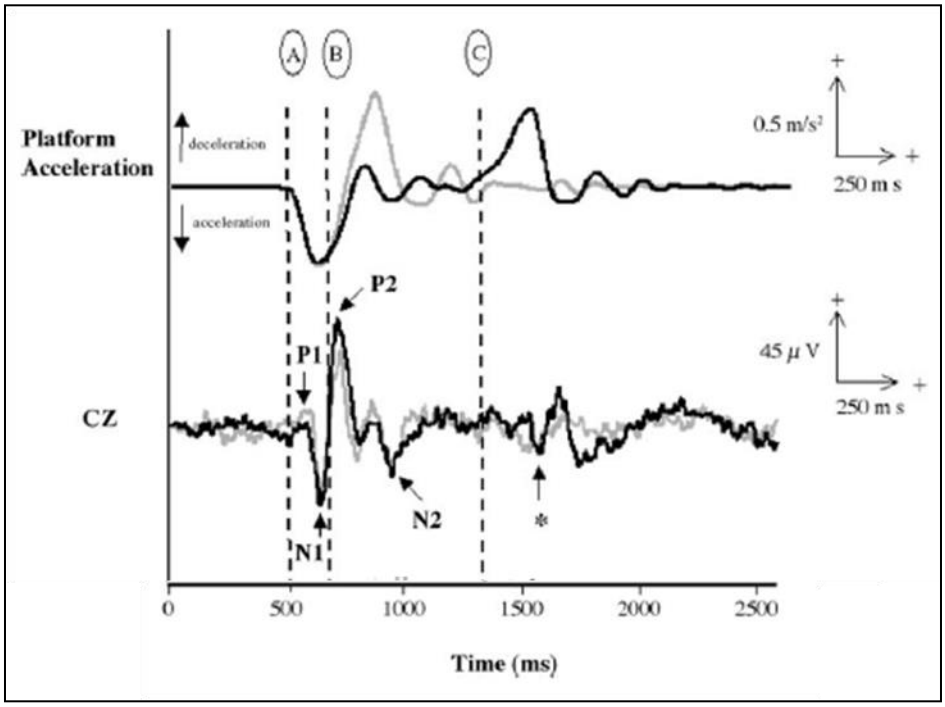


Figure 2.5. Perturbation evoked cortical potentials recorded at Cz electrode. Black dashed line A indicates the horizontal acceleration of platform. The P1 response observed in average 88ms after the perturbation followed by the N1 response with a latency of 137ms. Gray and Black lines represent to different task conditions. Adopted from Quant, Maki and McIlroy, 2005.

The first positive potential called as the P1 response and peaks around 40-50ms delay which is followed by a negative potential, called as the N1 response, peaks with a latency of 100-150ms post perturbations (Figure 5). Following the N1 response another positive potential, called the P2 response, is usually observed around 200-400ms of delay following the perturbation. Researchers considers the P1 response as the sensory representation of perturbation originated over the primary sensory cortex while the N1 response is considered

as the perceptual processing of this sensory representation over sensory-motor cortices. There is, however, no clear consensus on the role of P2 like late cortical potentials in balance control such that they may be related with various cognitive functions including the processing of task instructions or shifting the attention from initial perturbation to upcoming motor strategies (Quant, Maki & McIlroy, 2005). In a recent study by Quant, Maki and McIlroy (2005) healthy young subjects were exposed to translational perturbations on the antero-posterior directions while monitoring EMG responses at postural muscles and EEG responses at the vertex of the head (CZ electrode). They have found that early potentials were consistently associated with initial postural reactions while later cortical potentials such as the P2 and N2 showed no temporal variation based on changes in later postural reactions (Quant, Maki & McIlroy, 2005). Although these early studies have shed some light into the activation characteristics of cortical potentials in upright stance, they are mainly restricted with perturbed balance conditions, and thus do not represent the role of continuous cortical involvement in wide variety of postural tasks. Cortical activity was also only monitored over the vertex of the head covering part of sensorimotor cortices with a very limited set of electrodes, CZ, C1 and C3 electrodes, restricting to draw general conclusions about posture related cortical activity over the entire cortex.

Recording electrophysiological activity of the entire cortex during continuing balancing tasks is relatively a new approach as a result of recent advancements in non-invasive brain activity monitoring technologies. The first line of studies was reported by Slobounov and colleagues in 2005 (Slobounov et al. 2005; Slobounov, Sebastianelli & Moos, 2005). Scalp EEG was recorded during two dynamic postural tasks in which subjects were asked to perform (1) self-initiated oscillatory and (2) discrete postural sways at the ankle

joints with a maximum range of motion in the antero-posterior direction (Slobounov et al. 2005; Slobounov, Sebastianelli & Moos, 2005). Time domain analyses showed that the self-initiation of discrete postural sways were preceded with an increasing negativity in EEG signals called Movement Related Cortical Potentials (MRCP) predominantly at sensori-motor cortices (Cz electrode). Frequency analyses also showed significant increases in the gamma band (30-50Hz) at the central-frontal electrode sites 200ms prior to the maximal lean forward position indicating a signal modulation sensitive to changes in postural state of the person. Authors suggested that the human cortex may contain a specialized set of neural detectors for monitoring the postural state of the individual and triggering central motor commands (Slobounov et al. 2005).

Further support for the role cortical activity modulation in postural stability was provided by another study with the same research design in subjects with mild traumatic brain injury (Slobounov, Sebastianelli & Moos, 2005). University level athletes were recruited to participate in baseline measurements and eight athletes who experienced concussions during the year were re-tested at 3, 10 and 30 days after mild traumatic brain injury. Impairments in postural performances as quantified with reduced sway range in self-initiated oscillations were accompanied with reduced MRCPs indicating that residual disturbances in neural networks monitoring preparation and execution of postural related movements are related with postural sway characteristics (Slobounov, Sebastianelli & Moos, 2005).

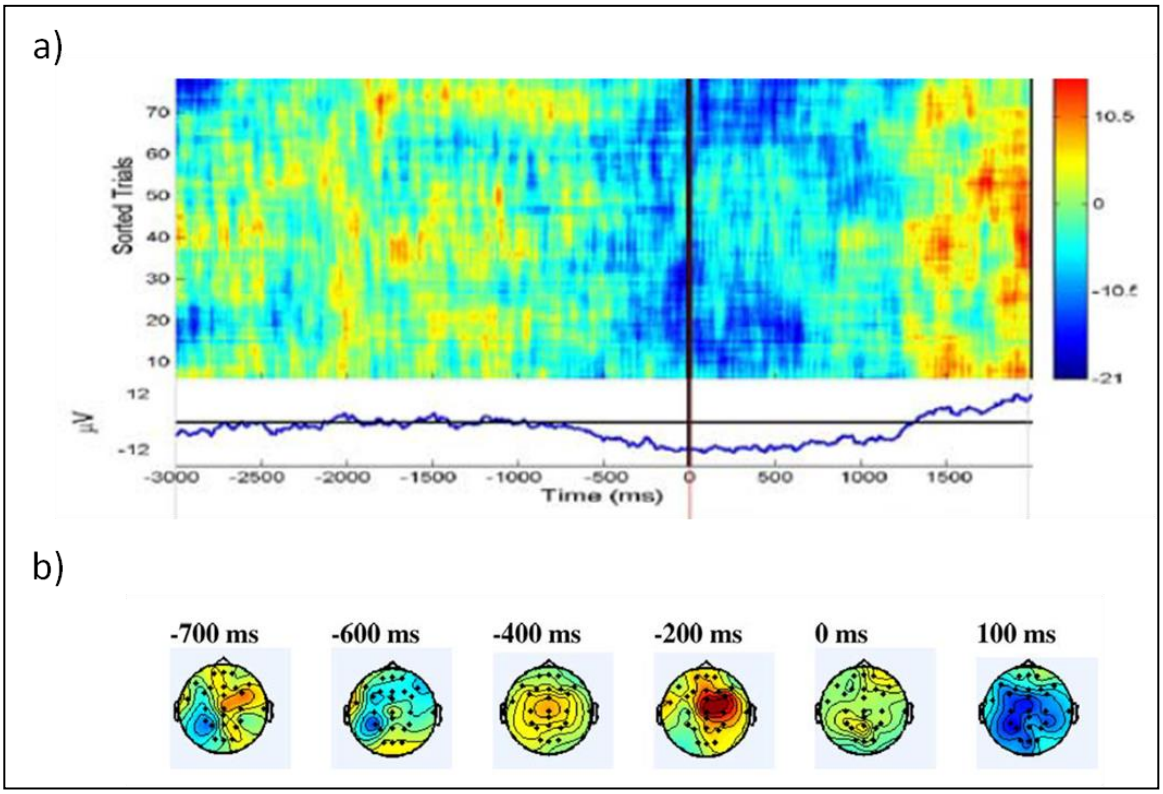


Figure 2.6. Slow wave EEG evolution along with MRCPs at Cz electrode preceding self initiated movement (a) and (b) scalp maps of EEG gamma (30-50Hz) evolution during self initiated maximum forward sway (0ms). Peak sway position is preceded (-200ms) with an increased gamma modulation. Adopted from Slobounov et al 2005.

Spatial organization of neural substrates involving in upright stance control was also identified in a recent study by Slobounov et al. 2009. In this study, researchers were primarily interested in how spatial-temporal dynamics of the COM characteristics, quantified by TTB measures, provide predictive information to neural substrates distributed throughout the cortical regions. Healthy young adult subjects were asked to stand on their dominant legs in the eyes closed condition until they were not able to maintain single leg stance and experienced falls. By using TTB values, postural data were segmented into stable and unstable stages, and time locked multi-channel (64channels) EEG data were used for continuous wavelet analyses to identify time-frequency evolution of EEG signals. Results

revealed significant increases in EEG low-theta (4-5Hz) power during unstable stage were predominantly observed at central frontal channels. Similarly the alpha (8-12Hz) power was also increased in unstable stage as compared to stable stage TTB values. The sources of manually selected Independent EEG Components (ICAs) were analyzed by Low-resolution tomography (LORETTA) and significant modulations were observed at the cingulated cortex and parietal-occipital cortices (Slobounov et al. 2009).

More recently, studies have also identified various aspects of cortical network functioning in upright stance control. Specifically these studies showed that the nature of cortical involvement can be modulated as a function of the subjects' training background (Percio et al. 2007; Percio et al. 2009), direction of voluntary postural sway (Slobounov, Harlett & Newell, 2008), predictability of future postural events (Jacobs et al., 2008; Mochizuki et al. 2009; Simith, Jacobs & Horak; 2012) and changes in sensory conditions (Zhavoronkova et al. 2012). In one related study, Percio and colleagues (2009) indicated that postural related cortical activity is reduced in elite karate athletes even during challenging postural tasks. Cortical activity was identified by event related de-synchronization (ERDs) in alpha (8-12Hz) band and results indicated that ERDs were lower in elite karate athletes, as compared to sedentary healthy controls, at left central, right central, middle parietal and right parietal areas. The authors suggests that athletes with intensive training backgrounds in posture-control tasks have more effective cortical functioning, and thus utilize less cognitive sources in accordance with the "neural efficiency" hypothesis (Percio et al. 2009).

Although all these studies have contributed to our understanding of neurophysiological processes underlying postural control, further studies are still needed to identify how cortical correlates of postural control mechanisms are functioning in response to

continuous changes in postural task requirements. Cortical representations of dual posture tasking mechanisms are also largely unknown. Moreover, age related changes in cortical control of upright stance are also remained to be examined.

2.5. Aging and upright stance control

Aging is known to affect almost all sensorimotor systems involving in upright stance control. In general, there is progressive decline both in musculoskeletal and sensory systems functioning with increasing age. Many studies have reported weak postural muscle strength (Horlings et al., 2008), distorted visual acuity and depth perception (Lord & Dayhew, 2001), reduced mechanoreceptor sensitivity (Thelen et al, 1998), and impaired vestibular system functioning (Rosenhall & Rubin, 1975). Cognitive impairments have also been reported in elderly populations, especially in a progressive manner after the age of 70 (Freedman et al., 2002). It is therefore not surprising that falls dramatically increase by increasing age and are among one of the main leading causes of death in elderly people (Woollacott & Shumway-Cook, 2000).

A number of studies have reported increased postural sway in older adults, even during non-challenging standings tasks, as compared to healthy young adults (Sheldon, 1963; Toupet et al. 1992; Slobounov et al., 1998). One of the earliest studies regarding quiet stance sway in all age groups (ranging from 6 to 80 years) was conducted by Sheldon in 1963, and results indicated increased sway both in young children and elderly people, compared to other age groups (Sheldon, 1963). Toupet and colleagues (1992) have also examined spontaneous body sway during quiet stance among 500 non-pathological participants aged between 40 to 80 years old. They found progressively increased postural sway with each decade of life (Toupet et al. 1992). Studies examining spatial-temporal characteristics of

COP dynamics with TTB measures also showed that ratio of the area of COP movements, within the functional stability limits, significantly increased in older adults when compared to younger participants (Slobounov et al., 1998).

Several studies have examined age related changes in postural control during changing sensory conditions by using posturography systems (Horak et al., 1989; Peterka & Black, 1990a; Teasdale et al., 1991). Peterka and Black (1990a) provided the first line of systematic research on effects of sensory manipulations on elderly postural control by using sensory organization tests. They found no age-related increases in postural sway in eyes closed condition on a fixed support surface. However significant increases in postural sway were observed in altered visual (sway surround) and proprioceptive (sway surface) conditions in people over 55 years of age, indicating deficits in posture-control related sensory re-weighting in older adults (Peterka & Black, 1990a). Previous studies have also reported that elderly people rely more on visual inputs for upright stance control (Lord & Webster, 1990; Wade et al., 1995).

Postural responses of elderly people during perturbed balance conditions have been largely investigated. It has been shown that older adults exhibit altered neuromuscular and motor strategies with a general decline in muscle response amplitudes and increased delay in muscle activation patterns (Woollacott & Shumway-Cook, 2000). In one of their early studies, Woollacott et al. (1986) examined postural muscle response characteristics of older adults, aged between 61 and 78 years, in response to platform perturbations. Similar muscle response synergies were observed in small perturbations in which muscle activation was first observed in ankle joints and move upward through hip joint muscles. However, significant differences were observed in muscle activation latencies in ankle dorsi-flexion muscles in

older adults causing an increased backward sway in response forward surface translations (Woollacott et al., 1986). Peterka and Black (1990b) reached similar conclusions in their complementary research. They asked 214 subjects to maintain balance during horizontally perturbed balance in antero-posterior directions. EMG analyses revealed that there was an increased delay in onset of muscle activations as well as increased time to reach peak muscle activations in elderly people (Peterka & Black, 1990b). Although behavioral studies consistently indicate that older adults exhibit slower muscle response characteristics to postural perturbations, the neurophysiological mechanisms underlying these responses have yet to be identified. For example, there is no conclusive evidence in the literature regarding the neurophysiological origins, whether in sensory or musculoskeletal mechanisms, of delayed postural responses in elderly people.

With respect to musculoskeletal system functioning, research has indicated that strength, amount of force and sustained power (endurance) capabilities of lower body musculature decrease by as much as 40% in elderly people (Anniansson et al., 1986). These impairments were reported to be more severe in nursing home residents with a history of increased falls (Whipple et al., 1987). Hughes et al. (2001), for example, reported 12 to 17% muscle strength loss on knee flexor and extensors over 10 years of period. Recent studies have also investigated the link between muscle strength parameters and upright stance performance in elderly people. Supporting evidence provided by studies showing reduced fall rates after strength training regimens in older adults or pathophysiological cases indicating a link between neuromuscular diseases and postural performance (Horlings et al,. 2008; Horlings et al. 2009). In a recent systematic and comprehensive review examining 74 peer-reviewed articles, Orr (2010) reported that 73% of studies showed significantly improved

balance performance after resistance/power exercise interventions, while 86% of cross sectional studies reported significant relationships between balance performance and muscle strength parameters. Despite these behavioral results, there is weak causal evidence for muscle strength and postural control associations in which changes in postural performance after therapeutic interventions is also attributed improved somatosensory functioning rather than changes in muscle strength per se (Orr, 2010).

2.5.1. Aging and dual postural tasking

Attentional requirements and cognitive components of upright standing have also been subject to numerous investigations in the elderly population. Majority of findings primarily rely on the behavioral outcomes obtained in dual-tasking studies, generally indicating impaired performance either in postural, secondary cognitive or both tasks in older adults. The general consensus is that there is a shift in control of upright stance from supra-spinally originated pathways to cortically controlled neural networks in elderly people, meaning that elderly people recruit more cognitive sources than younger counterparts in a given postural task, and thus exhibit impaired dual-tasking performance due to limited attentional capacity.

Most of these studies, originated from shared attention theory, reported cognitive performance interferences when attentional requirements of concurrently performed tasks exceed the total information processing capacity of the individual (Dault et al., 2001; Remaud et al., 2013). This understanding suggests declined cognitive and postural performance during dual tasking in elderly people due to the well-known deteriorative effects of aging on cognitive processing and sensorimotor functioning. For example, due to the

impairments in sensorimotor tracts underlying the -supra-spinally driven- automatic posture control mechanisms, elderly people are assumed to rely more on high level cortical processing loops as a compensatory strategy to control upright stance (Boisgontier & Nougier, 2013). This requires increased allocation of cognitive sources for posture control tasks and, thus, claimed to lead further performance decrements during dual tasking due to the limited attentional capacity (Goble et al. 2010). Shared attention theory can fairly explain a variety of experimental results reporting increased COM sway when older participants were asked to perform cognitive tasks (i.e. working memory task) during posture control testing (Teasdale et al., 1993; Lajoie et al., 1996; Brown et al., 1999; Marsh & Geel, 2000; Teasdale & Simoneau, 2001; Dault & Frank, 2004; Swan et al., 2004; Raymakers et al., 2005; Bernard-Demanze et al., 2009; Berger & Bernard-Demanze, 2011; Granacher et al., 2011).However, it also fails to account for considerable amount of recent research findings indicating either unchanged or decreased COM sway in older adults during dual tasking (Shumway-Cook et al., 1997; Melzer et al., 2001; Weeks et al., 2003; Prado et al., 2007; Dromey et al., 2010; Van Impe et al., 2013; Yogev-Seligmann et al., 2013).

Studies that report decreased COM sway in dual task settings attributed their findings to either "task prioritization model" or "facilitatory control" strategy employed by elderly people (Fraizer & Mitra 2008). The task prioritization model posits that elderly people prefer tighter postural control strategy during dual tasking and prioritize postural stability over cognitive performance, called the posture first strategy, with the major goal of preventing themselves from falling (Brauer et al, 2002). The facilitatory control hypothesis, on the other hand, assumes that postural control is a natural component of dual tasking since postural control mechanisms almost always coexist with numerous other cognitive functions (i.e.

memory, language, spatial orientation) in daily life settings. This view, therefore, interprets postural control system as naturally integrated part of other cognitions and considers posture-cognition dual-tasking as a single higher order skill rather than being independent with autonomous components (Frasier and Mitra 2008). Although these theoretical frameworks rely on the organization of cognitive processes in explaining current inconsistency in the results, no studies have monitored cortical activity during posture-cognition dual tasking. We still have no direct neurophysiological evidence regarding the reliance primarily on cognitive sources to maintain upright stance in elderly population.

2.6. Summary

The human upright stance is inherently unstable and depends on complex dynamical interactions between musculoskeletal and several neural systems. The postural control system integrates multiple sensory modalities to plan, coordinate and execute optimal postural responses in constantly changing environmental conditions. Neural subsystems involving in upright stance control are distributed to all levels of CNS. While posture control related neural systems residing at spinal or brain stem regions have been relatively well identified, there is a little consensus on the role of cerebral circuits involving in upright stance control. Additionally, how the proposed posture related cortical activity is changing as a function of aging and task requirements has yet to be documented.

CHAPTER III

Manuscript I: Cortical Involvement to Upright Stance Control: Age related changes during challenging quiet and perturbed stance conditions

3.1 Introduction

Most daily human activities require vertical orientation of the body to the gravitational vector. The human upright stance in gravitational fields, however, is inherently unstable due to biomechanical design of the body and external forces acting on it (Winter, 1995). Thus, control and establishment of upright stance depends on complex dynamical interactions between musculoskeletal and several neural systems, collectively described as the "postural control system" (Bernstein, 1967; Shumway-Cook & Woollacott, 2000). The postural control system constantly monitors the position and orientation of the body in space via multiple sensory channels, and initiates necessary motor actions to secure upright stability. This essential control system, unfortunately, is also subject to deteriorations and specific impairments, especially in the aging body, which in turn may cause falls.

Falls are a leading cause of severe traumatic injuries (i.e. hip fractures, head traumas) and early death among elderly population (Speechley & Tinetti, 1991; Sattin, 1992; Siracuse et al., 2012). Maintaining optimal mobility and postural functions will be one of the key health priorities for millions of senior citizens (National Center for Injury Prevention and Control, 2013). Thus, it is crucial to identify factors causing falls in the elderly. This, at the very first step, requires comprehension of the complex neurophysiological mechanisms of optimally functioning human posture control system in a variety of settings.

Although historical pioneers of neuromotor physiology (Sherrington, 1910; Sherrington, 1947; Magnus, 1926) mainly concluded that upright standing in mammals and vertebrates is predominantly governed by spinal and sub-cortical networks (Liddell & Sherrington, 1924; Magnus, 1926, Schaltenbrand, 1928), we now have ample experimental evidence to suggest involvement of several cerebral cortices to the control of standing balance in humans (for detailed reviews see Jacob & Horak, 2007; Papegaaij et al. 2014). Evidence from behavioral observations in healthy subjects shows that changes in cognitive loads (i.e. dual tasking) (Brown & Marsden, 1991), focus of attention (i.e. directing attention to primary or secondary task) (Kerr, Condon &McDonald; 1985), and mood states (anxiety, fear of falling) (Balaban & Thayer, 2001) of the person can affect behavioral response of the person to a postural task. Moreover, predictability of environment with respect to upcoming posture events can also change postural responses both in healthy and impaired populations (Hansen, Woollacott & Debu, 1988; Slijper et al. 2002). Healthy humans who expect or anticipate upcoming postural events (i.e. perturbations) are able to modify their neuromuscular responses accordingly (Shumway-Cook &Woollacott. 2000; Schmidt & Lee, 2005). All these mental functions, such as anticipation, attention, cognition, memory, and mood state, are thought to be controlled by the cortex, and thus supporting its influential role on postural control (Dehaene et al.,2004; Kaiser & Lutzenberger, 2005; Naghavi & Nyberg, 2005; Jacobs & Horak, 2007).

Electrocortical studies also provide further support for the role of cerebral cortex in human upright standing (Del Percio et al., 2007; Mihara et al., 2008; Mochizuki et al., 2009; Quant, Maki & McIlroy, 2005; Slobounov et al. 2005; 2009; Sipp et al., 2013). Early studies on perturbation evoked cortical potentials (PEPs) have consistently reported multi-

component large scalp potentials following unpredictable postural perturbations in young adults, indicating rapid involvement of cortical centers into control of upright stance when balance is threatened (Dietz et al. 1985; Ackermann et al. 1986; Dimitrov et al. 1996; Duckrow et al. 1999; Quant et al. 2004, 2005). Temporal analyses of PEPs have revealed a small amplitude positive potential (P1) with a latency of 50-80ms, representing initial cortical responses to sensory afference, followed by a larger negative deflection (N1) with a latency of 100-200ms. (Ackerman, Diener & Dichgans, 1986; Adkin et al. 2003; Dietz et al. 1985; Dimitrov, Gavrilenko & Gatey, 1996; Duckrow et al. 1999; Quant et al. 2004; Staines, McIlroy & Brookes, 2001). These studies, however, mostly focused on cortical potentials recorded from the vertex only at perturbed stance conditions, thus providing limited information regarding the involvement of cortical networks on balance control during quite stance with challenging sensory conditions.

Electroencephalographic (EEG) recordings from the whole-scalp during continuous balance tasks are relatively a new approach as a result of recent advancements in non-invasive brain activity monitoring technologies. Slobounov and colleagues reported the first set of studies recording whole scalp EEG activity during two dynamic postural tasks (Slobounov et al. 2005; Slobounov, Sebastianelli & Moos, 2005). Time domain analyses showed that the self-initiation of discrete postural sways were preceded with an increasing negativity in EEG signals called Movement Related Cortical Potentials (MRCP) predominantly observed over scalp areas above sensorimotor cortices (Cz electrode). Frequency analyses also showed significant increases in the gamma band (30-50Hz) at the central-frontal electrodes when standing balance is threatened. More recently, studies have also identified increased theta (4-7Hz) band activity in anterior cingulate, anterior parietal,

superior dorsolateral prefrontal and medial sensorimotor cortices when body sway increases during postural tasks (Hulskunder et al. 2015) or falling during a challenging walking task (Sipp et al., 2013). These EEG modulations, in general, are assumed to reflect increased attentional requirements or cognitive demands of the challenging balance tasks such that cortical networks are actively involving in updating internal models of upright stance control (Sipp et al., 2013).

While these studies provide some experimental support regarding the involvement of cortex in upright stance control, there is still insufficient understanding for the functional role of different cerebral cortices on monitoring postural state of the body during changing sensory and task conditions. To date, no systematic research has been conducted to identify the role of cerebral activity on postural control during quiet stance, challenges to sensory organization, recovery from biomechanical perturbations or divided attention. How, for example, posture related cortical activity is modulated as a function of the availability of different sensory modalities during upright stance tasks has yet to be examined. More importantly, the effects of aging on cortical correlates of postural control are also largely unknown. To our knowledge, there are no prior reports examining age differences in balance related whole scalp cortical activations during continuous postural tasks with challenging sensory conditions or biomechanical perturbations. A considerable amount of behavioral research, for example, showed that older adults are less able to maintain their upright stance during perturbed balance conditions, compared to young people due to prolonged response delays along with increased COM sway following postural perturbations (Nashner 1976; Stelmach, Teasdale, Di Fabio, & Phillips, 1989; Maki, Holliday, & Topper, 1994; Gu, Schultz, Shepard, &Alexander, 1996; Allum et al., 2002; Lin, Woollacott, & Jensen, 2004,

Mansfield & Maki, 2009). Although delayed muscular activations in response to postural perturbations have generally been attributed to morphological deformations, such as degenerated axons or decreased number of myelinated fibers (Verdu et al., 2000; McNeil et al., 2005) in the peripheral nervous system of the aging body, degraded cortical representations resulting in prolonged response delays in older adults have received little attention (Duckrow et al., 1999). Therefore, we undertook the current study by utilizing two experimental tasks with the main goal of understanding cortical representations of human posture control during varying environment and task related constraints both in young and elderly people. We designed the first component of the study (Experiment 1) to answer the basic neurophysiological question of whether or not unexpected changes in postural state of the person are monitored by cortical centers, and if so, how this cortical monitoring differs between healthy young and older adults. Here, the primary focus was to examine changes in cortical activity when unexpectedly altering the sensory conditions of upright stance, such as switching from stable (eyes open, fixed support surface) to less-stable (eyes closed, sway-referenced support surface) quiet stance conditions. We expected to observe increased cortical activity over the frontal, central-frontal, central and central-parietal cortices during challenging upright stance conditions (eyes closed-swayed reference) when standing balance is threatened. We also expected increased cortical activation in the elderly participants as a compensatory reorganization due to deformations in the peripheral pathways of the aging nervous system (for a detailed review see Papegaaij et al. 2014).

The second component of the study (Experiment 2), on the other hand, examined compensatory postural responses to unexpected postural perturbations while simultaneously recording Electroencephalography (EEG), Electromyography (EMG), and Center of Mass

(COM) dynamics. Perturbation experiments were designed to provide insights into the neurophysiological sources of prolonged response delays to postural perturbations in the elderly people.

3.2. Materials & Methods

3.2.1. Subjects

Ten healthy young (4 female and 6 male, M*age*=26.20±2.77 years old) and 9 healthy older (6 female and 3 male, M*age*=81.42±6.30 years old) adults participated in this study after reporting freedom from any neurological, cardiovascular, vestibular or musculoskeletal disorders, and no history of falls for at least 6 months prior to study. Overall health status of the prospective participants was assessed using the Physical Activity Readiness Questionnaire-PAR-Q (Canadian Society for Exercise Physiology, 2002). Cognitive functioning level of older adults was measured with the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) and those who scored <27 were excluded from the study. All participants were informed about the experimental protocols before they gave their written consent. The study protocol was approved by the Institutional Review Board of the University of Houston.

3.2.2. Instrumentation

Center of pressure data (COP) for postural performance were quantified by using standard computerized dynamic posturography platform (NeuroCom Balance Master NeuroCom Intl, Clackamas OR). The platform is equipped with a dynamic dual force plate system (18” X 18”), in which ground reaction forces under the feet of individuals were

collected at 100 Hz by four individual force transducers embedded within force plate and used to estimate COM projections. Surface muscle activation patterns were recorded with an 8 channel analogue surface electromyography (EMG) data acquisition system (DataLOG MWX8 EMG data collection unit, Biometrics Ltd., Cwmfelinfach, Gwent, UK). EMG data were collected from lower body musculature at a sampling frequency of 1000 Hz and passed through an amplifier with the gain set at 1000. Eight bipolar surface electrodes (SX230 EMG electrodes, Biometrics Ltd., Cwmfelinfach, Gwent, UK) with a fixed electrode distance of 20 mm were placed bilaterally (on both legs) over the following muscles; tibialis anterior (TA), gastrocnemius (Gast), biceps femoris (BF), and vastus lateralis (VL). Whole scalp 64-channel EEG data were collected (actiCap system, Brain Products GmbH, Munich, Germany) and labeled in accordance with the extended 10-20 international system. EEG data were online referenced to channel FCz. Electrode impedances were maintained below 5kΩ with a sampling rate of 1000 Hz. EEG signals were digitized using a BrainAmp DC amplifier linked to BrainVision Recorder software version 1.10. Head kinematics were captured using wireless motion sensors (OPAL, APDM Inc., Portlans, OR) placed on the frontal bone of the head. Kinematics data were sampled at 80 Hz.

3.2.3. Experimental Procedures.

Experiment 1 was primarily designed to investigate changes in EEG signal power when postural tasks are gradually and unexpectedly switched from non-challenging to challenging sensory conditions. The experiment started with resting EEG state measurements. Subjects were asked to sit on a chair (placed on the Neurocom platform) in a comfortable position for two minutes and whole scalp EEG was monitored to attain baseline cortical activity. At the end of two minutes, subjects were asked to stand up and perform a series of postural control tasks. Postural control tasks included bipedal stance trials with three

different sensory conditions: Stable Surface Eyes-Open (SEO), Stable Surface Eyes-Closed (SEC), and Unstable Surface Eyes-Closed (UEC). Two trials, each lasting 90 seconds with a 30 sec testing for each sensory condition, were performed in a specified order (SEO-SEC-UEC-SEC-UEC-SEO). All trials were performed continuously without having a break among sensory conditions. These continuous trials allowed us to manipulate the difficulty of the postural control task progressively while monitoring cortical (EEG) activity and postural (COP) responses simultaneously.

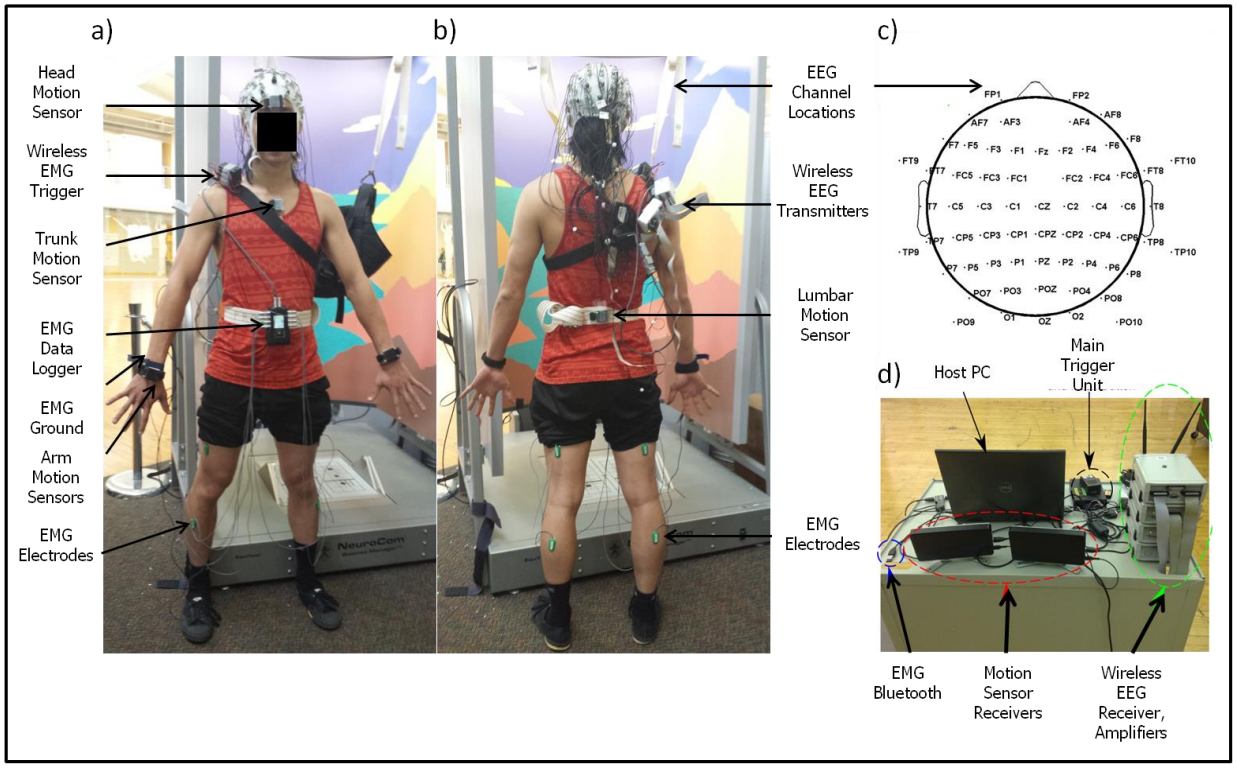


Figure 3.1. Data collection system mounted on a representative participant.

Experiment 2 was designed to examine neurophysiological sources of postural response delays to perturbed balance conditions. Subjects were asked to maintain their balance as much as possible when their upright stance was unexpectedly perturbed in different directions. Perturbation tasks included two surface translations (Forward and

Backward translations with 15.875cm/s amplitude within 400ms) and two surface rotations (Toes-Up and Toes-Down rotations with 8^0 amplitude and 200ms duration of the platform where the axis of rotation is ankle). Each perturbation test had 5 trials and each trial lasted for 5 sec. The order and timing (2 to 5s) of perturbations were fully randomized in order to minimize adaptation effects. A brief practice session including sample trials of each postural task was administered to familiarize participants with the experimental protocol. During all postural tasks, subjects were instructed to maintain their balance without taking steps or using their arms. During all postural tasks, subjects were also secured with a safety harness to prevent falls or injuries.

3.2.4. Data Reduction and Signal Processing

Posture control data processing steps were performed as explained in Ozdemir et al. (2013). Briefly, ground reaction force data collected from the Neurocom system (100 Hz) were combined to create center-of-pressure (COP) time series in the antero-posterior (AP) and medial-lateral (ML) directions for each trial (Ozdemir, Pourmoghaddam, & Paloski, 2013). Corresponding center-of-mass (COM) position was estimated by low pass filtering the COP data (second order Butterworth; f_c= 0.86 Hz), and COM velocity was estimated by differentiating the COM position using a 3-point central difference algorithm. Stability boundaries in the AP and ML directions were conservatively estimated at the outer extremes of the foot locations to create a rectangular stability zone for each subject, and distance-to-boundary (DTB) was estimated as the instantaneous differences between the COM position and the stability boundaries in the direction of COM movement. Time to boundary (TTB) time series were then calculated by dividing the DTB by the COM velocity for each direction. Two performance measures were derived from the TTB time series for each trial.

The minimum value of the TTB over each trial (TTBmin) represents the least stable moment during the trial and was considered to be the worst-case performance during the trial. The integrated area of TTB (iTTB) was also calculated below an arbitrary 10 sec threshold that represents an estimate of relative instability over the entire trial. iTTB is expressed as a fraction of the total area beneath the threshold during the trial.

EMG signals were band-pass filtered with an 8^{th} order Butterworth filter between 15 and 300 Hz. All signals were rectified and integrated over 30 ms to get linear envelopes of EMG activity (Bulea et al. 2013). EMG data were used to quantify compensatory postural responses during postural perturbations. First, linear envelope EMG signal of each channel was manually segmented into (1) no-perturbation and (2) perturbation periods by using digital channel triggers representing start of each perturbation. Then the mean and standard deviation of all no-perturbation periods were calculated for each channel and subtracted from the entire EMG time series data for each trial. Peak EMG latencies were determined in perturbation periods as the time points with the highest voltage values across muscles and trials. Finally grand means of peak activation latencies were calculated for each muscle.

The EEG data were processed offline using EEGLAB 5.03 (Delorme & Makeig, 2004) and Matlab open source toolbox (Mathworks, Natick, USA). First the EEG channels from the peripheral and temporal sites (FP1-2, AF7-8, F7-8, FT7-10, T7- 8, TP7-10, P7-8, PO7-8, PO9-10, in the extended 10–20 EEG system montage) were rejected and not used in any further analyses due to their sensitivity to a number of physiological artifacts including facial gestures, eye movements or cranial muscular activity. The EEG data were then band pass filtered with a zero phase 3rd order Butterworth filter from 0.1 to 50Hz for main analyses. Next, each EEG channel was standardized by subtracting the mean and dividing by

its standard deviation (Cruz-Garza et al., 2014). Furthermore, Independent Component (ICA), time-frequency, bivariate correlation and coherence analyses were performed to identify potential mechanical, motion, neuromuscular, and eye artifacts in the EEG signals. First, Independent Component Analyses (ICA) was run to identify and remove components related to potential mechanical artifacts and eye blinks for all channels.

Time-frequency spectrograms were then computed to compare evolution of power dynamics in EEG signals over selected (Fcz, Cz, Poz) channels, representing a sampling of neural activity over central-frontal, central and posterior scalp regions, with the gravity compensated antero-posterior head accelerometer data from the MARG sensor (Figure 3.2). Short-time Fourier transform (STFT) with overlapping windows (1024 samples for each window with 93% overlap) were computed to generate spectrograms (Cruz-Garza et al., 2014). Figure 3.2 shows increased power especially during transition from SEC to UEC postural condition in EEG channels at low delta oscillations (.01 to 2 Hz). Corresponding power changes, however, were not observed in gravity compensated antero-posterior head accelerometer data indicating motion artifact free EEG data during transition periods after ICA correction (Figure 3.2, lower panel). Furthermore, coherences between raw EEG signals and the antero-posterior head accelerometers signals were also estimated (Figure 3.3). Welch's overlapped segment approach (Carter, 1987) was used to compute mean squared coherences to estimate relations between previously selected EEG electrodes and head acceleration at the frequency domain. As shown in Figure 3.3, coherence estimates were mostly low (<0.2) with some short lived increases (= 0.8) at low delta band (.01 to 2 Hz) at the end of the SEC postural condition.

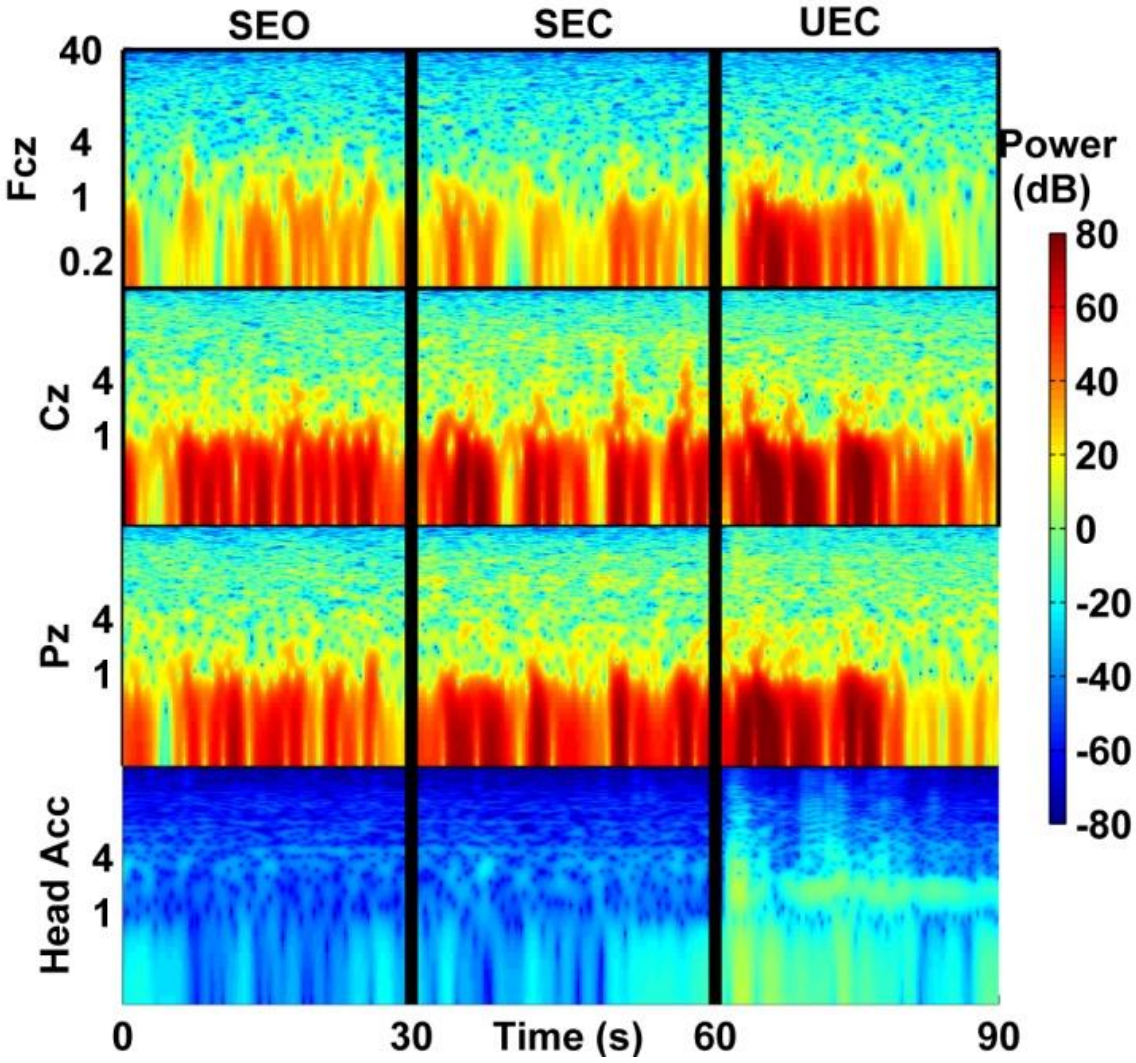


Figure 3.4. Time-frequency spectrograms representing fronto-central (Fcz), central (Cz) and posterior (Pz) scalp regions from a representative young subject. Gravity compensated antero-posterior head accelerometer data from the MARG sensor (Head Acc) were also shown in lower panel.Vertical solid black lines represent transition points between postural tasks. Continuous postural conditions: SEO-"Stable surface Eyes Open, SEC-"Stable surface Eyes Closed, UEC-"Unstable surface Eyes Closed"

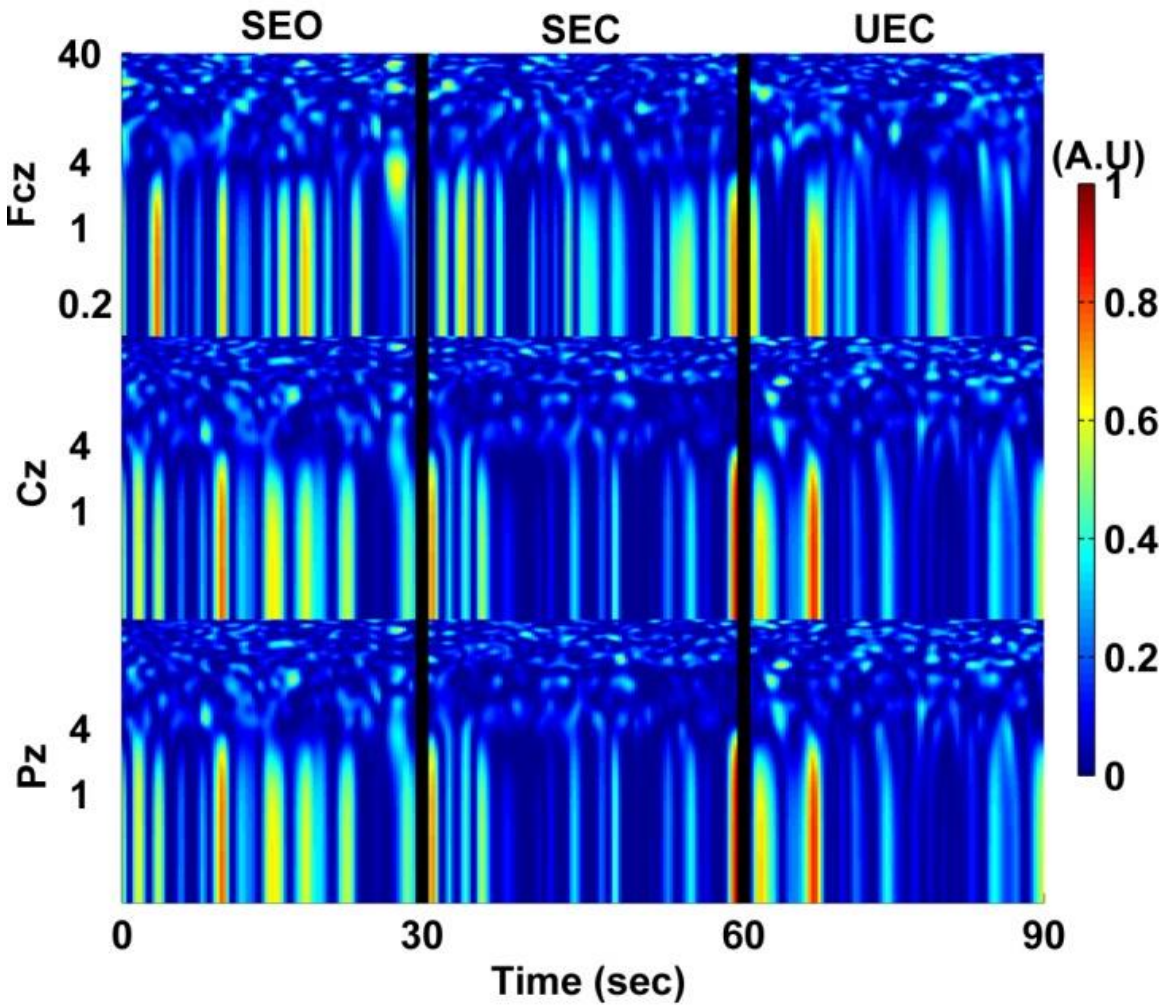


Figure 3.5. Spectrograms and short-term coherence between selected (raw) EEG channels (Fcz, Cz, and Pz) and the acceleration magnitude of the head MARG sensor for a representative young subject.Vertical solid black lines represents transition points between postural tasks.

Finally, bivariate correlations of the ICA corrected raw EEG signals (down sampled to 80 Hz) and the antero-posterior head acceleration were computed over the entire scalp (Figure 3.4) for each subject. Correlations were computed for UEC postural condition only since most body movements were observed in this condition due to the challenging nature of

the task. In general, weak (<0.2) and non-significant (p> 0.05) correlations were observed over the entire scalp except for one subject in the young group (Y8, see Figure 4 lower panel). Significant correlations for this subject were, however, ranging from .2 to .3 indicating that head movements can only account for 4 to 9% of variance in the EEG signals.

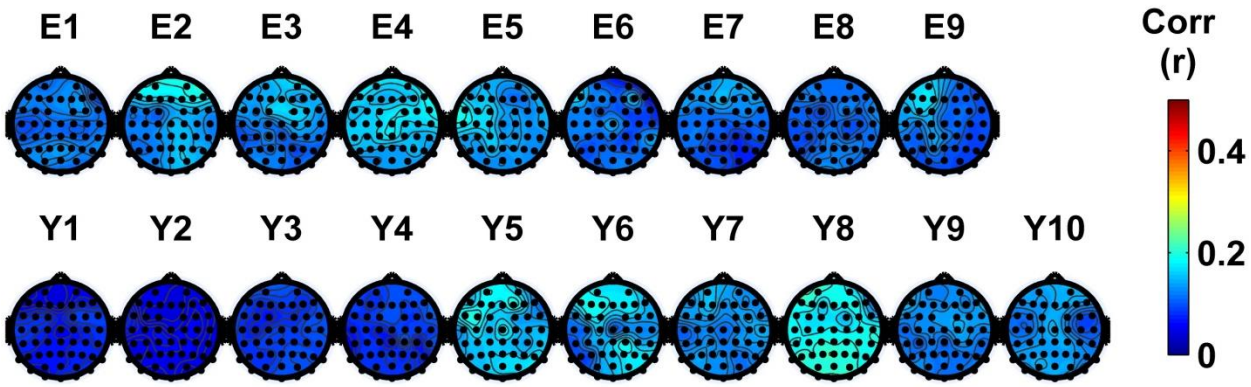


Figure 3.6. The topoplots show the distribution of bivariate correlation coefficients grand means between raw EEG signals and the magnitude acceleration data from the head MARG sensor during UEC postural condition for each subject. Keys: E: Elderly subject, Y: Young subject.

For main analyses a continuous complex morlet wavelet transform (CWT) was performed to quantify modulation of EEG signal power within delta (0.1-4 Hz), theta (4-7 Hz), alpha (8-12 Hz), beta (14-24 Hz) and gamma (30-50 Hz) bands over time throughout the duration of the postural trials (Slobounov et al. 2009). Specifically, EEG data were down sampled to 100 Hz and the Matlab wavelet toolbox including CWT algorithms (Misite et al. 1996) was used to compute two-dimensional representation of time-frequency energy of raw EEG data from low delta (0.2Hz) to high gamma (50Hz) oscillations. Then mean energy power in time-frequency series was calculated for every 1 second (corresponds 100 data points) for each EEG channel representing continuous power modulations in EEG signals within the postural condition. Finally, grand mean energy power was calculated from one-

second time-frequency energy means representing relative power changes in EEG channels across the entire duration of a given postural condition. For perturbation analyses, perturbation evoked potentials (PEPs) were analyzed. EEG data were epoched with 3 sec periods corresponding to -2000ms before and +1000ms after the perturbation (0 is the perturbation initiation). Each epoch was then baseline corrected with the average EEG amplitude between -2000 and -1500s before the perturbation onset. EEG signal mean amplitudes between -500ms to 1000ms were then averaged across all perturbation trials and subjects (younger adult vs older adult) for the given condition to examine PEP profiles. We focused on two main PEP responses. The first response is a small positive deflection (P1) usually observed 50-80ms following perturbation and thought to represent initial processing of perturbation related sensory information. The second response is a larger and longer negative deflection in EEG amplitude called the N1 response. N1 response has been studied in more detail and is thought to reflect higher order cortical processing of sensory information including error detection mechanisms (Ackerman, Diener & Dichgans, 1986; Adkin et al. 2003; Dietz et al. 1985; Dimitrov, Gavrilenko & Gatey, 1996; Duckrow et al. 1999; Quant et al. 2004; Staines, McIlroy & Brookes, 2001). The latency and the magnitude of these responses were calculated with respect to the initiation of perturbation (0 s). P1 latency was calculated as the time difference between initiation of perturbation and the sample point with the highest positive voltage within 100ms window, whereas N1 latency was determined based on the time point with the highest negative voltage within the 500ms window following perturbations. The amplitude was also calculated as the voltage difference between the initiation of perturbation (0s) and peak response time points.

3.2.5. Statistical Analyses

For statistical analyses of EEG power in experiment 1, cortical Region of Interests (ROI) were defined by calculating the grand mean EEG powers across all subjects, in each group, and channels for different cerebral regions including the frontal (F3, F1, Fz, F2, F4), central-frontal (FC5, FC3, FC1, FC2, FC4, FC6), central (C3, C1, Cz, C2, C4), central–parietal (CP3, CP1, CPz, CP2, CP4) and parietal (P3, P1, Pz, P2, P4) cortices. Series of 2(Group: Elderly vs Young) x 4(Condition: Baseline vs SEO vs SEC vs UEC) repeated measure variance analyses were performed to examine changes in grand mean EEG power in each ROI across groups and postural conditions for each frequency band. In order to examine whether short term (over one second period) quantitative changes in balance performance are associated with modulations in cortical activations, a series of bivariate correlations were calculated between TTB time series and EEG power data for each one sec period (corresponding 100 data points). Similarly, grand means of correlations between TTB time series and EEG power were calculated across channels and subjects in each group before (pre-transition: -2 : 0 sec, final phase of postural condition), during (transition: 0: +2sec, unexpectedly switching from one postural task to another), and after (post-transitions: +2: +5 sec after transition) switching from one postural task to another to examine whether modulations in cortical activity are sensitive to changes in postural conditions. A series of variance analyses were conducted to examine PEP latency and amplitude differences between groups for each ROI's. Statistical analyses for PEPs include grand means of FC3, FC1, FC2, FC4 channels for central-frontal, C3, C1, Cz, C2, C4 channels for central, and CP3, CP1, CPz, CP2, CP4 channels for central-parietal cortices. Finally, peak EMG response latencies of TA, Gast, BF and VL muscles to postural perturbations were compared between

groups by using independent sample t-tests. Significance level was set as ($p < .05$) for all statistical analyses.

3.3. Results

Experiment 1:

3.3.1. Descriptive Observations

Figure 3.5 shows time frequency evolution of EEG power (Cz channel) in delta band (0.1-4Hz), COM dynamics (COM position and velocity in antero-posterior direction), EMG activation profiles of selected postural muscles (TA and Gast), and Head kinematics (Velocity in AP) during continuous postural task conditions for a representative young subject. During stable surface eyes open (SEO) postural condition (Figure 3.5, panel a-, block SEO) no apparent changes were observed in EEG power dynamics, as compared to Rest condition (sitting on the chair). Stable surface eyes closed (SEC) postural condition seemed to slightly disturb COM dynamics (Figure 3.5, panel b), and increase EEG power in lower delta band (Figure 3.5, panel a- block SEC). Although EMG recordings showed some activation during SEC condition on TA and Gast muscles, the activity levels remained low (Figure 3.5, panel c). However, when postural task was unexpectedly switched from SEC to unstable surface eyes closed (UEC) condition dramatic changes were observed in postural performance (Figure 3.5, panel b), where the subject started to fall forward (AP direction) about 1.5 sec after the initiation of UEC condition as COM position moves towards anterior direction. During the falling phase, simultaneous modulations were identified in delta band EEG power (Figure 3.5, panel a- block UEC). EMG recordings also showed increased activation in Gast muscles during the falling phase in forward direction (Figure 3.5, panel c-

block UEC) followed by activations in TA muscles when the subject actively tries to recover COM position as noticed by the sudden change in the direction of COM velocity (see red line in panel b- block UEC). The overall trial suggests that cortical networks may be involved in posture control when the balance is threatened to recognize unstable posture of the body and control initiation of voluntary neuromuscular corrections.

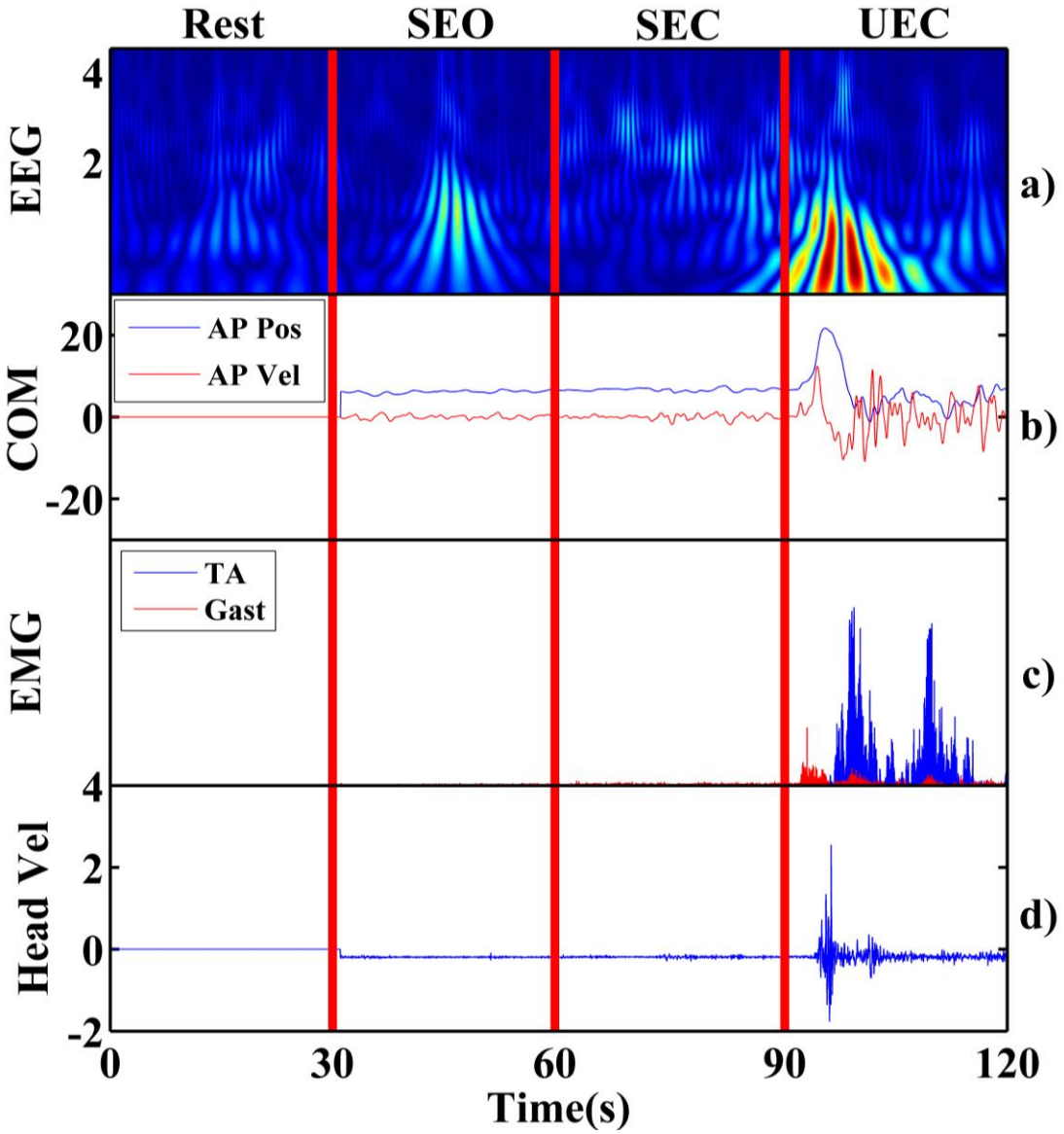


Figure 3.5 Time-frequency evolution of EEG (Cz), COM changes in AP, EMG activation profiles for TA and Gast muscles, and Head acceleration of representative young subject during continuous postural tasks. Vertical solid red lines represent transition points between postural tasks.

3.3.2. Cortical activity modulations as a function of postural task and ageing.

Topographical distribution of group means of EEG power in delta and gamma bands were plotted as scalp maps to show how EEG power is modulated over scalp channels across different postural task conditions (Figure 3.6). Although both groups showed significantly increased ($p < .05$) neural activity in the delta band during the most challenging postural task conditions (UEC), younger subjects show slightly higher EEG power as compared to elderly subjects.

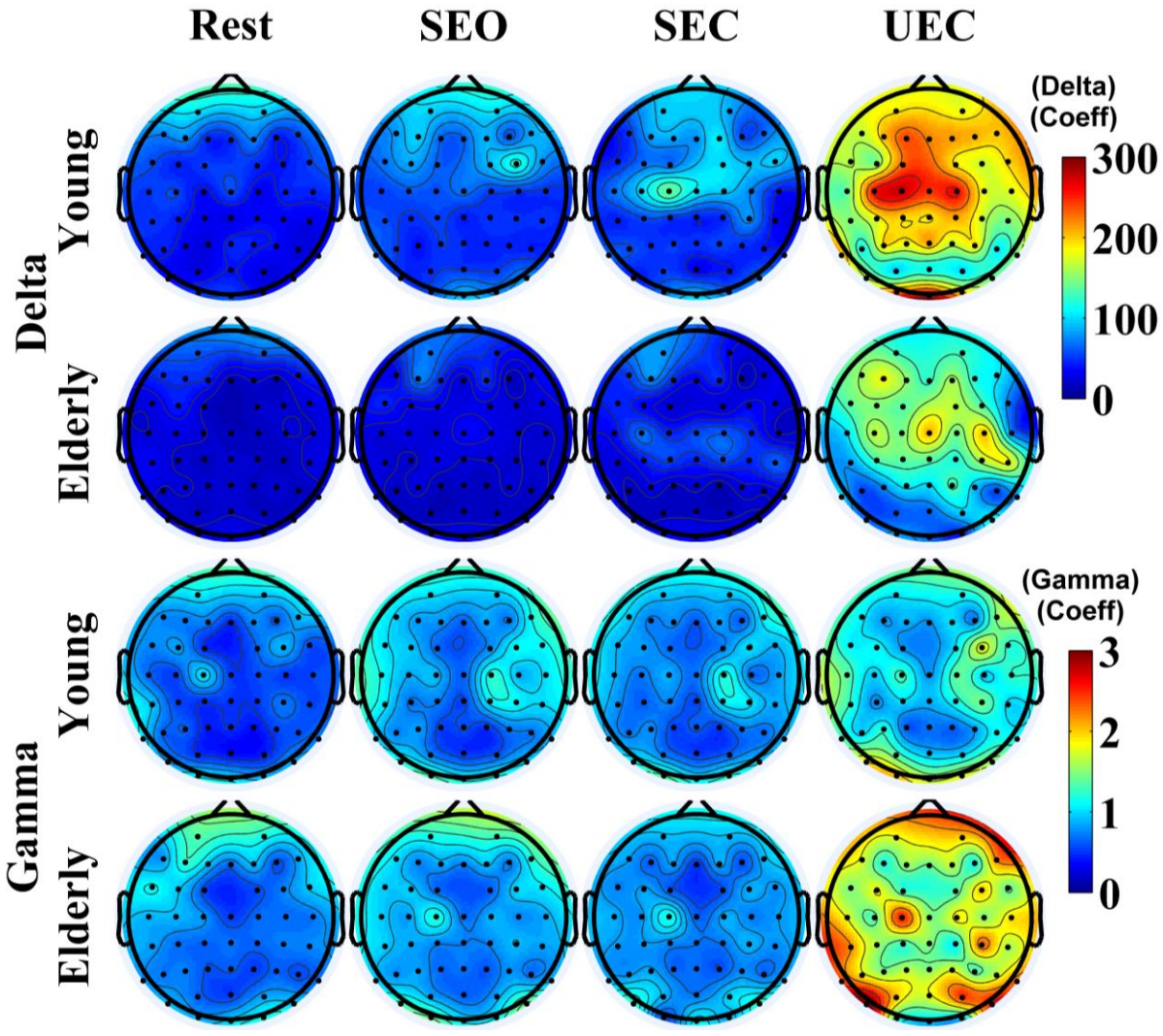


Figure 3.6 Scalp distributions of EEG power grand means in Delta and Gamma Band for Quiet stance postural conditions

Gamma band activity, on the other hand, appeared to be higher in the elderly group during UEC conditions, suggesting that younger individuals seemed to relay more on network processing as opposed to local processing as in elderly individual. Results for delta band neural activity showed significant main effect for postural condition over frontal (p=.041), central-frontal (p=.044), central (p=.039), central-parietal (p=.031), and parietal (p=.037) cortices, indicating increased neural activity due to changes in postural conditions when groups were combined. Pairwise comparisons revealed increased neural activity from SEC to UEC postural conditions in all ROI's (Figure 3.7).

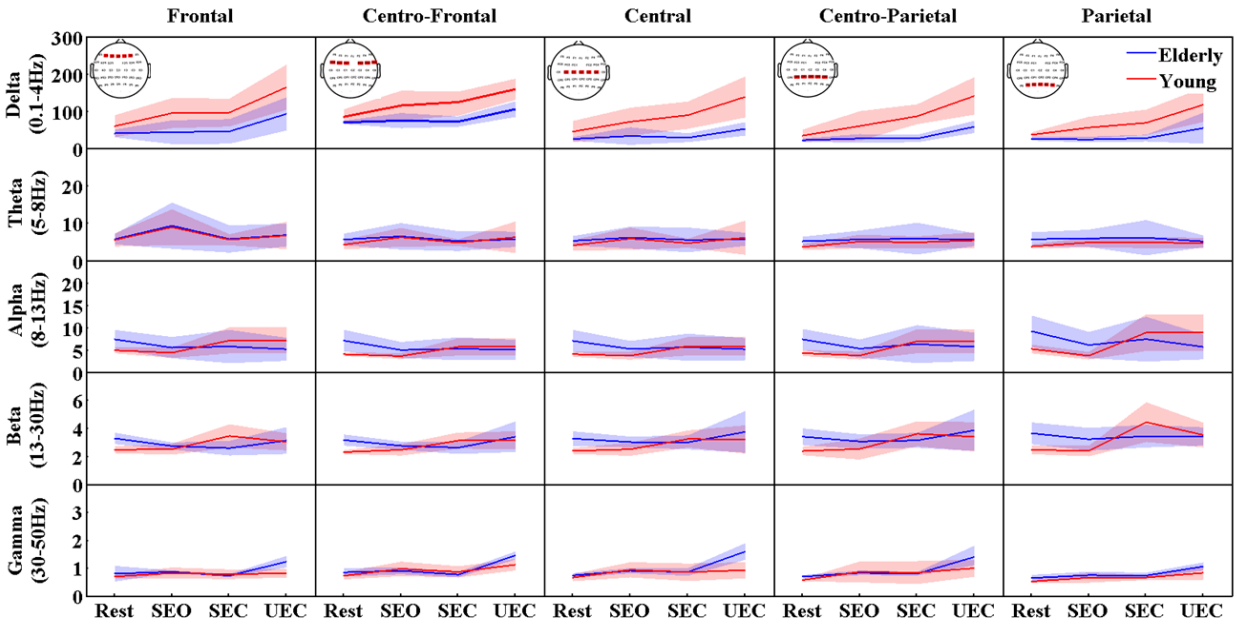


Figure 3.7. Grand means (solid lines) and standard deviations (shaded regions) of EEG power both in elderly (blue) and young (red) groups for all Region of Interests (red dotted channel locations in each topoplot) during quiet stance postural conditions.

Increased neural activity was also observed from SEO to SEC in central cortices only in younger subjects. Significant "group X postural condition" interactions were observed in central and central-parietal neural activity. Simple effect analyses were performed to break down interaction effects by comparing neural activity differences between groups at each

postural condition (Field, 2009). Simple effect analyses showed that the young group has higher neural activity during SEC (p<.05) and UEC (p<.05) at central-frontal, central and central-parietal regions, when compared to the elderly group (Figure 3.7).

No significant modulations were found in theta band power for any condition (p> .05). For alpha and beta bands, increased activity during SEC and UEC at frontal, central-parietal and parietal cortices in the young group was not considered meaningful due to an outlier (determined as Z-score > 3.29) in the data set (Figure 3.7). Results also became non-significant after removing the outlier from the data set. Results for gamma band activity, on the other hand, showed significant main effect for postural condition over central-frontal (p=.033), and central-parietal (p=.047) cortices, indicating modulated neural activity for both groups. Significant group X postural condition interactions were also observed for frontal (p=.048), central (p=.022) and central-parietal cortices (p=.029). Pairwise comparisons for main effects indicated increased activity during UEC condition (p< .05) at all ROI's, when compared to SEC, SEO and Rest conditions. Simple effects analyses showed that the elderly group has higher neural activity during UEC conditions at central-parietal (p=.041), central (p=.035), and frontal cortices (p=.027), when compared to the young group (Figure 3.7).

3.3.3. Sudden changes in postural stability evoke cortical activity.

A series of bivariate correlations were calculated to examine whether short term (over one second period) quantitative changes in balance performance are associated with modulations in cortical activations. We observed apparent changes in the magnitude of correlations between balance performance and cortical activity when TTB values are lower, representing poor balance performance periods (Figure 3. 8). Higher (r=.2 to .85) and

sustained correlations ($p < .05$) were especially observed between TTB and delta band power during the most challenging postural conditions (UEC).

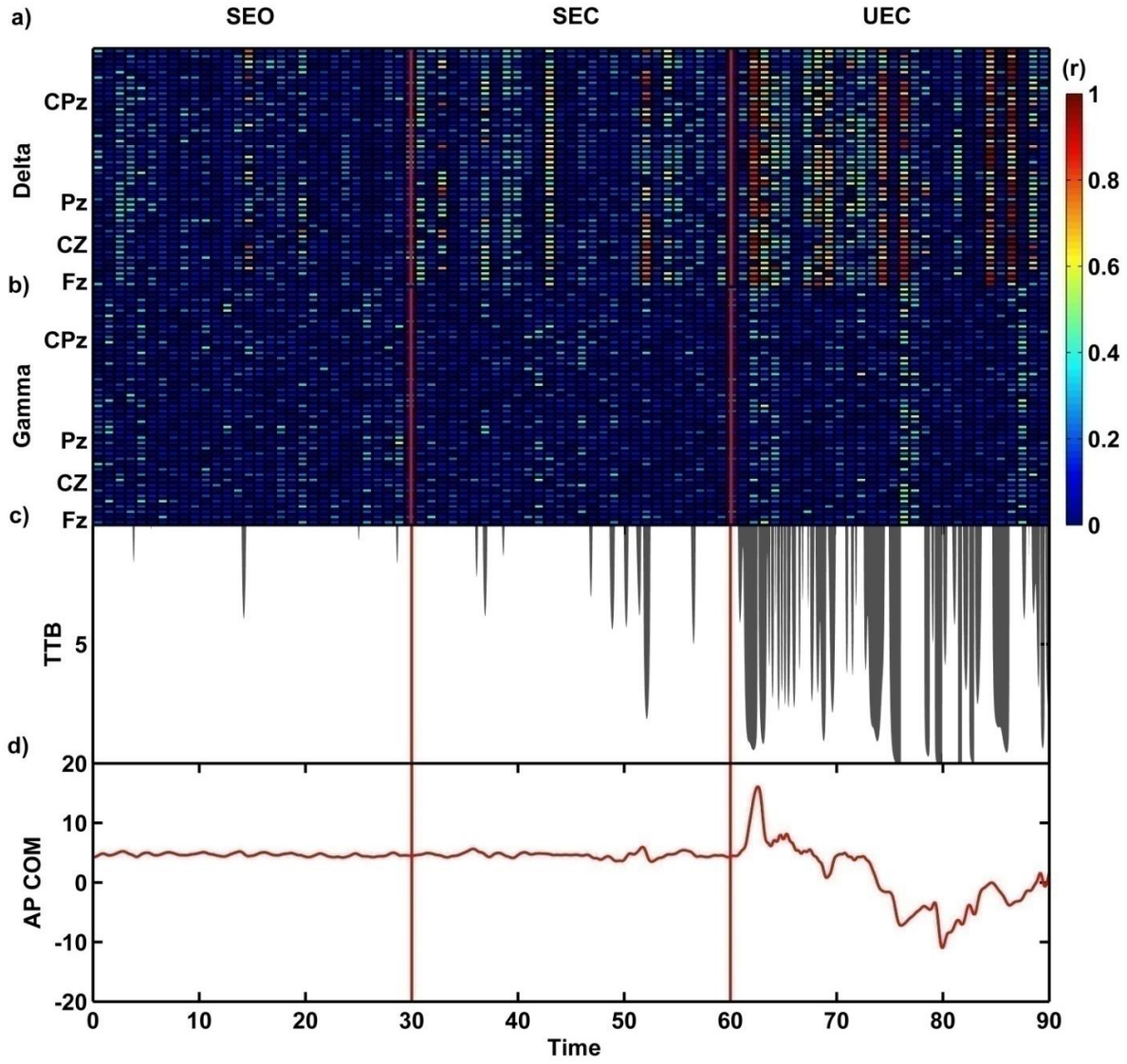


Figure 3.8. Bivariate correlations between time frequency evolution of EEG and TTB time series (panel a and b) computed continuously for each second (n=100), corresponding TTB (panel c), and COM time series (Panel d) during quiet stance postural conditions for a representative elderly subject. The small rectangle boxes with color maps (panel a and b) represent the magnitude of correlation between mean TTB and mean delta/gamma power over one second period for each channel. Each rectangle box over the Y axis represent one EEG channel and the location of representative channels for each ROI on the Y axis were labeled. Computed correlations over each second for were presented over the X axis. Vertical solid red lines represent transition points between postural tasks.

Although correlations for balance performance and cortical activity were lower (p> .05) at gamma band, increased correlations (up to r=.41) were observed at instances when balance was threatened or when the subject experienced a fall (TTB approaches 0; see figure 3. 8, panel c).

To further investigate balance performance and cortical activity associations, postural control (TTB) data were segmented into three stages based on selected TTB thresholds: unstable: TTB ≤ 1s, cautious: 1s<TTB<2s, and stable: TTB≥2s. These identified time points and corresponding EEG data across channels with power values at delta and gamma bands were then clustered by a hierarchical clustering algorithm using Matlab. It must be noted that TTB data clustering resulted in unequal number of sampling especially for unstable balance states (Figure 3.9) in which the young group had substantially less number of TTB samples for the unstable cluster (when TTB <1, Young: *M*samples=173±86 vs Elderly: Msamples=793±287), indicating better balance performance throughout postural trials when compared to the elderly group (Figure 3.9).

Topoplots in Figure 3.10 presents bivariate correlations between TTB and scalp distributions of EEG power in delta and gamma rhythms when upright balance was in unstable (TTB < 1s), in cautious (TTB =1-2s), and in stable (TTB > 2s) states. Scalp distribution of bivariate correlations were all very weak, ranging from r=0.004 to r=0.015, and non-significant (p> .05) for all frequency bands and groups when TTB is >2 s, indicating no association between cortical activity and postural control performance when balance is in stable state (Figure 3.10, Panel c). Although not significant (p> .05), increased correlations were observed in the elderly group between TTB and EEG delta rhythms when upright stance is cautious state (TTB>1s or <2s).

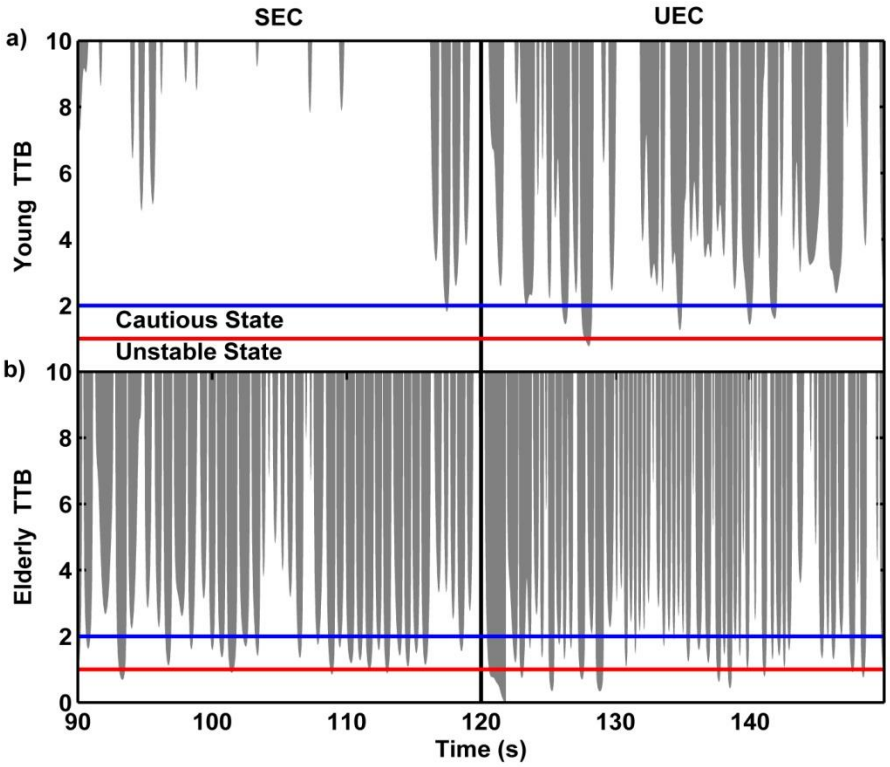


Figure 3.9.TTB time series for a representative Young (Panel a) and Elderly (Panel b) subject for SEC and UEC postural conditions. Unstable (TTB<1) and cautious (TTB > 1 or < 2) balance thresholds were shown with red and blue horizontal lines, respectively. Note that elderly subject spent more time in both balance states than young subject throughout postural trials.

Correlations for the elderly group ranged from r=0.10 to r=0.24 over central (C1, C2, C4 channels) and central-frontal (Fc2, Fc4) cortices (Figure 3.10, Panel b). Similar patterns were also observed between TTB and delta band (0.2-4Hz) filtered raw EEG signals in the elderly group with correlations ranging from *r*=0.14 to *r*=0.27 over frontal (F2, F4) and central cortices (C1, Cz, C2). Correlations for gamma band activity, although increased, were still weak and negligible (up to *r*=0.05). No apparent increase and pattern were also observed for scalp distribution of correlations between TTB and EEG variables in young participants when upright balance is in cautious state (TTB >1s or <2s). However, when upright balance is in unstable (TTB =< 1sec) state cortical activity was found to be related to postural control

performance, especially in the elderly group (Figure 3.10, Panel b). Significant bivariate correlations ($p < .05$) were observed between TTB and EEG delta power (0.2-4Hz) ranging from r=0.25 to r=0.33 over frontal (F3, Fz, F4), central-frontal (Fc1, Fc3), and central (C1, Cz, C2) cortices in the elderly group. For the young group, scalp distributions showed non-significant but increased TTB and EEG delta power correlations (r=0.17 to 0.24) over central-frontal (Fc1, Fc2) and central (C1, C2) cortices. TTB correlations with EEG gamma power (30-50Hz) were also found to be higher, but non-significant ($p > .05$), in the elderly group over central-frontal (Fc1 and Fc2) and central (C1, Cz, C2) cortices, when compared to the young group.

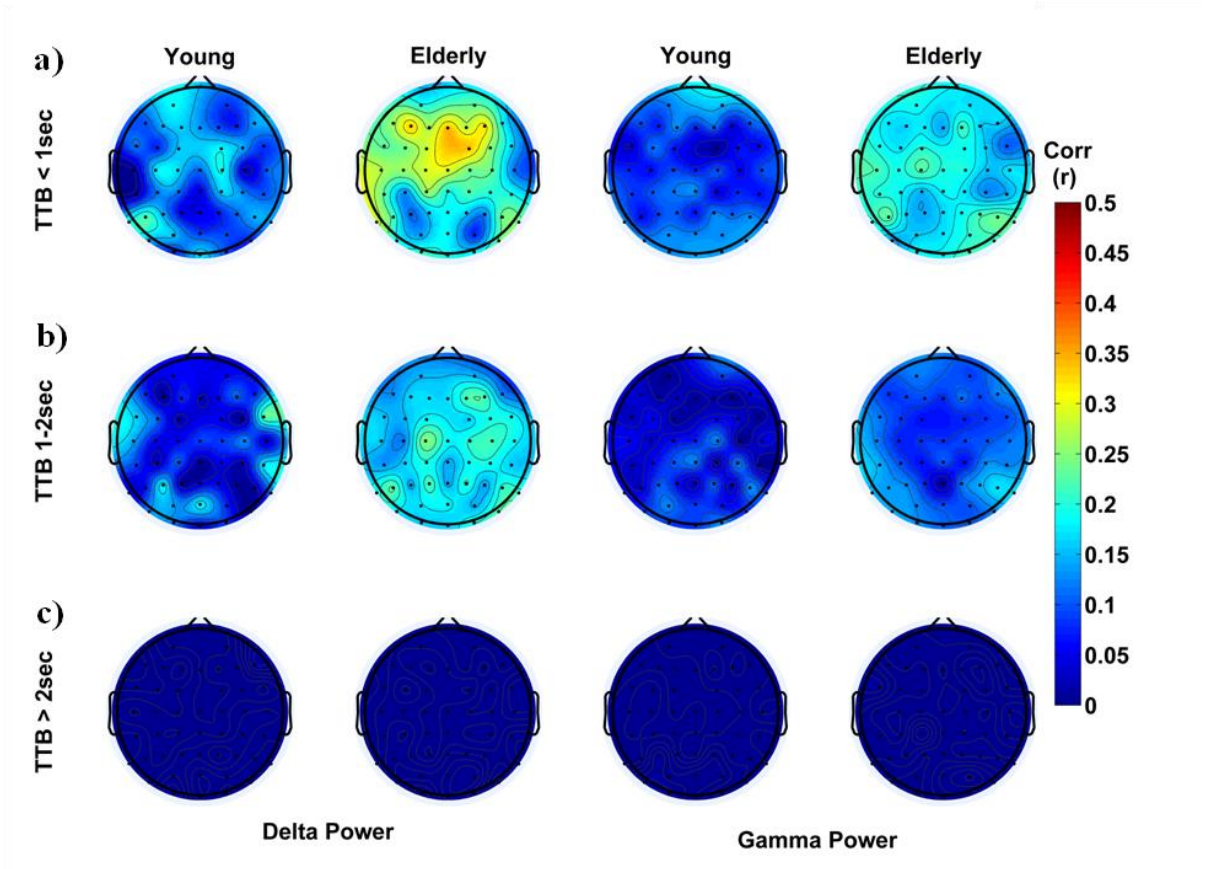


Figure 3.10. Scalp distribution of bivariate correlations between EEG power (Delta and Gamma power) and postural performance when stance balance is in stable (TTB > 2 sec), cautious (TTB 1 to2 sec), and unstable (TTB < 1 sec) states

3.3.4. Cortical activity is associated with balance performance during postural task transitions.

In order to examine whether modulations in cortical activity are sensitive to changes in postural conditions, grand means of correlations between TTB and EEG were calculated across channels and subjects in each group before (pre-transition), during (transition), and after (post-transitions) switching from one postural task to another (See Methods). Scalp distribution of correlation analyses between TTB and EEG power in delta and gamma rhythms during pre-transition (-2: 0sec; final phase of postural condition), transition (0: +2sec unexpectedly switching from one postural task to another) and post-transitions (+2: +5 sec after transition) periods were computed for both groups and shown in Figure 3. 11. When switching from SEO to SEC, TTB and EEG delta power correlations were very weak (p> .05) at pre-transition (r=0.01 to r=0.04), significantly increased at transition period (r=0.10 to r=0.35) over frontal, central-frontal and central cortices, and then again reduced to pre-transition values at post-transition period in elderly group (Figure 3.11, Panel a).

Although similar correlation patterns were observed for the young group, the magnitude of change in correlations was not significant (p > .05) during transition periods. Results for SEC to UEC transition phases revealed highest changes for TTB and EEG delta power correlations in both groups (Figure 3.11, Panel a). Similarly very weak correlations (p > .05) were observed during pre-transition period (r=0.01 to r=0.02) both in the elderly and the young group. However, when postural task was unexpectedly switched from SEC to UEC, significantly increased correlations were found in both groups during transition period (p <. 05). Scalp distributions for elderly people revealed strong correlations over frontal (r=0.59 to r=0.73) and central-parietal (r=0.57 to r=0.74), and moderate to strong

correlations over central-frontal (r=0.44 to r=0.70) and central (r=0.55 to r=0.65) cortices. During post-transition (+2: 5sec) period, on the other hand, significant correlations reduce or disappear over the entire scalp (p> .05). Similar patterns were also observed in young people, although lower increases were found during transition period compared to the elderly group. Results for the young group also showed that TTB and EEG delta band correlations were very weak during pre-transition (r=0.03 to r=0.04), significantly increased during transition period over frontal (r=0.45 to r=0.56), central-frontal (r=0.58 to r=0.60) and central (r=0.42 to r=0.63) cortices, and finally disappeared during post-transition period over the entire scalp. Scalp distribution of TTB and EEG gamma power correlations fail to reveal significant results (p> .05) for any transition period both in the elderly and the young group (Figure 3.11, Panel b).

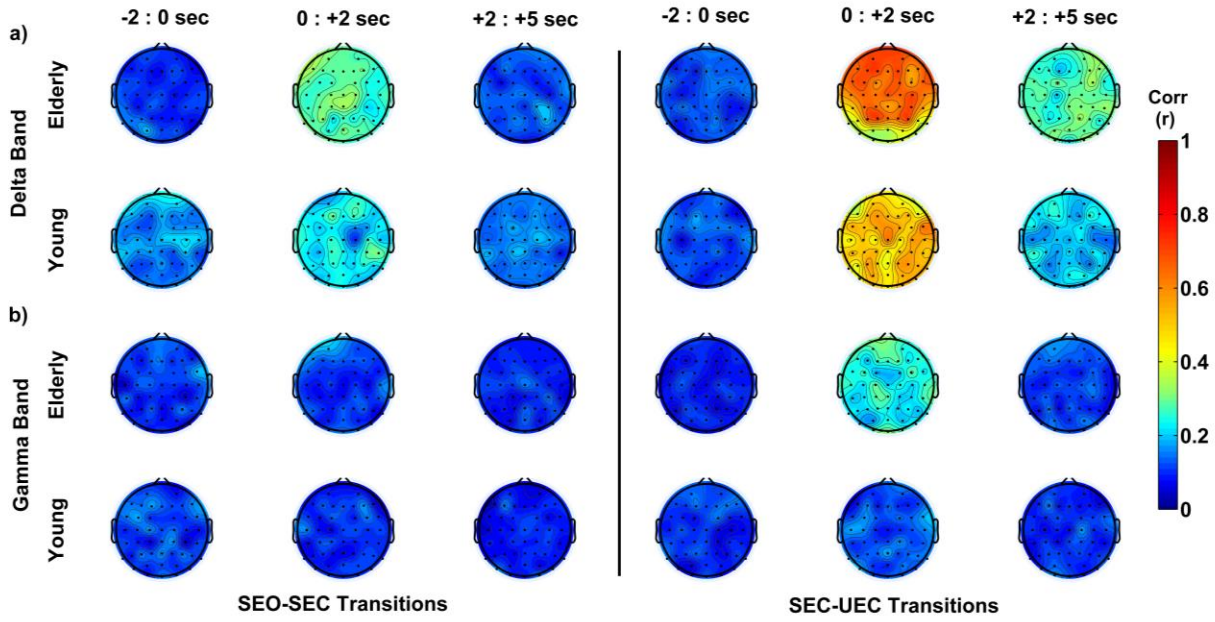


Figure 3.11.Scalp distributions of EEG and TTB correlations for transition periods during quiet stance conditions. Correlations were presented as group means, and calculated based on EEG power and TTB scores during pre-transition (2: 0 sec with n=200 samples), transition (0:+2 sec with n=200 samples), and post transition (2:+5 sec with n=300 samples) periods.

Experiment 2:

3.3.5. The latency and magnitude of perturbation evoked cortical potentials changes by age.

A representative example of TTB, EEG and EMG responses to postural perturbation (toes-up rotation) in a healthy young subject are shown in Figure 3.12.

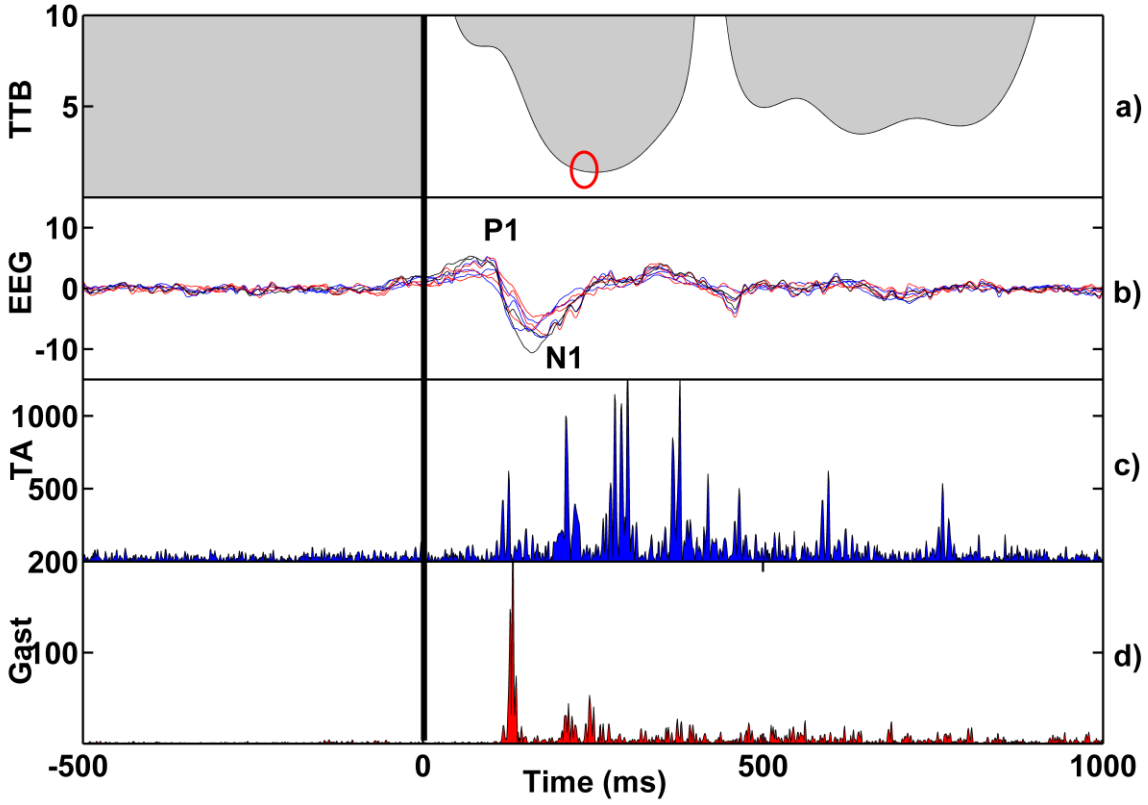


Figure 3.12. Postural (TTB), Cortical and Muscular responses to a perturbed balance (toes up rotation) in a representative young subject. Red circle (Panel a) shows the worst postural performance moment when the subject is close to falling. Panel b shows perturbation evoked potentials (PEPs) over central (C3, C1, Cz, C2, and C4) and central-parietal (Cp3, Cp1, Cpz, Cp2 and Cp4) cortices. P1 and N1 peak potentials were shown for the vertex (Cz) with a black line. Panel c and panel d shows EMG activations on two postural muscles (TA and Gast) respectively.

TTB started to decrease right after the perturbation, was below the 10 sec threshold 48 ms following perturbation, and reached to the minimum value, representing worst balance performance instance, 252 ms after the perturbation (Figure 3.12 panel a, red circle). Cortical potentials first showed a positive deflection around 36 ms followed by positive potential peaks with a latency of 69 ms post-perturbation representing P1 like cortical responses (Figure 3.12 panel b). A larger negative deflection was observed over central and central-parietal electrodes with a peak latency of 157 ms post perturbation representing N1 responses. EMG traces showed activations at the Gast and TA muscles around 120 ms post perturbation, representing sub-cortically initiated medium latency responses (Figure 3.12 panel c and d). TA muscle, on the other hand, was re-activated around 200 ms and peaks at 300 ms following the toes up rotation. The latter long latency activations in TA to toes-up perturbations represent cortically originated motor responses and resulted in a functional recovery from postural perturbations (Figure 12, Panel a, see change in TTB after TA muscle activation).

Figure 3.13 shows grand means of perturbation evoked cortical potentials (PEPs) over frontal, centro-frontal, central centro-parietal and parietal electrode locations for a representative young and elderly subject. One obvious observation is that the elderly subject has longer PEP latencies when compared to the young subject. Central and central-parietal cortices seem to produce stronger PEP responses as compared to parietal and frontal cortices. We also observed the P1 responses disappear for the elderly subject in frontal channels (F1, Fz and F2) and for both groups in posterior channels (P1, Pz, and P2). These regions, therefore, were not included in statistical comparisons.

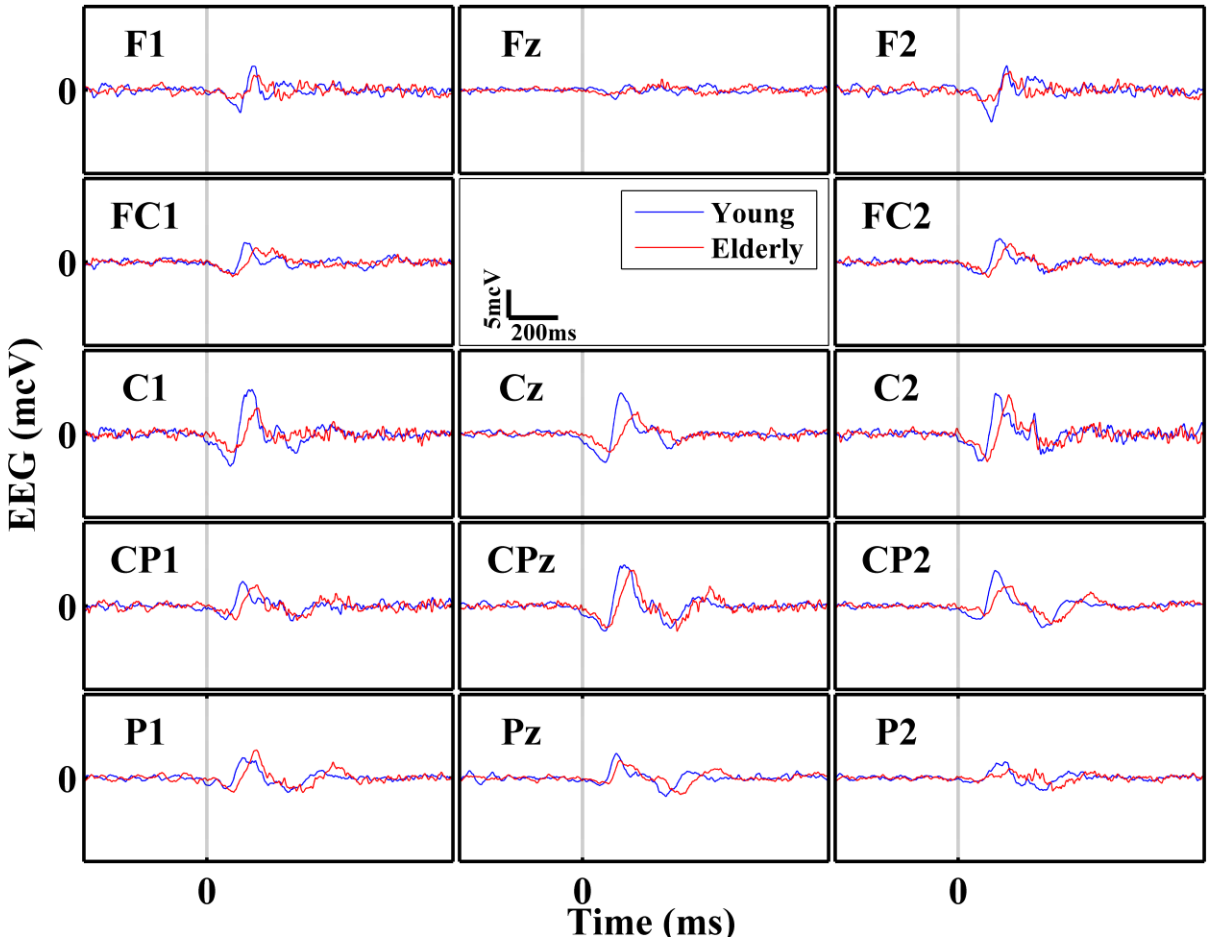


Figure 3.13. PEP responses over frontal, central-frontal, central, central-parietal and parietal cortices for a representative young and elderly subject

Topographical distribution of grand mean PEP latencies (panel b) and PEP magnitudes were shown in figure 3.14 for both groups. A series of variance analyses were conducted to examine PEP latency and amplitude differences between groups for each ROI's. Statistical analyses include grand means of FC3, FC1, FC2, FC4 channels for central-frontal, C3, C1, Cz, C2, C4 channels for central, and CP3, CP1, CPz, CP2, CP4 channels for central-parietal cortices. Results showed that postural perturbations evoked earlier ($p < .05$) P1 responses in the young group over central (Young: *M*latency=81±07ms vs Elderly:

*M*latency=115±13ms) and centro-parietal cortices (Young: *M*latency=73±11ms vs Elderly: *M*latency=112±12ms), when compared to the elderly group (Figure 3.14, P1 latency). Similarly, N1 responses were also observed earlier ($p < .05$) in the young group over centro-frontal (Young: *M*latency=186±19ms vs Elderly: *M*latency=238±23ms), central (Young: *M*latency=167±16ms vs Elderly: *M*latency=219±21ms), and centro parietal (Young: *M*latency=171±20ms vs Elderly: *M*latency=226±24ms) cortices. N1 amplitude differences, on the other hand, was found to be significantly higher ($p < .05$) only over the central region (Young: *M*amplitude=16±3mcV vs Elderly: *M*amplitude=11±2mcV) in the young group (Figure 3.14). No Significant differences were found for P1 response amplitudes ($p > .05$).

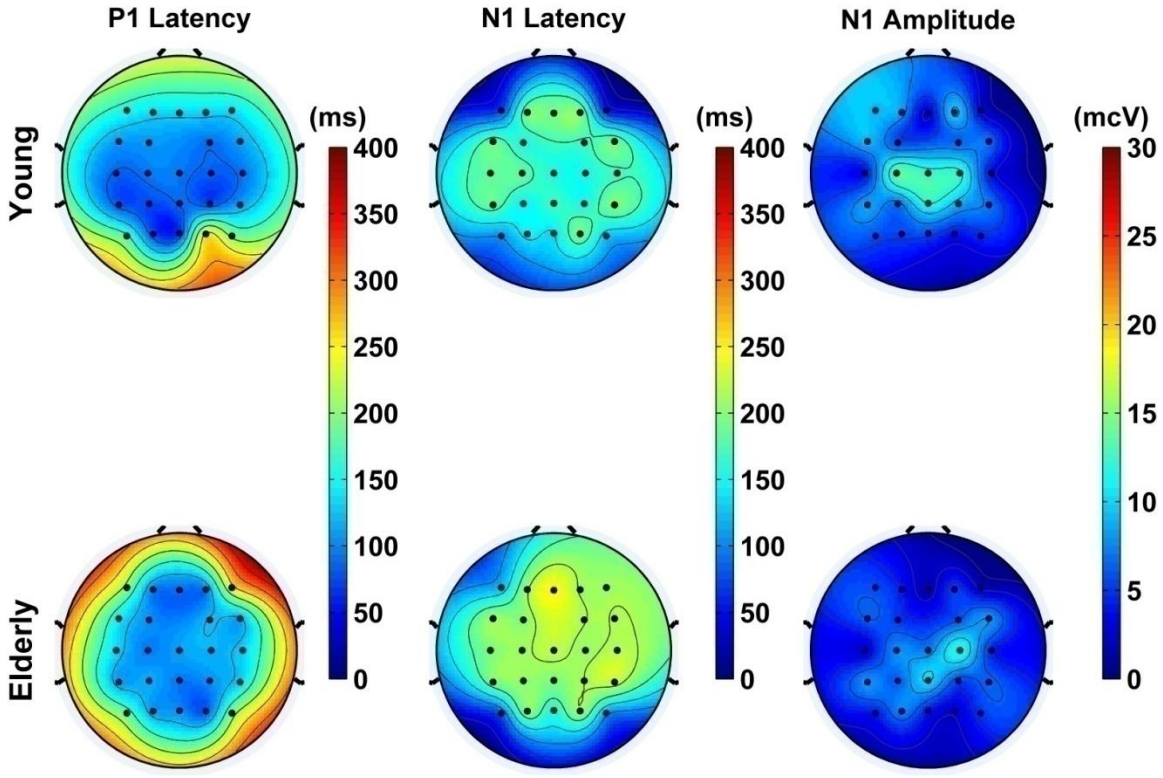


Figure 3.14. Scalp distribution of Grand mean P1 and N1 latencies, and P1-N1 amplitude differences.

Finally, peak EMG response latencies of TA, Gast, BF and VL muscles to postural perturbations were compared between groups (Figure 3.15). The young group have significantly shorter (p< .05) peak EMG latencies for TA (Young: *M*latency=306.16±26.77 vs Elderly: *M*latency=357.16±37.69) and Gast (Young: *M*latency=294.01±42.57 vs Elderly: *M*latency= 371.23±17.23) muscles in response to postural perturbation. However, when peak TA and Gast activations were referenced to N1 responses over central cortices in each group (the latency from N1 response to peak EMG in TA and Gast), no significant differences (p > .05) were found between groups both for TA (Young: *M*latency= 139.01±11.22 vs Elderly: *M*latency= 133.23±18.39) and Gast muscles (Young: *M*latency=117.01±10.52 vs Elderly: *M*latency= 133.11±14.53). Although similar patterns were found for VL and BF muscles with shorter peak EMG latencies in the young group, analyses failed to found significant differences (p>.05) when compared to the elderly group (Figure 3.15).

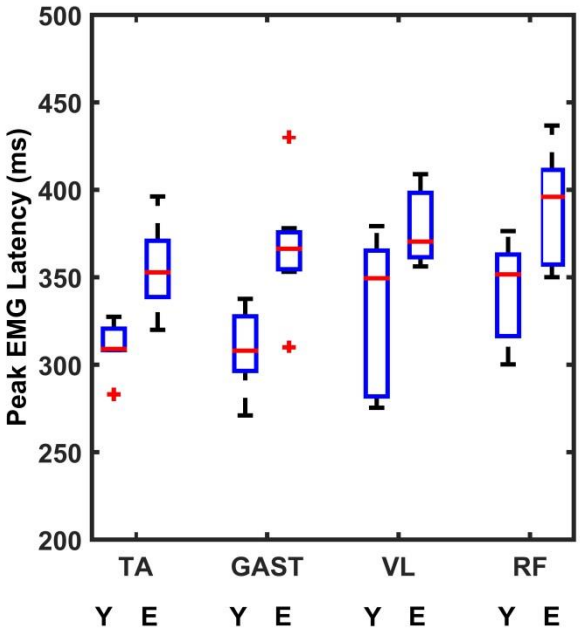


Figure 3.15. Boxplots showing grand mean Peak EMG latencies for Tibilalis Anterior (TA), Gastrocnemius (Gast), Vastus Lateralis (VL), and Rectus Femoris (RF) muscles both in young (Y) and elderly (E) groups. Red horizontal lines represent median values with edges represent 25th and 75th percentiles**.** Outliers were marked with red plus signs.

3.4. Discussion

We designed the current study to (1) understand cortical representations of human upright stance control during challenging sensory conditions and biomechanical perturbations, and more importantly, (2) age related changes in cortical control of upright stance. In general, our results support many previous reports suggesting involvement of cerebral cortices in human upright stance control (Slobounov et al. 2005; Slobounov, Sebastianelli & Moos, 2005; Slobounov, Harlett & Newell, 2008; Slobounov et al. 2009). In experiment 1, we demonstrate increased cortical activations in delta and gamma oscillations, primarily over central-frontal, central and central-parietal cortices. To our knowledge, this study is the first to show age differences in balance related cortical activations during continuous postural tasks with challenging sensory conditions. While increased delta rhythms were observed in both groups during challenging sensory conditions, elderly individuals also showed increased gamma activity over sensorimotor and parietal cortices, when compared to younger group. Correlation analyses also suggest that increased cerebral activity became more relevant to the control of COM dynamics when upright stance is threatened, especially in the elderly group. Finally, experiment 2 confirms the neurophysiological sources of prolonged compensatory responses to perturbed balance in elder individuals by showing increased delays both in cortical and muscular activations following postural perturbations.

3.4.1. EEG signal modulations during challenging postural conditions.

Although no consensus has yet to be established on the frequency specifications, there have been many recent studies reporting power modulations in EEG signals at different frequency bands during upright stance control tasks in humans (Slobounov et al. 2005, Slobounov et al. 2009; Sipp et al., 2009; Hülsdünker et al. 2015). In a recent study, for

example, Hülsdünker et al (2015) reported increased cortical theta activity (4-7 Hz) over frontal, central and parietal cortices during challenging balance tasks in healthy male university students. Sipp et al. (2013) also reported increased spectral power in theta band in anterior cingulate, anterior parietal, superior dorsolateral prefrontal and medial sensorimotor cortices along with decreased beta power (12-30 Hz) over sensorimotor cortices during beam walking task. In a series of studies, Slobounov and colleagues (2005, 2009), focused on cortical activity modulations when subjects are falling or when upright stance balance is threatened. They reported decreased alpha power (8-12 Hz) over occipital, and increased gamma activity (30-50 Hz) over parietal cortices preceding unstable balance states. Taken together, it is noticeable that previous research relating EEG oscillations to upright postural control have mostly focused on theta, alpha, beta and gamma bands and generally attributed balance related modulations in EEG recordings to the increased attentional requirements or cognitive demands of the challenging balance tasks. In particular, increased cortical theta band activity over sensorimotor and superior dorsolateral prefrontal cortices is reported to be generated in the anterior cingulate cortex (ACC) and assumed to be sub-serving to sensory information transformations for error detection mechanisms in feed-forward control of human upright stance (Sipp et al., 2013). Modulations on the alpha and gamma band cortical activations, on the other hand, were interpreted based on the cognitive aspects of the task such as allocation of attention to the demanding tasks and sustained arousal to monitor task performance (Slobounov et al., 2005, 2009).

Using a similar postural task paradigm, our results are in line with Slobounov et al. (2005) by showing significantly increased gamma activity during reduced sensory conditions (UEC) over central, central-parietal and frontal cortices in older individuals. In general, fast

oscillations in the cortex (> 30 Hz) are considered to be related to focal neural computations due to shorter temporal processing windows at high frequencies (Harmony, 2013). Regarding functional correlates of cortical processing, modulations in gamma power is attributed to focused arousal and sustained attention during both cognitive and motor tasks (Basar et al., 1995; Slobounov et al., 2005; Slobounov et al., 2009). Considering our findings for continuous balance tasks, increased gamma power among older adults during challenging postural conditions, thus, may reflect increased allocation of attentional sources to postural task as compared to healthy young adults.

Many posture-dual tasking studies in postural control have reported impaired cognitive performance during concurrent postural tasks among older adults (Brauer, Woollacott & Shumway-Cook, 2001; Brown, Shumway-Cook & Woollacott, 1999; Rapp, Krampe & Baltes, 2006; Redfern et al. 2001; Shumway-Cook & Woollacott, 2000; Teasdale & Simoneaau, 2001). Optimal performance in posture-dual tasking conditions requires allocating sufficient cognitive sources to each task, and impairments in secondary task performance (cognitive) indicates either declined attentional capacity or increased attentional demands, and thus cortical involvement, for primary postural tasks in the elderly population (Shumway-Cook & Woollacott, 2000). Our results not only support but also extended these behavioral findings by showing modulated gamma activity over frontal, sensorimotor and parietal cortices, indicating that postural tasks become more challenging for older adults, and thus, require more attentional capacity and cortical involvement when sensory information from visual and proprioceptive afferents are compromised.

In addition to increased gamma power in older adults our experiments also consistently exhibited increased delta band power (0.2-4 Hz) over central-frontal, central and

central-parietal cortices during the most challenging upright stance conditions (See figure 3.6). Although previous studies on cortical control of human stance have mostly reported EEG modulations in the theta band (4-7 Hz) and higher frequencies, our results regarding delta band modulations corroborate with recent research showing involvement of slow cortical oscillations in the control of coordinated multi-joint movements (Bradberry et al., 2010; Bulea et al., 2014; Gwin et al., 2010; Presacco et al., 2011; Agashe et al., 2013). In particular, recent research focusing on understanding neural signatures of movement control during various multi-joint tasks has consistently associated changes in delta band oscillations with planning and execution of coordinated body movements. It has been, for example, reported that low frequency EEG activations represents control parameters for various kinematics including direction (Liao et al., 2007; Vuckovic and Sepulveda, 2008; Waldert et al., 2008; Robinson et al., 2013), velocity (Bradberry et al., 2010), and type (Agashe & Contreras-Vidal, 2013) of multi-joint upper extremity movements. Regarding locomotion tasks, delta band oscillations have been shown to contain information about movement kinematics such that lower limb trajectories can be predicted and reconstructed by using delta band EEG with reasonably well accuracies up to 80% during continuous walking (Bradberry, Gentili & Contreras-Vidal; 2011; Presacco et al., 2011), and running (Gwin et al., 2010). In another line of research, pre-movement delta band signal features were extracted to successfully classify upcoming locomotive movement intentions such as start and stop walking (Kilicarslan et al., 2013) and 'sit to stand' or 'stand to sit' posture transitions preceding walking (Bulea et al., 2014). Our results, which showed modulated EEG in delta band during challenging postural conditions, also support these findings and provide preliminary evidence that slow EEG oscillations as low as 1 to 2 Hz can also be sensitive to

the changes in postural state of the body and involve in controlling motor aspects of human upright stance.

It must be noted that, we quantified modulations in EEG power by calculating grand mean of time-frequency wavelets across trials and channels for each postural condition, corresponding to 60 second periods of testing, to represent overall modulation of EEG during postural tasks. Broadly distributed increases in delta band activity over large population of neural networks during relatively longer periods of testing (60 sec) may also represent an overall change in the cognitive state of the person to reflect temporary transitions from sub-cortical (automatized) to cortical (controlled) processing strategies for efficient upright stance control. Optimal balance performance in our experimental design primarily depends on cognitive recognition of sudden and unexpected changes in continuous postural task conditions. This cognitive recognition would allow subjects to utilize cortical control strategies when challenging postural tasks require controlled processing of (1) sensory information, and (2) following compensatory motor adjustments within the close loop postural control system. Past research on neuromotor modeling of human upright stance control suggests that the nervous system relies on a close loop control strategy with an internal model of body mechanics in which current sensory information (feedback) is continually compared with expected sensory predictions generated by feed forward component, with a certain error during comparisons initiates corrective motor responses (Ahmed and Ashton-Miller 2005; 2004; 2007). Regarding cortical correlates of this close loop control system, increased delta over central-parietal cortices may represent cortical monitoring of posture related sensorimotor and vestibular feedback (Figure 3.6). Our results have also shown significant delta power changes over frontal and central-frontal electrodes

during challenging postural conditions. Cortical involvement over these brain regions to postural control is likely to reflect error detection and decision making computations when upright stance is threatened. Indeed, previous neuroimaging research has suggested that the anterior cingulate gyrus (ACC), located at ventral forebrain has strong connections to pre-frontal and pre-motor cortices, and may mainly function as an active monitoring unit of error recognition system during motor tasks (Allman et al., 2001). Accordingly, recent EEG work on neural basis of upright stability and walking have reported increased spectral power from source clusters located over or near ACC during unstable balance on one leg standing or walking (Sipp et al., 2013). Our findings regarding increased delta band activity over frontal and central-frontal regions seems to corroborate with these studies that, when subjects experience an unexpected switch from stable to unstable postural conditions, a sudden change in COM sway dynamics (see Figure 3.5, second panel) may change the rate of sensory information signaling from parietal to prefrontal cortices, specifically to ACC, and thus activates cortical error detection mechanism for upright stability. This explanation supports the time-frequency evolution of EEG data provided in figure 3.5 for a representative young subject that a sudden change in COM position toward anterior stability limits (see Figure 3.5, second panel), is accompanied by increased EEG power in lower delta band (Figure 3.5a, first panel) over the Cz electrode, indicating recognition of an unstable postural state. It is also important to note that this increased delta band activity may also possibly reflect motor computations for late phase compensatory postural adjustments and voluntary postural muscle activations (Figure 3.5a, third panel). These preliminary findings, therefore, should be further confirmed through additional research focusing on source analyses of EEG signal modulations constrained with structural magnetic resonance imaging data. These

analyses would allow us to better understand temporal relations among kinematic, cortical and neuromuscular responses during unstable postural conditions.

3.4.2. Age related differences in posture-related delta band activity

Although increased cortical activity in delta band was present in both groups, younger adults had slightly higher cerebral delta activations particularly over sensorimotor cortices in central regions and dorsolateral prefrontal cortices in central-frontal electrode sites. Currently, however, we do not have clear understanding regarding the underlying neuromotor mechanisms of age related differences in posture control related delta activity, , except that these slow-cortical potentials are related to motor intent or movement (Bradberry et al., 2010; Bulea et al., 2014; Gwin et al., 2010; Presacco et al., 2011; but see discussion below). One possible reason for relatively low delta activity in older adults could be attributed to functional declines in sensorimotor processing due to aging (Andrews-Hanna et al. 2007). Scalp distributions of time-frequency wavelets in figure 6 provide some preliminary support for declined sensorimotor processing in the elderly. Although we observed increased delta activity and gamma activity over frontal and central-frontal regions during UEC postural condition, parietal cortices responsible for cortical processing of somatosensory and vestibular afferents remains relatively silent in older adults (see Figure 3.6, second row). The lack of relative involvement in this region may also negatively affect cortical computations required for error estimation at dorsolateral prefrontal cortices including anterior cingulate cortex.

We should also mention that continuously challenging postural tasks (30 seconds of UEC postural condition) require considerable amount of perceptual integration, and thus,

continuous synchronization of many distant neural networks in order to detect constantly changes in upright stance orientation in relation to the gravitational vector . To date, only a few studies have attempted to relate the delta band with various cognitive and perceptual processes (for a detailed review see Harmony, 2013). Although high amplitude and slow EEG waves have been recognized as the main characteristics of non-REM sleep, Arellano and Schwab (1950) were the first to report increments in EEG delta band during the performance of cognitively demanding tasks. Since then, many neuroscientists have considered delta activity as a part of an inhibitory cognitive state that is involved in synchronization of distant neural networks while practicing automatized behaviors (Vogel et al., 1968; Knyazev, 2012), attending to and detecting motivationally relevant stimuli during cognitive processing (Knyazev 2007; Knyazev et al., 2009), selective attentional processing of threatening stimuli (Putman, 2011), and behavioral inhibition (Kamarajan et al., 2004; Knyazev, 2007). In order to explain how high amplitude slow EEG oscillations are associated with cognitive processing, it has been postulated that sustained delta activity during cognitively demanding tasks would selectively suppress non-relevant neural networks through functional connectivity at the global scale, and thus, inhibit neural activity that may distract or interfere with proficient execution of perceptual tasks (Harmony, 2013; Vogel et al., 1968). Considering the possibility that even disease free normal aging is accompanied by declined coordination among large-scale cortical connections, due to degenerations in white matter integrity (Andrews-Hanna et al. 2007), it is reasonable to conclude that these structural deformations may also be reflected by age associated changes in delta band activity during cognitively demanding motor tasks.

Taken together our time-frequency analyses of EEG data support the idea of cortical involvement to upright stance especially during challenging sensory-motor conditions. However, whether these cortical activations have functional role on balance recovery in elderly people is debatable and further research is needed to identify cortical correlates of postural control both in elderly fallers and non-fallers.

4.4.3. Cortical activity is coupled with postural performance when balance is threatened.

Previous studies on cortical mechanisms of postural control have suggested the idea of *"neural detectors"* referring specialized set of neural networks for recognizing postural instability in humans (Slobounov et al., 2000; 2005; 2006; and 2009). Specifically, research findings showed that: (1) subjects with high postural stability were also have greater cortical and sub-cortical activations at multiple areas of the brain when they were asked to recognize unstable postures during functional MRI scanning (Slobounov et al., 2006), and (2) more recently, significantly higher spectral power in low theta (4-5 Hz), and gamma (30-50 Hz) frequencies over anterior cingulate cortex and pre-frontal cortices during unstable balance when subjects were standing on one leg (Slobounov et al., 2009). In our study, we further examined whether short time changes in COM dynamics (one second) is related to cortical activity. First, we found significant correlations (r=0.4 to 0.9) between cortical activity, especially at the delta band activity, and postural performance at instances of low TTB scores, while no such correlations were present during stable postural moments, indicating activated cortical monitoring system when upright stance balance is threatened (Figure 8). Second, we segmented postural performance into unstable, cautious and stable balance states based on TTB thresholds and showed that both delta and gamma band activity over frontal

and central-frontal cortices was low-to-moderately correlated (r=0.2 to 0.4) with the orientation of COM in antero-posterior direction when TTB is lower than 1 second (Figure 9, upper panel). Finally, we focused on transition periods, representing last 2-seconds of an ending postural trial and first 2-seconds of the following postural trial, and found moderate to high correlations (r=0.5 to 0.7) between delta band EEG and TTB when unexpectedly switching postural tasks from stable surface support to swayed surface support conditions (Figure 10, upper panel).

Regarding group comparisons, we also found that cortical activity and postural performance correlations were higher in older adults, when compared to young subjects. At the first glance, this finding may seem counterintuitive when considering relatively low delta band activity in the elderly group during challenging postural conditions (Figure 3.6). One might expect that increased delta oscillations should also lead higher correlations between cortical activity and postural performance in the young group if cortical centers involves in active monitoring of postural sway. This can be explained by (1) obvious postural performance differences, and (2) unequal number of unstable balance state moments (TTB < 1) between young and older adults especially during challenging postural conditions. We noticed that although TTB scores decreased during transition periods, they also quickly returned to pre-transition values and remained relatively stable throughout the rest of the trial, indicating fast achieved functional recovery for postural control in young adults (figure 3.9). This, however, results in low bivariate correlations due to increased values in one factor (delta band activity) but relatively stable values in another factor (TTB scores) within the overall trial. As for the elderly group, on the other hand, unexpected postural task transitions not only cause sudden decreases but also persisting fluctuations in TTB scores, and

sometimes falls, within the entire postural trial, thus leading significantly moderate and '*negative*' correlations between cortical activity and postural performance in general. Another reason for higher correlations in the elderly group might be due to significantly low number of unstable balance state moments (on? average 173 data points corresponding TTB < 1) in the young, when compared to the elderly group (on average 793 data points corresponding TTB < 1). Such a sampling difference in comparisons may cause range restriction problem for correlation analyses. We, therefore, suggest that these high cortical activity-postural performance correlations in elderly people should be interpreted with caution. Overall correlation analyses seems to suggest that relatively increased cortical involvement during challenging postural conditions may not be sufficient to achieve functional balance recovery in older adults. Further research is needed to examine how modulations in cortical activity changes activation patterns in postural muscles both in elderly fallers and non-fallers.

3.4.4. Older adults have longer cortical and muscular response delays to postural perturbations

By simultaneously monitoring EMG activity from postural muscles and cortical activity from whole-scalp EEG recordings during unexpectedly perturbed balance conditions, we examined age related changes in cortical processing of perturbation related afferents and following corrective motor responses. Our main results consistently showed that older adults have prolonged PEP latencies, when compared to younger subjects, indicating a critical temporal delay regarding the perceptual recognition of threatening postural stimuli. Average P1 peak latency from the electrodes located over central-parietal (Cp1 Cpz and Cp2) and parietal cortices (P1 and Pz) in older adults was found to be 31 ms longer than the P1 responses in young adults. P1 is reported to be a relatively small amplitude response, and

assumed to reflect the initial cortical representation of sensory information related to postural perturbations (Duckrow et al. 1999, Quant et al. 2004, 2005). Although, previous studies (Quant et al., 2004; 2005) recording PEPs only from the vertex electrode (Cz) did not report P1 cortical responses due inconsistent observations across trials and subjects, our whole-scalp EEG recordings revealed greater P1 amplitudes over central (C1, Cz, C2) and central-parietal (Cp1, Cpz and Cp2) regions representing somatosensory and motor cortices.

Similarly, N1 responses in older adults were observed with considerable delays relative to young adults over central and central-parietal cortices with prolonged latencies of 47 and 51ms, respectively. Age related N1 latency differences could be attributed to well-documented deformations both in sensory (i.e. decreased myelinated fiber density) and neurocognitive mechanisms (i.e. declined white matter integrity) of aging postural control system (Jacobs & Love, 1985; Ota et al., 2006). Using variety of postural task conditions, however, N1 response was reported to be independent from corrective motor responses (Adkin et al. 2006), but involved in cortical processing of proprioceptive and cutaneous inputs (Dietz et al. 1985), and can be modified depending on predictability of postural perturbations or availability of sensory modalities (Dietz et al. 1985; Adkin et al., 2006), all of which suggesting sensory system deformations as underlying mechanism of modulated N1 response. In a recent study, for example, Adkin et al. (2006) reported that the N1 responses observed during unpredictable perturbations were absent in the predictable trials, although motor responses were present in both condition. These findings suggests that the N1 response is related to higher order cortical processing of perturbation related sensory information rather than planning and execution of corrective motor responses.

Earlier studies on aging neurophysiology proposed that even normal aging can cause deformations in myelinated nerves which account up to 10 to 20 ms conduction delays in peripheral afferences (Dorfman & Bosley, 1979; Allison et al., 1983; Kakigi, 1987). In their study, Duckrow and colleagues (1999) also examined age related differences in PEPs and found relatively comparable results with neurophysiological reports that older people have prolonged P1 (22ms longer) but similar N1 responses compared to young subjects. However, the latency of relative P1 and N1 delays in older adults observed in our study were considerably longer (52ms vs 22ms) than the delayed P1 responses reported by Duckrow et al. (1999).These increased temporal delays, therefore, cannot be solely explained by impaired peripheral nerves due to aging. Longer delays in P1 and N1 responses among older adults may be explained by differences in experimental protocols. Duckrow and colleagues (1999) employed 36 to 72 consecutive forward translations with random intervals (1.5 to 2s) to perturb upright stability in older adults. Although the timing of perturbations was semi-random, the type of postural task was constant for all trials (forward translation only) and thus remained predictable. Prior knowledge regarding the characteristics of upcoming postural events might alter the cortical processing strategies associated with upright stability. There is a high possibility for older adults to become adapted to consecutive forward translations and may adopt an anticipatory control strategy which may allow them to predict sensory consequences of subsequent postural perturbations. We, on the other hand, applied four different types of postural perturbations (toes up and toes down rotations, backward and forward translations) with fully randomized order and timing (2 to 5s) to minimize adaptation effects. Unpredictable postural perturbations, employed in our study, seem to require longer central processing for perceptual recognition of perturbation related sensory afference. We,

therefore, concluded that prolonged P1 and N1 response delays in older adults can be attributed to impairments in aging sensory systems both at the peripheral and cortical levels. Future studies, however, should further examine spatial-temporal changes in PEPs by varying postural task characteristics (predictable timing and type vs unpredictable timing and order) both in elderly fallers non-fallers.

Finally, our analyses of EMG activation patterns during stance perturbations revealed longer latencies in voluntary postural muscle responses for older adults (on average 20 to 60ms longer latencies in older adults) similar to that of observed in N1 response comparisons. Furthermore, when EMG activations were referenced to N1 responses in both groups, no differences were found in postural muscle activation latencies between older and young adults. Taken together these results seem to suggest that, rather than motor system malfunctioning, impairments in perceptual processing of sensory afference forms the basis of prolonged postural responses to perturbed stance conditions in non-faller older adults. Future research with longitudinal designs should target both elderly fallers and non-fallers, and employ functional balance exercises as therapeutic interventions to monitor changes in PEPs and motor responses perturbed balance.

CHAPTER IV

Manuscript II: Cortical activity modulations underlying age related performance differences on posture control dual tasking conditions.

4.1. Introduction

Daily life human activities often require performing various motor and cognitive tasks concurrently and thus often involve continuous integration of multiple neurocognitive processes and neuromotor control systems. In such multi-tasking situations, upright stance is considered to be a baseline motor skill to accomplish a variety of goal directed motor and cognitive tasks (Haddad et al. 2013). Although control of upright stance is a seemingly effortless and autonomous motor task predominantly governed by spinal and sub-cortical networks in the optimally functioning nervous system, it may become a challenging and attentionally demanding task with increased cognitive involvement at the cortical level, in the aging nervous system (Woollacott, & Shumway-Cook, 2002).

Dual tasking paradigms, originating from shared attention theory, have been commonly used to investigate attentional demands of postural control (Brown & Shumway-Cook, 1999; Brauer, Woollacott, & Shumway-Cook, 2002) as well as the interaction between cognitive tasks and postural control performance in relation to aging (Boisgontier et al., 2013). A majority of studies indicated impaired performance either in postural, cognitive or both tasks during challenging dual task conditions (Doumas, Rapp & Krampe, 2009; Makizako et al., 2013; Olivier et al., 2010; Teasdale & Simoneau, 2001; Van impe et al., 2013; Woollacott & Velde, 2008). In regards to dual task cognitive performance, it has generally been reported that challenging postural tasks impair cognitive performance especially in the elderly people, as compared to healthy young adults (Brauer, Woollacott &

Shumway-Cook, 2001; Brown, Shumway-Cook & Woollacott, 1999; Rapp, Krampe & Baltes, 2006; Redfern et al. 2001; Shumway-Cook & Woollacott, 2000; Teasdale et al. 1993). The general consensus is that there is a shift in the control of upright stance from supra-spinally originated neural pathways to higher order cortical networks in elderly people, suggesting that elderly people may recruit more cognitive sources than younger counterparts in a given postural task, and thus exhibit impaired dual-tasking performance during challenging task conditions.

Many previous dual tasking studies also reported increased postural sway when attentional requirements of concurrently performed cognitive tasks exceed the total information processing capacity of the individual (Dault et al., 2001; Remaud et al., 2013). Decreased cognitive or postural performance during dual tasking in elderly people is generally attributed to the well-known deteriorative effects of aging on cognitive processing and sensorimotor functioning. For example, due to the impairments in sensorimotor tracts underlying the supra-spinally driven automatic posture control mechanisms, elderly people are assumed to rely more on high level cortical processing loops as a compensatory strategy to control upright stance (Boisgontier & Nougier, 2013). This requires increased allocation of cognitive resources for posture control tasks and, thus, is considered to lead to further performance impairments during dual tasking conditions due to the limited attentional capacity (Goble et al. 2010). Shared attention theory can fairly explain a variety of experimental results reporting increased center of mass (COM) sway when elderly people were asked to perform cognitive tasks (i.e. working memory task) during posture control testing (Teasdale et al., 1993; Lajoie et al., 1996; Brown et al., 1999; Marsh & Geel, 2000; Teasdale &Simoneau, 2001; Dault & Frank, 2004; Swan et al., 2004; Raymakers et al., 2005;

Bernard-Demanze et al., 2009; Berger & Bernard-Demanze, 2011; Granacher et al., 2011). However, it fails to account for recent research findings indicating either unchanged or decreased COM sway in older adults during dual tasking (Shumway-Cook et al., 1997; Melzer et al., 2001; Weeks et al., 2003; Prado et al., 2007; Dromey et al., 2010; Van Impe et al., 2013; Yogev-Seligmann et al., 2013).

Studies that report decreased COM sway in dual task settings attributed their findings to either “task prioritization model” or “facilitatory control” strategy employed by elderly people (Fraizer & Mitra 2008). The task prioritization model suggests that elderly people prefer tighter postural control strategy "posture first" during dual tasking conditions by prioritizing postural stability over cognitive performance with the main goal of preventing themselves from falling (Brauer et al, 2002). The facilitatory control hypothesis, on the other hand, assumes that postural control is a natural component of dual tasking since postural control mechanisms almost always coexist with numerous other cognitive functions (i.e. memory, language, spatial orientation) in daily life settings. This view, therefore, interprets the postural control system as a naturally integrated part of other cognitions and considers posture-cognition dual-tasking as a single higher order rather than being an independent skill with autonomous components (Frasier and Mitra 2008).

Most of these theoretical interpretations have been heavily based on behavioral performance observations without having neurophysiological evidence regarding the conflicting nature of dual-tasking performance. To date, no systematic research investigating cortical correlates of performance changes in dual tasking has been reported in the elderly population. Thus, in this study we monitored whole scalp cortical activations during both single task (cognitive only) and postural dual tasking with the main goal of understanding

cortical activity modulations underlying age related performance differences on dual tasking conditions. We designed a 2 (challenging/non-challenging cognitive task) by 2 (challenging/non-challenging postural task) experiment to better understand cognition and posture control interactions. Regarding behavioral performance, we expected to find similar cognitive and postural performance between elderly and young subjects during non-challenging single or dual tasking conditions. Increased cognitive load, on the other hand, was expected to increase postural sway even during non-challenging postural tasks in the elderly people due to declined attentional capacity. As for the cortical activation patterns, we expected to observe increased cortical activity in elderly people during non-challenging dual tasking conditions as a compensatory strategy due to increased attentional demands of postural control. Despite increased cortical activity, however, we expected to find similar postural and cognitive performance levels between elderly and young subjects when standing balance is not threatened during non-challenging postural and cognitive tasks.

4.2. Methods

4.2.1. Subjects

Ten healthy young (4 female and 6 male, M*age*=26.20±2.77 years old) and 9 healthy older (6 female and 3 male, M*age*=81.42±6.30 years old) adults participated in this study after reporting freedom from any neurological, cardiovascular, vestibular or musculoskeletal disorders, and no history of falls for at least 6 months prior to study. Overall health status of the prospective participants was assessed using the Physical Activity Readiness Questionnaire-PAR-Q (Canadian Society for Exercise Physiology, 2002).Cognitive functioning level of older adults was measured with the Mini Mental State Examination

(MMSE; Folstein, Folstein, & McHugh, 1975) and those who scored <27 were excluded from the study. All participants were informed about the experimental protocols before they gave their written consent. The study protocol was approved by the Institutional Review Board of the University of Houston.

4.2.2. Instrumentation

Center of pressure data (COP) for postural performance were quantified using standard computerized dynamic posturography platform (NeuroCom Balance Master, NeuroCom Intl, Clackamas OR) and used to estimate center of mass (COM) projections. The platform is equipped with a dynamic dual force plate system (18" X 18"), in which ground reaction forces under the feet of individuals were collected at 100 Hz by four individual force transducers embedded within the force plate. Whole scalp 64-channel EEG data were collected (actiCap system, Brain Products GmbH, Munich, Germany) and labeled in accordance with the extended 10-20 international system. EEG data were online referenced to channel FCz. Electrode impedances were maintained below 5kΩ with a sampling rate of 1000 Hz. EEG signals were digitized using a BrainAmp DC amplifier linked to BrainVision Recorder software version 1.10. Cognitive performance was evaluated via series of working memory (WM) tasks. WM data were collected by using custom-made software that provides time locked presentation of words. The custom-made software was developed using Microsoft Visual C++ and provides 26 alphabetic characters randomly which recognizes the participant's speech in real time.

4.2.3. Experimental procedures

Prior to the beginning of WM trials, each subject was required to perform a familiarization procedure so that the custom-made software could better understand the participant's voice and intonation. The N-Back working memory paradigm was employed audibly, and subjects were instructed to respond verbally. Specifically, subjects were presented with a series of words via headphones where the first word was presented at the beginning of each trial and subsequent words were presented with 3 seconds intervals. Subjects were asked to recall previously presented words depending on the N-back condition. In the one-back condition (N1), subjects were asked to immediately recall the word that was presented before the current one, whereas in the two-back condition (N2) subjects were required to recall the target word presented two stimuli ago in the row. The WM task was also synched to both the postural data (COM) and EEG monitoring systems during dual tasking conditions.

Each experiment trial started with single task conditions (balance task only and cognitive task only). For single balance tasks participants were asked to perform quiet stance fixed platform surface (S1) as non-challenging and quiet stance sway platform surface (S4) as challenging balance task with their eyes open. Each single balance task was performed for 30 sec. Single cognitive task conditions included one-back (N1) as non-challenging and two-back (N2) as challenging WM tasks. After completing the four single task conditions, a 2-by-2 experimental design was followed for posture-control dual tasking measurements (Figure 1). In the dual tasking paradigm, S1 and S4 balance tasks were concurrently performed with N1 (S1+N1, S4+N1) and N2 (S1+N2, S4+N2) cognitive tasks, respectively. Three trials, each lasting 60 sec, were performed for dual tasking conditions. Twenty word recalls were

performed during each trial, making 60 recalls in total for each dual tasking condition. The order of trials was randomized. During all postural tasks subjects were instructed to focus on their WM task performance. The main purpose in directing focus of attention to cognitive instead of postural tasks was to examine postural control performance in an ecologically valid setting. In daily life functioning we don't usually focus primarily on automatized motor skills such as posture-control during multi-tasking activities (McNevin & Wulf, 2002). Maintaining upright stance is not considered to be the main focus of attention unless standing balance is threatened. Thus, we aimed to investigate effects of cognitive load on standing balance as it occurs in daily life settings in which people has to maintain upright stance without consciously focusing on their balance while performing other tasks.

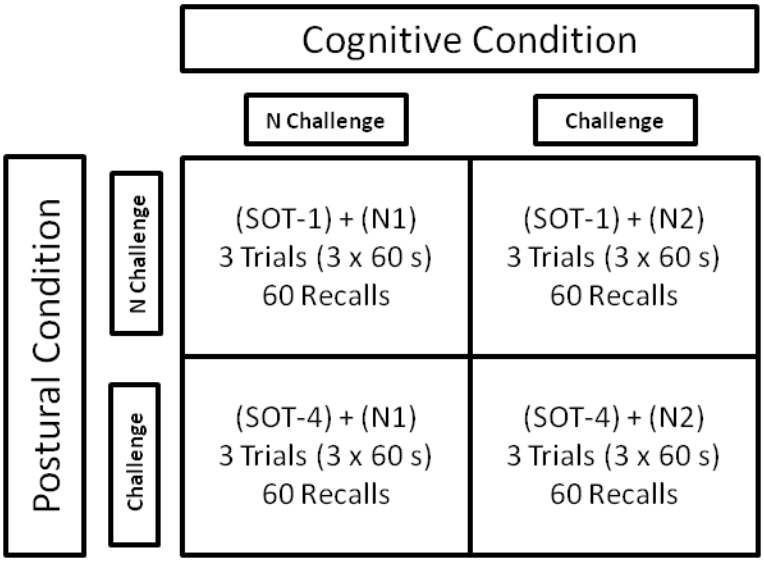


Figure 4.1. Dual tasking conditions

4.2.4. Data Reduction and Signal Processing

Posture control data processing steps were performed as explained in Ozdemir et al. (2013). Briefly, ground reaction force data collected from the Neurocom system were

combined to create center-of-pressure (COP) time series in the antero-posterior (AP) and medial-lateral (ML) directions for each trial (Ozdemir, Pourmoghaddam, & Paloski, 2013). Corresponding center-of-mass (COM) position was estimated by low pass filtering the COP data (second order Butterworth; f_c= 0.86 Hz), and COM velocity was estimated by differentiating the COM position using a 3-point central difference algorithm. Stability boundaries in the AP and ML directions were conservatively estimated at the outer extremes of the foot locations to create a rectangular stability zone for each subject, and distance-to-boundary (DTB) was estimated as the instantaneous differences between the COM position and the stability boundaries in the direction of COM movement. Time to boundary (TTB) time series were then calculated by dividing the DTB by the COM velocity for each direction. Two performance measures were derived from the TTB time series for each trial. The minimum value of the TTB over each trial (TTBmin) represents the least stable moment during the trial and was considered to be the worst-case performance during the trial. The integrated area of TTB (iTTB) was also calculated below an arbitrary 10 s threshold that represents an estimate of relative instability over the entire trial. iTTB is expressed as a fraction of the total area beneath the threshold during the trial.

The EEG data were processed offline using EEGLAB 5.03 (Delorme & Makeig, 2004) and Matlab open source toolbox (Mathworks, Natick, USA). First the EEG channels from the peripheral and temporal sites (FP1-2, AF7-8, F7-8, FT7-10, T7- 8, TP7-10, P7-8, PO7-8, PO9-10, in the extended 10–20 EEG system montage) were rejected and not used in any further analyses due to their sensitivity to a number of physiological artifacts including facial gestures, eye movements or cranial muscular activity. The EEG data were then band-pass filtered with a zero phase 3rd order Butterworth filter from 0.1 to 50 Hz for main

analyses. After band-pass filtering, the EEG data were standardized by subtracting the mean and dividing by the standard deviation across channels (Cruz-Garza et al., 2014). Furthermore, a series of Independent Component Analyses (ICA), were performed to further identify possible mechanical, motion, or neuromuscular artifacts in the EEG signals. For main analyses a continuous complex morlet wavelet transform (CWT) was performed to quantify modulation of EEG signal power within delta (0.1-4 Hz), theta (4-7 Hz), alpha (8-12 Hz), beta (14-24 Hz) and gamma (30-50 Hz) bands over time throughout the duration of the postural trials (Slobounov et al. 2009). Specifically, EEG data were down sampled to 100 Hz and the Matlab wavelet toolbox including CWT algorithms (Misite et al. 1996) was used to compute a two-dimensional representation of time-frequency energy of raw EEG data from low delta (0.2Hz) to high gamma (50Hz) oscillations. Then mean energy power in the time-frequency series was calculated for every 1 second (100 data points) for each EEG channel, representing continuous modulations in EEG signals within the postural condition. Finally, a grand mean energy power was calculated from one second time-frequency energy means representing relative power changes in EEG channels across the entire duration of a given postural condition

As for the WM tests, response time (RT) in seconds and response accuracy (RA) in percentages were measured to quantify cognitive performance. RA was calculated as the ratio of number of incorrect responses to total number of responses. RT analyses were also performed both for correct and incorrect responses.

4.2.5. Statistical Analyses

A series of 2 x 3 mixed design repeated measures ANOVA with Group (Young vs Elderly), as the between subject factor, and Condition (N-back single vs N-back SOT1 vs N-back SOT4), as the within subject factor, were conducted to examine effects of cognitive tasks on postural performance. Simple effect analyses with Bonferroni corrections (p=0.05/number of comparisons) were performed to understand group differences among conditions. Similarly, the effect of postural task on cognitive performance was also tested with series of 2 x 3 mixed design ANOVA.

For statistical analyses of EEG data, cortical Region of Interests (ROI) were defined by calculating the grand mean EEG powers across all subjects, in each group, and channels for different cerebral regions including the frontal (F3, F1, Fz, F2, F4), central-frontal (FC5, FC3, FC1, FC2, FC4, FC6), central (C3, C1, Cz, C2, C4), central–parietal (CP3, CP1, CPz, CP2, CP4) and parietal (P3, P1, Pz, P2, P4) cortices. Series of 2 (Group: Elderly vs Young) x 2(Condition: Single task vs Dual task) repeated measure variance analyses were performed to examine changes in grand mean EEG power in ROI's across groups and postural conditions for each frequency band

4.3. Results

4.3.1. Postural Performance

Figure 4.2 shows postural performance as TTB time series during both single (postural only) and dual tasking conditions for a representative young and elderly subject. During single postural tasks (S1 panels and S4 panels), especially during the non-challenging posture task, S1, similar postural sway characteristics were observed for the elderly and the

young subjects. This was also true when subjects were performing dual tasking with the two non-challenging conditions (S1/N1). However, when subjects were performing dual tasking containing either (S1/N2, S4/N1 or both S4/N2) of the challenging conditions postural sway increased considerably more in the elderly subject than the young subject indicating limited cognitive capacity in the elderly when compared to single task conditions.

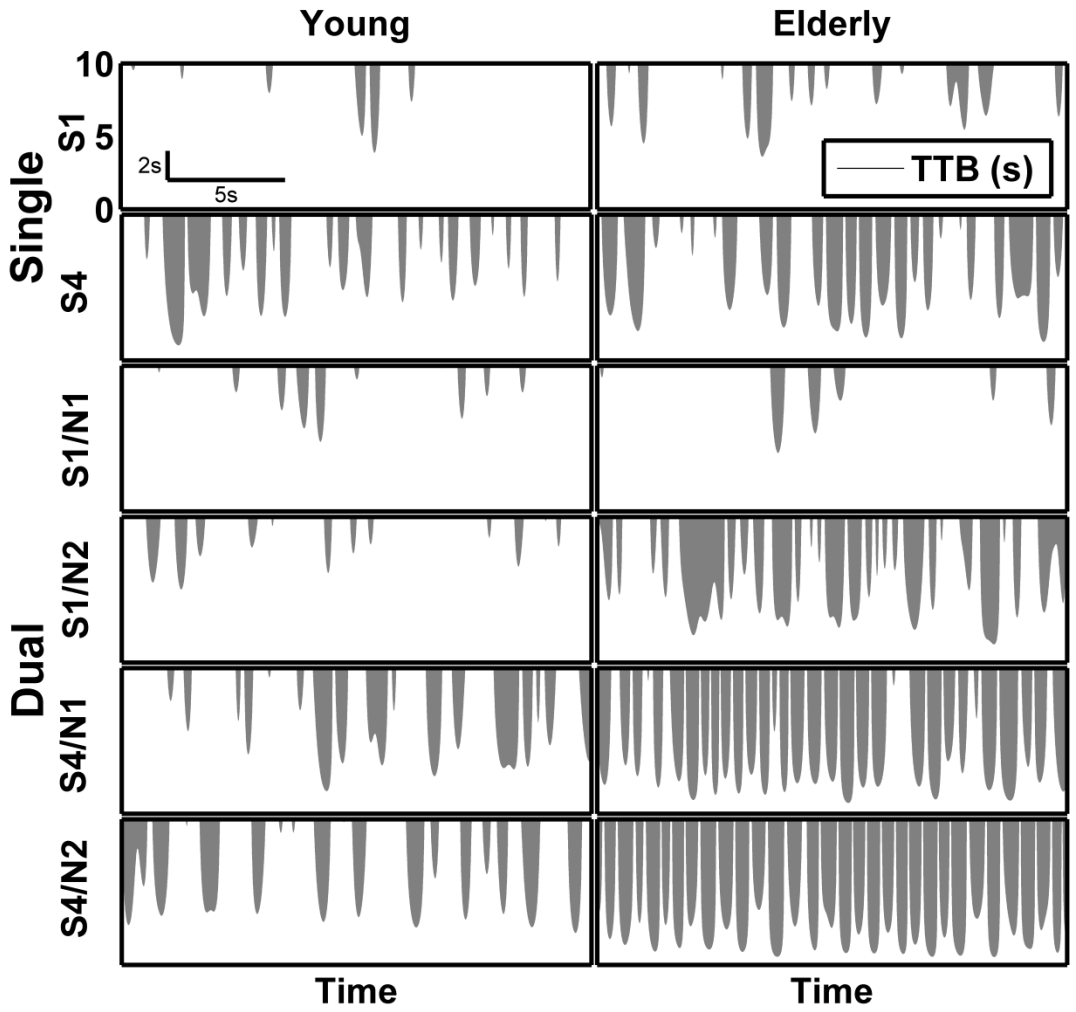


Figure 4.2. TTB time series for single task postural (S1 and S4) and dual taskingpostural plus working memory (N1 and N2) conditions in representative young (left) and elderly (right) subjects.

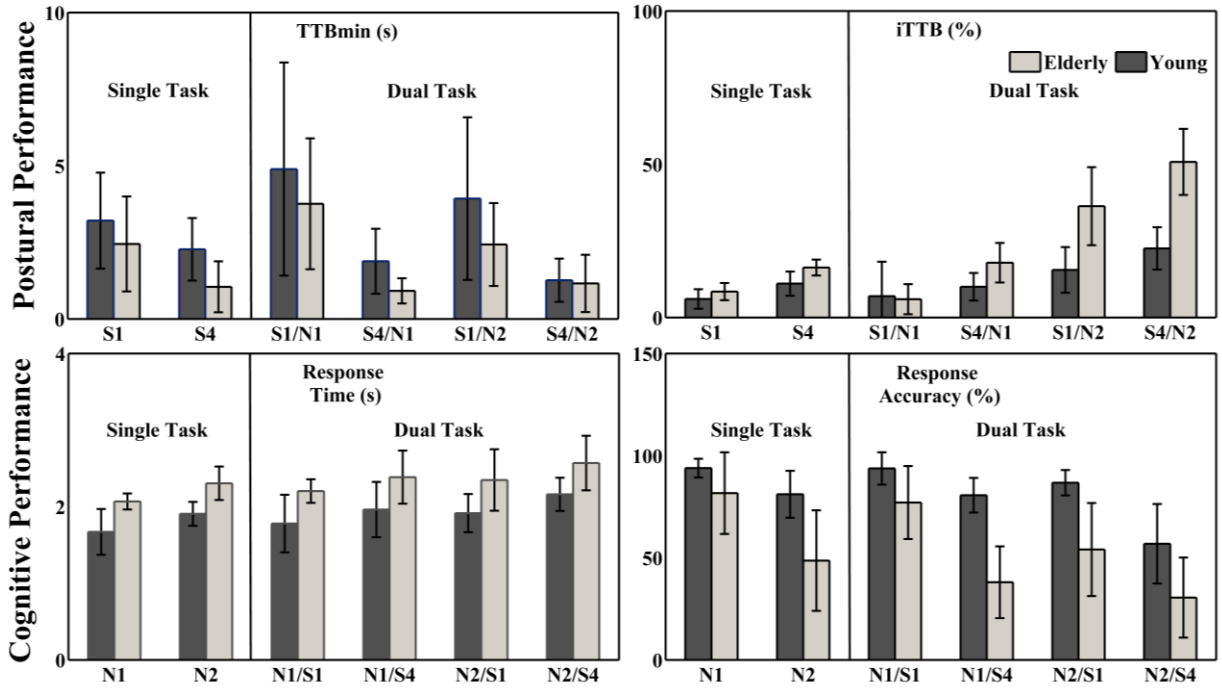


Figure 4.3. Postural (TTBmin, iTTB) and Cognitive (Response time, Response Accuracy) performance (Mean±SD) for young and elderly subject groups during single and dual tasking conditions

Figure 4.3 shows group means (±SD) for postural and cognitive performance during single and dual task conditions. Mixed design repeated measure variance analyses for S1 trials showed a significant multivariate effect for TTBmin across dual tasking conditions (S1/N1 and S1/N2; p=0.029).

Follow up paired sample comparisons revealed that TTBmin was significantly (p=0.041) higher for the S1/N1 dual task when compared to the S1 single task, indicating improved balance performance during low cognitive load dual tasking condition in both groups. For the more challenging S1/N2 dual task condition, TTBmin values decreased (p=0.010) in the elderly group, but not in the young group when compared to S1/N1 dual task condition, suggesting that the elderly group relied more heavily on cognitive resources to maintain upright stance, even under non-threatening conditions. Repeated ANOVA for S4

trials showed no significant within subject change in TTBmin across dual tasking conditions in both groups (p >.05). Group comparisons, on the other hand, indicated poor balance performance for elderly group during the S4/N1 dual task conditions compared to young group (p=0.042). No significant group difference was found also for TTBmin values during the S4/N2 dual task condition.

iTTB analyses for S1 trials showed significant condition effect (p=0.004) and "group x condition" (p=0.004) interaction effect across dual tasking conditions. Follow up paired sample comparisons revealed that iTTB values significantly decreased (p=0.021) from S1 single task to S1+N1 dual tasking condition, however significantly increased (p=0.003) from S1+N1 to S1+N2 dual taking condition in the elderly group indicating increased postural sway for the entire postural trial during challenging cognitive conditions. Non-significant condition effect (p >.05) for the young group, on the other hand, suggests that, despite challenging

cognitive condition, postural sway did not increase across dual tasking trials (figure 4.3). Simple effect analyses were performed to break down "group x condition" interaction effects by comparing iTTB differences between groups at each postural condition (Field, 2009). Simple effect analyses showed that elderly subjects have higher iTTB (p=0.009) than their younger counterparts at S1+N2 dual tasking condition indicating increased postural sway even at fixed platform postural task when they performed a challenging cognitive task. For S4 trials repeated measure analyses revealed significant condition effect (p=0.000) and "group x condition" interaction effect (p=0.000). Follow up paired sample comparisons for condition effect showed remarkably increased iTTB in the elderly group from S4+N1 to S4+N2 (p=0.000) dual tasking conditions (figure 4.3). Follow up analyses in the young

group, on the other hand, only showed significant iTTB differences between S4 single and S4+N2 dual tasking conditions (p=0.021).

4.3.2. Cognitive Performance

Repeated measure analyses showed significant condition effect (p=0.000) for response time (RT) values at N1 trials. RT was longer only during N1+S4 dual tasking condition in both groups (figure 4.3, panel c) when compared to N1 single tasking. No significant "group x condition" effect (p >.05) was found, but group comparisons indicated faster RT performance for the young group both during single (p <.05) and dual tasking (p <.05) trials (figure 4.3, panel c). Response accuracy (RA) analyses, on the other hand, indicated a significant interaction effect (p=0.021) for N1 trials (figure 4.3, panel d). Follow up comparisons showed declined RA only in the elderly group during N1+S4 dual tasking when compared to both N1 single (p=0.000) and N1+S4 (p=0.002) dual tasking conditions indicating even low cognitive loads can be demanding during challenging postural conditions. No condition effect was found in the young group (p >.05) that younger subject can maintain similar cognitive performance across dual tasking conditions (figure 4.3, panel d). Compared to the elderly group, RA was also higher in the young group (p <.05) both in N1 single and dual tasking conditions.

For the challenging N2 cognitive trials, RT significantly increased (p=0.001) from N2 single to N2+S4 dual tasking conditions in both groups (figure 4.3, panel c). RT was also found to be longer in the elderly group (p <.05) when compared to the young group in N2 conditions. Response accuracy analyses also revealed significant condition effect (p=0.002). Follow up comparisons showed that RA significantly declined from N2 single task to N2+S4

dual tasking conditions (p=0.041) in the elderly group (figure 4.3, panel d). No significant RA differences (p >.05) were found between N2 single and N2+S1 dual tasking conditions in the young group. Declined RA performance was only observed during N2+S2 dual tasking conditions in the young group indicating that challenging postural task also effect cognitive performance in young subjects (figure 4.3, panel d).

To better understand cognitive and postural performance interactions, bivariate scatter plots with regression lines were computed for iTTB and RA and presented in figure 4.4. In general, scatter plots indicated that as dual tasking conditions becomes challenging both RA and iTTB performance declines in both group (figure 4.4). One important observation is the significant negative correlation (r=.66, p<.05) between iTTB and RA during S4+N2 dual tasking condition in the elderly group that individuals with high cognitive capacity have reduced postural sway suggesting the important role of sustained attentional sources on postural performance during challenging dual tasking conditions (figure 4.4, left panel).

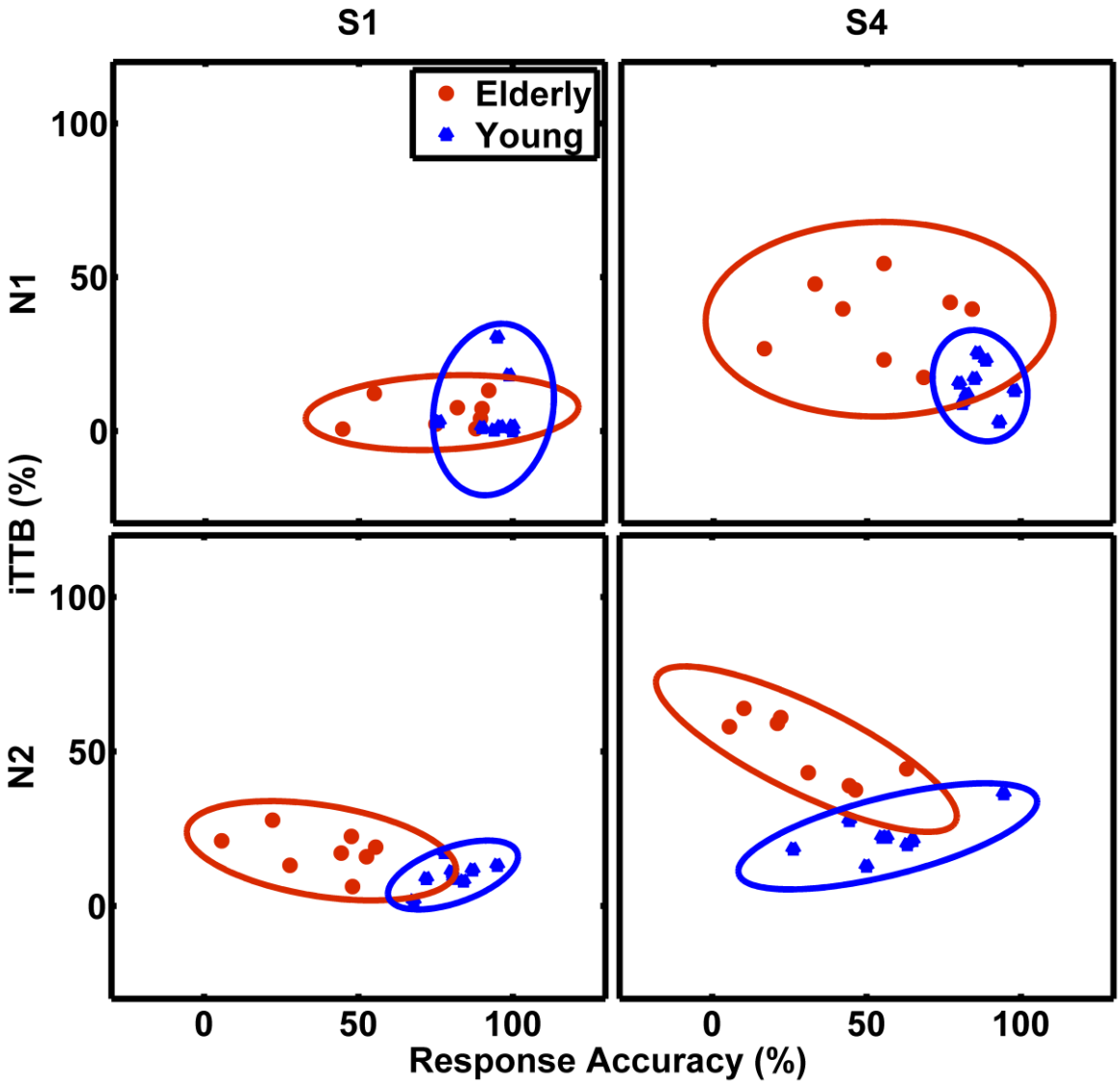


Figure 4.4. Bivariate scatter Plots (circles represents area with 2 standard deviations for the given data set) for iTTB (postural performance) and Response Accuracy (cognitive performance) both for the elderly and the young group during dual tasking conditions.

4.3.3. Cortical Activity Modulations during Dual Tasking

Topographical distribution of group means of EEG power in delta, theta, alpha and gamma waves were plotted as scalp maps to show how EEG power is modulated over the entire scalp across different cognitive-postural dual tasking conditions (See, figure 4.5). Delta

activity seems to increase in both groups, especially over the frontal, central-frontal and central regions, only when dual tasking includes challenging postural condition (S4) with a more pronounced increase in the young group (figure 4.5, first column). Theta band EEG activity, on the other hand, is seems to be more responsive to working memory performance in dual tasking conditions with challenging cognitive tasks (N2) in both groups over frontal, central-frontal and central cortices (figure 4.5, 3rd and 4th columns). Increase alpha activity was also observed over central-parietal and parietal cortices in both groups with increasing dual tasking difficulty. Increased alpha is, however, more pronounced in the young group especially over parietal cortices during N1+S4 and N2+S4 dual tasking conditions (figure 4.5, column 5). As for the Gamma band, increased activity was observed only in the elderly group especially over central and central-parietal cortices during dual tasking conditions with challenging (S4) postural control tasks (figure 4.5, column 8).

Figure 4.6 shows group means and standard deviations of EEG activity for each ROI at different frequency bands and across dual tasking conditions. Repeated measure variance analyses were performed to examine changes in grand mean EEG power in ROI's across groups and postural conditions for each frequency band. For delta band analyses, results showed significant main effect for dual tasking conditions over frontal (p=.040), central-frontal (p=.044), central (p=.037), and central-parietal regions (p=.033). Pairwise comparisons with bonferroni corrections indicated significantly increased delta activity during N1+S4 and N2+S4 dual tasking conditions, when compared to single cognitive (N1 and N2) and dual conditions with non-challenging postural tasks (S1) at central-frontal (p< .05), central (p< .05) and central-parietal (p< .05) regions in the young group (figure 4.6, Upper panels). The elderly group also showed increased delta during N1+S2 dual tasking

condition at the central region. Although, in general, the young group had higher delta activity across all experimental conditions and ROIs, significant differences were only found during dual tasking with challenging postural tasks (S4) in all ROI's, when compared to the elderly group.

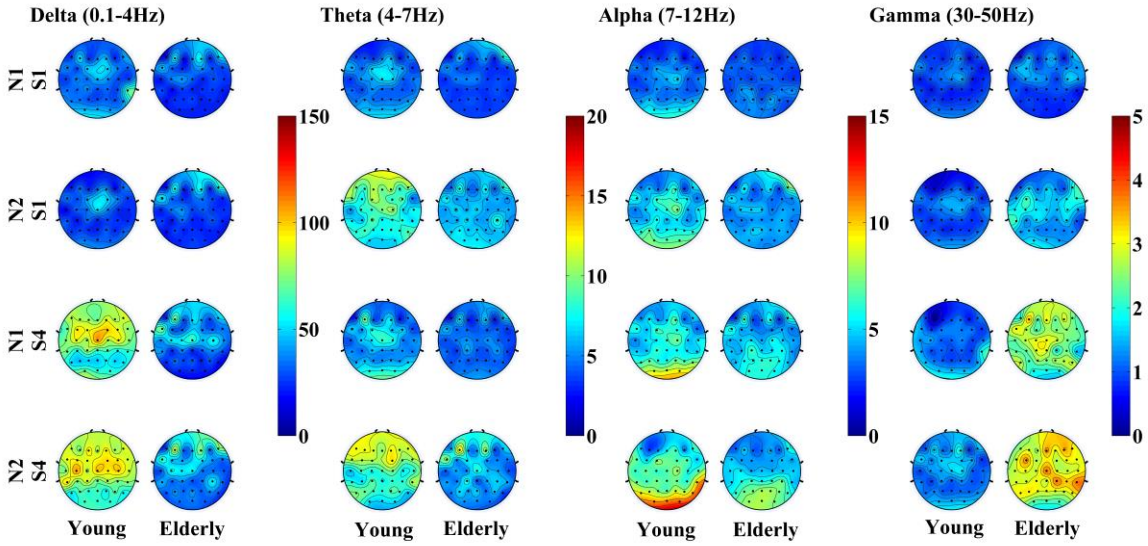
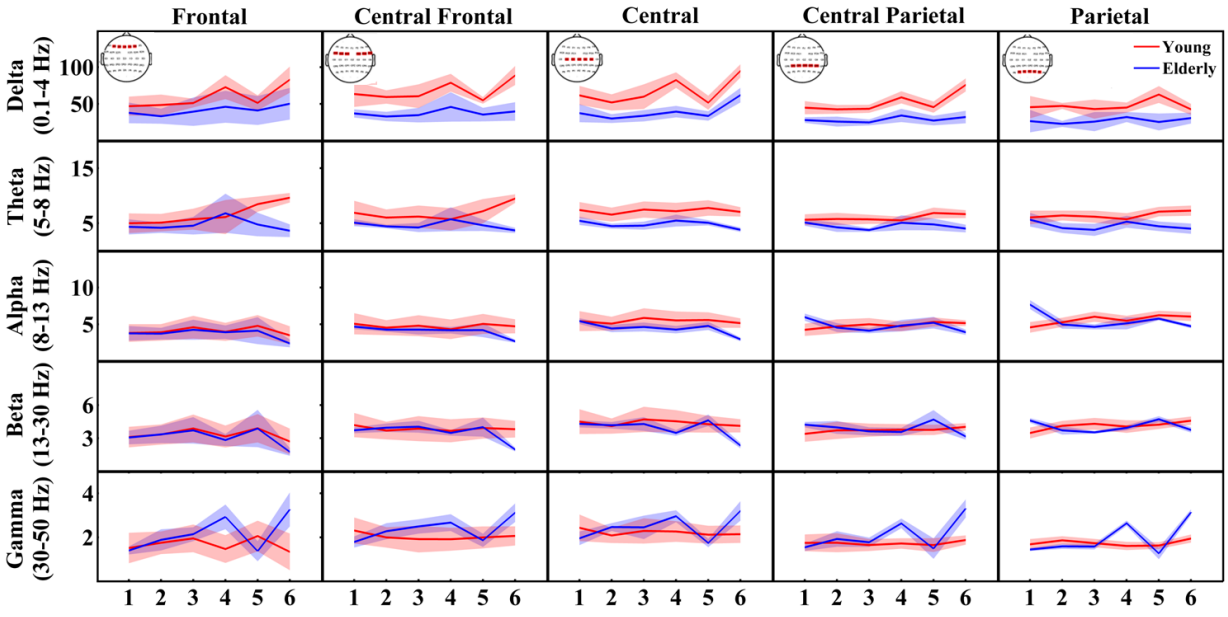


Figure 4.5. Scalp maps of group mean EEG power for Delta, Theta, Alpha and Gamma bands under the four experimental conditions for young and elderly subjects. Regional activity ranges from low (0; dark blue) to high (150; dark red).

Theta band EEG activity was found to be significantly higher during dual tasking with challenging cognitive task conditions (N2+S1 and N2+S4) over frontal (p=.039) and central-frontal (p=.044) regions when compared to single cognitive tasks and dual tasking with non-challenging cognitive task conditions (Figure 4.6, second row panels). Group comparisons also showed higher theta activity in the young group over frontal (p< .05) and central-frontal (p< .05) regions during challenging cognitive dual tasking conditions, when compared to the elderly group. Significant increases in alpha activity were observed in both groups over central-parietal and parietal regions during dual tasking conditions with

challenging postural conditions (N1+S4 and N2+S4). Similarly group comparisons indicated higher alpha activity increases over parietal region during challenging cognitive and dual tasking (N2+S4) condition (Figure 4.6, 3rd row panels). No significant differences were observed for beta activity (p> .05) across experimental conditions and groups (Figure 6, 4th row panels). Gamma band activity, however, was found to be higher in the elderly group over frontal (p=.042), central-parietal (p=.029), and parietal regions (p=.026) during dual tasking with challenging postural control task conditions (figure 4.6, 5th row panels).

Figure 4.6. Group means (Bold lines) and standard deviations (Shaded regions) of EEG activity for each ROI at different frequency bands and across dual tasking conditions. 1=N1, 2=N2, 3=N1/S1, 4=N1/S4, 5=N2/S1 and 6=N2/S4



4.4. Discussion

The main objective of this study was to (1) better understand age related changes in dual tasking postural control performance along with (2) task related cortical activity modulations. In general, our results are in line with most of the previous studies reporting impaired performance during challenging posture-dual tasking conditions in the elderly population (Brauer ,Woollacott & Shumway-Cook, 2001; Brown, Shumway-Cook & Woollacott, 1999; Rapp , Krampe & Baltes, 2006; Redfern et al. 2001; Shumway-Cook & Woollacott, 2000; Teasdale et al. 1993). Postural and cognitive data analyses showed elderly people had no performance deficits during single postural task conditions (single S1 and S4), but decreased response accuracy even during challenging single cognitive tasks (Single N2). Dual tasking analyses mainly indicated that working memory impairments in the elderly group occurred when a challenging cognitive task (N2) was performed in any postural condition (either S1 or S4), but postural control performance differences only became significant during dual tasking with challenging postural and cognitive (N2+S4) task conditions (Figure 4.3). During challenging postural and cognitive dual tasking we also noticed that elderly subjects with high cognitive capacity exhibited less postural sway during the entire trial (Figure 4.4). Our EEG analyses showed increased delta, theta and gamma oscillations, primarily over frontal, central-frontal, central and central-parietal cortices during challenging dual tasking conditions (Figure 4.5). To our knowledge, this study is also the first to show age-related differences in cortical activation patterns during dual tasking. We found that delta oscillations were more responsive to challenging postural conditions presumably related to cortical representations of changing sensory conditions in postural tasks. Theta rhythms, on the other hand, were more responsive to cognitive task difficulty in

both groups, with more pronounced increases in younger subjects which may underlie neural correlates of high level cognitive computations including encoding and retrieval. Gamma oscillations also appeared to increase in the elderly group primarily over central and central-parietal cortices during dual tasking is performed with a challenging postural task indicating increased allocation of attentional sources to postural tasks.

4.4.1. Age related changes in Cognitive and Postural performance during dual tasking conditions

Despite inconsistent findings in the posture control related dual tasking literature (for details see the recent review by Boisgontier & Nougier, 2013), one strong consensus derived from many studies is that posture control and higher order cognitive skills share common attentional resources (Fraizer & Mitra, 2008), and decrements in cognitive performance during dual tasking can be explained by impaired cognition in elderly people (Woollacott, & Shumway-Cook, 2002). Our results regarding cognitive performance difference between young and elderly subjects also suggests decreased attentional capacity in the elderly such that, even during single task conditions, response accuracy was lower in the elderly group when the high cognitive load (N2) task was performed. We also found that although there was no performance difference between the groups for a non-challenging cognitive task during single (N1) and non-challenging dual tasking (N1+S1), decreased cognitive performance in N1 was observed only in the elderly group when they concurrently performed N1 with a challenging postural task (N1+S4). These results suggests that a challenging postural task requires more attentional sources in the elderly, as compared to the young group, thus it can further impairs cognitive performance even for low cognitive load tasks during dual tasking. Decreased cognitive performance during challenging postural conditions

in the elderly group may also reflect that elderly people may prioritize balance performance and thus intentionally allocate more cognitive sources to postural tasks when upright stance is threatened (figure 4.3, response accuracy panel, notice group differences in N1 and N1+S1 vs N1+S4 conditions).

Our results for postural performance, on the other hand, seem to support both "shared attention or capacity" theory and " facilitatory control" hypothesis depending on the challenging nature of dual tasking conditions. Increased postural sway and decreased response accuracy in both groups during dual tasking with challenging postural task (N2+S4) conditions suggested that concurrent performing of high load cognitive task (N2) with a sway platform postural task (S4) may challenge available attentional resources and impairs both cognitive and postural performance. Decreased dual-tasking performance was also more dramatic in the elderly group presumably due to reduced capacity in overall cognition.

Supporting evidence for "facilitation hypothesis" comes from non-challenging dual tasking conditions that, compared to single postural task performance (S1), concurrent low load cognitive task (N1) increases TTBmin (figure 4.3, TTBmin panel) and slightly decreases iTTB (figure 4.3, iTTB panel) indicating reduced sway during a fixed platform (S1) postural task. This facilitatory effect of concurrent N1 task on postural performance, however, disappear during sway platform conditions (N1+S4) suggesting that a non-challenging cognitive task may facilitate postural performance only during natural standing (S1) conditions. Previous research tends to explain facilitatory effects of simple cognitive task on postural performance by the functional role of upright stance in everyday posture-cognitions tasks. According to this understanding postural control for functional activities in daily life settings is mostly used as a primary tool to achieve variety of perceptual or motor tasks

which often require certain degree of cognitive processing. This suggests that life-long acquired automated postural skills such as natural standing on a fixed surface might be presumably well integrated with cognitive faculties and, thus, does not pose further challenge to the posture control system.

Another possible explanation could be attributed to methodological issues such that, in our study, we asked subjects to perform their best for recalling words in the working memory task during dual tasking. The main purpose was to mimic ecological settings and quantify postural performance as it is performed in daily life contexts. During single postural tasks, alternatively, subjects may consciously focus on their standing balance which has been shown to negatively interfere with well automated processes underlying postural control (for details see Fraizer & Mitra; 2008). Contrarily, release of attention from postural tasks by employing an external focus or switching attention from postural to secondary tasks has been shown to enhance postural stability (Vuillerme & Nafati, 2007). Thus, future studies can also manipulate task instructions to better understand underlying mechanisms of enhanced postural performance during non-challenging dual tasking.

Taken together, our overall posture-dual tasking performance analyses suggests that elderly subjects may adopt a non-automated conscious control strategy to maintain upright stance to a certain point when postural tasks become more challenging (see figure 4.3 N1/S4 postural performance comparison between groups). This increased cognitive involvement during challenging postural tasks, however, significantly degrades response accuracy even for non-challenging cognitive tasks in the elderly, suggesting that elderly people may prioritize postural stability over cognitive performance (see figure 4.3 N1/S4 cognitive performance comparison between groups). Finally, postural performance impairments during

challenging cognitive dual tasking conditions also indicates limited cognitive capacity in the elderly that they are no longer able to control their postural sway when they engage in a challenging cognitive task.

4.4.2. Modulated cortical activity during dual tasking

Many recent studies have investigated neural correlates of human upright stance and reported modulated cortical activity at different frequency bands during challenging postural conditions in healthy young adults (Slobounov et al. 2005; Slobounov, Sebastianelli & Moos, 2005; Slobounov, Harlett & Newell, 2008; Slobounov et al. 2009; Sipp et al., 2013). In particular, increased theta power over anterior parietal, frontal and sensorimotor cortices during challenging postural tasks (Sipp et al., 2009; Hülsdünker et al. 2015), and increased gamma activity over parietal cortices during unstable balance moments were reported (Slobounov et al. 2005, Slobounov et al. 2009). Our EEG results are predominantly in line with previous reports. We found increased cortical activity in theta and gamma oscillations as a function of task difficulty. However, we were also able to examine age and dual tasking related cortical activity modulations during challenging and non-challenging postural conditions, which have not been reported previously. In regards to dual tasking conditions, theta activity was found to be responsive to cognitive task difficulty such that increased theta was predominantly observed during challenging cognitive dual tasking (N2) conditions over frontal and central-frontal cortices with more pronounced increases in the young group. In particular, recent reports in neurocognitive studies have relate increased theta oscillations over frontal brain areas to high level cognitive computations including cognitive mapping during spatial navigation (Lithfous et al., 2015), memory encoding and retrieval during working memory tasks (Jensen & Tesche, 2002), novelty detection and error monitoring

during learning tasks (Cavanagh, Zambrani-Vazquez & Allen, 2013). Previous postural control studies also reported significantly higher spectral power in theta oscillations located over anterior cingulate, medial sensorimotor cortex during loss of walking or standing balance (Sipp, et al., 2013, Slobounov et al., 2009). In regards to standing balance, increased dorsolateral and prefrontal theta is considered to originate especially from the anterior cingulate cortex and assumed to have a functional role on sensory information integration and error detection related to decision making mechanisms in internal feed-forward models of posture control (Ahmed and Ashton-Miller 2005; 2004; 2007). Our findings, however, indicated increased theta activity over central-frontal brain areas only during dual tasks with challenging cognitive, but not during challenging postural conditions. We also found that this increased theta is more pronounced in the young group, as compared to the elderly group, who also had higher WM performance for challenging (N2) tasks. Considering the fact that our challenging postural condition (S4) did not lead to loss of balance in the young group, increased theta activity seems to reflect demanding cognitive computations for memory encoding and retrieval functions when performing N2 working memory tasks concurrently with postural tasks. Indeed a recent study on neural correlates of cognitive mapping for spatial navigation tasks found a significant correlation between increased theta and accuracy of cognitive mapping only in young but not in elderly subjects, due to reduced theta power during encoding in the elderly group (Lifthous et al., 2015).

Our findings modulated gamma activity differences between the groups may also reflect increased attentional demands for challenging postural conditions in the elderly group. In general, fast oscillations in the cortex (> 30 Hz) are considered to be related to focal neural computations due to shorter temporal processing windows at high frequencies (Harmony,

2013). Regarding functional correlates of cortical processing, modulations in gamma power is attributed to focused arousal and sustained attention during both cognitive and motor tasks (Basar et al., 1995; Slobounov et al., 2005;Slobounov et al., 2009). Considering our findings for continuous balance tasks, increased gamma power among older adults during challenging postural conditions, thus, may reflect increased allocation of attentional sources to postural task as compared to healthy young adults.

Apart from increased power in theta and gamma oscillations, however, we also found significantly higher delta band activity over central-frontal, central and central-parietal cortices during dual tasking with challenging postural conditions (Figure 4.6). Although previous studies on cortical control of human stance have mostly reported EEG modulations in the theta band (4-7 Hz) and higher frequencies, our results regarding delta band modulations corroborate with recent research showing involvement of slow cortical oscillations in the control of coordinated multi-joint movements (Bradberry et al., 2010; Bulea et al., 2014; Gwin et al., 2010; Presacco et al., 2011). During locomotion tasks, for example, lower limb kinematics were reconstructed with high accuracies by using delta band EEG, suggesting that high amplitude low frequency cortical signals can contain motor information regarding coordination of multi joint tasks (Bradberry, Gentili & Contreras-Vidal; 2011; Presacco et al., 2011). Our results, which showed modulated EEG in delta band during challenging postural conditions, also support these findings and provide preliminary evidence that slow EEG oscillations as low as 1 to 2 Hz can also be sensitive to the changes in postural state of the body and involve in controlling motor aspects of human upright stance.

CHAPTER V

Summary-Conclusions, Limitations and Future Directions

5.1. Summary-Conclusions

The results of this dissertation provide novel insights regarding the neurophysiological basis of human upright stance control obtained from systematic examination of cortical activity (EEG) modulations in a variety of settings. We were able to show, for the first time, how aging can affect cortical control of upright posture during (1) quiet stance with normal and altered sensory stimulation, (2) biomechanical perturbations, and (2) dual tasking conditions.

The results presented in Manuscript I (Chapter III), showed that the cortex becomes involves in upright stance control when standing balance is threatened. They also showed age specific balance related cortical activity modulations during altered sensory conditions. While increased delta rhythms were observed in both groups during challenging sensory conditions, elderly individuals also showed increased gamma activity over sensorimotor and parietal cortices, when compared to the younger group. Our postural perturbation condition results also suggested that, rather than motor system malfunctioning, impairments in perceptual processing of sensory afferences forms the basis of prolonged postural responses to perturbed stance conditions in non-faller older adults.

The results presented in Manuscript II (Chapter IV) revealed the cortical activity modulations underlying age related performance differences during dual tasking conditions. We found that cognitive performance declines in the elderly group either (1) when they performed a challenging cognitive task or (2) when they performed a non-challenging

cognitive task (N1) concurrently with a challenging postural task (S4). Postural performance, on the other hand, was only impaired when elderly people performed postural tasks (either S1 or S4) concurrently with a challenging cognitive task (N2). These results suggest that elderly subjects may adopt a non-automated conscious control strategy that prioritizes postural performance over cognitive to maintain upright stance when the cognitive load is low. When the cognitive load was high, on the other hand, the elderly subjects were not able to control balance well, as evidenced by dramatically increased postural sway and high risk of falling, in the elderly. Regarding the cortical basis of age related performance differences during dual tasking conditions, EEG analyses suggest that while increased theta over frontal and central-frontal cortices may underlie the cortical correlates of to high level cognitive computations including encoding and retrieval for working memory tasks, delta oscillations, in general, maybe underlie cortical monitoring of changes in postural state when sensory conditions of upright stance is compromised.

5.2. Limitations and future directions

Several limitations of this study have been identified. First, we only selected healthy older adults with no history of falls or neurological disorders for this study. Thus our results regarding cortical correlates of upright stance control cannot be generalized to elderly fallers or individuals with pathological postural control deficits. Second, our cortical activity analyses had limited spatial resolution due to use of EEG. Although we were able to identify modulations in cortical activity over the whole scalp, neural sources of these activations cannot be clearly identified with the current design. Finally, we found that our EEG data during the second study was highly contaminated with EMG artifacts due to the use of auditory feedback for the working memory task. Verbal responses with high volume created

facial EMG artifacts over much of the cortex during response periods, thus we were unable to achieve our goal of identifying event related potential (ERPs). Considering these limitations, therefore, future studies should target clinical populations and focus on source analyses of EEG signal modulations constrained with structural magnetic resonance imaging data. These analyses would allow us to better understand temporal relations among kinematic, cortical and neuromuscular responses during unstable postural conditions.

CHAPTER VI

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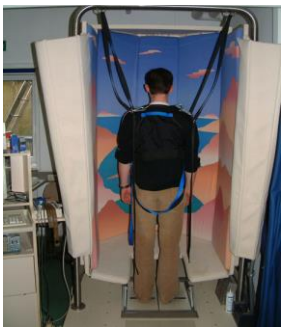
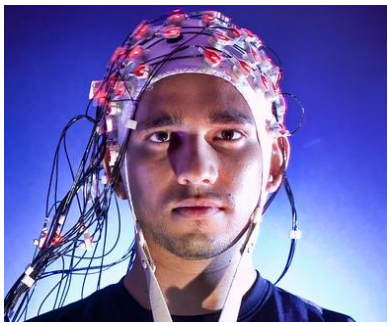
CHAPTER VII

Appendix 1





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(1) Test your balance during different tasks
(2) Test your short term memory
Then you might be eligible to participate

For information on participating in this study, please contact us at **832 921 5220** or **nsnever61@gmail.com**

This project has been reviewed by the University of Houston Committee for the Protection of Human Subjects (713) 743 9204

Appendix 2

UNIVERSITY OF HOUSTON
CONSENT TO PARTICIPATE IN RESEARCH

INFORMED CONSENT

PROJECT TITLE: Cortical Control of Human Upright Stance

You are being invited to participate in a research project conducted by Recep Ali Ozdemir and Dr. William Paloski from the Department of Health and Human Performance at the University of Houston.

NON-PARTICIPATION STATEMENT

Your participation is voluntary and you may refuse to participate or withdraw at any time without penalty or loss of benefits to which you are otherwise entitled. You may also refuse to answer any question.

PURPOSE OF THE STUDY

You have been invited to participate in a research study that uses noninvasive scalp electroencephalography (EEG) to learn specific brain wave patterns associated with balance control. The findings will be used to design future studies to develop effective cognitive and motor interventions to improve posture control in elderly population.

PROCEDURES

You will be one of approximately 20 subjects to be asked to participate in this project. You will be asked to perform the following procedures at the Center for Neuro-Motor and Biomechanics Research, at Texas Medical Center John P. McGovern Campus, 2450 Holcombe Boulevard.

To participate in the study, you will be required to travel to the Center for Neuromotor and Biomechanics Research (CNBR) at the Texas Medical Center. You must provide your own transportation to the Center for Neuromotor and Biomechanics Research and researchers will pay for parking. You will be required to wear a sport short during the testing period. Firstly, you will be asked a series of questions about your health status, injury history and physical activity background to determine your eligibility to participate.

If you are eligible to participate, we will measure your weight, height and foot size and then you will complete a series of balance and memory tests while we are monitoring your brain waves and activation of your leg muscles. The complete set of procedures for eligible participants is as follows.

(As you read please check the boxes).

☐ Procedure 1: Preparation stage (up to 60 minutes):

1. You will have your head fitted with an EEG cap (similar to a swim cap) that will measure the activity of your brain.
2. The EEG cap may be filled with gel to ensure good contact.
3. Stickers will be placed above and below your eyes in order to record eye blinks, and behind your ears to secure EEG electrodes. These sensor sites will be lightly rubbed with alcohol and a special gel to improve the connection between the skin of the scalp and the sensors. Using a blunt applicator and syringe, the gel will be applied to each electrode site. You will feel a rubbing sensation but the skin will not be broken.
4. Small disks with light emitting diodes (LEDs) or small wireless motion sensors may be placed on your arms, trunk and head in order to measure your body movements during balance tasks. Also, muscle activity will be recorded from muscles of the legs by attaching sensors to the muscles (i.e., electromyography or EMG) with adhesive patches and tape. These sensor sites for muscle recording will be lightly rubbed with alcohol prep pads prior to placing the electrodes.
5. You will wear a gait belt for safety as a research team member spots you as you Stand on Balance platform during testing.

☐ Procedure 2: Testing (up to 90 minutes):

Experiment 1:

1. During the first set of balance tasks you will be asked to sit quietly for 2min while your brain activity is recorded. After 2 min you will be asked to stand up on balance platform and maintain your stand as still as possible for 3 min. During balance testing you will be also instructed to keep your eyes closed for at least 30sec. The balance platform may also sway without your knowledge during testing. There will be a 2 min resting period after the completion of these tests.

2. At the second phase of Experiment-1 you will be asked to stand on balance platform. During the testing the platform will move suddenly on different

directions (forward, backward, up and down) without your knowledge. You will be asked to stand as still as possible.

Experiment 2:

3. At the beginning of this experiment you will be asked to perform a series of memory tests first while seated. During memory test you will hear a series of words presented audible via ear phones and you will be asked to recall certain words on the series. After the completion of first set of memory tests you will be asked to stand on balance platform and perform another set of memory tests while simultaneously performing certain balance tasks. The platform may also sway without your knowledge during testing. You will be asked to focus on memory task performance.

You will be allowed to rest if needed and there will be a spotter for each trial to ensure your safety. **During all balance tests, you also will be required to wear, a safety harness to prevent falls or injury**

☐ I agree to participate in the session today.

CONFIDENTIALITY

Every effort will be made to maintain the confidentiality of your participation in this project. Each subject's name will be paired with a code number by the principal investigator. This code number will appear on all written materials. The list pairing the subject's name to the assigned code number will be kept separate from all research materials and will be available only to the principal investigator. Confidentiality will be maintained within legal limits.

RISKS/DISCOMFORTS

The procedures described above are widely used in research and are not known to be physically harmful to you. There are no known long-term effects associated with the tasks or events experienced during this study. The procedures of this study involve minimal risk and are non-invasive. It is possible that you may experience some discomfort and slight sensations and skin irritation when fitted with the EEG cap or the EMG sensors. Also, a small number of people may be allergic to the conducting gel and/or adhesive used to attach the other sensors on the skin, but this is very rare. It is also possible that you may show fatigue and/or muscle soreness from balance tasks. There is a minimal risk of falling during the balance tasks. To minimize this risk, you will wear a safety harnesss and a research assistant will be next to you at all times during these assessments. There are no known risks associated with measuring EEG, motion analysis, or muscle activity. There are no other

known risks and no long-term effects associated with your participation in this study. Your participation is completely voluntary.

BENEFITS

While you will not directly benefit from participation, your participation may help investigators better understand how the brain controls balance in different task conditions.

ALTERNATIVES

Participation in this project is voluntary and the only alternative to this project is non-participation.

PUBLICATION STATEMENT

The results of this study may be published in professional and/or scientific journals. It may also be used for educational purposes or for professional presentations. However, no individual subject will be identified.

CIRCUMSTANCES FOR DISMISSAL FROM PROJECT

Your participation in this project may be terminated by the principal investigator:

- If you do not keep study appointments:
- If you do not follow the instructions you are given;
- If the principal investigator determines that staying in the project is harmful to your health or is not in your best interest.

AGREEMENT FOR THE USE OF AUDIO/VIDEO TAPES

If you consent to participate in this study, please indicate whether you agree to be audio/video taped during the study by checking the appropriate box below. If you agree, please also indicate whether the audio/video tapes can be used for publication/presentations.

☐ I agree to be audio/video taped during the interview.

☐ I agree that the audio/ video tape(s) can be used in publication/presentations.

☐ I do not agree that the audio/ video tape(s) can be used in publication/presentations.

☐ I do not agree to be audio/video taped during the interview.

SUBJECT RIGHTS

1. I understand that informed consent is required of all persons participating in this project.

2. All procedures have been explained to me and all my questions have been answered to my satisfaction.

3. Any risks and/or discomforts have been explained to me.

4. Any benefits have been explained to me.

5. I understand that, if I have any questions, I may contact Mr Recep Ali Ozdemir at 832-921-5220.

6. I have been told that I may refuse to participate or to stop my participation in this project at any time before or during the project. I may also refuse to answer any question.

7. ANY QUESTIONS REGARDING MY RIGHTS AS A RESEARCH SUBJECT MAY BE ADDRESSED TO THE UNIVERSITY OF HOUSTON COMMITTEE FOR THE PROTECTION OF HUMAN SUBJECTS (713-743-9204). ALL RESEARCH PROJECTS THAT ARE CARRIED OUT BY INVESTIGATORS AT THE UNIVERSITY OF HOUSTON ARE GOVERNED BY REQUIREMENTS OF THE UNIVERSITY AND THE FEDERAL GOVERNMENT.

8. All information that is obtained in connection with this project and that can be identified with me will remain confidential as far as possible within legal limits. Information gained from this study that can be identified with me may be released to no one other than the principal investigator. The results may be published in scientific journals, professional publications, or educational presentations without identifying me by name.

I HAVE READ (OR HAVE HAD READ TO ME) THE CONTENTS OF THIS CONSENT FORM AND HAVE BEEN ENCOURAGED TO ASK QUESTIONS. I HAVE RECEIVED ANSWERS TO MY QUESTIONS. I GIVE MY CONSENT TO PARTICIPATE IN THIS

STUDY. I HAVE RECEIVED (OR WILL RECEIVE) A COPY OF THIS FORM FOR MY RECORDS AND FUTURE REFERENCE.

Study Subject (print name): _____

Signature of Study Subject: _____

Date: _____

I HAVE READ THIS FORM TO THE SUBJECT AND/OR THE SUBJECT HAS READ THIS FORM. AN EXPLANATION OF THE RESEARCH WAS GIVEN AND QUESTIONS FROM THE SUBJECT WERE SOLICITED AND ANSWERED TO THE SUBJECT'S SATISFACTION. IN MY JUDGMENT, THE SUBJECT HAS DEMONSTRATED COMPREHENSION OF THE INFORMATION.

Principal Investigator (print name and title): _____

Signature of Principal Investigator: _____

Date: _____

Appendix 3

Cortical Control of Human Upright Stance (Data Collection Sheet)

Date: Operator:

Subject ID:

A) Questionnaires

1) Physical Activity Readiness Questionnaire.
2) Rapid Assessment of Physical Activity (only for E\elderly people)
3) Mini Mental State Examination (only for elderly people)
4) Exercise Stages of Change.
5) If eligible have the subject sign the consent form

B) Subject Preparation

Height (cm): **Weight (lbs):** **Foot length (cm):**

EEG system

1) Replace EEG cap to the subject head and connect electrodes to the ANTI-CAP control box.
2) Start gelling electrodes.
3) Place the Velcro straps over the chest of the subject.
4) Turn on EEG wireless transmitters and check the quality of EEG signals (eyes closed and teeth clinch).
5) Attach the wireless EEG hardware on Velcro straps mounted on the subject.

EMG system

1) Delete all existing files in the data logger
2) Make sure that the batteries are full
3) Place the data logger over the belly of the subject
4) Apply skin cleaning on designated muscle sites (shaving, abrasion and alcohol).
5) Replace electrodes to the cleaned muscle sites.
6) Check the quality of EMG signals.

Motion Sensors

1) Calibrate sensors through the software (80 hz)

2) Check sensor synchronization
3) Replace sensors over designated areas (Forehead, trunk, lumbar, wrists).
4) Check the triggers

C) Experiment 1

1) Ask subject to sit on chair in a comfortable position
2) Initiate all data collection systems.
3) Send initiation and termination triggers (2 minute interval)
4) Place subject over the neurocom (ankle joint corresponds to axis of platform rotation).
5) Have subject wear the safety harness
6) Initiate neurocom testing (check neurocom triggers)
7) Check neurocom condition and provide necessary task instructions (eyes closed etc.)
8) Initiate each neurocom condition immediately.
9) Save eeg, emg and opal data into different files Before perturbation trials
10) Re-start eeg, emg and opal systems for perturbation trials.
11) Apply one leg stance trials **(for young subjects only)**

D) Experiment 2

1) Re-start eeg, for single 1 back WM trials (3 x 60sec)
2) Re-start eeg, for single 2 back WM trials (3 x 60sec)
3) Re-start eeg, emg and opal systems neurocom trials.
4) Start with single postural task conditions (SOT-1, SOT-4)
5) Complete dual task conditions (3X 60 sec for each condition)
    a. 1 back WM + SOT-1 (3 x 60 sec)
    b. 1 back WM + SOT-4 (3 x 60 sec)
    c. 2 back WM + SOT-1 (3 x 60 sec)
    d. 2 back WM + SOT-4 (3 x 60 sec)

Appendix 4

Participant ID:

Date:

MODIEFIED PHYSICAL ACTIVITY READINESS QUESTIONNAIRE (PAR-Q)

For most people physical activity should not pose any problem or hazard. PAR-Q has been designed to identify the small number of adults for whom physical activity might be inappropriate or those who should have medical advice concerning the type of activity most suitable for them. Common sense is your best guide in answering these few questions. Please read them carefully and mark the yes or no opposite the question as it applies to you.

Yes__	No__	Can you walk at a comfortable steady pace for 4-5 minutes without stopping?
Yes__	No__	Has a physician ever said you have a heart condition and you should only do physical activity recommended by a physician?
Yes__	No__	When you do physical activity, do you feel pain in your chest?
Yes__	No__	When you were not doing physical activity, have you had chest pain in the past month?
Yes__	No__	Do you ever lose consciousness or do you lose your balance because of dizziness?
Yes__	No__	Do you have any problems of the circulatory system (e.g. problems with veins)?
		If so, specify:
Yes__	No__	Do you have a joint or a bone condition or problems with your feet?
		If so, specify:
Yes__	No__	Do you have insulin dependent diabetes or related conditions?
		If so, specify:
Yes__	No__	Do you have any breathing difficulties or suffer from asthma?
Yes__	No__	Do you suffer from epilepsy?
Yes__	No__	Do you have any neurological conditions?
		If so, specify:
Yes__	No__	Do you use (have been recommended to use) corrective lenses?
		If so, specify:
Yes__	No__	Is a physician currently prescribing medications?

If so, specify which medication and for which condition(s):

Yes__ No__ Have you had a major operation?

If so, specify (what, when):

Yes__ No__ Do you suffer from any other medical conditions?

If so, specify:

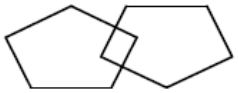
Yes__ No__ Do you know of any other reason you should not exercise or increase your physical activity

Appendix 5

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

Interpretation of the MMSE:

Method	Score	Interpretation
Single Cutoff	<24	Abnormal
Range	<21	Increased odds of dementia
	>25	Decreased odds of dementia
Education	21	Abnormal for 8th grade education
	<23	Abnormal for high school education
	<24	Abnormal for college education
Severity	24-30	No cognitive impairment
	18-23	Mild cognitive impairment
	0-17	Severe cognitive impairment

Interpretation of MMSE Scores:

Score	Degree of Impairment	Formal Psychometric Assessment	Day-to-Day Functioning
25-30	Questionably significant	If clinical signs of cognitive impairment are present, formal assessment of cognition may be valuable.	May have clinically significant but mild deficits. Likely to affect only most demanding activities of daily living.
20-25	Mild	Formal assessment may be helpful to better determine pattern and extent of deficits.	Significant effect. May require some supervision, support and assistance.
10-20	Moderate	Formal assessment may be helpful if there are specific clinical indications.	Clear impairment. May require 24-hour supervision.
0-10	Severe	Patient not likely to be testable.	Marked impairment. Likely to require 24-hour supervision and assistance with ADL.

Source:

- Folstein MF, Folstein SE, McHugh PR: "Mini-mental state: A practical method for grading the cognitive state of patients for the clinician." *J Psychiatr Res* 1975;12:189-198.

Appendix 6

Exercise Stages of Change Questionnaire

Regular Exercise is any *planned* physical activity (e.g., brisk walking, aerobics, jogging, bicycling, swimming, rowing, etc.) performed to increase physical fitness. Such activity should be performed *3 to 5 times* per week for *20-60 minutes* per session. Exercise does not have to be painful to be effective but should be done at a level that increases your breathing rate and causes you to break a sweat.

Question:

Do you exercise regularly according to that definition?

- Yes, I have been for MORE than 6 months.
- Yes, I have been for LESS than 6 months.
- No, but I intend to in the next 30 days.
- No, but I intend to in the next 6 months.
- No, and I do NOT intend to in the next 6 months.

Scoring

- answered with choice #1: stage = Maintenance
- answered with choice #2: stage = Action
- answered with choice #3: stage = Preparation
- answered with choice #4: stage = Contemplation
- answered with choice #5: stage = Precontemplation

Appendix 7

How Physically Active Are You?

An assessment of level and intensity of physical activity

Rapid Assessment of Physical Activity

Physical Activities are activities where you move and increase your heart rate above its resting rate, whether you do them for pleasure, work, or transportation.

The following questions ask about the amount and intensity of physical activity you usually do. The intensity of the activity is related to the amount of energy you use to do these activities.

Examples of physical activity intensity levels:

Light activities • your heart beats slightly faster than normal • you can talk and sing	 Walking Leisurely  Stretching  Vacuuming or Light Yard Work
Moderate activities • your heart beats faster than normal • you can talk but not sing	 Fast Walking  Aerobics Class  Strength Training  Swimming Gently
Vigorous activities • your heart rate increases a lot • you can't talk or your talking is broken up by large breaths	 Stair Machine  Jogging or Running  Tennis, Racquetball, Pickleball or Badminton

How physically active are you? *(Check one answer on each line)*

		Does this accurately describe you?	
RAPA 1			
1	I rarely or never do any physical activities.	Yes ☐	No ☐
2	I do some **light** or **moderate** physical activities, but not every week.	Yes ☐	No ☐
3	I do some **light** physical activity every week.	Yes ☐	No ☐
4	I do **moderate** physical activities every week, but less than 30 minutes a day or 5 days a week.	Yes ☐	No ☐
5	I do **vigorous** physical activities every week, but less than 20 minutes a day or 3 days a week.	Yes ☐	No ☐
6	I do 30 minutes or more a day of **moderate** physical activities, 5 or more days a week.	Yes ☐	No ☐
7	I do 20 minutes or more a day of **vigorous** physical activities, 3 or more days a week.	Yes ☐	No ☐
RAPA 2 (3 = Both 1 & 2)			
1	I do activities to increase muscle **strength**, such as lifting weights or calisthenics, once a week or more.	Yes ☐	No ☐
2	I do activities to improve **flexibility**, such as stretching or yoga, once a week or more.	Yes ☐	No ☐

ID # _____

Today's Date _____

Scoring Instructions

RAPA 1: Aerobic

To score, choose the question with the highest score with an affirmative response. Any number less than 6 is suboptimal.

For scoring or summarizing categorically:

Score as sedentary:

1. I rarely or never do any physical activities.

Score as under-active:

2. I do some light or moderate physical activities, but not every week.

Score as under-active regular – light activities:

3. I do some light physical activity every week.

Score as under-active regular:

4. I do moderate physical activities every week, but less than 30 minutes a day or 5 days a week.
5. I do vigorous physical activities every week, but less than 20 minutes a day or 3 days a week.

Score as active:

6. I do 30 minutes or more a day of moderate physical activities, 5 or more days a week.
7. I do 20 minutes or more a day of vigorous physical activities, 3 or more days a week.

RAPA 2: Strength & Flexibility

I do activities to increase muscle strength, such as lifting weights or calisthenics, once a week or more. (1)

I do activities to improve flexibility, such as stretching or yoga, once a week or more. (2)

Both. (3)

None (0)