Cortical activations underlying human bipedal balance control

by

Jessy Parokaran Varghese

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners. I understand that my thesis may be made electronically available to the public.

Jessy Parokaran Varghese

Abstract

Human bipedal balance is a complex sensorimotor task controlled by the central nervous system. Balance impairments, caused by aging or neuromuscular diseases, often lead to falls which are one of the leading causes of injury and subsequent increases in health care costs. Hence, understanding the mechanisms underlying human bipedal balance control has many functional and clinical implications. Traditionally, it was believed that balance control is mediated by subcortical structures. However, evidence from research in the past few decades has shown that the cerebral cortex plays a major role in bipedal balance control. Nevertheless, the cortical contributions in balance control are still unclear. Hence, the purpose of this thesis was to extend the understanding of cortical involvement in human bipedal balance control. Specifically, the two overarching goals of this thesis were to examine evidence of a cortical network involvement and its generalizability across reactive and predictive balance control. These two overarching goals were addressed through four different studies. Study 1 explored the frequency characteristics and mechanisms underlying the generation of perturbation-evoked potentials. Study 2 investigated cortical activity linked to 'automatic' balance reactions that occur continuously while standing still and its dependence on the amplitude of these balance reactions. Study 3 examined the cortical activations related to the preparation and execution of anticipatory postural adjustments that precede a step and whether the activations are dependent on the context of control. Study 4 was designed to examine the functional connectivity in balance control and whether similar networks underlie reactive and predictive balance control. Studies were conducted on young healthy adults and cortical activations were acquired using electroencephalography during feet-in-place balance reactions, standing still, and voluntary stepping. Overall, the findings of these studies provided direct and indirect evidence for the

involvement of a cortical network in balance control and its generalizability across different classes of balance control. This work reinforces the view that cortical networks likely play an important role in the control of stability. It is proposed that the synchronized activation of neural assemblies distributed across the cortex might have contributed to the balance-related cortical activations. The findings of this thesis extend the understanding of cortical control of human bipedal balance that may help to inform future, more precise models of the cortical contributions to balance control. This, in turn, can inform future diagnostic and therapeutic approaches to improve mobility among those with balance impairments.

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Table of Contents

List of Figures

List of Tables

List of Abbreviations

ANOVA - Analysis of variance

AP - Anterior-posterior/anteroposterior

APA - Anticipatory postural adjustment

APR - Automatic postural reaction

BMLL - Bimanual load lifting

BOS - Base of support

BP - Bereitschaftspotential

CNS - Central nervous system

CNV - Contingent negative variation

COM - Center of mass

COP - Center of pressure

CPA - Compensatory postural adjustment

CPL - Characteristic path length

ECG - Electrocardiography

EEG - Electroencephalography

EMG - Electromyography

EOG - Electrooculography

EPSP - Excitatory postsynaptic potential

ERD - Event-related desynchronization

ERN - Error-related negativity

ERP - Event-related potential

ERPC - Event-related phase coherence

ERS - Event-related synchronization

ERSP - Event-related spectral perturbation

FFT - Fast Fourier transform

fMRI - Functional magnetic resonance imaging

fNIRS - Functional near-infrared spectroscopy

FO - Foot-off

GTA - Graph theoretical analysis

IC - Independent component

ICA - Independent component analysis

ITC - Inter-trial coherence

IPSP - Inhibitory postsynaptic potential

M1 - Primary motor cortex

MEG - Magnetoencephalography

ML - Medial-lateral/ mediolateral

MMP - Movement monitoring potential

MP - Motor potential

MRI - Magnetic resonance imaging

MRP - Movement-related potential

NS - Negative slope

PD - Parkinson’s disease

PEP - Perturbation-evoked potential

PET - Positron emission tomography

PFC - Prefrontal cortex

PMC - Premotor cortex

PMP - Pre-motion positivity

PPC - Posterior parietal cortex

RMS - Root-mean-square

RP - Readiness potential

SMA - Supplementary motor area

SPECT - Single photon emission tomography

TMS - Transcranial magnetic stimulation

Chapter 1

Introduction

1.1 Background

The ability to stand bipedally in both static and dynamic environments is an extraordinary characteristic of humans. Humans often perform secondary tasks during upright stance without paying attention to balance control, hence bipedal balance control appears to be highly automatic. However, the ability to maintain upright stance is a remarkably complex balance control challenge because the human body is an inherently unstable system. This is due to two-thirds of the body mass being located above the two legs providing only a narrow base of support and the intrinsic instability of the musculoskeletal linkage caused by gravitational forces (Maki and Ostrovski, 1993; Winter, 1995b). The ability to maintain balance often deteriorates as a result of aging and/or neuromuscular disorders such as Parkinson's disease (PD), multiple sclerosis, stroke, peripheral neuropathy, muscular dystrophies, cerebellar ataxia, amyotrophic lateral sclerosis, cerebral palsy, and spinal cord injuries (Maki et al., 1994; Winter, 1995b; Horlings et al., 2008). Among the elderly population, falls are the leading cause of injury and accidental death (Maki et al., 1987; Rubenstein, 2006; Billette and Janz, 2011). According to Statistics Canada, falls injured 63% of seniors and 35% of working-age adults (Billette and Janz, 2011). In the United States, falls occur in 30-60% of the geriatric population resulting in injury, hospitalization, and even death (Rubenstein, 2006). This in turn has led to an increased economic burden to society in terms of health care costs, reduced activity due to post-fall syndrome, and reduced productivity due to sprains, strains, and fractures (Maki et al., 1987; Billette and Janz, 2011).

Among the many distinct causes, impaired balance is the major reason for falls in the elderly whereby the postural control system is unable to correct for unexpected perturbations such as slips or trips during gait, standing, bending, reaching, pushing or pulling (Maki et al., 1987; Rubenstein, 2006). Age-related or neurological injury-related impairments in the sensory, motor, and nervous system deteriorate the performance of the postural control system leading to impaired balance and falls (Berg, 1989). Hence, understanding the mechanisms underlying human bipedal balance control has many functional and clinical implications, especially in physical therapy practice (Horak et al., 1997; Maki and McIlroy, 1997). In order to adequately interpret balance disorders, develop appropriate diagnostic tools to assess balance, develop therapeutic approaches for rehabilitation of balance disorders, and design effective interventions to improve balance, we need to first understand how the postural control system maintains human bipedal balance (Horak et al., 1997; Maki and McIlroy, 1997). Specifically, understanding the neural control of human bipedal balance could help identify the causes of balance impairments associated with various neurological disorders and develop diagnostic and therapeutic tools, in turn reducing healthcare costs and improving quality of life.

Historically, the neural control of balance was thought to be subcortically mediated and hence ‘automatic’ (Sherrington, 1910; Magnus, 1926; Horak et al., 1997). Early reflex studies in which decerebrate cats and dogs exhibited reflex standing have led to the notion that balance is a reflex response evoked by sensory stimuli and is controlled by the neural substrates of the brain stem and spinal cord (Sherrington, 1910; Magnus, 1926). However, evidence from recent human studies using dual-task paradigms, electroencephalography (EEG), magnetoencephalography (MEG), transcranial magnetic stimulation (TMS), positron emission tomography (PET), single photon emission tomography (SPECT), functional near-infrared spectroscopy (fNIRS), visual-

attention studies, and lesion studies suggest that balance control is a complex skill which is likely to be learned and regulated by a distributed neural network system with a potential role for the cerebral cortex (Dietz et al., 1984; Fukuyama et al., 1997; Ouchi et al., 1999; McIlroy et al., 1999; Miyai et al., 2001; Malouin et al., 2003; Jahn et al., 2004; Jacobs and Horak, 2007; Maki and McIlroy, 2007; Mihara et al., 2008; la Fougère et al., 2010; Marlin et al., 2014). Nevertheless, cortical involvement in human bipedal balance control is still unclear. Hence, the overarching goal of this thesis was to extend the understanding of cortical contributions in balance control by examining the cortical activations associated with predictive (anticipatory postural adjustments (APAs)) and reactive (compensatory postural adjustments (CPAs)) balance control.

1.2 Rationale

Human bipedal balance control is maintained reactively and predictively by the postural control system. Even though there is recent literature exploring the cortical involvement in balance control, there is still scarce research that explores cortical activations related to both reactive and predictive balance control. For instance, previous studies that examined cortical activations related to reactive balance control have explored the amplitudes and latencies (time domain analysis) of perturbation-evoked potentials (PEPs) that occur after a balance perturbation (Dietz et al., 1984). However, the frequency characteristics of PEPs have not been explored. In addition, cortical activations related to reactive balance control during standing still and generation of APAs in predictive balance control during stepping have yet to be revealed. Moreover, the research to date has shown that various cortical regions are involved in balance control. However, there have been no studies examining the involvement of a cortical network in balance control. Even though some studies have proposed a network or multiple dipole model for balance

control, there remains debate/challenges in the interpretation regarding a network involvement at the level of the cortex. In addition, the generalizability of this network has to be explored to examine whether the cortical contributions to balance control are generalizable across different balance tasks. Most of the studies to date have limited their focus to a single task (e.g. perturbation evoked reactions) and in some cases complex tasks are used that likely include more than just balance control (e.g. gait). To address this gap in knowledge, the studies of this thesis were designed to provide evidence for the potential involvement of a cortical network and its generalizability by examining cortical activations and functional connectivity associated with reactive and predictive balance control during three balance tasks: standing still, compensatory feet-in-place reactions, and voluntary stepping. It is anticipated that the findings of this thesis work will extend the understanding of cortical control of human bipedal balance. In addition, this work would lead to future work exploring the mechanisms underlying disordered balance control associated with neurological injury and aging, and applying this knowledge to develop more effective diagnostic and therapeutic measures to improve mobility and quality of life of elderly and balance-impaired individuals.

1.3 Research Objectives

The two overarching questions addressed in this thesis were:

1. Is the cortical contribution to balance control reflective of a network of activity of cortical regions or the activity of a specific focal loci?
2. Is the potential cortical network generalizable across a range of balance control tasks from reactive to predictive or is the network specific to each type of task?

These two overarching questions were addressed using four studies that made up this thesis, in which the following specific research objectives were addressed:

Study 1: Frequency characteristics of cortical activity associated with perturbations to upright stability

- To explore the frequency characteristics of the perturbation-evoked N1 response.
- To investigate evidence for the partial phase reset mechanism in the genesis of the perturbation-evoked N1 response.

Study 2: **Standing still: Is there a role for the cortex?**

- To reveal the cortical activity linked to the 'automatic' balance reactions that occur continuously when one is standing still.
- To determine whether the amplitude of this cortical activity is associated with the amplitude of balance reactions.

Study 3: Cortical control of anticipatory postural adjustments prior to stepping

- To examine the cortical activations related to the preparation and execution of APAs that precede a step.
- To investigate whether cortical activations related to a specific movement are associated with the context of control (postural component vs. focal component).

Study 4: Functional networks underlying human bipedal balance control

- To explore the functional connectivity during reactive and predictive balance control.
- To examine whether similar patterns and strengths of connectivity exist between reactive and predictive balance control as well as between reactive balance control to internally and externally generated perturbations.

In summary, the four studies constituting this thesis specifically examined evidence of a cortical network involvement associated with balance control by analyzing spatial, frequency, and

connectivity characteristics of ERPs. Study 1 used frequency analysis to reveal the potential involvement of a cortical network in reactive balance control to external perturbations. Study 2 was a novel assessment of automatic reactive control during standing still to determine if such cortical activity, revealed in response to external perturbations, is evident when perturbations arise from internal causes. Study 3 examined cortical activations related to predictive balance control to determine if the spatial and frequency characteristics paralleled that observed during reactive control. Study 4 employed functional connectivity techniques to determine the potential cortical network and its generalizability across the tasks used in studies 1 through 3 (reactive external, reactive internal and predictive).

1.4 Overarching Hypotheses

Through various lines of evidence, it is likely that a cortical network is involved in balance control. Research from the past few decades using various neuroimaging modalities like PET, TMS, EEG, FNIRS, dual-task paradigms, and lesion studies have shown that different cortical areas are active during balance control (Dietz et al., 1984; Di Fabio et al., 1986; McIlroy et al., 1999; Ouchi et al., 1999; Solopova et al., 2003; Mihara et al., 2008; Marlin et al., 2014). In addition, the research to date suggests that various cortical regions are involved in the detection of postural instability, generation, and execution of APAs and CPAs (Chan et al., 1979; Diener et al., 1985; Gurfinkel and Elner, 1988; Viallet et al., 1992; Beloozerova et al., 2003; Taube et al., 2006; Yakovenko and Drew, 2009; Chang et al., 2010). From these studies, it can be inferred that a distributed network of cortical areas might be involved in balance control. It is also likely that a similar pattern of cortical connectivity may exist for reactive and predictive balance control. Electrophysiological studies have shown that both APA and CPA-related ERPs have similar widespread fronto-central topographic distributions (Mochizuki et al., 2008). Behavioral

studies have shown that both APAs and CPAs share the same set of postural synergies. For instance, the CPA in response to backward platform translation and the APA prior to voluntary pull on a stiff handle activates posterior muscles in a distal-to-proximal order (Nashner, 1977; Cordo and Nashner, 1982; Frank and Earl, 1990). The parallels in cortical activations and behavioral control of APAs and CPAs suggest that a similar cortical network underlies reactive and predictive balance control. Hence, the two overarching hypotheses of this thesis were:

1. Cortical contributions to balance control will be associated with a network of activity involving multiple cortical regions.
2. The pattern of this cortical network will be generalizable across balance tasks (reactive and predictive, reactive balance control to internally and externally generated perturbations).

Chapter 2

Literature Review

This literature review provides an overview of the postural control system, strategies used to maintain bipedal balance, techniques to characterize balance control, neural control of balance, and cortical activations associated with reactive and predictive balance control.

2.1 Postural Control System

Postural control is a complex sensorimotor task required to maintain human upright stance by accomplishing two major goals: postural orientation and postural equilibrium (Winter et al., 1990; Horak, 2006). Postural orientation refers to actively aligning the body parts with respect to each other and with respect to the external world such as gravitational vertical, visual vertical, and support surfaces (Massion, 1994; Winter, 1995b; Horak, 2006). Postural equilibrium (commonly referred to as 'balance' or 'stability') refers to maintaining the relationship between the center of mass (COM) and base of support (BOS) (Massion, 1994; Winter, 1995b; Maki and McIlroy, 1997; Horak, 2006). While the COM refers to the point location equivalent to the total body mass, BOS refers to the area demarcated by the body parts that are in contact with the supporting surface (Massion, 1992; Winter, 1995b). The present thesis focused on the cortical control of balance and hence the following sections will summarize the literature with respect to postural equilibrium.

The postural control system that regulates human upright stability is made up of three subsystems: (1) the sensory system that provides information about body position relative to the environment, position and motion of the head with respect to gravity, and movement of body segments relative to each other through visual, vestibular (otoliths and semicircular canals), and somatosensory (muscles, joints, skin) inputs, (2) the central nervous system (CNS) that evaluates

and integrates the sensory information to generate appropriate postural commands, and (3) the musculo-skeletal system which are the effectors that execute the postural commands by generating complex patterns of muscle activation appropriate for balance control (Berg, 1989; Frank and Earl, 1990; Winter et al., 1990; Horak, 2006). The different variables controlled by the postural control system include COM, limb geometry, head stabilization and gaze fixation, energy expenditure, and contact forces (Horak et al., 1997). The redundancy in sensory information from various sensory inputs enables the CNS to compensate for deterioration from one input, to re-weight the sensory input with respect to the sensory context, and also to verify sensory information prior to generating the postural command (Winter et al., 1990; Horak, 2006). For instance, the linear acceleration of the whole body relative to the environment is signaled by otoliths of the vestibular system, optic flow in the visual system, and somatosensory input provided by the mechanoreceptors in the human feet and proprioceptors in the muscles and joints (Lee and Lishman, 1975).

2.2 Bipedal Balance Control Strategies

The CNS uses two strategies, namely feed-forward (predictive balance control) and feed-back (reactive balance control) strategies for maintaining stability (Frank and Earl, 1990; Massion, 1994; Winter, 1995b; Maki and McIlroy, 1997; Horak, 2006). While the feed-forward strategy is triggered in advance of destabilization, the feed-back strategy follows an internal or external destabilizing perturbation (Cordo and Nashner, 1982; Frank and Earl, 1990). These balance control strategies are usually task-specific (e.g. standing vs. walking) and also specific to the velocity, amplitude, and direction of perturbation (Cordo and Nashner, 1982; Diener et al., 1988; Moore et al., 1988).

2.2.1 Anticipatory Postural Adjustments

APAs are feed-forward strategies that occur prior to or simultaneous with the onset of a voluntary movement or an expected perturbation in order to prevent or minimize the forthcoming postural disturbance induced by the movement or perturbation (Winter et al., 1990; Frank and Earl, 1990; Massion, 1992; Maki and McIlroy, 1997). For example, externally cued and self-initiated rapid pulls on a stiff handle while standing unsupported activate the postural muscles (gastrocnemius and hamstrings) in advance of the focal muscle (biceps brachii) (Cordo and Nashner, 1982; Frank and Earl, 1990). APAs are pre-programmed postural commands that are generated separately from the focal commands and are executed prior to the focal task with a specific direction, amplitude, and timing depending upon the required degree of postural compensation (Cordo and Nashner, 1982; Brown and Frank, 1987; Frank and Earl, 1990; Winter et al., 1990; Massion, 1992). APAs are mainly acquired by learning, likely during early childhood, and are adaptable to the conditions in which the movement is performed (Massion, 1984, 1992). For instance, if the rapid pulls were performed while standing supported, the postural muscle activations are absent (Cordo and Nashner, 1982). APAs are also influenced by prior instructions regarding task requirements (Massion, 1984, 1992). The latency of APAs also depend on the speed of the voluntary movement, with shorter latencies for fast movements and vice versa (Brown and Frank, 1987; Massion, 1992).

2.2.2 Compensatory Postural Adjustments

CPAs are feed-back strategies that compensate for unexpected internal perturbations during standing still and external perturbations either self-induced or experimentally induced (Frank and Earl, 1990; Winter et al., 1990; Maki and McIlroy, 1997). These are rapid reactions manifested as coordinated muscular activities that occur within 100 ms after the perturbation onset and are

the primary defense mechanism against sudden unexpected perturbations such as slips, trips or missteps (Nashner et al., 1979; Allum, 1983; Horak and Nashner, 1986; Maki and McIlroy, 1997). Unlike APAs, CPAs are triggered by sensory inputs that detect the instability. The three sensory systems, somatosensory, vision, and vestibular systems, signal the orientation and movement of the body parts relative to each other, to the surrounding environment, and to inertia and gravity, whenever there is a deviation from the upright posture (Winter et al., 1990).

In reactive balance control, standing posture is maintained by two major types of strategies: fixed-support and change-in-support strategies (Nashner, 1977). Fixed-support strategies maintain stability without changing the BOS (Maki and McIlroy, 1997). Ankle strategy, hip strategy, suspensory synergy, and exerting force on a handhold are examples of fixed-support reactions (also known as automatic postural reactions (APRs)) (Maki and McIlroy, 1997). APRs have shorter latencies (70-180 ms) than voluntary reactions (180-250 ms) but have longer latencies than stretch reflex responses (40-50 ms) (Horak et al., 1997; Maki and McIlroy, 1997). Selection of a particular strategy depends on environmental constraints (e.g. length of support surface), available sensory information, size of the perturbation, and prior experience (Horak and Nashner, 1986; Horak et al., 1997). Ankle strategy is applied in quiet stance or small perturbations on a firm, wide support surface utilizing the torque generated about the ankle by plantarflexors/dorsiflexors to restore stability (Nashner, 1977; Horak and Nashner, 1986; Winter, 1995b). Hip strategy is triggered when the support surface is narrow or large perturbations are applied and utilizes forward and backward movements of the hips that generate shear forces on the support surface to restore balance (Nashner and McCollum, 1985; Horak et al., 1990; Winter, 1995b). Suspensory synergy utilizes calf and thigh muscles to resist load changes on the lower limbs caused by the vertical displacement of a platform (Nashner, 1977; Nashner and McCollum,

1985; Winter et al., 1990). It has been suggested that the APR is mainly triggered by muscle proprioceptive input, whereas cutaneous and joint somatosensory information is not critical (Horak et al., 1990). This is evident by a normal APR latency in somatosensory loss due to ischemic hypoxia at the ankles but a delayed onset of APR in patients with diabetic peripheral neuropathy (Horak et al., 1990). However, cutaneous and joint somatosensory input is necessary to select and control appropriate APR strategy (Horak et al., 1990). Vestibular input contributes to the magnitude of the APR and advances selection of APR strategies as evident by the normal latency, but the abnormal amplitude of postural responses in vestibular loss patients and their inability to use hip strategy when it was required to maintain stability while standing on a narrow support surface (Nashner et al., 1979; Horak et al., 1990; Allum et al., 2003). Visual information processing is too slow to trigger an APR and hence contributes to the later stages of postural response (after 300 ms) (Allum et al., 2003). Moreover, onset of the APR was not affected by loss of visual input from birth (Nakata and Yabe, 2001; Allum et al., 2003). However, visuospatial information about the environment obtained prior to the perturbation is incorporated to initiate the change-in-support strategies (Ghafouri et al., 2004; Zettel et al., 2005). Change-in-support strategies often involve lower or upper limb movements that alter the base of support and are commonly used to counteract large perturbations (Maki and McIlroy, 1997). Stepping and grasping movements are two commonly used change-in-support strategies (Maki and McIlroy, 1997).

Balance control in quiet stance is thought to be composed of both open-loop and closed-loop postural control mechanisms (Collins and De Luca, 1993). The postural control system utilizes open-loop control schemes over short term intervals, whereas it uses the closed-loop feedback mechanism over long term intervals (Collins and De Luca, 1993). The postural control

system utilizes ankle strategy in the AP direction using plantar/dorsiflexors and ML weight transfer (hip load/unload strategy) using hip abductors/adductors in the ML direction to maintain stability during quiet stance (Winter, 1995b).

2.3 Techniques to Characterize Balance Control

There are several kinetic, kinematic, electrophysiological, and neuroimaging techniques used in research and clinical settings to characterize, assess, and quantify the neural control of balance. However, this review summarizes only those techniques that were used in the four studies that comprised this thesis work.

2.3.1 Electromyography

Surface electromyography (EMG) is the most widely used electrophysiological technique for characterization and assessment of the neural control of balance. Postural commands are executed with a specific spatiotemporal muscle activation pattern known as postural synergies which can be monitored using EMG (Winter et al., 1990). For instance, ankle strategy in APRs manifests a distal-to-proximal muscle activation pattern in functionally related muscles of the legs and lower trunk, whereas hip strategy exhibits a proximal-to-distal muscle activation pattern (Nashner, 1977). In addition, while standing, pulling on a handle activates an APA in the posterior muscles of the leg and trunk in a distal-to-proximal order, whereas pushing on the handle activates anterior muscles in a distal-to-proximal order (Cordo and Nashner, 1982; Winter et al., 1990; Massion, 1992). Surface EMG is widely used to assess these muscle activation patterns in both healthy individuals and those with balance impairments (Winter et al., 1990). The onset (latency) and amplitude of EMG signals are two frequently used parameters to assess the neural control of balance (Nashner, 1977; Nashner et al., 1979). The latency of postural muscle activations during CPAs and APAs are shorter than the voluntary reaction time of the

same muscles (Nashner and Cordo, 1981; Cordo and Nashner, 1982; Diener et al., 1984). The amplitude of EMG responses of the postural muscles varies with the perturbation amplitude, velocity, direction, and central-set conditions (Moore et al., 1988; Horak et al., 1989). Normal EMG patterns of APRs can be used as a reference to assess impaired balance control associated with various neuromuscular pathologies and to examine the roles of somatosensory, vestibular, and visual inputs in the control of posture (Horak et al., 1990). For instance, the onset of postural muscles in APRs is delayed in diabetic peripheral neuropathic patients due to the slowed sensory or motor conduction (Horak et al., 1997).

2.3.2 Force Plates

Kinetic analysis provides insight into the integrated activity of the neuromuscular system to achieve specific goals of the CNS (Winter, 1995a). Postural synergies generate forces that correct for instability. This action can be observed by recording the ground reaction forces using force plates. Vertical and horizontal ground reaction forces and moments generated during CPAs and APAs are used to calculate the center of pressure (COP) which reflects the CNS response to correct imbalance (Winter et al., 1990). COP is the neural control variable to control the passive variable COM (Murray et al., 1967; Winter, 1995a, b). In a quiet stance condition, COP oscillates on either side of the COM to control it by maintaining the COM position between the two feet (Murray et al., 1967; Winter et al., 1996,1998). While CPAs have a characteristic muscle activation pattern and share the same set of postural synergies with APAs (e.g. CPAs in response to backward platform translation and APAs prior to voluntary pulls on a stiff handle activate posterior muscles in a distal-to-proximal order), generation of APAs sometimes lack a consistent postural synergy among subjects due to inter-subject variability associated with voluntary movements (Cordo and Nashner, 1982; Frank and Earl, 1990; Winter et al., 1990,

Winter, 1995b). For instance, generation of a lateral weight shift prior to leg flexion can be accomplished using either ankle evertors/invertors or hip abductors/adductors. In such cases, ground reaction forces and COP variables provide an appropriate measurement to assess balance control (Rogers and Pai, 1990, 1993; Mouchnino et al., 1992). In addition, COP sway is the most frequently used parameter in both research and clinical settings to assess balance control, examine and quantify the sensory contributions, and diagnose impaired balance control in patients with neuromuscular disorders (e.g. sensory neuropathy, ataxia, cerebellar atrophy, cerebral palsy, PD) (Diener et al., 1984; Winter et al., 1990; Maki and Ostrovski, 1993).

2.3.3 Electroencephalography

While force plate measurements reveal the integrated control of the distributed neural network, EEG activity reveals the cortical activations related to balance control. EEG recorded from the scalp reflects the synchronous activation (summation of post-synaptic potentials) of the cortical pyramidal neurons (layer III, V, VI) within a cortical area of macroscopic extent (Gloor, 1985; Olejniczak, 2006; Avitan et al., 2009). The parallel arrangement of these pyramidal neurons and the perpendicular orientation of their apical dendrites with respect to the cortical surface facilitate their synchronized activation to be detectable on the scalp (Gloor, 1985). The major advantages of EEG over other neurophysiological techniques (e.g. microelectrode recordings, PET, SPECT, and functional magnetic resonance imaging (fMRI)) are that it is noninvasive, has excellent temporal resolution (< 1 ms), relatively inexpensive, and is suitable for balance studies that require tasks to be performed while standing (Luck, 2005). EEG recorded during postural adjustments can be analyzed in both time and frequency domains to reveal the cortical activations associated with balance control (Dietz et al., 1984; Mochizuki et al., 2010; Slobounov et al., 2009; Jacobs et al., 2015).

2.3.3.1 Event-related Potentials

Event-related potentials (ERPs) correspond to time-locked changes in EEG activity induced by several types of events (e.g. sensory stimuli) and are detected using averaging techniques (Pfurtscheller and Lopes da Silva, 1999). There exist two different assumptions underlying the generation of ERPs. The evoked model (additive model) suggests that ERPs are generated by the addition of stimulus-evoked, fixed latency, fixed polarity neuronal activity onto the ongoing background oscillatory activity, which can be retrieved by averaging techniques (Jervis et al., 1983; Makinen et al., 2005). In contrast, the phase-reset model (phase reorganization model) suggests that ERPs arise from the event-related reorganization of the phase, latency, and/or modulation of amplitude of the ongoing (background) EEG activity resulting in the phase synchronization of different oscillatory EEG rhythms (Sayers et al., 1974; Brandt, 1997; Jansen et al., 2003; Rizzuto et al., 2003; Klimesch et al., 2004). Alternatively, the partial phase reset model suggests that ERPs result from a combination of both the additive and phase reset models (Makeig et al., 2002; Fell et al., 2004; Gruber et al., 2005; Fuentemilla et al., 2006). Phase synchronization of EEG signals from a single electrode is quantified in terms of event-related inter-trial coherence (ITC) which is a frequency domain measure that quantifies the synchronization between EEG data and time-locking events (Kolev and Yordanova, 1997; Delorme and Makeig, 2004; Roach and Mathalon, 2008).

The two ERPs explored in this thesis are PEPs and movement-related potentials (MRPs). PEPs are ERPs evoked by balance perturbations (discussed in section 2.6.2). Both voluntary and externally triggered movements are preceded and accompanied by MRPs which consist of mainly 4 components. First, the Bereitschaftspotential (BP) or readiness potential (RP) which occurs approximately 1.5-2 s prior to the onset of movement as a slow negative potential over

parietal and precentral areas with maximum over vertex (Cz) and is bilaterally symmetrical (Kornhuber and Deecke, 1965; Deecke et al., 1969, 1976). However, BP increases its gradient over the contralateral primary motor cortex (M1) and lateral premotor cortex (PMC) approximately 400 ms prior to the movement onset, hence the late steeper slope is termed as late BP or negative slope (NS) whereas the initial slow segment is termed as early BP which arises from the supplementary motor area (SMA) (Shibasaki and Hallett, 2006). BPs reflect the motor preparatory process and are assumed to be generated by the summation of postsynaptic potentials in the dendritic network of upper layers of the cortical areas that are involved in the movement (Deecke et al., 1976). Second, the pre-motion positivity (PMP) which starts about 80-90 ms prior to EMG onset and is bilaterally symmetrical over the parietal and precentral region with maximum amplitude over anterior parietal areas (e.g. BA 5) (Kornhuber and Deecke, 1965; Deecke et al., 1976). PMP represents the cortical activity related to the initiation of movement, most likely the motor command (spatiotemporal patterns of movement) itself (Deecke et al., 1976). The third component, the motor potential (MP), arises approximately 50-60 ms prior to EMG onset and is unilateral with maximum amplitude over the contralateral M1 (Kornhuber and Deecke, 1965; Deecke et al., 1969, 1976). MP is assumed to be triggered by subcortical circuits, especially the cerebellum via the thalamus, and reflects motor cortical activity immediately preceding the voluntary movement (Deecke et al., 1976). Lastly, the movement monitoring potential (MMP) or goal-directed movement potential is the increased negativity that occurs after EMG onset and persists during the execution of movement (Grünewald-Zuberbier et al., 1981). The MMP reflects cortical activity related to movement execution (Grünewald-Zuberbier and Grünewald, 1978).

2.3.3.2 Event-related Spectral Perturbation

It is likely that the partial phase reset mechanism contributes to the generation of ERPs. In that case, the stimulus-evoked response of the brain cannot be fully captured by averaging techniques because ongoing background oscillations modified by the stimulus are not exactly synchronized in both time and phase to the stimulus onset and will therefore cancel out (Makeig, 1993). In addition, even the fixed-latency and fixed-polarity additive component is not stable across the trials due to within subject variability (Makeig, 1993). Hence, the analysis of EEG in the frequency domain is required to reveal phase-locked and non-phase locked responses evoked by experimental stimuli or other events (Makeig, 1993). While the power spectral density plot, based on Fourier transform, decomposes the EEG/ERP waveforms into a set of sine waves of different frequencies and amplitudes, it lacks temporal information (Makeig, 1993). The event-related spectral perturbation (ERSP) technique is used to retain temporal information in the frequency domain analysis using moving window techniques (Makeig, 1993). ERSP computes the Fourier transform of a brief time window at the beginning of each EEG epoch (time-locked to experimental events) to quantify the amplitude at each frequency (Makeig, 1993). The process repeats as the window is moved over the entire range of the trial (Makeig, 1993). The Fourier transform at a given time point are then averaged across all the EEG epochs (called time-locked spectral averaging) and subtracted or divided from a baseline spectral estimate to generate an ERSP plot displaying the event-related changes in spectral amplitudes (Makeig, 1993).

ERSP is a generalization of event-related desynchronization (ERD) and event-related synchronization (ERS) measures (Makeig, 1993; Pfurtscheller and Lopes da Silva, 1999; Delorme and Makeig, 2004). ERD represents an electrophysiological measure of activated cortical areas related to information processing, selective attention, motor preparation, and/or

motor execution (Pfurtscheller et al., 1996). ERS reflects either the cortical idling state (deactivated cortical area) or the synchronized activation of a large number of cortical modules (Pfurtscheller et al., 1996). For instance, during the planning and execution of voluntary hand movements, ERD of central mu (8-12 Hz) and beta (13-28 Hz) rhythms corresponds to the activation of the sensorimotor cortex and SMA whereas the ERS of gamma waves (40 Hz) reflects the neural interactions (intra-cortical and inter-cortical information transfer) between sensorimotor areas (Pfurtscheller, 1981; Pfurtscheller et al., 1993, 1996; Rubino et al., 2006). It has been suggested that the massive projection of basal ganglia to the thalamus influences the thalamo-cortical rhythmic circuits resulting in the ERD of mu and beta rhythms prior to movement (Pfurtscheller, 1981). Even though both ERD and MRPs have similar latencies (1.5-2 s prior to movement onset), similar topographies (primary sensorimotor areas and SMA), and start prior to movement onset, they reflect different aspects of sensorimotor cortical processes (Babiloni et al., 1999). While alpha ERD reflects changes in ongoing oscillatory activity in wide sensorimotor cortical areas and depends on thalamo-cortical feedback loops, MRPs reflect increased, task-specific excitability of the SMA and contralateral primary sensorimotor areas and depend on cerebellar-thalamo-cortical circuitry (Babiloni et al., 1999).

2.3.3.3 Independent Component Analysis

It is now believed that information processing in the brain is performed in a parallel fashion by the simultaneous activation of several neural assemblies in anatomically distinct cortical areas and the integration of these distributed sets of neuronal activities leading to the coherent representation of sensory input and generation of motor output (Lopes da Silva, 1991). Hence, EEG activity recorded from the scalp is composed of activity from these different neural networks. In addition, EEG signals are often contaminated with noise arising from both

biological and non-biological sources. The frequently observed EEG artifacts include alpha waves around 10 Hz from posterior electrode sites (due to tiredness or boredom) and non-EEG biological signals such as skin potentials (slow voltage shifts), electrocardiographic (ECG) artifacts, electroocoulographic (EOG) artifacts caused by blinks (monophasic deflection of 50-100 μV and 200-400 ms duration) and eye movements, as well as muscle activity (typically > 100 Hz) from the neck, jaw, and forehead (Luck, 2005; Thompson et al., 2008; Keil et al., 2014). Non-biological artifacts include slow voltage shifts (0-20 Hz) due to changes in electrode position caused by head movements and cable movement artifacts, inherent noise in electronic equipment, and electrical noise from sources such as AC power lines (50 or 60 Hz), video monitors (60-75 Hz), AC lights, and other devices powered by AC line voltage (Luck, 2005; Keil et al., 2014). Independent component analysis (ICA) is frequently used in EEG research to remove artifacts and identify the brain sources from the raw EEG data (Keil et al., 2014). ICA identifies a set of independent components (ICs) with spatially fixed scalp distributions and temporally independent time courses by performing blind source separation (without prior knowledge of the physical location or configuration of the source generators) on the EEG data (Makeig et al., 1996). Among the various ICA algorithms, infomax ICA is one of the most popular algorithms used in EEG research (Bell and Sejnowski, 1995; Keil et al., 2014). The infomax ICA algorithm is based on the 'infomax' neural network that uses the EEG data recorded from multiple scalp electrodes to train an 'unmixing' weight matrix which then acts as linear spatial filters decomposing the N-channel EEG data in to N ICs (Makeig et al., 1997).

2.4 Neural Control of Balance in Animals

Postural control mechanisms have been extensively studied in various aquatic and terrestrial animals such as mollusc Clione, lamprey, rats, rabbits, cats, and dogs (see Deliagina and

Orlovsky, 2002; Deliagina et al., 2006 for review). While the neural control of postural orientation has been explored in aquatic animals, neural control of both APAs and CPAs have been explored in terrestrial animals (Deliagina et al., 2006). It was found that Clione and lamprey use postural reflexes driven by their gravitational inputs for maintaining postural orientation and these reflexes are mediated by the spinal cord (Clione) and brainstem (lamprey) (Deliagina et al., 2006). Lesion studies in cats and dogs by Sherrington (1910) have shown that the spinal preparation was not able to stand, whereas decerebrate cats exhibited reflex rigidity that maintained an erect posture when passively set upright. This proprioceptive triggered reflex standing employs tonic contraction of the extensor antigravity muscles and inhibition of flexors and was controlled by a brain stem center located between the anterior colliculus and posterior edge of pons (Sherrington, 1910). However, this tonic postural reflex persisted even when the decerebrate preparation was completely inverted and reflex stepping lacked sufficient balance control (Sherrington, 1910). In addition, the spinal cats (spinalized at T6 level) exhibited poor (increased latencies and amplitudes) or absent APR response to support surface translation and were unable to maintain balance (Macpherson and Fung, 1999). The response to the platform translation was observed from antigravity muscles but there was no response from flexor muscles (Macpherson and Fung, 1999). The decerebrate cats exhibited similar directionally specific tuning of postural muscles to that of intact cats in response to support surface translations in different directions (Honeycutt et al., 2009). The authors suggested that the directional tuning is mediated by the brain stem and spinal circuits with no role for the cortex (Honeycutt et al., 2009). Even though directionally appropriate, the responses lacked sufficient strength and duration to counteract the perturbation (Honeycutt et al., 2009). Furthermore, the

head and tail of the decerebrate cats were fixed during the experiment and the extent to which this external support assisted the balance was not discussed in the study.

The cerebellar control in maintaining balance is well documented in animals (see Morton and Bastian, 2004 for review). It has been demonstrated that the medial regions of the cerebellum (vermis, fastigial nuclei, and flocculonodular lobe) play a major role in regulating the extensor tone, maintaining upright stance, and dynamic balance control in animals, whereas the intermediate and lateral cerebellar regions are less important for balance control (Morton and Bastian, 2004). Thus, these animal studies have led to the notion that the neural control of balance is subcortically mediated by the brain stem, cerebellum, and spinal cord.

However, in the last few decades, evidence for cortical involvement in balance control has been explored in animals (Birjukova et al., 1989; Beloozerova et al., 2003, 2005; Yakovenko and Drew, 2009). The role of the sensorimotor cortex in APAs was studied in cats during conditioned paw lifting movements by inducing a contralateral sensorimotor lesion (Birjukova et al., 1989). It was reported that after the lesion, the inborn postural pattern was not affected, whereas learned postural patterns were altered, suggesting the sensorimotor cortex is involved in learning new postural patterns (Birjukova et al., 1989). Single neuron recordings in the motor cortex of rabbits revealed strong activation of layer 5 corticofugal neurons (that project to the thalamus, subcortical motor nuclei, and spinal cord) while maintaining balance in response to periodic platform tilts in the frontal plane and during locomotion, suggesting that the motor cortex is involved in the generation of CPAs (Beloozerova et al., 2003). In another study using the same experimental paradigm, the authors found that the activity of pyramidal tract neurons from the forelimb representation area of the motor cortex of cats was strongly modulated during postural corrections (Beloozerova et al., 2005). These pyramidal tract neurons also contributed to

the generation of an APA that precedes the onset of a reaching movement in standing cats (Yakovenko and Drew, 2009). In summary, the studies using various animal models suggest that quadrupedal balance control is mediated by a distributed neural network including both cortical and subcortical structures.

2.5 Neural Control of Balance in Humans

Postural control studies in animal models have attempted to generalize the results to human postural control mechanisms. However, human bipedal stance is more challenging than the quadrupedal stance of animals and might require more complex and greater cortical input for the control of balance. Maintaining human upright stance requires the execution of appropriate postural commands to counteract perturbations caused by the voluntary movement of limbs and trunk, naturally occurring instability during standing still, self-initiated external perturbations, and unexpected external perturbations. The generation of postural command is thought to be an integrated activity of a distributed neural network, but the specific role of each nuclei or region is not fully understood. Research to date suggests that the neural control of bipedal balance is mediated by both spinal and supra spinal circuits which include the brain stem (midbrain, pons, and medulla), cerebellum, basal ganglia, thalamus, limbic system, and cerebral cortex (Babinski, 1899; Nashner et al., 1979; Massion, 1992; Maki and McIlroy 2007).

2.5.1 Spinal Cord and Brain Stem

It has been suggested that local networks responsible for APAs are located on the spinal cord and brain stem based on the absence of APAs in the spastic leg of children with cerebral palsy or the delayed onset of APAs in hemiplegic individuals during voluntary arm movements (Nashner et al., 1983; Horak et al., 1984; Massion, 1992). In addition, brain stem areas seem to be responsible for the basic motor programs underlying APAs prior to stepping (Timmann and

Horak, 2001). It is proposed that the basic activity patterns for CPAs are organized by neuronal circuitry at the spinal cord and brain stem level (Nashner et al., 1979). The spinal neural generators organize individual limb movements and inter-limb coordination based on the somatosensory inputs from muscles, joints, and cutaneous receptors of the legs (Nashner et al., 1979). For instance, abnormal muscle coordination patterns during APRs evoked by platform rotations were observed in the spastic leg of children with cerebral palsy (Nashner et al., 1983). Spinal cord and brain stem areas also play a major role in the adaptive control of APAs and CPAs (Timmann and Horak, 2001). APR responses to unexpected perturbations were absent or delayed in patients with spinal cord lesions (Chan et al., 1979; Diener et al., 1985). In summary, it appears that the basic postural networks responsible for APAs and CPAs are located in the spinal cord and brain stem.

2.5.2 Cerebellum

The cerebellum plays a major role in maintaining human upright posture, utilizing both anticipatory and compensatory mechanisms, as evidenced by impaired standing and walking balance associated with cerebellar damage (Horak and Diener, 1994; Timmann and Horak, 2001; Morton and Bastian, 2004; Diedrichsen et al., 2005; Ilg et al., 2008). However, the cerebellum appears not to be involved in the generation of APAs and CPAs as evident by similar temporal characteristics of APAs and CPAs observed in cerebellar patients compared to that of normal subjects (Nashner, 1976; Timmann and Horak, 2001). In addition, the adaptive control of APAs and CPAs are also intact in cerebellar patients as they were able to use perturbation velocity feedback to scale the magnitude of the postural response (Horak and Diener, 1994; Timmann and Horak, 2001; Diedrichsen et al., 2005). However, the cerebellum controls the magnitude of APAs as indicated by the reduced peak vertical force production during APAs prior to stepping

in cerebellar patients (Timmann and Horak, 2001). The cerebellum also contributes to the acquisition of APAs as evidenced by the difficulty of cerebellar patients in acquiring an APA (anticipatory inhibition of the forearm flexor biceps brachii) during a bimanual load lifting (BMLL) task where the subjects used their one arm to unload the weight on the other arm (postural forearm) (Diedrichsen et al., 2005). Likewise, the anterior lobe of the cerebellum plays a major role in tuning the magnitude of APRs based on prior experience (Horak and Diener, 1994). Cerebellar patients have exhibited hypermetric postural muscle responses and coactivation of postural and its antagonist muscles to backward surface displacements (Horak and Diener, 1994).

The cerebellum also contributes to the coordination of posture and movement (Massion, 1984). Balance control during quiet stance is a complex motor task by the combined effort of two separate and independent motor groups that generate ankle and hip load/unload strategies (Winter, 1995b; Winter et al., 1996). It has been suggested that the cerebellum coordinates these separate motor strategies as evident from postural instability in cerebellar patients during quiet stance (Diener et al., 1984). Studies in cerebellar ataxic patients revealed that the medial, lateral, and intermediate zones of the cerebellum are involved in balance control during locomotion (Ilg et al., 2008).

2.5.3 Basal ganglia

Basal ganglia appear to be involved in both reactive and predictive balance control. The well-documented ‘stooped’ posture of PD patients during quiet stance reveals the dominant role of the basal ganglia and its dopaminergic pathways and the impact of its degeneration on bipedal balance control (Halliday et al., 1998). Basal ganglia seem to be primarily involved in the motor preparatory process by coordinating postural and focal commands during voluntary movements

(Rogers et al., 1987; Winter et al., 1990). Self-paced rapid arm flexion movements during standing were preceded by activations in postural muscles (biceps femoris and erector spinae) for normal subjects (Rogers et al., 1987). However, these APAs were less frequent with shorter duration and there were multiple EMG bursts in PD patients (Rogers et al., 1987). Similarly, abnormal APAs were observed in PD patients during voluntary gait initiation with decreased swing limb force production that resulted in delayed execution and variable duration of the APA phase (Burleigh-Jacobs et al., 1997). However, these PD patients exhibited a normal APA phase with levodopa medication suggesting that dopamine deficiency led to the impaired APA (Burleigh-Jacobs et al., 1997). Basal ganglia also play a major role in the acquisition of APAs as evidenced by the difficulty in acquiring an APA pattern during a modified BMLL task for PD patients (Massion et al., 1999). Basal ganglia are not involved in triggering APRs since PD patients have normal response latencies to postural perturbations (Horak et al., 1992). However, they do exhibit abnormal APR patterns including excessive antagonist activity and the inability to adapt to the changing support surface conditions (Horak et al., 1992).

2.5.4 Cerebral Cortex

Various lines of evidence from lesion, attention, dual-tasking, and TMS studies have shown the potential role of cortical motor areas in human bipedal balance control (see Jacobs and Horak, 2007; Maki and McIlroy, 2007 for review). The studies using dual-task paradigms, where subjects concurrently perform both balance and cognitive tasks, have shown attentional switching to the balance task indicating the requirement of attentional resources in compensatory balance control (McIlroy et al., 1999; Maki et al., 2001; Norrie et al., 2002). In addition, the longer latency of APAs and CPAs compared to the spinal stretch reflex suggests the potential role of the cerebral cortex in human bipedal balance control (Jacobs and Horak, 2007).

Neuroimaging studies using SPECT, PET, and fNIRS showed activations in the frontal cortex, prefrontal cortex (PFC), PMC, SMA, primary sensorimotor areas, posterior parietal cortex (PPC), visual association cortex, and visual cortex during stance, stepping, gait, and postural responses to platform perturbations whereas fMRI studies during imagined stance and walking have showed similar activation patterns in these cortical areas, revealing the cortical involvement in bipedal balance control (Fukuyama et al., 1997; Ouchi et al., 1999; Miyai et al., 2001; Malouin et al., 2003; Jahn et al., 2004; Mihara et al., 2008; la Fougère et al., 2010).

Impaired APAs (delayed onset or absence of trunk and leg muscle activation) associated with rapid arm movements were observed in patients with SMA lesions suggesting a role for the SMA in the generation of APAs (Gurfinkel and Elner, 1988). The authors proposed that the SMA generates and stores the motor programs for complex interconnected actions, whereas the M1, basal ganglia, and brain stem (red nucleus) are involved in the execution of these programs (Gurfinkel and Elner, 1988). The PMC also contributes to the generation of APAs (Chang et al., 2010). For instance, delayed onset of postural muscle activity in both affected and unaffected legs was observed in patients with unilateral PMC lesions during a forward step (Chang et al., 2010). Viallet and colleagues (1992) examined the role of the SMA and M1 in APAs by comparing APAs of healthy normal subjects with that of patients with unilateral lesions of the SMA and spastic hemiparesis while performing a BMLL task. They found impaired APAs (less inhibition of forearm flexor activity) in SMA lesion patients when the postural forearm was contralateral to the lesion and absence of APAs in spastic patients when the postural forearm was the spastic arm (Viallet et al., 1992). The authors suggested that the contralateral SMA, PMC, and M1 areas are involved in the organization of an APA (Viallet et al., 1992; Massion et al., 1999). M1 and premotor areas (along with the basal ganglia and cerebellum) are also involved in

the acquisition of APA patterns as evidenced by the absence of learning ability in hemiparetic patients (with lesions involving the internal capsule) during a modified BMLL task (Massion et al., 1999). The role of the M1 in learning a new APA pattern was further confirmed in a TMS study during a modified BMLL task (Kazennikov et al., 2008). TMS studies during voluntary stepping demonstrated that the SMA and M1 contribute to the timing and initiation of APAs, respectively (MacKinnon et al., 2007; Jacobs et al., 2009).

Lesion studies examining postural responses to unexpected perturbations have revealed cortical involvement in reactive balance control. APR responses were absent or delayed in patients with cerebral lesions in response to sudden unexpected perturbations suggesting that APR responses are cortically mediated (Chan et al., 1979; Diener et al., 1985). Both feet-in-place and stepping responses were impaired in patients affected by stroke involving the cerebral cortex (Di Fabio et al., 1986; Mansfield et al., 2012). TMS of the motor cortex during stance perturbation exhibited increased corticospinal excitability approximately 86 ms after the perturbation onset suggesting that the APR is mediated by direct corticospinal pathways (Taube et al., 2006). In addition, TMS of the motor cortex when balancing on a rocking platform resulted in increased motor evoked potentials from postural muscles (tibialis anterior and soleus) when compared to standing on a rigid floor (Solopova et al., 2003). The polymodal sensory cortex (temporoparietal junction) also plays a major role in balance control, specifically maintaining lateral body stability (Perennou et al., 2000). Stroke patients with vascular lesions on the temporoparietal junction exhibited increased body instability while maintaining balance on a rocking platform (Perennou et al., 2000).

From these various lines of evidence, it can be summarized that a distributed network within the CNS is maintaining human bipedal balance and the cortex plays a major role in

balance control. Moreover, within the cortex there are multiple regions that are involved in balance control, and therefore it is possible that the integrated activity of various sensory, motor, and association cortical areas leads to the generation of complex bipedal balance control strategies.

2.6 Cortical Activations related to Balance Control

Cortical activation recorded using EEG and MEG during APA and CPA provide additional key insight in to cortical contributions in human bipedal balance control. EEG analysis in the time domain was focused on ERPs such as PEPs, MRPs, and contingent negative variation (CNV) whereas the frequency domain analysis was focused on power spectral density and ERD of various EEG rhythms prior to and during APAs and CPAs.

2.6.1 Cortical Activations related to APAs

Time domain analysis of EEG recorded during a voluntary rising on tip-toe showed that MRPs precede the onset of APA with maximum amplitude at the Cz electrode and are more negative than the MRPs that precede the focal movement (Saitou et al., 1996). MRPs that preceded a shoulder flexion movement (by time-locking EEG to the onset of the deltoid muscle) were larger during standing (APA in postural leg muscles) than sitting (no APA) with the maximum amplitude difference observed at the Cz electrode (Yoshida et al., 2008). The authors suggested that the increased MRPs in the standing condition correspond to postural control by the SMA (Yoshida et al., 2008). Jacobs and colleagues (2010) examined MRPs time-locked to postural muscle onset during a voluntary arm raise movement and found MRPs specifically related to APAs with maximum amplitude at Cz. MRPs were also observed prior to stepping and gait initiation in forward, backward, and lateral directions and the amplitude of these MRPs changed with the direction of stepping and gait initiation (Do Nascimento et al., 2005). CNVs preceded

the onset of externally triggered gait initiation with maximum amplitude at Cz and the late CNVs were significantly larger than that of foot dorsiflexion, suggesting the increased amplitude accounts for cortical activity related to initiating the gait which includes a postural component (Yazawa et al., 1997). ERPs recorded during a BMLL task revealed a negative wave over the ipsilateral M1 and a positive wave over the M1 contralateral to the postural arm (Barlaam et al., 2011). The authors proposed that the negative wave reflects the cortical motor command to initiate the focal arm movement, whereas the positive wave corresponds to the cortical postural command to generate an APA (inhibit the flexor activity) (Barlaam et al., 2011).

Frequency domain analysis of MEG signals recorded during a BMLL task showed a robust ERD of beta rhythm (16-30 Hz) over the sensorimotor cortex associated with the APA suggesting cortical involvement in the generation of an APA (Ng et al., 2011, 2013). In addition to beta ERD, a mu (10-13 Hz) ERD was also observed during APA from C3 and C4 electrodes (Barlaam et al., 2011). It was inferred that the ipsilateral mu ERD over the postural M1 was related to the focal arm movement, whereas the contralateral mu ERD was related to the APA (Barlaam et al., 2011). An ERD of 6-8 Hz frequency band from C3 and C4 was also observed in children during an APA in a BMLL task (Martineau et al, 2004). Mu ERD was also observed prior to the onset of an APA during a voluntary arm raise movement (Jacobs et al., 2010). In addition, alpha ERD in central-parietal areas was observed during standing suggesting that alpha ERD corresponds to cortical information processing for balance control (Del Percio et al., 2007).

2.6.2 Cortical Activations related to CPAs

Time domain analysis of EEG following a balance disturbance has mainly focused on PEPs, also known as perturbation-evoked responses or mechanically-evoked cerebral potentials. PEPs are ERPs evoked by various types of perturbations during stance, gait or seated conditions such as

platform translations, trunk perturbations, and perturbations using the lean and release system (Dietz et al., 1984, Staines et al., 2001; Quant et al., 2004a; Adkin et al., 2008; Mochizuki et al., 2010). PEPs are widely distributed over frontal, central, and parietal areas with maximum amplitude at FCz or Cz (Dietz et al., 1984, Dimitrov et al., 1996; Marlin et al., 2014). PEPs are comprised of an initial small positive peak (P1) that peaks within 40-90 ms after the perturbation onset followed by a large negative wave (N1, also known as the perturbation-evoked N1) peaking within 100-200 ms and a succeeding positive wave (P2) that peaks within 200-400 ms (Dietz et al., 1984, 1985; Quant et al., 2004a). The P1 corresponds to the earliest unspecific primary sensory cortical response to the perturbation-evoked somatosensory (from muscle, joint, and cutaneous receptors) input (Dietz et al., 1984, 1985; Ackermann et al., 1986). There have been several interpretations regarding the role of the perturbation-evoked N1. Dietz and colleagues (1984, 1985) suggested that the N1 represents cerebral processing of the somatosensory afferent information of balance disturbance for the control and coordination of compensatory responses. Likewise, Quant and coworkers (2004a, b) suggested that the N1 corresponds to the sensory processing of postural instability caused by perturbation. In contrast, Adkin et al. (2006) suggested that the N1 represents an error signal that arises due to the difference between expected and actual state and is independent of sensorimotor processing associated with postural responses. Dimitrov and associates (1996) suggested that the N1 reflects cortico-cortical transfer of afferent input to the frontal motor areas, mainly to bilateral SMA. They suggested that the enduring afferent input in the primary sensory areas and cortico-cortical transfer accounts for the widespread distribution of PEPs on the scalp (Dimitrov et al., 1996). More recently, source localization of the N1 revealed the location of the N1 dipole in the SMA and the authors suggested that the N1 is related to the planning and execution of compensatory

postural responses rather than error detection (Marlin et al., 2014). P2, also known as the late PEP, is suggested to represent sensory and motor processing related to the execution of postural responses (Quant et al., 2004a).

The amplitude of the perturbation-evoked N1, which is normally between 20-40 μV, is altered by age, postural threat, perturbation magnitude, concurrent peripheral stimuli, concurrent cognitive tasks, initial condition (stance vs. gait), stance width, learning effects (first vs. last trial), perturbation triggering mode (self-induced vs. externally triggered), and predictability of perturbation (Dietz et al., 1985; Quintern et al., 1985; Dimitrov et al., 1996; Duckrow et al., 1999; Staines et al., 2001; Quant et al., 2004b, Adkin et al., 2006,2008; Mochizuki et al., 2008). Hence, it is assumed that the processing of perturbation-evoked somatosensory afferent input is dependent on psychological and environmental conditions leading to different PEP amplitudes in the aforementioned conditions (Dietz et al., 1985). PEPs (P1 and N1) are thought to be somatosensory in origin since there is no difference in PEPs between bilateral vestibular loss patients and normal subjects, whereas the PEP latency of patients with peroneal muscular atrophy is significantly longer than that of normal subjects (Dietz et al., 1985).

While PEPs represent cortical activations after the onset of a postural perturbation, some studies have examined pre-movement potentials such as the RP and CNV that occur prior to predictable or self-initiated postural perturbations and the influence of such preparatory activity on PEPs and APRs (Adkin et al., 2008; Jacobs et al., 2008; Mochizuki et al., 2008; Fujiwara et al., 2011; Smith et al., 2012). It has been suggested that these pre-perturbation cortical potentials represent motor preparation for the postural responses and thus modify the ensuing postural performance based on predictability of perturbation characteristics and initial standing position (Jacobs et al., 2008; Fujiwara et al., 2011; Smith et al., 2012). Alternatively, Mochizuki et al.

(2008, 2010) suggested that pre-perturbation cortical activity corresponds to altering the central set prior to the perturbation onset and is independent of PEPs.

Frequency domain analysis of EEG signals associated with CPAs has shown event-related power changes in theta, alpha, beta, and gamma rhythms. A transient increase in theta band (4-7 Hz) power over prefrontal, cingulate, parietal, and sensorimotor areas was present when subjects lost their balance while walking on a balance beam and stepped off (Sipp et al., 2013). The authors proposed that the increased theta power corresponds to the activity of a widespread cortical network in planning a compensatory postural response (Sipp et al., 2013). In addition, the modulation of theta band activity (4-7 Hz) at fronto-central areas was observed prior to the onset of visually-induced perturbations (Slobounov et al., 2013). Moreover, increased midline frontal theta (4-5 Hz) band activity occurred during the unstable stage of single leg stance indicating the role of theta band activity in monitoring postural stability (Slobounov et al., 2009). ERD of upper alpha (10-12 Hz) and beta (20-29 Hz) rhythms at central-parietal electrodes occurred prior to temporally predictable perturbations (Smith et al., 2012). The authors suggested that the alpha ERD prior to the perturbation onset corresponds to sensory processing and integration for preparing anticipated postural responses, whereas the beta ERD represents motor preparation (Smith et al., 2012). Similarly, alpha (8-12 Hz) and beta (14-25 Hz) ERD at central electrode sites were also observed prior to the onset of voluntary postural sway (Slobounov et al., 2008). ERS of gamma (30-50 Hz) band activity at frontal, central, and parietal areas was observed during the visual recognition of non-stable postures of a computer generated 3-D human model (Slobounov et al., 2000). The authors suggested that the gamma ERS is related to the detection of postural instability (Slobounov et al., 2000). In addition, gamma ERS at fronto-central electrode sites occurred prior to the onset of compensatory postural movements to self-

induced postural perturbations, emphasizing the role of gamma band activity as a neural detector for postural instability and triggering the CPA (Slobounov et al., 2005). Thus, it appears that theta and gamma band activations are related to the monitoring and signaling of postural instability, whereas alpha and beta activations are related to the generation and execution of postural responses.

In summary, cortical activations revealed by time and frequency domain analysis of EEG and MEG signals recorded prior to and during APAs and CPAs reveal the potential cortical contributions in human bipedal balance control. In addition, both ERPs and frequency modulations are widely distributed over frontal, central, and parietal areas. It seems likely that rather than a focal region, a distributed network of cortical areas is involved and their integrated activity gives rise to the generation and execution of postural adjustments. It is therefore necessary to examine activations in these distinct cortical areas and how these cortical areas are connected to facilitate the information flow to generate complex bipedal balance control strategies. Brain connectivity techniques are now widely used to explore cortical connectivity and information flow which is discussed in the following section.

2.7 Brain Connectivity

Postural control is a complex sensorimotor task utilizing sensory inputs to generate anticipatory and compensatory postural responses. Hence, to further explore cortical involvement in balance control it is necessary to examine both the activation within different cortical areas and the functional interactions between them. Cortical information flow in a sensorimotor activity has been suggested to flow from the primary sensory areas to the unimodal sensory association areas to high-order multisensory association areas to motor association areas and finally end at M1 generating a specific motor output for the detected sensory input (Cheney, 1985; Rizzolatti,

1998; Cunnington et al., 2002). For instance, the tactile sensorimotor transformation network consists of cortical areas responsible for processing a tactile input (primary and secondary somatosensory cortex), transforming the tactile input to a motor output (PPC, SMA), and executing the movement (M1 and PMC) (Nelson et al., 2004). Brain connectivity techniques are used to measure the coordinated activation of different cortical areas during a sensorimotor activity (Sakkalis, 2011).

Brain connectivity techniques can be used to explore structural, functional, and effective connectivity (Fingelkurts et al., 2005). Structural connectivity (neuroanatomical connectivity) refers to brain connectivity at the neuronal level by exploring the anatomical connectivity of the white matter fiber tracts that connect different regions of the brain, usually examined using diffusion-weighted MRI (diffusion tensor imaging) (Fingelkurts et al., 2005; Sakkalis, 2011). Functional connectivity refers to the temporal correlation in activity between local or distant cortical areas and can be examined using neurophysiological signals acquired using single unit recordings, local field potential recordings, EEG, MEG, PET, and fMRI (Fingelkurts et al., 2005; Sakkalis, 2011). Effective connectivity refers to directional (causal) interactions between different brain regions (the influence that one neural population exerts on another) and can be assessed using data-driven methods or model-based methods (Horwitz, 2003; Sakkalis, 2011). Since EEG provides excellent temporal resolution (< 1 ms) compared to fMRI or PET and is also noninvasive compared to single neuron or local field recordings, EEG signals are widely used for examining functional and data-driven effective connectivity (Sakkalis, 2011).

There are several techniques used to assess and quantify functional connectivity from EEG signals. Functional connectivity techniques are classified in to linear, non-linear, and information-based techniques (Sakkalis, 2011). Linear functional connectivity is measured in

both time (e.g. cross-correlation) and frequency domains (e.g. phase coherence). While cross-correlation techniques measure the correlation of EEG signals in different brain regions, coherence techniques measure the spatial correlation of EEG signals in different frequency bands and provide information about the stability of the relationship between these signals based on the spectral power and phase relationship (Brazier and Casby, 1952; Sakkalis, 2011). Phase synchronization of EEG signals recorded from two different electrodes can be quantified in terms of event-related phase coherence (ERPC) which is a frequency domain measure that quantifies the synchronization in activity between two EEG channels (Delorme and Makeig, 2004). Non-linear methods are based on the nonlinear characteristics of neural processes and provide information of functional connectivity complementary to linear methods (Sakkalis, 2011). Information-based functional connectivity techniques are based on either mutual dependence between two EEG signals or on the degree of predictability of one signal as a function of the other (Sakkalis, 2011). In summary, all these aforementioned techniques serve as valuable tools for assessing brain connectivity. However, there is no single optimum connectivity measure and hence the selection of a connectivity measure depends on the specific objectives of the research study and the instrumentation used to answer the research questions (Sakkalis, 2011).

The following chapters detail four studies that explored the cortical activations and connectivity during reactive and predictive balance control in young healthy adults and introduce new approaches of analyzing balance-related ERPs that can be applied in the future to assess impaired balance control associated with aging and various neural diseases.

Chapter 3

Study 1: Frequency characteristics of cortical activity associated with perturbations to upright stability

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3.1 Abstract

Cortical evoked potentials are evident in the control of whole-body balance reactions in response to transient instability. The focus of this work is to continue to advance understanding of the potential cortical contributions to bipedal balance control. Temporally unpredictable postural perturbations evoke a negative potential (N1), which has drawn parallels to error-related negativity (ERN) as well as visual and auditory evoked N1 responses. The mechanism underlying the generation of ERPs has been a matter of debate for the past few decades. While the evoked model proposes that ERPs are generated by the addition of fixed latency and fixed polarity responses, the phase reorganization model suggests that ERPs are the result of stimulus-induced phase reorganization of the ongoing oscillations. Previous studies have suggested phase reorganization as a possible mechanism in auditory N1, visual N1, and ERN. The purpose of the current study was to explore the frequency characteristics of the cortical responses to whole-body balance perturbations. Perturbations were evoked using a lean and release protocol. The results revealed a significant power increase and phase-locking of delta, theta, alpha, and beta band activity during perturbation-evoked N1. This may suggest that the stimulus-induced phase

reorganization of the ongoing EEG activity could account for the features of cortical ERPs in response to perturbation of upright stability.

3.2 Introduction

Cortical activity evoked by external stimuli or events provide important insight into the underlying spatial and temporal aspects of nervous system control of behavior. We have a specific interest in understanding the potential role of such cortical evoked potentials that are evident in the control of whole-body balance reactions in response to transient instability. Numerous studies have shown that temporally unpredictable postural perturbations such as platform translations, chair tilt, and standing lean and release elicit a negative potential (N1), which is a pronounced and consistent feature of the perturbation-evoked cortical response (see Jacobs and Horak, 2007; Maki and McIlroy, 2007 for review). The peak of the N1 response occurs approximately 100-200 ms after the perturbation onset in the fronto-central region of the cerebral cortex with peak amplitude at FCz (Adkin et al., 2006, 2008; Mochizuki et al., 2009; Marlin et al., 2014). It has been suggested that the N1 represents the sensory processing of balance disturbances (Marlin et al., 2014). In addition, it has been speculated that the N1 may represent an ERN that may be associated with a specific cortical area (anterior cingulate) (Adkin et al., 2006; Slobounov et al., 2009). Understanding of the cortical role in balance control may be found in parallel to ERPs evoked by other stimuli. As noted, there are proposed links between the perturbation-evoked N1 and the ERN (Adkin et al., 2006; Slobounov et al., 2009; Marlin et al., 2014). In addition, there are stimulus-evoked N1 responses to visual or auditory stimuli that share some characteristics with perturbation-evoked N1 (Sayers et al., 1974; Brandt, 1997; Makeig et al., 2002; Jansen et al., 2003). One intriguing characteristic is that there is a temporal synchronization of the evoked frequency components.

For the past few decades there has been ongoing debate regarding the genesis of ERPs (Sayers et al., 1974; Jervis et al., 1983; Brandt, 1997; Makeig et al., 2002; Jansen et al., 2003; Rizzuto et al., 2003; Klimesch et al., 2004; Luu et al., 2004; Yeung et al., 2004; Gruber et al., 2005; Makinen et al., 2005; Klimesch et al., 2007; Min et al., 2007; Sauseng et al., 2007). A conventional view is that ERPs are generated by superposition of fixed latency and fixed polarity responses on to the ongoing EEG activity (evoked or additive model). Alternatively, the cortical potentials may instead reflect event-related phase reorganization of the ongoing EEG oscillations (phase resetting or reorganization model) (see Klimesch et al., 2007; Sauseng et al., 2007 for review of both models). The distinction between these different explanations for the genesis of the ERP is important as they may have a significant impact on the interpretation of the associated cortical events. EEG phase reorganization has already been reported in response to auditory and visual stimuli (Sayers et al., 1974; Brandt, 1997; Makeig et al., 2002; Jansen et al., 2003). In addition, the ERN associated with incorrect motor responses has been suggested to be the result of the partial phase-locking of theta band (4-7 Hz) EEG activity (Luu et al., 2004). The intracranial EEG recordings also showed phase resetting of ongoing oscillations during a working memory task (Rizzuto et al., 2003). Such work leads to the view that the characteristics of the frequency responses to such stimulus-evoked responses may have the potential to yield insight into underlying control.

Unlike stimulus-evoked responses associated with visual or auditory stimuli, there has been little attention paid to the frequency characteristics of the perturbation-evoked N1 response. The purpose of the current study was to explore the frequency characteristics of the cortical responses to whole-body balance perturbations. This will allow a comparison of cortical activity

associated with the control of balance reactions to other stimulus-evoked negativities which may, in turn, provide some insight into the genesis of the perturbation-evoked N1 response.

3.3 Materials and Methods

Adults (n = 14, 5 females) aged 26.6 ± 4.4 years voluntarily consented to participate. The study protocol was approved by the Office of Research Ethics at the University of Waterloo. Perturbations were induced using a custom-made lean and release cable system (Mochizuki et al., 2010). The participants stood on a force plate (AMTI, Watertown, MA) (McIlroy and Maki, 1997) and leaned forward at load on a horizontal cable of 5-7% of body weight. Temporally unpredictable perturbations were triggered by manually releasing the cable (Figure 3.1). The lean angle was selected to evoke a feet-in-place reaction to recover balance (no stepping or grasping). A total of 40 trials were collected from each participant (interstimulus interval ranged 1-15 s).

Figure 3.1: Experimental set up: Lean and release system to evoke perturbations. Perturbations to standing balance were achieved using a custom-made lean and release cable system that reliably

evokes compensatory balance reactions. The participant stood on a force plate in a standardized foot position. Subjects leaned forward at load on a horizontal cable of 5-7% of body weight. The experimenter applied the perturbation by unpredictably releasing the cable causing the participant to fall in a forward direction, evoking a compensatory reaction. The magnitude of the perturbation, determined by the standardized lean angle, was only large enough to evoke a feet-in-place reaction to recover balance (no stepping or grasping). The timing of the perturbations was randomized; varying from 1 to 15 seconds once the participant was relaxed in the forward lean position. A total of 40 trials were collected per participant.

EMG (bilateral medial gastrocnemius and tibialis anterior), COP, and cable force were collected along with synchronized 64-channel EEG referenced to linked mastoids (Neuroscan, El Paso, TX). All the data were sampled at a rate of 1000 Hz. Electrooculographic signals were also recorded using four electrodes. Impedance of all electrodes was kept less than 5 kΩ throughout the experiment. EEG signals were recorded, amplified, and filtered (DC-300 Hz) online using a SynAmps2 amplifier and SCAN 4.3 (Neuroscan, El Paso, TX). EMG, COP, and cable force were filtered and analyzed for the measurement of reaction time and any evidence of pre-perturbation activity. Cable force was used to determine the onset of perturbation (Mochizuki et al., 2010).

EEG signals were preprocessed using Neuroscan EDIT 4.3. Data were band pass filtered (1-30 Hz), epoched around the perturbation onset (-600 ms to +500 ms), and baseline corrected (baseline period: -600 ms to -500 ms). Post-processing was performed using EEGLAB (Delorme and Makeig, 2004). ICA was performed on EEG data to remove ocular, muscular, cardiac, and line noise artifacts. ICA-pruned EEG data was once again visually inspected to further remove epochs contaminated by gross movements that were not removed by ICA noise reduction. ICA was also used to identify the independent components that mainly contributed to generation of perturbation-evoked N1. ERP scalp maps were plotted to visualize the scalp topography of the perturbation-evoked cortical response. To visualize the phase-locking across trials, phase-sorted

ERP-images (a two-dimensional image with color-coded single-trials sorted in order of phase and stacked) were plotted (Delorme and Makeig, 2004). Power spectral analyses using the Matlab pwelch function were performed for averaged ERP and unaveraged EEG epochs at specific frequencies. This computed the mean log power spectrum of data epochs and plotted the scalp distribution of power at discrete frequencies (2, 6, 8, 10, 12, 14, 20 Hz). The similar topography of EEG and ERP power indicates that ERPs are generated by the synchronization of ongoing EEG oscillations (Makeig et al., 2002; Yeung et al., 2004). ERSP, which measure the mean event-related changes in spectral power over time, were computed at the FCz electrode site using fast Fourier transform (FFT) and the corresponding significant ($p < 0.01$) time-frequency maps were plotted. Event-related ITC (also called 'phase-locking factor') was computed to verify significant ($p < 0.01$) phase-locking across trials with respect to perturbation onset (Makeig et al., 2002; Delorme and Makeig, 2004).

3.4 Results

Compensatory balance reactions were consistently evoked as reflected by medial gastrocnemius EMG activation and associated COP excursion. On average, the onset of balance reactions was 182.4 ms (SD 10.3) and 184.1 ms (SD 7.3) for the left and right medial gastrocnemius, respectively. The peak of the perturbation-evoked N1 response at FCz had a mean latency of 107.9 (SD 8.3) ms and mean amplitude of 30.85 (SD 10.95) μV (Figure 3.4C, bottom panel). The scalp topography showing N1 concentrated in fronto-central areas (Figure 3.2A) is consistent with previous studies (Adkin et al., 2006, 2008; Jacobs and Horak, 2007; Maki and McIlroy, 2007; Mochizuki et al., 2009; Marlin et al., 2014). The power spectral maps of unaveraged EEG (Figure 3.2B) and averaged ERP (Figure 3.2C) data during the 20-180 ms post-stimulus interval showed similar scalp topography. The scalp distribution of power in the delta,

theta, alpha, and beta frequencies showed power increases concentrated at fronto-central midline electrode sites. There was considerable inter-subject variability in the N1 latency as seen in the ERP-image at the FCz electrode site (Figure 3.4A). The ERSP plot (Figure 3.4B), which gives the total power without regard to the phase of the signal, showed a significant increase ($p < 0.01$) in delta, theta, alpha, and beta power during the N1 period. The event-related ITC plot (Figure 3.4B), which gives the degree of event-related phase consistency across trials, revealed significant ($p < 0.01$) phase-locking of 1-20 Hz activity during the N1 period. Power increase and phase coherence in the lower frequency bands appear to occur before the perturbation onset, but this may be an artifact associated with the poor time resolution of windowed FFT in lower frequency bands. Phase-sorted ERP-image plots (Figure 3.3) also showed significant synchronization of delta, theta, alpha, and beta activity during N1. The variability in the phases across trials seen in the phase-sorted ERP-images is likely due to the difference in N1 latencies between subjects. ICA analysis revealed that a fronto-central component (FC) mainly accounted for the generation of N1 (Figure 3.5). The scalp topography (Figure 3.6A) of FC showed fronto-central concentration and, indeed, the component ERP-image (Figure 3.6B) and average component ERP (Figure 3.6D, bottom panel) of the FC closely resembled those of the FCz electrode site. The ERSP plot (Figure 3.6C) and ITC plot (Figure 3.6D) of the FC showed significant ($p < 0.01$) power modulation and phase consistency across trials, respectively, during the N1 period.

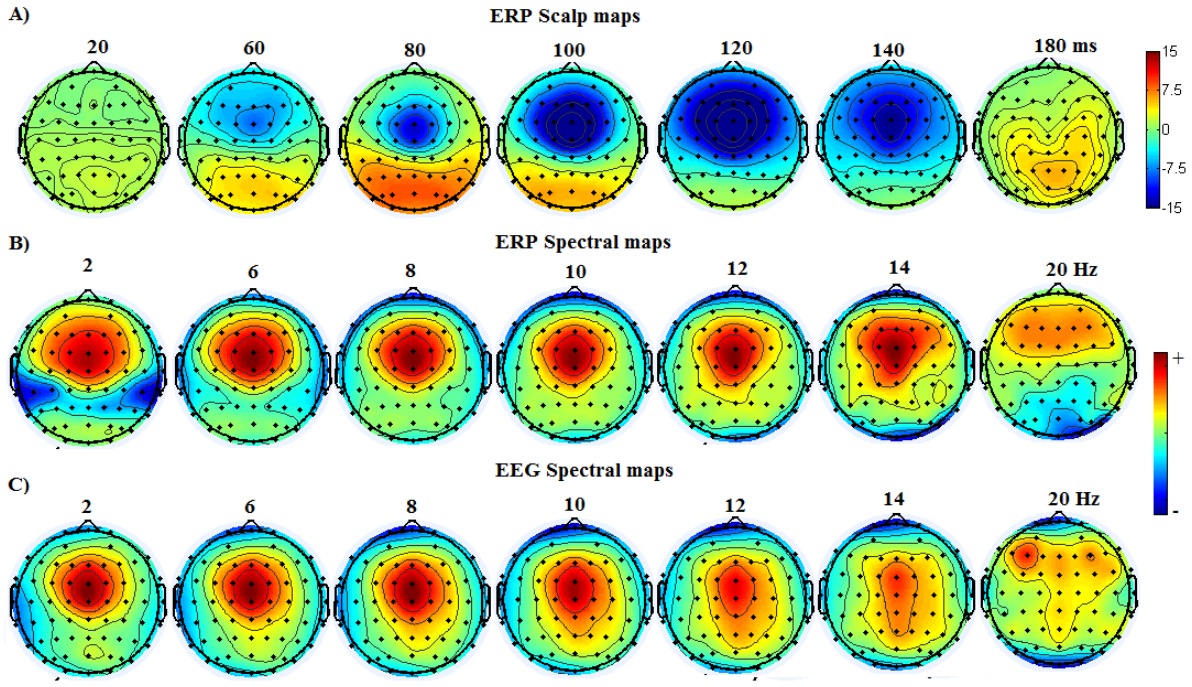

Figure 3.2: (A) ERP scalp maps showing the topography of perturbation-evoked N1 averaged across subjects. Scalp distribution of power in the (B) mean single-trial EEG and (C) trial-average ERP at seven frequencies during 20-180 ms post-stimulus period.

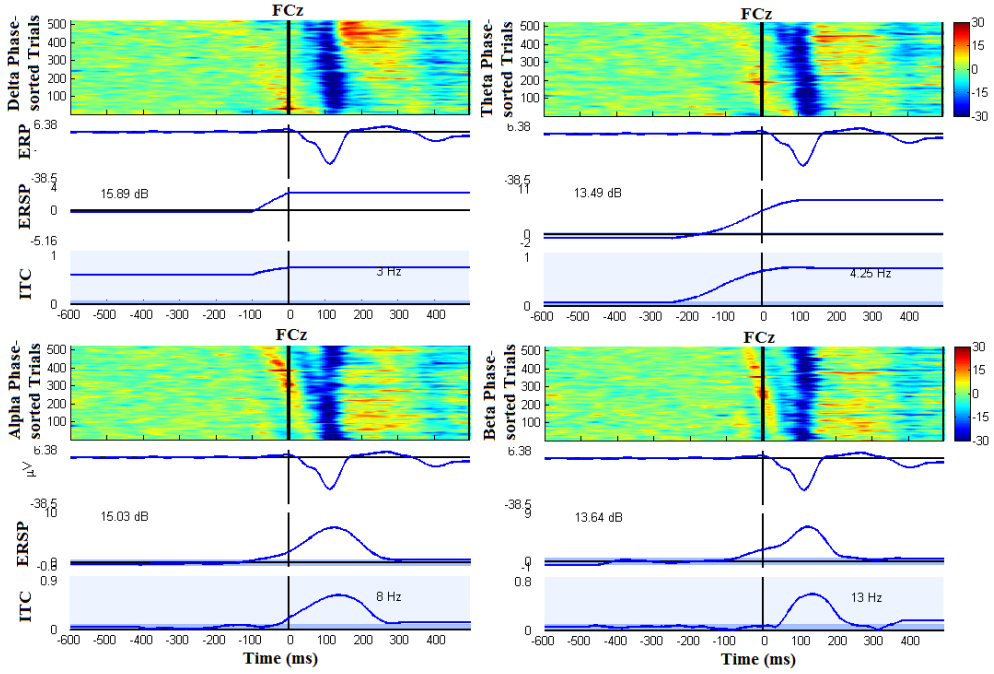

Figure 3.3: Phase distribution and coherence analysis: ERP-image plots at FCz showing color-coded single trial data sorted by delta, theta, alpha, and beta phases. Lower traces show the time

courses of ERSP and ITC at the peak frequencies. A marked increase of ITC at all frequency bands can be seen during N1. The vertical dashed line at time = 0 represents the perturbation onset. The variability in the N1 latency among subjects (main fig 1(A)) causes the variability in the phases across trails seen in these phase-sorted ERP images.

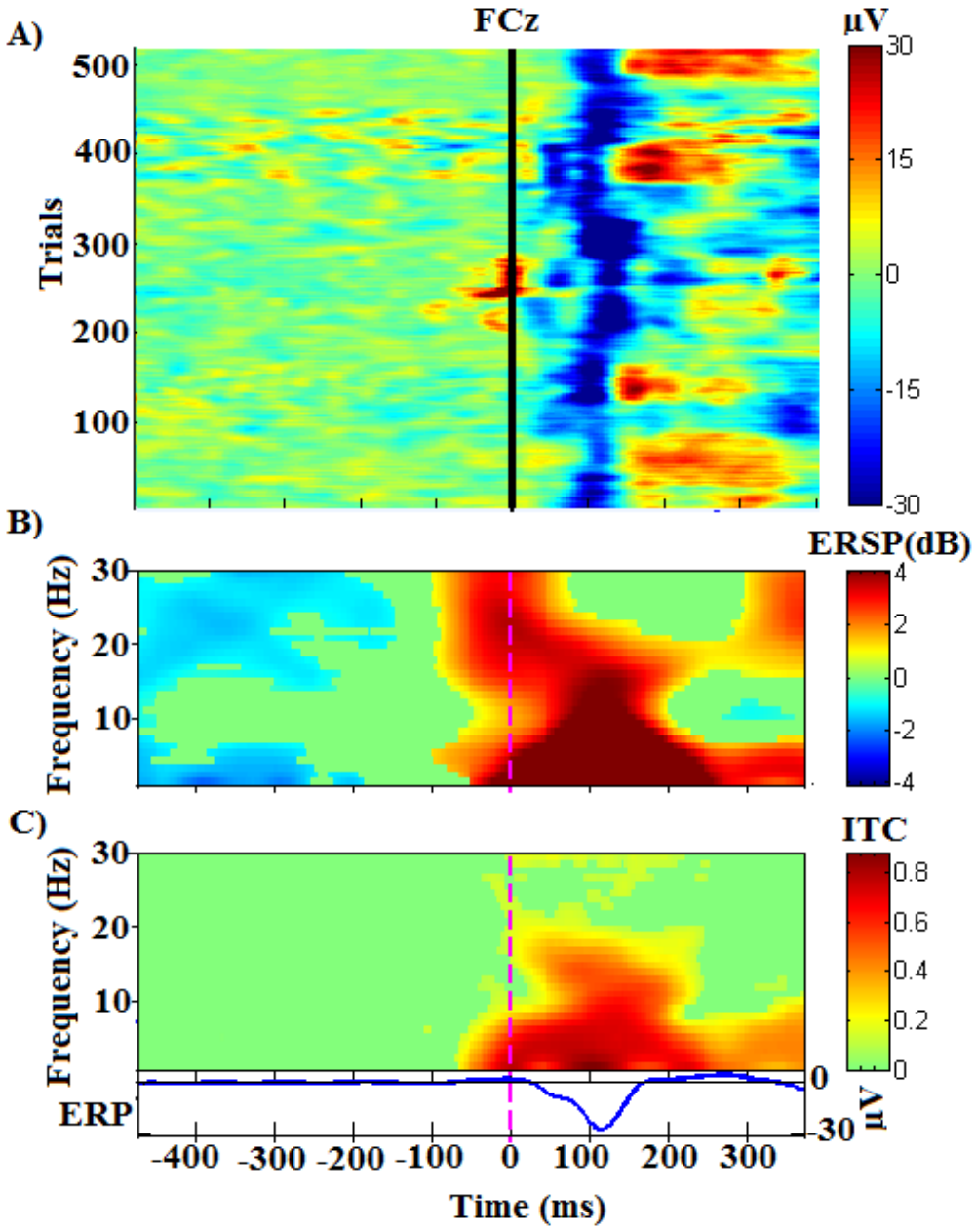

Figure 3.4: (A) ERP-image plot of single-trial EEG epochs across all subjects sorted by trial order at the FCz electrode. Each horizontal line represents a color-coded single trial with

negative voltages in blue and positive voltages in red. (B) ERSP and (C) ITC plots at the FCz electrode site. The vertical dashed line at time = 0 represents the perturbation onset. Non-green areas show significant ($p < 0.01$) event-related increase or decrease in (B) log spectral power or (C) phase-locking in the averaged ERP data. The bottom trace shows the perturbation-evoked N1 averaged across trials.

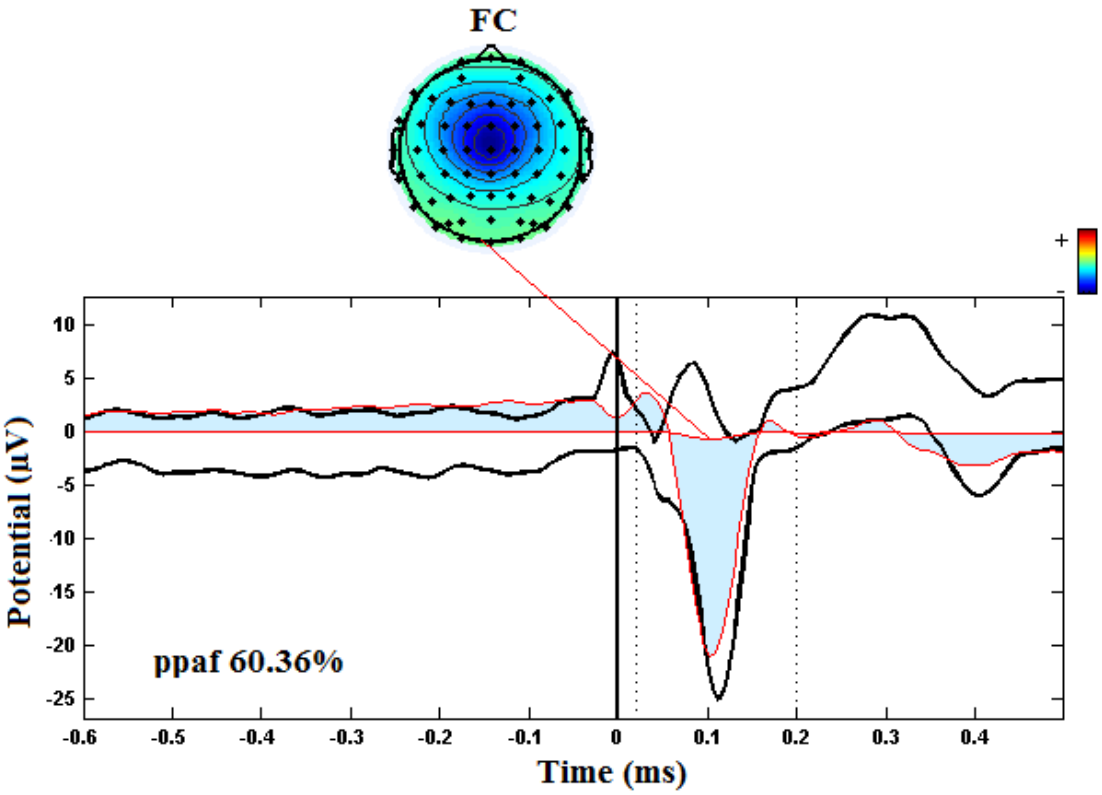

Figure 3.5: ERP scalp map of fronto-central component (FC). Among the 64 ICs decomposed using infomax algorithm, FC contributes 60.36 % to the total power during the N1 (ppaf-percentage power accounted for).

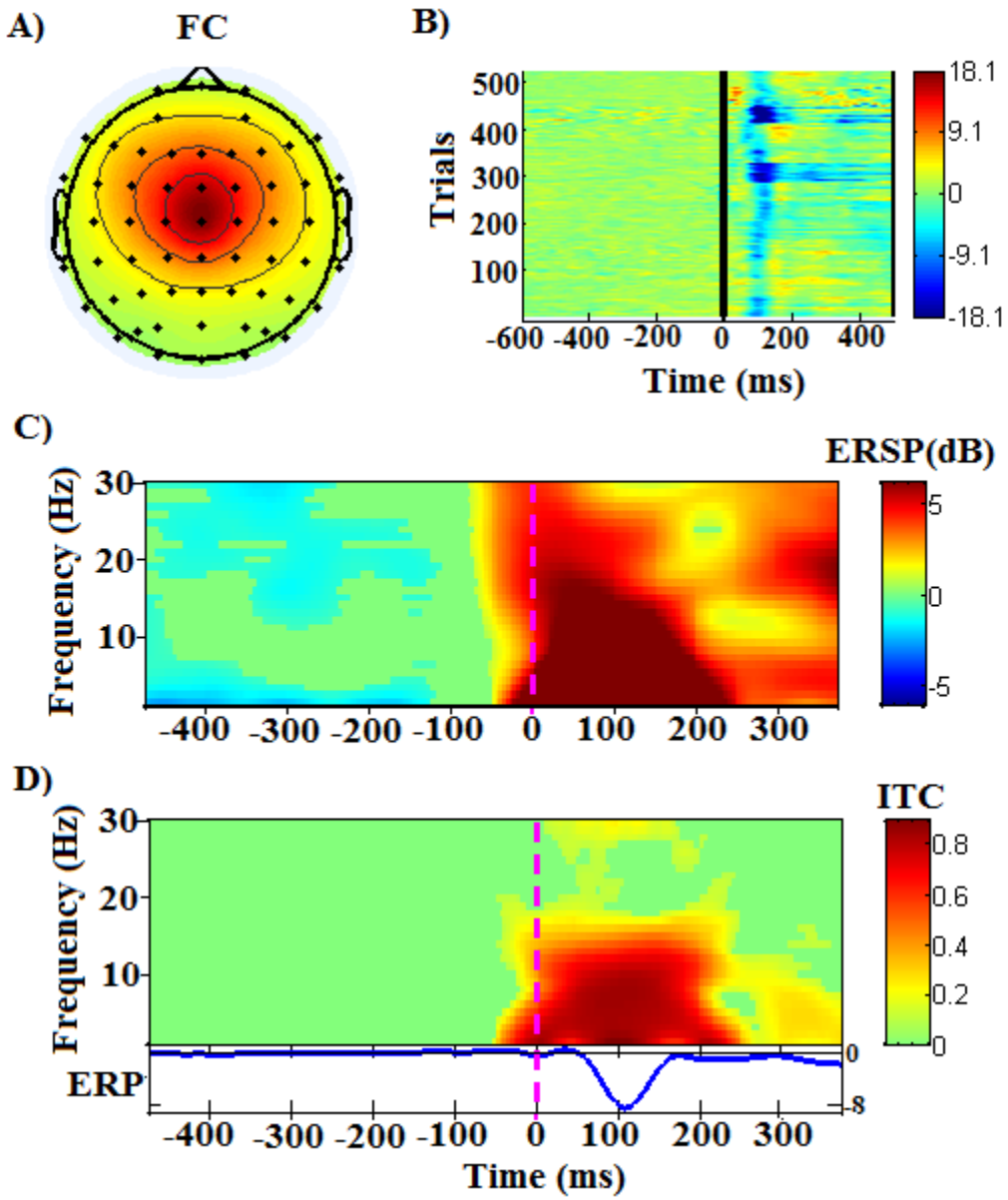

Figure 3.6: Characteristics of the fronto-central component (FC) that largely contribute to the generation of the perturbation-evoked N1. (A) The component scalp map and (B) component ERP-image for FC. (C) ERSP plot of FC highlighting significant ($p < 0.01$) increase in spectral power at delta, theta, alpha, and beta frequency bands during the N1 period. (D) ITC plot of FC which shows significant ($p < 0.05$) phase-locking of 1-20 Hz activity during the N1 period.

3.5 Discussion

This study is the first to examine the frequency modulations associated with the cortical N1 response evoked by unpredictable whole-body balance perturbations. The present results reveal

evidence of phase synchronization associated with the perturbation-evoked N1 response. This observation is consistent with the previous findings for visual N1, auditory N1, ERN, and ERP during a working memory task (Sayers et al., 1974; Brandt, 1997; Makeig et al., 2002; Jansen et al., 2003; Rizzuto et al., 2003; Luu et al., 2004; Klimesch et al., 2004; Gruber et al., 2005). In the present study, phase-locking of ongoing oscillations is most clearly revealed by the uniform phase distribution across trials in the phase-sorted ERP-image and event-related ITC plots. It is interesting to note that the perturbation-evoked N1 was composed of frequencies across the spectrum which is similar to the frequency content for auditory and visual N1 potentials, and working memory ERPs that includes delta to beta range (Brandt, 1997; Makeig et al., 2002; Jansen et al., 2003; Rizzuto et al., 2003; Klimesch et al., 2004; Gruber et al., 2005; Min et al., 2007). Arguably, the range of frequencies is associated with the spectrum of sensorimotor and cognitive process associated with the control of reactive balance (Başar-Eroglu et al., 1992). Synchronization of delta, theta, alpha, and beta oscillations may reflect the role of multiple concurrent sensorimotor cognitive processes and the integrated activity of these oscillations might have contributed to the generation of the perturbation-evoked N1.

The current results, as proposed in other studies, may indicate that a phase reorganization mechanism may underpin the perturbation-evoked N1 response. Such an explanation has been proposed for the visual N1, auditory N1, ERN, and P1-N1 complex during a memory task. The evidence for the phase resetting mechanism given by Sayers et al. (1974) in the auditory ERP suggests a stimulus-evoked phase reorganization of the ongoing EEG activity. They concluded that an effective stimulus generates an ERP by controlling the phases of spectral components of the ongoing EEG oscillations. This phase reset model was further explored in visual and auditory evoked ERPs in the alpha band at parieto-occipital sites. The first two post-stimulus negative

peaks are proposed to be the result of phase resetting during presentation of both visual and auditory stimuli (Brandt, 1997). In a human visual selective attention task, Makeig and colleagues (2002) showed that the visual N1 at the central parietal electrode site, evoked by brief visual stimuli, was generated by stimulus-induced partial phase resetting of multiple EEG processes below 20 Hz. The phase reset model was also further demonstrated in ERN seen in behavioral studies. The ERN (an event-related negative potential that occurs 50-150 ms after an error response) was found to be resulting from phase-locking of theta band EEG activity that accounts for 57% of peak amplitude of the ERN (Luu et al., 2004). Gruber et al. (2005) proposed an oscillatory phase-resetting model suggesting that the P1-N1 complex during a memory task is generated by phase reorganization of delta, theta, alpha, and beta activity. While the above-mentioned findings were obtained using scalp EEG, similar results were demonstrated with intracranial EEG studies. Rizzuto et al. (2003) were able to show the resetting of ongoing brain oscillations in 7-16 Hz range during a short term recognition memory task.

Alongside these previous findings, the present findings contribute to the evolving body of literature debating the genesis of ERPs. The 'evoked model' suggests that ERPs are generated by the addition of fixed latency-fixed polarity evoked responses on to the ongoing EEG activity during each trial, thus, considering the ongoing oscillations as 'random noise' and the ERP as independent of this background EEG (Jervis et al., 1983; Makinen et al., 2005). On the other hand, the 'phase reorganization model' states that ERPs are generated by the stimulus-induced phase reorganization of the ongoing EEG oscillations, thereby considering the background oscillations as serving specific functions (Klimesch et al., 2007; Sauseng et al., 2007). Oscillatory activity in the ongoing EEG mainly represents the summated activity of postsynaptic potentials: excitatory post-synaptic potentials (EPSPs) and inhibitory post-synaptic potentials

(IPSPs) in the dendritic tree of pyramidal neurons (Olejniczak, 2006). These oscillations are functionally important and play a major role in the timing of neural activity (Klimesch et al., 2007). Thus, it is likely that rather than simply representing background noise; the ongoing EEG activity plays an important role in generating the ERPs. However, while the current study does demonstrate that changes in the frequency characteristics of the EEG signal are evident during postural responses to balance perturbation, the findings cannot specifically disentangle whether the N1 potential represents result from an additive signal or phase resetting (Sauseng et al., 2007).

It is believed that the different frequencies represent the activity of different neuronal cell assemblies (Klimesch et al., 2007). If this assumption is true, it is likely that the postural perturbations induce synchronized activity of different neuronal assemblies in the fronto-central cortical area that might be related to 'event detection', specifically detection of postural instability. This synchronized fronto-central activity results in the generation of the perturbation-evoked N1, which may parallel the ERN. However, recent source localization studies have shown that dipole locations of the N1 may lie in the SMA (Marlin et al., 2014). As such, an alternate explanation might be that the perturbation-evoked N1 is involved in the compensatory response to postural perturbations. That is, postural perturbations induce phase reorganization of the ongoing oscillations in the SMA that synchronously act together to generate compensatory reactions to counteract the postural perturbations, thereby maintaining postural equilibrium. However, future investigations will be needed to further explore the specific function of the perturbation-evoked N1.

Previous literature has reported frequency modulation in the theta, alpha, and beta bands in association with postural instability (Slobounov et al., 2008, 2009). Midline theta burst during

single leg stance was interpreted as involvement of the anterior cingulate cortex in monitoring postural instability (Slobounov et al., 2009). Our present findings also suggest that midline theta burst might be associated with high-level cortical processing involved in detecting postural instability. In the present study, we also found a significant modulation of alpha and beta rhythms associated with the perturbation-evoked N1 response. High frequency modulations (10-45 Hz) in the motor cortex during motor preparations have been reported in monkeys, suggesting that these high frequency modulations represent the intra- and inter-cortical information transfer during movement preparation and execution (Rubino et al., 2006). Our present findings suggest a relationship between synchronized activation of delta, theta, alpha, and beta oscillations and the perturbation-evoked N1. It appears the N1 may be a product of complex waveforms rather than a singular event or dipole as mentioned by previous studies (Marlin et al., 2014). Further research is needed to disentangle the specific cognitive functions underlying these oscillations and how the integrated activity of these multiple cognitive processes may participate in the control of reactive balance.

3.6 Conclusions

In summary, the present study reveals the frequency characteristics of cortical activity evoked by whole-body instability. Consistent with previous studies, the findings may be reflective of partial phase resetting of ongoing oscillations as a possible source for the generation for such ERPs. Further investigation is needed to explore the neurophysiology underlying the genesis of ERPs and to determine the specific role for phase reorganization.

Chapter 4

Study 2: Standing still: Is there a role for the cortex?

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4.1 Abstract

In humans, standing still appears so automatic that high-level cortical processes seem unnecessary. However, by measuring cortical activity time-locked to reactive control events arising from naturally occurring instability while standing still, we detected cortical involvement in the form of an evoked N1 potential prior to the onset of balance reactions. Peak amplitude and spectral power of this event-related activity increased as postural challenges and demand for reactive control increased.

4.2 Introduction

Humans take years to develop the ability to maintain static upright bipedal stance until it eventually becomes automatic. The apparent automaticity of balance control during upright stance led to a view that it may be largely reflexive, occurring at subcortical levels (Sherrington, 1910; Magnus, 1926). The support came originally from research on quadrupeds, where control of biomechanical demands, ontogenetic development, and habitual stance are very different (Lockhart and Ting, 2007). However, bipedal stance is a remarkably complex task involving biomechanical and neuromotor challenges to position a high COM over a relatively small base of support through the control of a series of linked moveable segments (Winter, 1995b). The challenges to balance control become profoundly evident in the face of disorders such as Parkinson's disease, multiple sclerosis, stroke, peripheral neuropathy, and cerebellar ataxia

(Maki and McIlroy, 1997). Evidence from dual task paradigms, imaging, and EEG reveals a potential role for a cortical contribution into reactive balance control in response to externally or self-generated perturbations (Jacobs and Horak, 2007; Maki and McIlroy, 2007; Marlin et al., 2014; Varghese et al., 2014). However, what is not clear is whether the cortex participates to control balance even when someone stands still.

Previous studies have used various imaging modalities PET, TMS, fMRI, and EEG to study the cortical activations during unperturbed and imagined stance. PET imaging during standing with eyes open and closed has shown activation in the right visual cortex and PFC, respectively (Ouchi et al., 1999). Tandem stance with eyes open activated the visual association cortex (Ouchi et al., 1999). TMS-evoked EMG responses were significantly increased while standing on a rocking platform as compared to standing on a rigid floor suggesting a potential role for the motor cortex in postural control (Solopova et al., 2003). fMRI during imagined stance has shown activations mainly in basal ganglia, cerebellar vermis and thalamus, but has also shown significant cortical activations in left superior frontal gyrus, left inferior frontal gyrus and bilateral medial temporal gyri (Jahn et al., 2004). More recently, EEG studies during standing with eyes open have reported ERD of alpha (8-12 Hz) rhythm and power increase in beta (13-19 Hz) and sigma (30-40 Hz) bands in the centro-parietal areas (Del Percio et al., 2007; Tse et al., 2013). However, these studies considered stance as a continuous event and have not delineated the role of cortex in reactive balance control during stance.

The current study adopted a novel approach to reveal if the control of standing still involved the cerebral cortex. We assume that standing still is comprised of a series of discrete balance reactions to naturally-occurring time-varying instability and examined cortical activity associated with these reactions by time-locking EEG activity to transient center-of-pressure

(COP) excursions that occur while standing still. To determine the dependence of cortical activation on the amplitude of these balance reactions, we evaluated the cortical activity associated with two tasks of varying postural challenges: standard and tandem Romberg stances.

4.3 Materials and Methods

Twelve healthy volunteers (6 females and 6 males; age range 19-37 years) participated in this study. No subjects reported any history of neuromuscular disorders. Written informed consent was obtained from each participant, and the experimental procedures were performed in accordance with the declaration of Helsinki. The study was approved by the Research Ethics Board of the University of Waterloo.

The participants were instructed to maintain upright stance with equal weight on each foot while standing with eyes closed and arms crossed in two different postures: (1) Low balance challenge stance with two feet placed together (standard Romberg stance) and (2) high balance challenge stance with heel-to-toe (tandem Romberg stance). Romberg stances have been used in clinical balance assessment to examine the integrity of corrective postural control mechanisms (Black et al., 1982). The tasks, especially the standard Romberg stance, were easy for healthy young adults tested in this study. They did represent a modest increase in task challenge from standard stance position to tandem stance position which we exploited in the current study to ensure that we could more easily detect the discrete balance reaction events. Participants stood with each foot on a force plate. Prior to data collection, the participants rehearsed the two standing postures required to establish a standardized foot position on the force plates and the outline of the feet was traced in each stance to allow the same foot position to be maintained in all trials (McIlroy and Maki, 1997). They were instructed to stand as still as possible in one of

the stance position for 30 s with bare feet. For each participant, the order of the stance position was randomized and three trails were performed for each stance condition.

Spontaneous postural sway during standard and tandem Romberg stances were recorded using two force plates (AMTI OR6-5) that were positioned side by side underneath the subject's foot without touching (<1 mm apart). Ground reaction forces (Fx, Fy, and Fz) and moment components (Mx, My, and Mz) from the force plates were acquired and recorded using a custom-made program (LabVIEW, National Instruments, TX, USA). Force plate data were amplified (gain: 1000), low-pass filtered using two pole low-pass 1000 Hz filter (built in AMTI MSA-6 MiniAmp amplifier), sampled at a rate of 1000 Hz, and stored for subsequent analysis. To synchronize the posturography with EEG, a triggering pulse was delivered to the EEG amplifier whenever the force plate starts collecting the data and the corresponding time point served as the starting point of 30 s stance.

EEG data were recorded continuously with Ag/AgCl electrodes mounted on a 32-channel electrode cap (Neuroscan, El Paso, TX, USA) based on the international 10-20 lead system. To monitor vertical and horizontal eye movements, EOG signals were also recorded simultaneously using four surface electrodes (VEOU, VEOL, HEOR, and HEOL) situated above and below the left eye and both outer canthi. All channels were referenced to linked mastoids (A1 and A2). The impedances of all electrodes were maintained below 5 kΩs throughout the recording period. EEG signals were amplified (gain: 19), sampled at 1000 Hz, filtered online (band pass: DC-300 Hz) using a NuAmps digital amplifier (Neuroscan, El Paso, TX, USA), and stored for offline analysis.

Post-processing of posturographic data was performed using a custom-built LabVIEW program. The digitized force plate data were at first low-pass filtered (6 Hz, 2nd order

Butterworth filter). Spontaneous postural sway during standard and tandem Romberg stances were quantified in terms of root-mean-square (RMS) anterior-posterior (AP) and medial-lateral (ML) COP displacement, relative to the mean COP location. COP reflects the central nervous system control to correct the COM excursions during quiet standing (Winter, 1995b). We currently use the COP as method of inferring the temporal and spatial properties of the CNS response to instability. AP and ML RMS COP values of standard and tandem Romberg stances were compared to verify whether tandem Romberg stance resulted in greater postural sway than the standard Romberg stance. ML COP displacement and velocity were used to identify discrete reactive control events to naturally occurring instability. ML COP velocity was determined by taking the first derivative of the ML COP displacement signals. Discrete events of balance corrections were noted by large amplitude peaks in ML COP velocity. ML COP velocity peaks with amplitude greater than the threshold value were used to find the corresponding peaks in the ML COP displacement and the time points of those peak COP displacements (the starting of the discrete reactive control events to naturally occurring postural instability) were written to an event file which was later used for epoch extraction of the EEG data. Due to the differences in spontaneous sway between the two stances the threshold for detection of a compensatory event was 0.1 m/s and 0.02 m/s for tandem and standard Romberg stances, respectively.

Offline analyses of continuous EEG data included band pass filtering (2-50 Hz) followed by epoch extraction (2 s before and 2 s after the peak ML COP displacement (t = 0)) and baseline correction (baseline period: -2000 to -1900 ms) using EEGLAB (Delorme and Makeig, 2004). Ocular, muscular, cardiac, and line noise artifacts were corrected using ICA algorithm (Jung et al., 2000). ICA was also used to extract the brain components that contributed to the generation of naturally occurring instability-evoked N1 based on the percentage of power contributed by

each component. Since the scalp electrode activities represent the summated activities of multiple brain sources, ICA analysis separated the recorded multichannel scalp electrode activity in to a sum of maximally independent components (Makeig et al., 1996). The epoched EEG data were then visually inspected and any additional noisy epochs were removed manually. After artifact rejection, a total of 972 (range: 14-164 per subject) and 929 (21-177) epochs were obtained from all 12 subjects for standard and tandem Romberg stance conditions, respectively.

ERPs were obtained by grand averaging (n = 12) the EEG epochs that were time-locked to peak ML COP displacement. Natural instability-evoked N1 was identified as the largest negative component between the -150 ms and -20 ms time window of the ERPs. N1 amplitude was quantified as the difference in voltage between the N1 peak and baseline. ERP-scalp maps were plotted to visualize the topographic distribution of natural instability-evoked N1. Data analyses (time domain and frequency domain) were focused on Cz as the N1 amplitude was found to be maximum at Cz electrode. Power spectral analysis of 500 ms (-250 ms to 250 ms) time window and 2-50 Hz frequency range were carried out using Matlab pwelch function and mean log power spectrum of standard and tandem Romberg stances were plotted. In order to obtain the spectral power changes during natural instability evoked N1, ERSP, which represents the mean log event-related changes in spectral power, relative to a pre-event baseline at each frequency, was computed using Morlet-based wavelet transform in a 2-50 Hz frequency range (Delorme and Makeig, 2004). To visualize the spectral changes during N1, the mean baseline log spectrum was divided from each spectral estimate, resulting in a baseline normalized time-frequency distribution (Delorme and Makeig, 2004).

Two-sided paired t-tests with alpha level set at 0.05 were conducted to compare the spectral power, N1 amplitude, N1 latency, AP COP displacement, and ML COP displacement between standard and tandem Romberg stances.

4.4 Results

EEG from twelve young healthy adults was recorded while standing quietly with their eyes closed for 30 s with each foot on a separate force plate (Figure 4.1A and B). The task challenge during standard Romberg stance, as reflected by the RMS AP and ML COP displacement was small (mean ± s.d., ML:0.57 ± 0.15 cm; AP: 0.67 ± 0.19 cm). As expected, ML COP displacement was significantly greater during tandem Romberg stance (1.01 ± 0.17 cm; t_{11} = 8.99, $p < 0.01$) but AP COP displacement was not (0.81 ± 0.39 cm; t_{11} = 1.44, $p = 0.18$). In summary, tandem Romberg stance posed a larger challenge to upright stability than standard Romberg stance though all subjects were able to maintain stability even during this more difficult challenge. Discrete COP events denoting balance corrections to naturally occurring instability from the 30 s stance (Figure 4.1A and B) were identified by ML COP velocity peaks (Figure 4.1D) that exceeded specific threshold values for both stances, which in turn is used to identify the corresponding ML COP displacement peaks (Figure 4.1C).

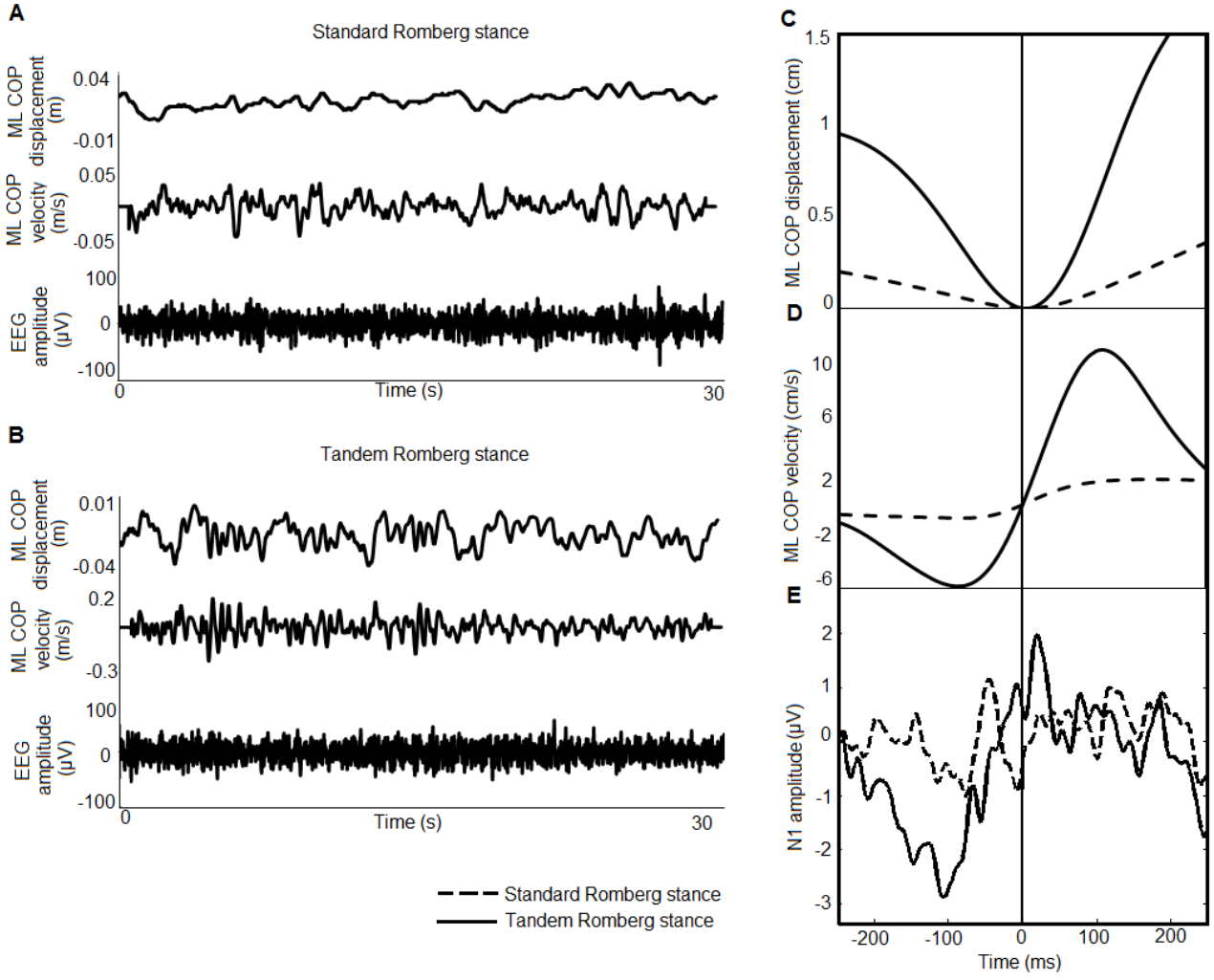

Figure 4.1: ML COP excursions and naturally occurring instability-evoked N1. Single trial EEG, ML COP displacement, and ML COP velocity during 30 s of standard (A) and tandem (B) Romberg stances. Grand averaged (*n* = 12) ML COP displacement (C), ML COP velocity (D), and ERP at Cz electrode (E) in response to naturally occurring instability during standard (dashed line) and tandem (solid line) Romberg stances. t = 0 is the peak ML COP displacement which estimates the onset of corrective balance reactions to spontaneous postural sway.

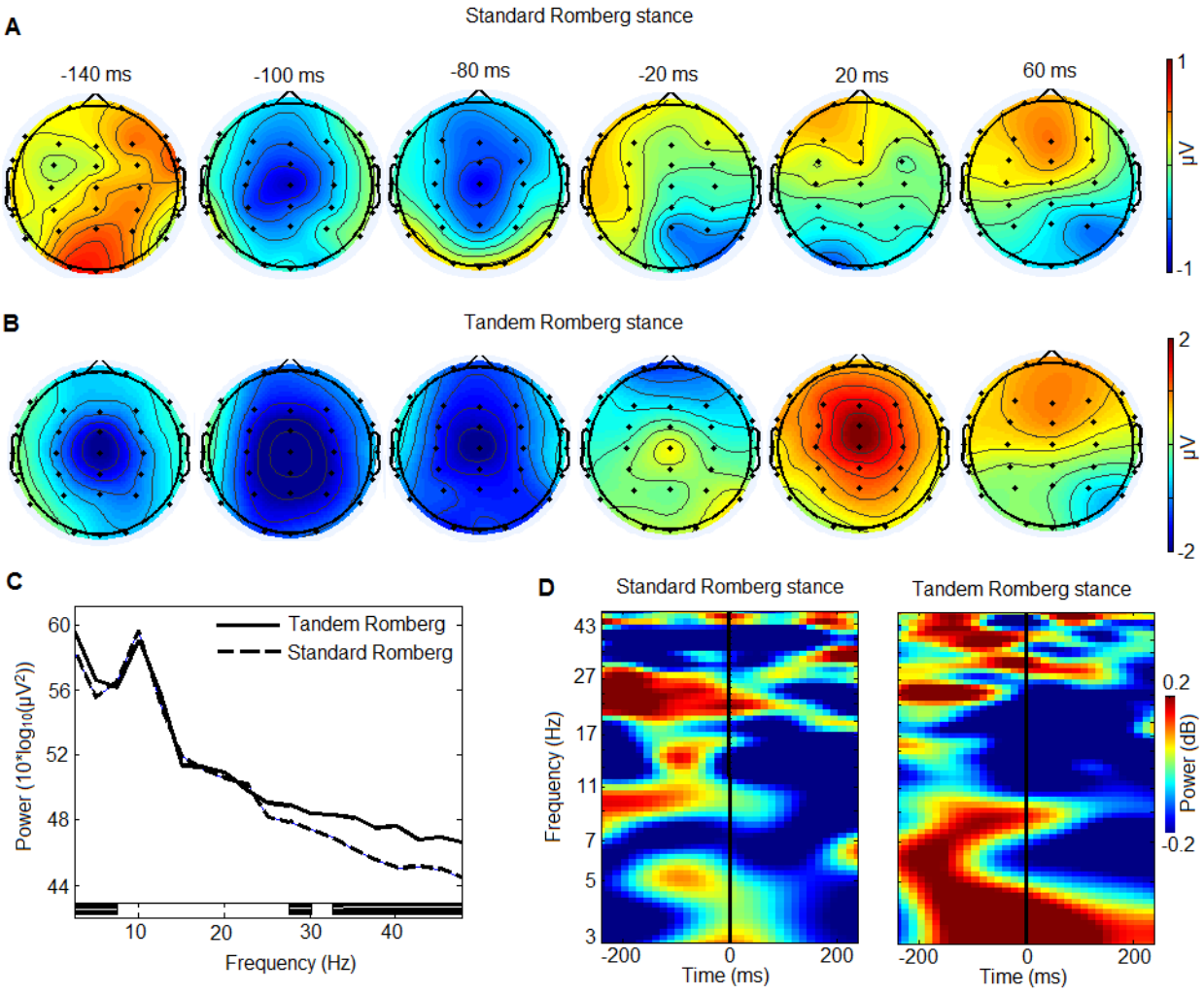

Figure 4.2: Scalp topographies and power spectral analysis. ERP-scalp maps of naturally occurring instability-evoked cortical response at selected time points during standard (A) and tandem (B) Romberg stances. (C) Grand averaged power spectral density of ERP (-250 ms to +250 ms) at Cz electrode during standard (dashed line) and tandem (solid line) Romberg stances. Black rectangles under the spectral plot indicate regions of significant ($p < 0.05$) differences in spectral power between the two stances. (D) Time-frequency maps of natural instability-evoked response during standard (left) and tandem (right) Romberg stances at Cz electrode.

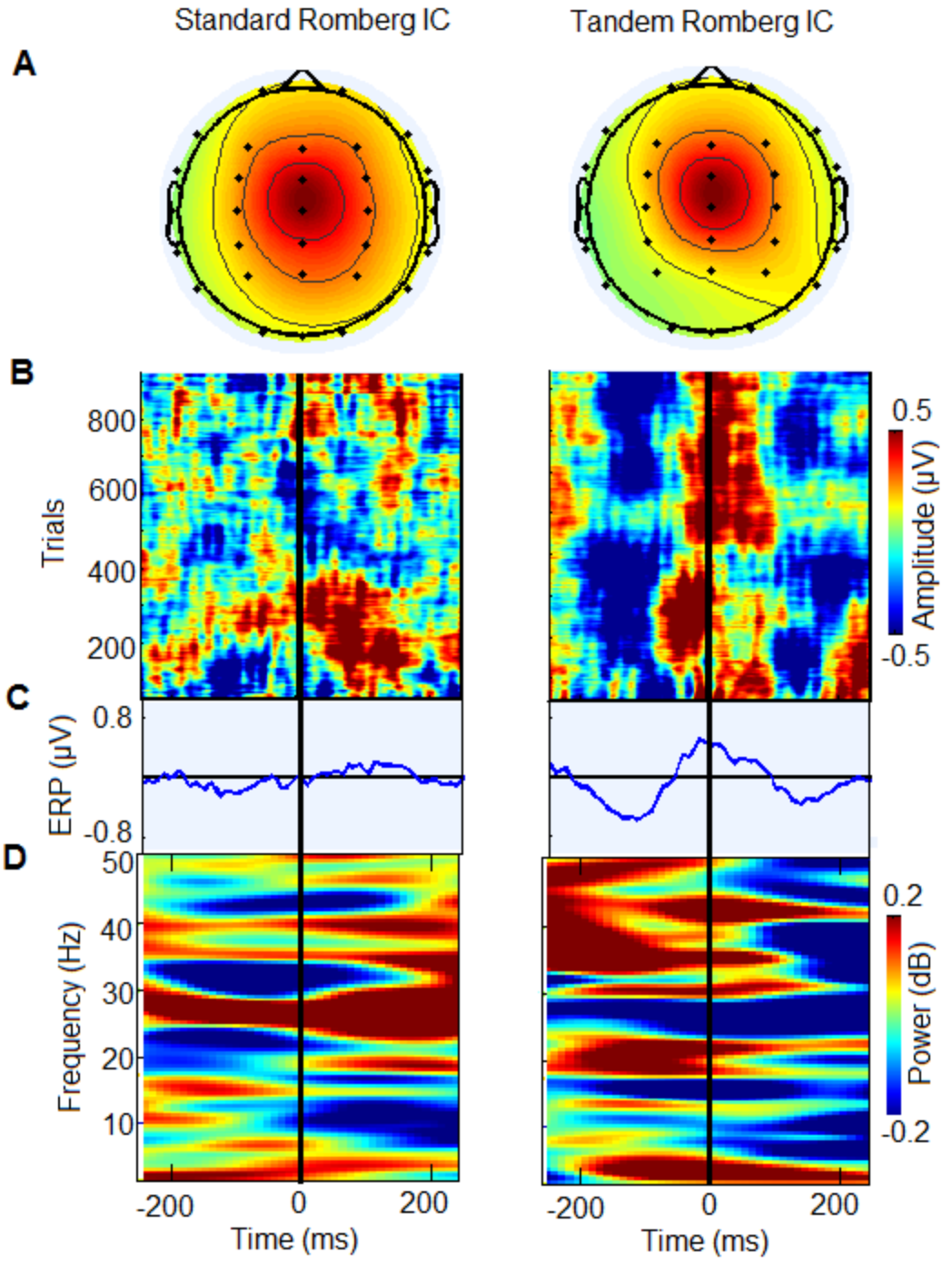

Figure 4.3: ICA of naturally occurring instability-evoked cortical response. (A) Scalp maps of fronto-central IC that mainly contributed to the generation of the natural instability-evoked N1 during standard (left) and tandem (right) Romberg stances. (B) Color-coded single trials of the fronto-central component stacked in the trial order. (C) Averaged ERP and (D) time-frequency plot of fronto-central IC during standard (left) and tandem (right) Romberg stances.

Cortical activity during standard and tandem stances (Figure 4.1A and B) was time-locked to each ML COP displacement peak. ERP analysis showed a consistently evoked N1 potential prior to peak COP displacement with maximum amplitude at Cz (Figure 4.1E). N1 peak latency did not differ between stances (tandem: -100 ± 27.80 ms; standard: -84 ± 30.70 ms; t_{11} = 1.64, p = 0.13), but N1 peak amplitude was significantly greater in tandem than standard Romberg stance (-4.80 ± 2.32 μV vs. -2.88 ± 2.34 μV; t_{11} = 2.3, p = 0.04). Note that the amplitude of the N1 response during standard stance was within the band of amplitude variability associated with data generated from randomly selected epochs. Scalp topography of N1 during both stances (Figure 4.2A and B) showed a wide distribution over fronto-central-parietal areas. Power spectral analysis revealed that spectral power in the delta (1-4 Hz), theta (4.1-7 Hz), and gamma (28-30 Hz and 33-50 Hz) frequency bands was significantly higher ($p < 0.05$) during tandem compared to standard Romberg stance (Figure 4.2C). Time-frequency analysis showed power increases in various frequency bands from 2 to 50 Hz during N1 for both stances (Figure 4.2D). ICA revealed that a fronto-central component contributed to the generation of evoked N1 in both stances. The scalp topography (Figure 4.3A), trial-by-trial activity (Figure 4.3B), trial-averaged ERP (Figure 4.3C), and time-frequency activity (Figure 4.3D) of this component were consistent with the N1 potential at the Cz electrode site.

4.5 Discussion

The focus of the current study was to reveal the potential presence of cortical activity temporally linked to the ‘automatic’ balance reactions that occur continuously when one is standing still. While recent studies (Marlin et al., 2014; Varghese et al., 2014) have highlighted the role for the cortex in reactive balance control during large destabilizing conditions (applied perturbations), this is the first study to explicitly reveal comparable cortical activity during naturally occurring

postural sway. The other distinguishing feature of this study is to focus on the discrete episodes of reactions during the continuous and ongoing postural sway. The standing tasks selected including standard and tandem Romberg stances resulted in the expected spatial and frequency of the COP excursions. The focus on specific discrete COP balance reactions during the continuous balance control task reflects the episodes of automatic balance reactions (events) that naturally occur during standing to maintain stability. Importantly this study revealed the complexity of the associated cortical activity that was temporally coupled to the measured balance reactions. The overall message is that even under the circumstances of standing still, highlighted by events of small automatic corrective reactions and associated COP sway, there is significant temporally coupled cortical activity. The current technique of specifically isolating the analysis to the behavioral markers of the reactive control avoided the potential problem of confounding feed forward control that can occur during standing.

The major finding of this study is a pronounced cortical negativity prior to the onset of discrete balance reactions to naturally-occurring instability while standing still. This cortical activity is evident even in a relatively stable stance but increases significantly during a more demanding stance characterized by larger reactive events. It should be noted that the potential evoked in the standard stance was modest and on amplitude alone would not have been distinguished from variability expected from randomly selected epochs. However, the timing and spatial characteristics of the associated activity support the idea that the N1 in the standard condition was a smaller but related potential to that measured during the tandem stance condition. Previous studies have reported large fronto-central negativity that peaks approximately 100-200 ms after the onset of external perturbations. This negativity originates in the SMA and may be attributed to increased power and phase-locking of oscillations at certain

frequencies (Dietz et al., 1984; Maki and McIlroy, 2007; Marlin et al., 2014; Varghese et al., 2014). Our present results suggest that this negative potential also arises for very small naturally occurring perturbations with significantly increased amplitude for more challenging postures. Perturbation-evoked N1 was shown to be generated by the power increase and phase-locking of 1-30 Hz frequency oscillations (Varghese et al., 2014). Differential modulation within alpha, beta, and gamma frequency bands were also shown during voluntary postural sways (Slobounov et al., 2005, 2008). Furthermore, significant modulation of theta, alpha, and gamma frequency bands was reported during transition-to-instability stage of single leg stance (Slobounov et al., 2009). High frequency oscillations in 10-45 Hz range has been reported to reflect intra- and inter-cortical information transfer during movement preparation (Rubino et al., 2006). Based on these previous findings, it may be likely that the modulation of different frequency oscillations, may contribute to the naturally occurring instability-evoked N1. The increased power in delta, theta, and gamma bands during tandem Romberg stance may reflect the increased cortical contributions to reactive control associated with increased task challenge.

4.6 Conclusions

In summary, we used a novel approach to identify stereotyped cortical activity that consistently precedes small automatic corrective balance reactions to naturally-occurring instability while standing still. This finding demonstrates cortical involvement in reactive balance control even during quiet, seemingly unperturbed, stance. This cortical activity increases in amplitude as the postural challenge increases and is likely associated with perturbation-evoked N1 responses. The work importantly contributes to the understanding of the CNS control of human bipedal balance.

Chapter 5

Study 3: Cortical control of anticipatory postural adjustments prior to stepping

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5.1 Abstract

Human bipedal balance control is achieved reactively and predictively by a distributed network of neural areas within the central nervous system with a potential role for cerebral cortex. While the role of the cortex in reactive balance has been widely explored, only few studies have addressed the cortical activations related to predictive balance control. The present study investigated the cortical activations related to the preparation and execution of APA that precede a step. This study also examined whether the preparatory cortical activations related to a specific movement is dependent on the context of control (postural component vs. focal component). Ground reaction forces and EEG data were recorded from fourteen healthy adults while they performed lateral weight shift and lateral stepping with and without initially preloading their weight to the stance leg. EEG analysis revealed that there were distinct MRPs with concurrent ERD of mu and beta rhythms prior to the onset of APA and also to the onset of foot-off (FO) during lateral stepping in the fronto-central cortical areas. Also, the MRPs and ERD prior to the onset of APA and onset of lateral weight shift were not significantly different suggesting the comparable cortical activations for the generation of postural and focal movements. The present study reveals the occurrence of cortical activation prior to the execution of an APA that precedes a step. Importantly, this cortical activity appears independent of the context of the movement.

5.2 Introduction

Human bipedal balance control is a remarkable complex sensorimotor task which is controlled both reactively and predictively by the CNS. While reactive balance control compensates for unpredictable postural perturbations, predictive (anticipatory) balance control minimizes the destabilizing effect of predictable perturbations and voluntary movements (Massion, 1992; Maki and McIlroy, 1997; Jacobs and Horak, 2007). For instance, prior to stepping, it is necessary to transfer the COM laterally to the stance leg in order to maintain equilibrium. This lateral weight shift, which is also referred to as ML APA, involves an initial increase in vertical loading on the swing leg with a concurrent ML COP displacement toward this leg to propel the COM toward the stance limb (Halliday et al., 1998; McIlroy and Maki, 1999). The APA (e.g., lateral weight shift) and focal movement (e.g., stepping) must be coordinated by the CNS in order to achieve the desired movement while also maintaining stability. The focus of the present study is to advance the understanding of the cortical contributions to balance control with specific attention to anticipatory control during stepping.

It has been proposed that a distributed neural network including cerebellum, basal ganglia, thalamus, and cortex are involved in the generation and execution of APA (Massion, 1984, 1992; Ng et al., 2011). During gait initiation, parkinsonian patients and cerebellar patients display APA impairments including decreased force production, reduced COP excursion, delayed APA execution, and prolonged anticipatory phase. These impairments reveal the potential role of basal ganglia and cerebellum in APA (Burleigh-Jacobs et al., 1997; Timmann and Horak, 2001). Clinical studies that examined the location of brain damage and impairment of APAs associated with rapid arm raising, BMLL, leg lift, and step initiation suggested a potential role for PMC, SMA and M1 in the generation and execution of APA (Gurfinkel and Elner, 1988;

Birjukova et al., 1989; Massion, 1992; Yakovenko and Drew 2009; Chang et al., 2010). MEG studies of APAs during the BMLL task in healthy adults also showed activation associated with the SMA and M1 (Ng et al., 2011, 2013).

EEG studies have revealed the cortical activations associated with APA during voluntary movements in both frequency and voltage domains as ERD of mu and beta rhythms and MRPs, respectively. APA during the BMLL task (reduction in the biceps brachii muscle activity of the load-bearing arm) was associated with an ERD of mu (8-13 Hz) and central beta rhythms (16-30 Hz) over M1 and SMA (Barlaam et al., 2011; Ng et al., 2011). MRPs preceded the onset of APA during voluntary rising on tiptoes with maximum amplitude over Cz (Saitou et al., 1996). A late CNV wave related to APAs during gait initiation and during bilateral shoulder flexion while standing was also reported using CNV paradigms (Yazawa et al., 1997; Maeda and Fujiwara, 2007). These studies all appear to point to an important role for fronto-central cortical sites for the execution of APA; however, in many of these studies it is difficult to disentangle the cortical activity that maybe linked to the APA and the concurrent or subsequent focal movement. For example, in forward stepping while the ML APA is being executed the CNS is concurrently generating force to cause anteroposterior (AP) instability (i.e., to move the COM forward for stepping). In arm raise studies, the timing between the onset of the APA and the onset of arm movement can be quite compressed making it difficult to separate them temporally. As a result, in many tasks studied, the APA phase may be temporally entangled with the control of the focal task.

To better understand the potential role of cortical activity for the predictive postural elements it is necessary to isolate the APA phase from the focal task. Yoshida and associates (2008) isolated the APA-related component in MRPs by comparing unilateral shoulder flexion

movements while standing and sitting. They found increased amplitude on all three components of the MRPs (RP, MP, and MMP) in the standing condition. Ng et al. (2013) isolated the APA in the BMLL task by comparing with a control task that has no APA and found ERD of beta rhythm associated with APA over the sensorimotor cortical areas. The challenge in gait initiation or forward stepping, as noted, is that the period of control that encompasses the APA is composed of two elements: (1) the APA involving the ML motion of the COM prior to limb unloading and (2) the AP movement of the COM to advance the body forward for a forward step. In this way the cortical control of the events prior to unloading are comprised of a predictive balance component and the focal task of moving forward. To better isolate the ML APA the current study explores laterally directed stepping removing concurrent control of the ML APA and the focal AP movement.

The present study advances the understanding of the cortical involvement in the control of anticipatory balance control. The primary objective of this study was to isolate cortical activity related to the preparation of an APA. To do this we examined the cortical events prior to the ML APA preceding a lateral stepping task. To isolate the cortical activity specifically associated with the execution of an APA, we compared the cortical events prior to the focal task of lateral stepping between conditions with and without a preceding APA (i.e., the limb is unweighted prior to stepping reducing the need for an ML APA). An additional objective was to determine if observed APA-related cortical activity was unique to the performance of a movement as part of an APA or, rather, was comparable to execution of the same movement as part of a focal task. To address this objective, we compared the pre-motor cortical events of an ML APA that automatically precedes lateral stepping with a voluntary ML weight shift that was not associated with any stepping reaction.

5.3 Materials and Methods

5.3.1 Participants

Fourteen healthy volunteers (19-33 years, three females) participated in this study. No subjects reported any history of neuromuscular or CNS disorders. The experimental procedures were performed in accordance with the declaration of Helsinki and approved by the Research Ethics Board of the University of Waterloo. Prior to the experiment, the subjects were given a description of the study and each participant provided written informed consent.

5.3.2 Experimental Design

Participants stood barefoot with each foot on one of the two force plates with arms by their sides and eyes open. They selected a comfortable stance width (approximately shoulder width) and the outline of their feet was traced using tape markers to maintain the same starting foot position throughout the experiment. Subjects fixed their gaze on a cross sign placed at eye level on the wall in front of them and maintained that gaze while performing the task.

Participants performed the following three motor tasks in response to an auditory cue: (1) equal-weighted lateral stepping (stepping preceded by APA), (2) unloaded lateral stepping (stepping with no APA) and (3) lateral weight shift (APA-like movement without the subsequent step). Four blocks of trials were performed for each of the three tasks for a total of 12 blocks. The order of these blocks was randomized. Each block consisted of 10 trials for a total of 120 trials (i.e., 40 trials for each task). In equal-weighted lateral stepping, participants initially stood on the force plate with equal weight over each limb and responded to the auditory cue by quickly stepping laterally with their right leg over a rectangular foam barrier placed to their right. The use of a foam barrier standardized the stepping height required in stepping tasks and also ensured an APA phase with sufficient amplitude in equal-weighted lateral stepping. In unloaded lateral

stepping, participants initially stood with their body weight transferred over the left leg to unload the right leg while keeping it in contact with the ground. They remained in that position until, upon hearing the auditory cue, they stepped over the foam barrier with their right leg. Thus, in unloaded lateral stepping there was no APA phase. After the stepping trials, subjects returned to the initial stance position at their own pace. In the lateral weight shift task, participants initially stood on the force plate with equal weight over each limb. Upon the auditory cue they performed a quick weight transfer to the left leg and returned to the initial stance position at their own pace. They were allowed to rest between blocks and practice trials were given prior to data collection.

5.3.3 Data acquisition

Vertical and horizontal ground reaction forces and corresponding moments from two force plates (AMTI model OR 6-5, Watertown, MA, USA) that were positioned side by side were recorded using a custom-built LabVIEW (National Instruments, TX, USA) program. Prior to data collection, the force plates were calibrated with the foam barrier on the right force plate. During the experiment, force plate signals were monitored online especially in the unloaded stepping trials to ensure the absence of APA. Unloaded stepping trials that contained an APA phase were discarded from further analysis. Force plate data were amplified (gain: 1000), analog low-pass filtered using two-pole low-pass 1000-Hz filter (built in AMTI MSA-6 MiniAmp amplifier), sampled online at a rate of 1000 Hz, and stored for subsequent analysis.

EEG data were acquired online using 32 Ag/AgCl electrodes mounted on a cap (Quick-cap, Compumedics Neuroscan, USA) and Neuroscan 4.3 software. EOG signals were also recorded using four EOG electrodes positioned above and below the left eye and lateral to the outer canthi of both eyes. The impedances of all EEG and EOG electrodes were kept below 5 KΩ throughout the experiment and they were referenced to linked mastoids. The acquired EEG

signals were amplified (gain: 19), sampled (1000 Hz), filtered (DC-260 Hz) online using 40-channel digital EEG amplifier (Nuamps, Compumedics Neuroscan, USA), and then stored for offline analysis.

5.3.4 Data analysis

Post-processing of force plate data (using a custom-built LabVIEW program) included low-pass filtering (6-Hz, dual-pass 2nd-order Butterworth filter), ML COP calculation, feature extraction, and writing event files that contain the time points of APA and FO onset. These event files were later used to mark the APA and FO time points on EEG data. Since the APA phase of equal-weighted lateral stepping consist of a lateral weight shift, we used the term 'APA onset' to refer the onset of lateral weight shift (in terms of ML COP displacement) in both equal-weighted stepping and lateral weight shift tasks. All latencies were expressed with respect to the onset of the auditory cue. Reaction time was expressed as the APA onset for lateral weight shift and equal-weighted stepping and the onset of unloading for unloaded stepping. These onsets were defined as the time points when the ML COP displacement toward the right limb deviated by 4 mm from the mean baseline ML COP (baseline was calculated over a time window of 200 ms after the auditory cue). The onset of unloading for equal-weighted stepping was the time of peak APA (peak amplitude of ML COP excursion toward the right limb)**.** The onset of stepping was defined as the onset of APA for equal-weighted stepping and the onset of unloading for unloaded stepping. Magnitude of APA was expressed as the peak APA amplitude relative to the mean baseline ML COP. Time to peak APA was the time of peak amplitude of ML COP excursion toward the right limb. Duration to peak APA was measured from the onset of APA until time to peak APA. The onset of FO was defined to be the time when the loading on the right force plate dropped to less than 1% of the body weight. The time required to unload the swing foot

(unloading phase duration) for both stepping tasks was measured from the onset of unloading until the onset of FO. Total stepping time was defined as the time between onset of FO and onset of stepping (McIlroy and Maki, 1993, 1996, 1999; Zettel et al., 2002; Lakhani et al., 2011).

Offline analyses of EEG data were performed in MATLAB (The Mathworks, Natick, MA, USA) using custom-made scripts written to run in EEGLAB v13.0.1 (Delorme and Makeig, 2004). EEG data were band pass filtered (0.05-50 Hz), segmented into 3-s epochs with respect to APA and FO onsets (1.5 s before and after the trigger points), and baseline corrected (baseline period: -1.2 s to -1 s). Ocular, muscular, cardiac, movement, and line noise artifacts were eliminated using ICA. One of the major artifacts that can encounter in stepping studies is the movement artifact (Thompson et al., 2008); however, ICA has been used to remove movement artifacts (Thompson et al., 2008; Gwin et al., 2011; Wagner et al., 2012). ICA decomposes the multi-channel EEG data into spatially fixed and temporally independent components statistically without prior knowledge about the signal and noise components in the input EEG data (blind source separation) thereby separating the contributions of brain sources and artifactual sources (Bell and Sejnowski, 1995; Makeig et al., 1996, 1997; Jung et al., 1998; Delorme et al., 2002). The ICA pruned epoched data were once again visually inspected and any additional noisy epochs were rejected manually.

MRPs related to APA and FO were obtained by grand averaging (n = 14) the individual-averaged epochs that were time-locked to the onset of APA and FO, respectively. MRP waveform morphology and topographic voltage maps were characterized using the grand-averaged data. The peak amplitudes of specific components within MRPs related to both APA and FO were extracted from averaged single-subject data for each condition as follows: (1) the peak negativity of the RP measured between -600 ms and -500 ms, (2) the peak negativity of the

MP measured between -100 ms and 0 ms, and (3) the NS by subtracting the RP amplitude from MP amplitude (Singh et al., 1992; do Nascimento et al., 2005; Yoshida et al., 2008). For equal-weighted stepping and lateral weight shift, the amplitude of MMP was also measured which is defined as the peak negativity between 0 ms and time of peak APA. The topographic voltage maps were plotted at discrete time points to visualize the scalp distribution of MRPs related to APA and FO. Brain ICs that contributed to the MRPs were selected based on the percentage of power contributed to the grand-averaged waveform.

In the frequency domain, the spectral power changes were characterized in terms of ERSPs, which is a generalization of ERD. The ERSP computes the mean log event-related spectral power changes relative to a mean pre-event baseline spectra using Morlet wavelet transform techniques and plots the spectral changes at discrete frequencies as a function of time (Makeig, 1993; Delorme and Makeig, 2004; Roach and Mathalon, 2008). Both ERP and ERSP analysis were focused on mid fronto-central electrodes.

5.3.5 Statistical Analysis

Two-tailed paired *t*-tests were used to assess the significant differences ($p < .05$) in the postural and EEG dynamics related to APA (between lateral weight shift and equal-weighted stepping) and FO (between equal-weighted stepping and unloaded stepping).

5.4 Results

5.4.1 Movement Characteristics

All 14 participants performed the three task conditions with a mean reaction time of 290 ± 41 ms (mean ± SD), 270 ± 42 ms, and 309 ± 55 ms for lateral weight shift, equal-weighted lateral stepping, and unloaded lateral stepping, respectively. Example of single-trial responses for each task condition is provided in Figure 5.1. As instructed, participants stood initially with equal

weight on both legs for lateral weight shift (baseline ML COP: -0.02 ± 0.02 m) and equal-weighted stepping (baseline ML COP: -0.03 ± 0.03 m) and preloaded their weight to the left leg in unloaded stepping (baseline ML COP: -0.15 ± 0.05 m). The magnitude of APA did not differ between task conditions (lateral weight shift: 0.077 ± 0.02 m; equal-weighted stepping: 0.078 ± 0.02 m; t_{14} = -0.09, p = .93). However, the duration to peak APA was significantly shorter for equal-weighted stepping than lateral weight shift (197 ± 49 ms vs. 248 ± 40 ms; t_{14} = 6.86, p < .05). The presence of the APA phase significantly delayed the onset of FO for equal-weighted stepping compared to unloaded stepping (661 ± 94 ms vs. 384 ± 64 ms; t_{14} = 13.15, p < .05). Subsequently, the unloading phase duration (193 ± 30 ms vs. 76 ± 23 ms; t_{14} = 10.63, p < .05) and total stepping time (390. 83 ± 69 ms vs. 76 ± 23 ms; t_{14} = 16.01, p < .05) were also significantly greater for equal-weighted stepping compared to those of unloaded stepping.

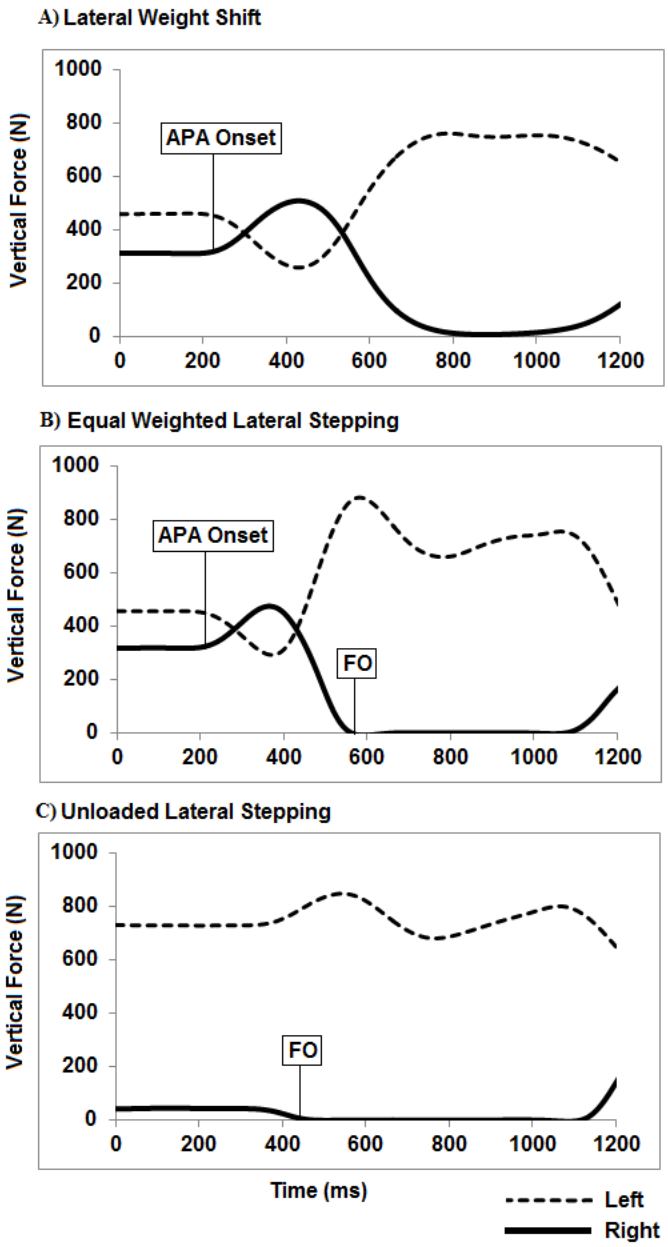

Figure 5.1: Example of single-trial responses. Vertical ground reaction forces under the swing (solid line) and stance (broken line) foot for lateral weight shift (A), equal-weighted lateral stepping (B), and unloaded lateral stepping (C). Time = 0 indicates the onset of auditory cue. The trials were selected, at random, from a single subject. The onset of lateral weight shift is labelled as APA Onset for lateral weight shift condition and equal-weighted lateral stepping. The onset of foot-off is labelled as FO for equal-weighted lateral stepping and unloaded lateral stepping. Note that there is no FO in the lateral weight shift condition and no APA in the unloaded lateral stepping.

5.4.2 Movement-related potentials

Figure 5.2 illustrates the grand-averaged (n = 14) MRPs related to APA and FO at Cz electrode site. The MRPs had maximum amplitude at Cz electrode, hence further analysis was focused on the Cz electrode. The grand-averaged plot (Figure 5.2A) revealed that there is a specific MRP related to the preparation and execution of APA with no significant difference between lateral weight shift and equal-weighted stepping for peak amplitude of RP, MP, NS, and MMP (Table 1). In addition, a paired *t*-test performed at each time point also showed no significant difference ($p > .05$) in the MRP related to APA between lateral weight shift and equal-weighted stepping. The grand-averaged plot of MRP related to FO (Figure 5.2B) revealed that there is a specific MRP related to the preparation and execution of FO, which differed significantly between equal-weighted stepping and unloaded stepping for peak amplitude of MP and NS (Table 5.1). However, even though the RP amplitude of equal weighed stepping was greater than that of unloaded stepping, this difference was not statistically significant (Table 5.1). The paired *t*-test performed at each time point also showed a significant difference ($p < .05$) in the MRPs prior to FO between equal-weighted stepping and unloaded stepping. The topographic maps plotted at the different time points before and after APA and FO onset are shown in Figure 5.3. RP related to APA begins approximately 800 ms prior to the onset of APA and is localized to mid-central areas, whereas MP and MMP are widely distributed over the fronto-central-parietal areas.

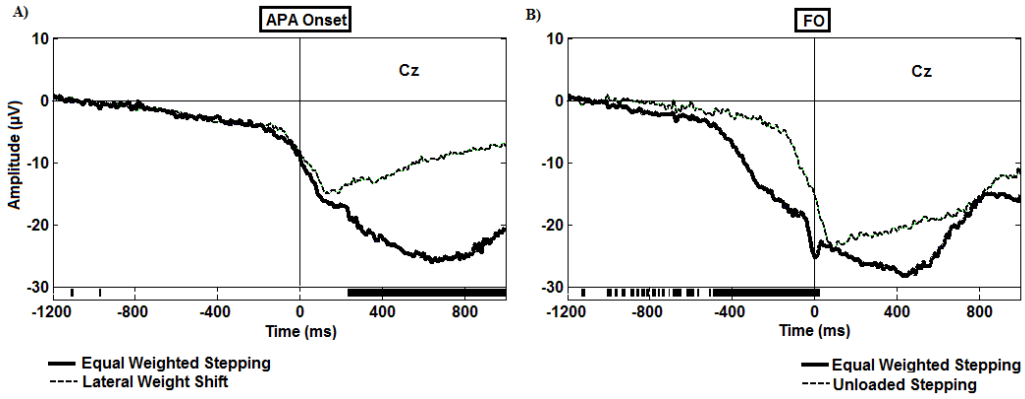

Figure 5.2: MRPs at Cz electrode. Grand-averaged (n = 14) MRPs of equal-weighted lateral stepping (solid line) and lateral weight shift (broken line) epoched around (t = 0) APA onset (A) and foot-off onset (B). Black rectangles under the MRP plots indicate regions of significant (p < .05) differences in MRP amplitudes between task conditions.

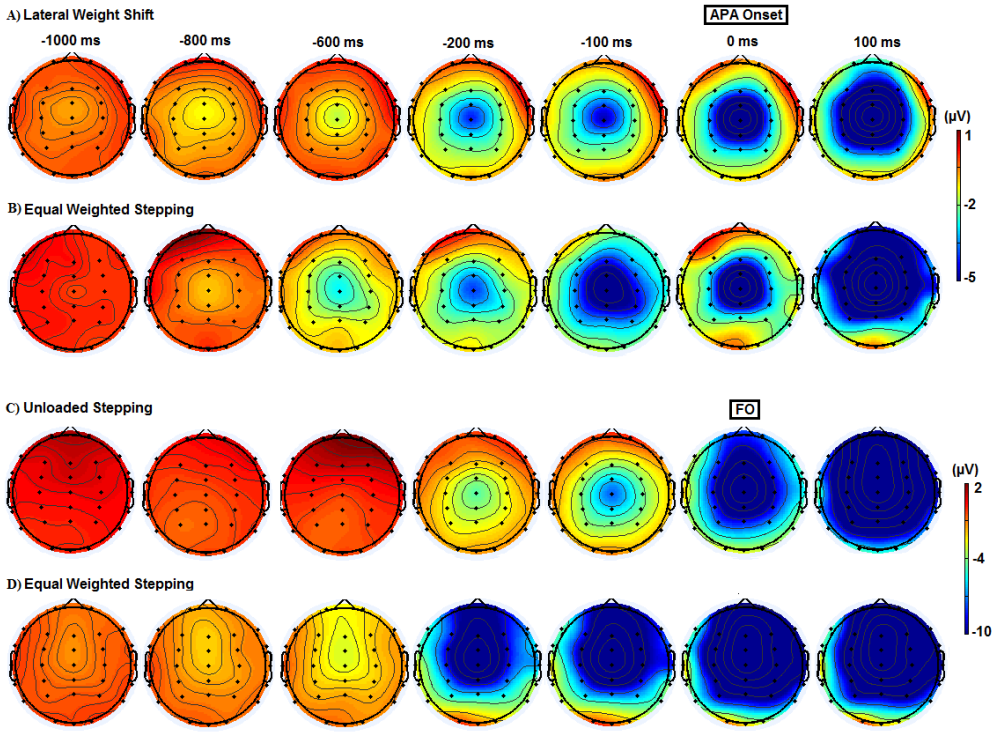

Figure 5.3: Scalp topographies of MRPs. Topographic voltage maps of grand-averaged MRPs (n = 14) related to APA (0 ms denotes the onset of APA) at different time points during lateral weight shift (A) and equal-weighted stepping (B). Topographic voltage maps of grand-averaged MRPs (n = 14) related to FO (0 ms denotes the onset of FO) at different time points during

equal-weighted stepping (C) and unloaded stepping (D). Color scales depict MRP amplitudes in microvolts and black dots depict the electrode locations.

Table 5.1: Peak amplitudes of MRPs related to APA and FO

	APA			FO		
	Lateral weight Shift (μV)	Equal-weighted stepping (μV)	*p* Value	Equal-Weighted stepping (μV)	Unloaded stepping (μV)	*p* Value
RP	-4.10 ± 3.31	-4.39 ± 3.41	.77	-5.43 ± 3.71	-4.54 ± 2.74	.33
MP	-9.19 ± 7.82	-10.96 ± 9.08	.20	-26.43 ± 14.11	-17.19 ± 13.16	< .05
NS	-5.09 ± 6.04	-6.57 ± 6.54	.06	-21.00 ± 11.21	-12.17 ± 11.24	< .05
MMP	-16.92 ± 11.67	-18.56 ± 11.50	.36			

Grand-averaged (n = 14) MRP amplitude values at Cz are presented as mean ± standard deviation. RP: readiness potential, MP: motor potential, NS: negative slope, and MMP: movement-monitoring potential. MMP values were measured only for MRPs related to APA.

5.4.3 Event-related spectral perturbations

The grand-averaged ERSP plots at the Cz electrode are depicted in Figure 5.4. ERSP analysis revealed the power spectral changes at specific frequencies (3-50 Hz) and time points relative to the onset of APA and FO. The time-frequency analysis of MRP related to APA during lateral weight shift and equal-weighted stepping (Figure 5.4A, B) revealed a robust mu ERD and phasic beta ERD during RP with no significant difference in spectral power between two task conditions ($p > .05$). This ERD was followed by mu ERS which started approximately 200 ms prior to the APA onset and lasted until the end of APA for lateral weight shift and until the FO for equal-weighted stepping. The time-frequency analysis of MRP related to FO during equal-weighted and unloaded stepping (Figure 5.4C, D) also showed mu and beta ERD during RP with

no significant difference between the two task conditions ($p > .05$). For unloaded stepping this ERD was followed by robust mu ERS and phasic beta ERS which started approximately 200 ms prior to the onset of FO. However, for the equal-weighted stepping the ERS started around 400 ms prior to the FO onset (this early ERS corresponds to the ERS that occurred during APA) and there was a robust mu and beta ERS during MP which was significantly different ($p < .05$) than that of unloaded stepping. A phasic gamma ERS (30 - 40 Hz) was also observable during RP for both APA- and FO-related MRPs.

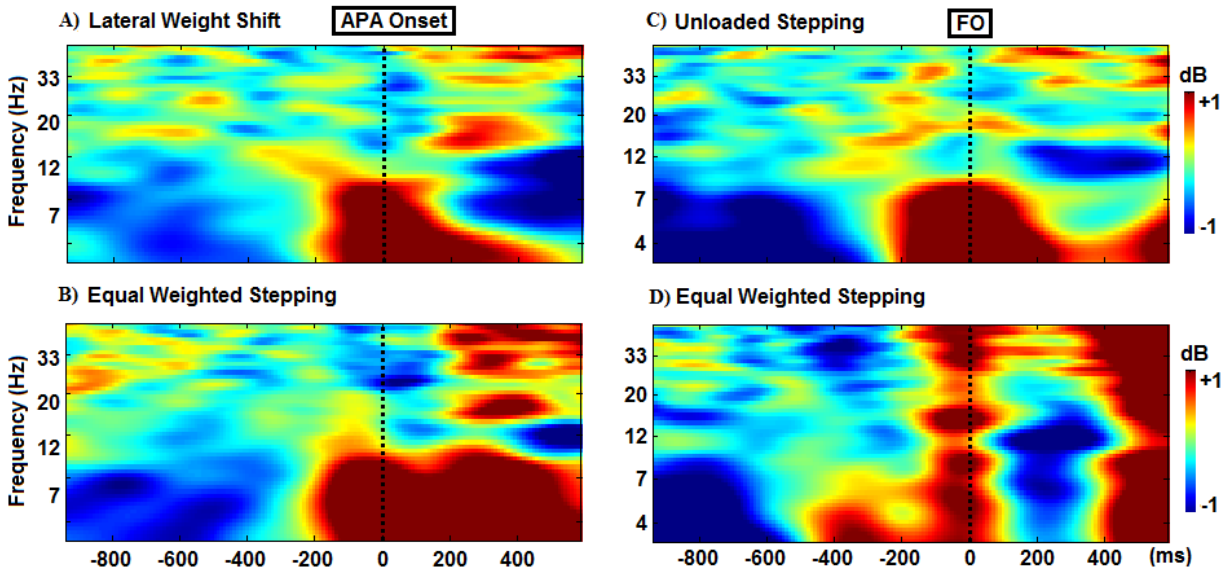

Figure 5.4: ERSP Plots. Time-frequency maps of grand-averaged (n = 14) MRPs related to APA (0 ms denotes the onset of APA) during lateral weight shift (A) and equal-weighted stepping (B). Time-frequency maps of grand-averaged (n = 14) MRPs related to FO (0 ms denotes the onset of FO) during equal-weighted stepping (C) and unloaded stepping (D). Color scale depicts the spectral power of MRPs in decibels. Blue color indicates an ERD whereas red color indicates an ERS.

5.4.4 Movement-related ICs

The brain ICs were identified based on the amount of power they contributed to the generation of the MRP (Delorme and Makeig, 2004). Component scalp maps of the brain ICs that show relative projection strength and time course of activity are provided in Figure 5.5. The scalp topography of the brain ICs of all MRPs demonstrated a mid fronto-central activation. The component activity of the brain ICs resembled that of the Cz electrode activity.

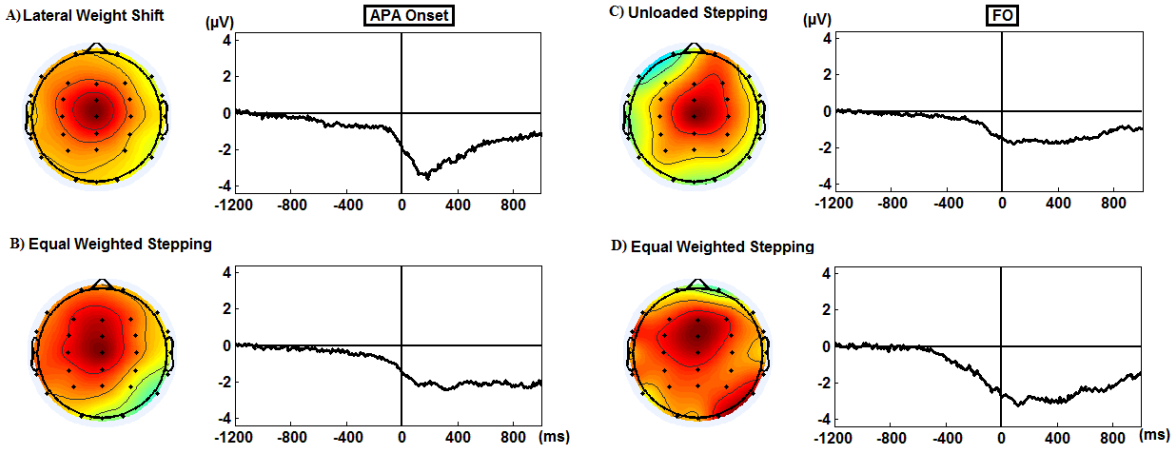

Figure 5.5: MRP-related ICs. Scalp maps (left frame) and time course of activity (right frame) of the ICs that contributed maximum power to the MRPs related to APA (0 ms denotes the onset of APA) during lateral weight shift (A) and equal-weighted stepping (B). Scalp maps (left frame) and time course of activity (right frame) of the ICs that contributed maximum power to the MRPs related to FO (0 ms denotes the onset of FO) during equal-weighted stepping (C) and unloaded stepping (D).

5.5 Discussion

To our knowledge, this is the first study to explicitly examine the cortical activity related to the preparation of an APA prior to stepping using ERP and time-frequency analysis. The results were highlighted by discrete cortical events in the voltage and frequency domain linked to APA and FO during lateral stepping.

5.5.1 Movement-related potentials

In the present study, the MRPs measured prior to the APA that preceded equal-weighted stepping was similar to the MRPs measured prior to the execution of a lateral weight shift. By having participants step laterally, we were able to isolate the MRPs that are solely related to the generation of ML APA. In our lateral stepping task, the anticipatory control occurred prior to the voluntary step unlike voluntary forward stepping where the lateral anticipatory control occurs concurrent with the AP advancement of the COM for the purpose of forward progression (McIlroy and Maki, 1993; Halliday et al., 1998). As such, we were able to isolate RPs and MPs specifically related to the APA and not the focal stepping task. RPs during voluntary movements begin 0.8-1.5 s prior to movement onset and are distributed bilaterally over frontal, central, and parietal areas with maximum amplitude at vertex (Cz) (Kornhuber and Deecke; 1965; Vaughan et al., 1968; Deecke et al., 1976; Boschert et al., 1983; Lang et al., 1991; Jahanshahi et al., 1995). It is suggested that the RP reflects the facilitatory events in the dendritic network of those cortical areas related to the preparation of movement (Gilden et al., 1966; Vaughan et al., 1968; Deecke et al., 1976). In addition, lesion studies, intracranial recordings, and source localization studies have shown that RP arises from SMA and M1 (Vaughan et al., 1968; Deecke et al., 1976; Boschert et al., 1983; Lang et al., 1991; Ikeda el al., 1992). MPs have been shown to start 50-100 ms prior to the movement onset and have maximum amplitude over the vertex for voluntary foot movements (Gilden et al., 1966; Deecke et al., 1976; Ikeda el al., 1992). MP reflects the synaptic potentials related to the pyramidal tract neuronal discharge in the motor cortex (Gilden et al., 1966; Deecke et al., 1976; Ikeda el al., 1992). Thus, it is proposed that the MRPs are indicators of cortical activation, which is a combination of decreased membrane potential and increased EPSPs of cortical cells (Gilden et al., 1966; Deecke et al., 1976). In the present study, the

characteristics of the RPs and MPs observed prior to the APA onset are in line with RP and MP characteristics from these previous studies. The present results emphasize the important role of the cortex in anticipatory balance control even when it is automatic.

The postural results revealed that the magnitude of APA did not differ between voluntary lateral weight shift and the automatic response that precedes equal-weighted stepping. Hence, it might be possible that the CNS controls the APA as a sequentially independent movement separate from the limb unloading associated with the step phase. Previous studies have shown the existence of MRPs prior to the APA in addition to the MRPs prior to the focal task during voluntary rising on tip toes (Saitou et al., 1996). The authors concluded that the CNS relies on separate motor programs to generate APA and focal movement as suggested by Nardone and Schieppati (1988). In addition, during a BMLL task, Barlaam et al. (2011) reported a negative wave over the left M1 hand area and a simultaneous positive wave over the right M1 hand area. The authors interpreted these results as evidence of a separate postural command that generates the APA (inhibition of the postural muscle activity as reflected by the positive wave over the contralateral M1 of postural arm) and motor command that generates the focal task (activation of the focal arm for load-lifting as reflected by the negative wave over the ipsilateral M1 of the postural arm). They supported the 'parallel' mode of coordination between posture and movement suggested by Massion (1992) that the postural and motor commands develop independently and in parallel. In the present study, the MRPs prior to the APA during lateral weight shift and equal-weighted stepping did not differ between the task conditions. In addition, the MMP that might be related to the execution of APA did not differ between lateral weight shift and equal-weighted stepping. The absence of a significant difference in APA-related MRPs between lateral weight shift and equal-weighted stepping suggests that the CNS utilizes the same

motor program for the generation of lateral weight shift regardless of whether it precedes stepping or is the focal task. We speculate that the MRPs associated with the APA reflect the postural command in the 'parallel' mode of postural control even though the present results provide no direct evidence of parallel processing of APA and focal task.

Even though the MRPs related to FO were not the primary focus of this study, we observed MRPs prior to FO which were significantly different between equal-weighted stepping and unloaded stepping conditions in both the voltage and frequency domains. While the MRP prior to FO corresponds to the activation of the cortical processes involved in the preparation of FO, the increased negativity in MRP of equal-weighted stepping might be accounted for by the parallel cortical processing required for both the execution of APA (part of the postural command) and preparation of FO. Thus the specific MRPs related to APA and FO in the present study suggest that APAs and focal tasks are organized independently by parallel descending pathways as separate postural and motor commands and are coordinated either subcortically or cortically (Massion 1992; Viallet el al., 1992; Ng et al., 2013).

In the current study, the duration to peak APA in equal-weighted stepping was significantly shorter than that of lateral weight shift. It has been shown that the duration of APA is reduced when the gait initiation is performed under triggered conditions (auditory cue) than that of self-initiated situations (Delval et al., 2005; Yiou et al., 2012). The shortened duration of time to peak APA in equal-weighted stepping might be due to the subsequent stepping task that the participants need to perform in response to the auditory cue.

5.5.2 Event-related spectral perturbations

The time-frequency analysis demonstrates that a robust mu and phasic beta ERD occurs during the RP related to both the APA and FO followed by mu and beta ERS during the MP and MMP.

ERD reflects the state of increased cortical excitability and serves as another indicator of cortical activation apart from the MRPs. Previous EEG studies reported that the RP that starts 2 s prior to the onset of a voluntary self-paced movement was paralleled by mu and beta ERD with similar onset timing and maximum amplitude at Cz for foot movements (Jasper and Penfield, 1949; Pfurtscheller and Aranibar, 1979; Pfurtscheller and Berghold, 1989). This ERD was followed by mu and beta ERS (Neuper and Pfurscheller, 1996). It was suggested that the involvement of the basal ganglia in motor planning and their projection to the M1 through the thalamus influences the thalamo-cortical rhythmic system which results in mu and beta ERD that precedes a voluntary movement (Pfurtscheller, 1981; Pfurtscheller and Berghold, 1989). However, the beta ERD usually had a phasic character and smaller amplitude compared to that of mu ERD thereby suggesting different functional significances for mu and beta ERD (Jasper and Penfield, 1949; Pfurtscheller, 1981; Pfurtscheller and Berghold, 1989). ERS was interpreted as a correlate of activated neural structures and reflects the sensorimotor integration prior to and during the activation of pyramidal neurons in the M1 (Pfurscheller et al., 1993; Neuper and Pfurscheller, 1996). Apart from the mu and beta ERD, a concurrent gamma ERS (30-40 Hz) close to the primary sensorimotor areas was also reported during externally triggered finger, toe, and tongue movements (Pfurscheller et al., 1993). The gamma ERS reflects the neural interactions between sensorimotor areas during motor programming (Pfurscheller et al., 1993). Electrocorticographic and stereo-EEG studies in epileptic patients also reported mu and beta ERD in the 5-40 Hz frequency range during RP associated with self-paced finger movements over SMA proper, M1, and primary sensorimotor areas with earliest ERD observed over SMA proper. This ERD was followed by mu and beta ERS in all the three areas (Ohara et al., 2000; Szurhaj et al., 2003). In

the present results, the ERD and ERS during the MRP related to APA and FO might reflect the frequency counterpart of the MRPs.

Moreover, mu and beta ERD were reported to be associated with APA during BMLL tasks. Mu ERD related to APA during a BMLL task was observed in healthy adults and children over the postural M1 hand area that corresponds to the postural forearm stabilization (Martineau et al., 2004; Barlaam et al., 2011). In addition, MEG studies showed pre-movement beta ERD associated with APA during BMLL task over the SMA and postural M1 which began approximately 4 s prior to the movement onset (Ng et al., 2011, 2013). The authors suggested that the beta ERD corresponds to the control of APA. The ERSP results in the present study are also in line with these previous results suggesting the role of cortex in generating postural and motor commands in a stepping task.

5.5.3 Movement-related ICs

The ICs that mainly contributed to the MRPs showed a mid-line fronto-central source identification with maximum activation at FCz and Cz. FCz and Cz electrodes are located above SMA and primary motor foot area (Deecke and Kornhuber, 1978; Pfurtscheller and Berghold, 1989). An extensive body of literature has reported the role of SMA and M1 in voluntary and externally triggered movements. It has been proposed that the SMA proper and M1 is involved in programing, preparation, and execution of voluntary and externally triggered movements whereas the pre-SMA is involved in internal selection of movement (decision making) (Roland et al., 1980; Thaler et al., 1988; Deiber el al., 1991,1996, 1999; Humberstone et al., 1997; Cunnington et al., 2002). Both pre-SMA and SMA proper receive input from distinct regions within the dentate nucleus of the cerebellum and internal segment of the globus pallidus. SMA proper and M1 have direct corticospinal projections and, as a consequence, both of them can

independently generate and control movements (Dum and Strick, 1991; Picard and Strick, 1996; Akkal et al., 2007). Intracranial recordings using subdural electrodes have shown the generation of MRPs that occur prior to the foot movements (RPs and MPs) from contralateral primary motor foot area and bilateral SMA (Ikeda et al., 1992). fMRI studies of motor imagery and observation of gait initiation and stepping reported activations in dorsal PMC, SMA, and dorsal PFC (Malouin et al., 2003; Iseki et al., 2008). In addition, there were significant activations in SMA and M1 in a study that compared real locomotion imaged using PET and imagined locomotion imaged using fMRI. In both experiments, the task included gait initiation (la Fougère et al., 2010). Impaired APAs during voluntary upper limb movements were found in patients with SMA lesions (Gurfinkel and Elner, 1988; Viallet et al., 1992). Also, impaired APAs associated with self-initiated stepping were found in PD patients. The APAs were significantly improved with Levodopa medication in these patients (Burleigh-Jacobs et al., 1997). Since one of the major outputs of the basal ganglia is to SMA, the impaired APAs seen in PD patients might be evidence of SMA involvement in APA. The role of SMA in generating APA during stepping was examined by disrupting SMA using repetitive TMS. The authors found decreased duration of APA and proposed that SMA is involved in the timing of APA (Jacobs et al., 2009). Impaired APAs during stepping were also found in patients with stroke who had lesions in PMC (Chang et al., 2010). Single-neuron recording in standing cats during APA prior to the onset of a reach revealed the role of M1 in the generation of APA (Yakovenko and Drew, 2009). The role of M1 in postural control was further explored using single-neuron recordings during posture and reaching tasks in macaque monkeys suggesting specialized control processes for posture and movement (Kurtzer et al., 2005). Based on all these findings, it is possible that the ICs that contribute to the MRPs in our study might represent activations in SMA, PMC, and M1.

5.6 Conclusions

In summary, the current study reveals cortical activations associated with the preparation of the automatic APA that occurs prior to stepping. Comparable preparatory activation was also observed prior to voluntary lateral weight shift and the APA phase of equal-weighted lateral stepping. These findings reinforce the important role of the cortex in anticipatory balance control and also reveal parallels in cortical activation regardless of the context of control (postural component vs. focal component). In addition, we speculate that the specific MRPs related to the APA and focal task appear to indirectly support the 'parallel mode' of control of posture and movement (Massion, 1992). This study enhances our understanding of the role of the cortex in the generation and execution of APA during lower limb movements.

Chapter 6

Study 4: Functional networks underlying human bipedal balance control

6.1 Abstract

Human bipedal balance control is proposed to involve the activity of distributed neural areas in the cortex and subcortical structures. The focus of recent work has been directed to advancing understanding of the role of the cerebral cortex in this highly automated behavior. While evidence exists for cortical activity temporally linked to balance control, little is known about the functional interaction of potential cortical regions. Here, we used ERPC and graph theoretical analysis (GTA) to derive cortical functional networks from ERPs recorded during reactive and predictive balance control events. The results suggest that there might exist a balance control network while standing (baseline period) and frequency-specific reorganization occurs in this network during balance control events (ERPs). This reorganization was characterized by increased connectivity strength, increased transitivity, and decreased modularity in theta (4-7 Hz), alpha (8-12 Hz), and beta (13-30 Hz) frequency bands. A similar pattern of connectivity was found between reactive and predictive balance control events as well as between reactive balance control to internally and externally generated perturbations. Hence, it is proposed that similar cortical areas are involved in balance control regardless of whether it is of reactive or predictive mode. To our knowledge, this is the first study to report the existence of functional networks during bipedal balance control. The results of the present study have potential implications on assessing impaired balance associated with aging and various neural diseases.

6.2 Introduction

Human bipedal balance control is a complex sensorimotor task accomplished reactively and predictively by the CNS. The CNS utilizes sensory input from visual, vestibular, and

somatosensory systems to generate APAs or CPAs to maintain balance (stability/equilibrium) (Winter et al., 1990). APAs (predictive balance control) aim to minimize the disturbances of balance and postural orientation associated with predictable perturbations and voluntary movements, whereas CPAs counteract the postural disturbance induced by unpredictable external postural perturbations (reactive balance control/reactive-external) or internal perturbations caused by naturally-occurring instability (reactive-internal) (Massion, 1992; Maki and McIlroy, 1997; Massion et al., 1999; Varghese et al., 2015). Understanding the mechanisms underlying the neural control of balance seems to be particularly important to identify the causes of balance impairments associated with aging and various neural diseases.

It is now generally believed that a distributed network of neural areas in the CNS is involved in balance control with a potential role for the cerebral cortex. Research to date in bipedal and quadrupedal balance control using neuroimaging techniques, single-neuron recordings, behavioral studies, and lesion studies have led to the view that different cortical areas are involved in balance control (see Massion, 1992; Jacobs and Horak, 2007; Maki and McIlroy, 2007 for review). In addition, evidence of the potential involvement of the cortex during reactive balance control in humans has come from ERPs that are time-locked to periods of instability. An unexpected postural perturbation evokes a negative potential (termed as the perturbation-evoked N1) that peaks 100-200 ms after the perturbation onset and is thought to be associated with CPAs (reactive-external) (Dietz et al., 1984; Staines et al., 2001; Marlin et al., 2014; Varghese et al., 2014). This negativity even exists prior to the small automatic corrective reactions to naturally-occurring instability (termed as the natural instability-evoked N1) while standing still (reactive-internal) (Varghese et al., 2015). Several studies have reported that there exists a negativity related to the preparation and execution of APAs that precede a voluntary tiptoe movement

(Saitou et al., 1996), unilateral shoulder flexion (Yoshida et al., 2008), lateral step (Varghese et al., 2016) and prior to a temporally expected perturbation (Adkin et al., 2008; Mochizuki et al., 2008). Furthermore, the spectral analysis of balance-related ERPs revealed modulation of theta (4-7 Hz), alpha (8-12 Hz), and beta (14-30 Hz) frequency bands distributed over fronto-centro-parietal areas (Slobounov et al., 2008, 2009; Varghese et al., 2014, 2015, 2016). While there has been speculation about the potential dipole contribution to such ERPs (Marlin et al., 2014) the widespread fronto-centro-parietal distribution of these APA- and CPA-related ERPs increases speculation that a complex network involving multiple dipoles may underpin this activation. The balance control studies done thus far have focused primarily on specific cortical regions (Solopova et al., 2003; Mihara et la., 2008; Marlin et al. 2014) or single electrode sites (Cz/FCz) (Dietz et al., 1984; Varghese et al., 2014) and to our knowledge, there have been no studies that characterize the functional interaction between various cortical regions during bipedal balance control. Indeed, understanding a brain function (e.g. balance control) requires identification of both functional segregation (the activation of functionally specialized neural assemblies) and neural integration/connectivity (the functional interaction between activated neural assemblies that are distributed across distinct brain areas) (Horwitz, 2003; Fingelkurts et al., 2005; Sakkalis, 2011). Hence, a better understanding of the cortical control of balance requires the knowledge of activation in different cortical areas as well as the functional connectivity between these regions. To this end, the current study adopts the additional approach of measuring brain functional connectivity using EEG and graph theory to reveal the functional networks underlying bipedal balance control, in turn providing additional insight into the time-varying cortical contributions to balance control.

Functional connectivity, as defined in this study, examines the temporal coherence between EEG signals at spatially separated electrodes during reactive (internal and external) and predictive balance control tasks (Horwitz, 2003; Fingelkurts et al., 2005; Sargolzaei et al., 2015). While the amplitude of an ERP from a single electrode reflects the synchronized activation of a localized neural population, coherence between two electrodes reflects the linear functional interactions between spatially remote but functionally collaborating cortical areas in specific frequency bands (Horwitz, 2003; Sakkalis, 2011). EEG offers excellent temporal resolution in the order of milliseconds to capture the transient synchronization of neural assemblies to perform a complex brain function (Fingelkurts et al., 2005). ERPC is used to measure the correlation between all pairs of electrodes to construct the functional connectivity matrices in theta, alpha, and beta frequency bands. ERPC, as with the ERP technique, is based on averaging across trials and measures the degree of phase synchronization in activity between the two channels (Andrew and Pfurtscheller, 1996; Delorme and Makeig, 2004; Perfetti et al., 2011). The advantage of phase coherence over linear coherence is that it considers only the phase relationship between two signals and is therefore less sensitive to erroneous estimates of connectivity due to external factors, volume conduction, and field spread, whereas the latter is sensitive to both amplitude and phase dynamics (Delorme and Makeig, 2004; Lachaux et al., 2002; Van Diessen et al., 2015). In addition, it has been suggested that the phase synchronization between participating neural assemblies is the most likely mechanism of neural integration (Varela et al., 2001). To explore functional brain networks, GTA provides a unique approach for both visualization and characterization of complex brain networks and has been widely used in neuroscience to characterize structural and functional brain networks under resting-state and task-state such as

during a visual discrimination task and emotional face processing (Bullmore and Sporns, 2009; Bola and Sabel, 2015; Li et al., 2015, Bernhardt et al., 2016).

In the present study, we aimed to examine the functional connectivity during reactive (perturbation-evoked N1) and predictive balance control (APA-related ERP) using ERPC and GTA. From several lines of evidence, it is likely that a similar pattern of cortical connectivity exists for reactive and predictive balance control. Both APA and CPA movements rely on similar postural synergies to maintain balance. For instance, the ankle strategy in CPAs and APAs that precede a voluntary handle pull exhibits the same distal-to-proximal muscle activation pattern (Nashner, 1977; Cordo and Nashner, 1982). In addition, both APA and CPA-related ERPs have similar widespread topographic distributions. Furthermore, the single-neuron recordings, TMS, and lesion studies have shown the involvement of similar cortical regions such as M1, SMA, and parietal cortex in reactive and predictive balance control (Nieoullon and Gahery, 1978; Gurfinkel and Elner 1988; Birjukova et al., 1989; Perennou et al., 2000; Solopova et al., 2003; Beloozerova et al., 2005; MacKinnon et al., 2007; Kazennikov et al., 2008). While the pattern of connectivity may be similar, it is likely that the specific details of cortical connectivity may be different. The rationale for these differences arises from the distinct sequence of events associated with sensory-evoked (CPAs) and self-initiated (APAs) actions. CPAs are triggered by sensory inputs, especially the somatosensory inputs from lower limbs (Horak et al., 1990). In contrast, APAs are pre-programmed postural commands that are executed prior to or during the focal task in order to minimize the postural perturbation that could be caused by the focal task (Massion, 1992). Hence, APAs are not triggered by sensory inputs. Instead, they are executed depending on the focal task requirements (Cordo and Nashner, 1982; Brown and Frank, 1987). For instance, externally cued or self-initiated rapid pulls on a stiff handle while standing unsupported is

preceded by an APA whereas this APA is absent if rapid pulls were performed while standing supported (Cordo and Nashner, 1982; Brown and Frank, 1987). Therefore, even though there might be parallels in the underlying control of APAs and CPAs, the specific details of the cortical connectivity are likely different for reactive and predictive balance control as would be evidenced by different connectivity strengths.

In the current study, we also aim to explore whether similar patterns and strengths of connectivity exist during reactive-internal (natural instability-evoked N1) and reactive-external (perturbation-evoked N1). Previous work has revealed a comparable topographic distribution for the perturbation-evoked N1 and natural instability-evoked N1 (Varghese et al., 2014, 2015). This is particularly noteworthy as it diminishes the concern that the ERPs observed in induced perturbation studies are associated with the expectation of a forthcoming perturbation or with the voluntary awareness of the imposed perturbation. With respect to the expected pattern of functional connectivity, it is likely that there exists the same underlying cortical network for both reactive-internal and reactive-external balance control. However, it is also expected that the connectivity strength would be different largely due to the amplitude of perturbation and associated difference in sensory inputs and response amplitudes. It has been suggested that the perturbation-evoked N1 represents the cortico-cortical transfer of perturbation information from primary sensory areas to frontal motor areas (Dimitrov et al., 1996). In addition, visual, vestibular, and somatosensory inputs are to be integrated to generate complex muscle activation patterns to regain balance (Winter et al., 1990). As such, greater neural integration is required to counteract balance disturbances caused by large-magnitude external unpredictable perturbations compared to very small-magnitude perturbations that occur during standing still which would be reflected in different strengths of connectivity.

To this end, the present study examined functional connectivity during three different balance control tasks: (1) external postural perturbations (lean and release in AP direction) to evoke feet-in-place balance reactions (reactive-external), (2) tandem Romberg stance to evoke naturally occurring reactive events measured in the ML direction (reactive-internal), and (3) voluntary lateral stepping to evoke APAs in the ML direction (predictive balance control). In spite of the very different behavior states and sensorimotor control, it was hypothesized that there would exist a similar pattern of functional connectivity between reactive and predictive balance control as well as between reactive-internal and reactive-external balance control. However, it was also hypothesized the strength of these connections would be different between reactive and predictive balance control as well as between reactive-internal and reactive-external balance control.

6.3 Materials and Methods

6.3.1 Participants

The current study was based on a secondary analysis of data collected in the first three studies of this thesis. Fourteen healthy young adults (5 females and 9 males, age range: 19-31 years) participated in the reactive balance control experiment (original data reported in study 1). Twelve healthy individuals (6 females and 6 males, age range: 19-37 years) participated in the reactive-internal experiment (original data reported in study 2). Fourteen healthy subjects (3 females and 11 males, age range: 19-33 years) participated in the predictive balance control experiment (original data reported in study 3). No subjects reported any history of neuromuscular disorders. All subjects voluntarily participated in the study and gave written informed consent. The experimental procedures were conducted in accordance with the Declaration of Helsinki and were approved by the Research Ethics Board of the University of Waterloo.

6.3.2 Experimental Setup and Balance Tasks

In the reactive balance control experiment, compensatory feet-in place reactions were evoked by temporally unpredictable postural perturbations triggered using a lean and release system (Marlin et al., 2014). A total of 40 trials were collected for each participant. In the reactive-internal experiment, the participants were instructed to maintain tandem Romberg stance with arms crossed, eyes closed, and equal weight on each foot for 30 s (Black et al., 1982, Varghese et al., 2015). Three trials were collected for each participant. In the predictive balance control experiment, subjects initially stood with equal weight over each limb and performed a lateral stepping with the right leg that was preceded by an APA phase (weight shift to the left leg) in response to an auditory cue (Varghese et al., 2016). A total of 40 trials were collected for each participant. In all three balance tasks, the participants initially stood in a standardized foot position on the force plates (AMTI model OR6-5, Watertown, MA, USA) and the outline of the feet was marked on the force plate to ensure that the same initial foot position was maintained in all trials.

6.3.3 Data Acquisition and Preprocessing

Postural data were acquired by recording ground reaction forces and moments from the two force plates using a custom-built LabVIEW program (National Instruments, TX, USA). Prior to data collection the force plates were calibrated. Force plate data were amplified, analog low-pass filtered using a two pole low-pass 1000 Hz filter (built in an AMTI MSA-6 MiniAmp amplifier), sampled online at a rate of 1000 Hz, and stored for subsequent analysis. In addition, cable force was recorded in the reactive-external experiment using a load cell to measure the onset of perturbation. To synchronize the posturography with EEG, a triggering pulse was delivered to the EEG amplifier at the start of postural data collection.

Offline analyses of postural data (using a custom-made LabVIEW program) included low pass filtering (6 Hz, dual-pass 2nd order Butterworth filter), computing ML COP displacement, and writing event files that contained the latencies of APA onset in the stepping task and peak ML COP displacement (onset of discrete reactive balance control events to naturally occurring instability) in the Romberg stance. APA onset was defined as the time point when the ML COP displacement toward the right limb deviated by 4 mm from the mean baseline ML COP (baseline was calculated over a time window of 200 ms after the auditory cue) (Varghese et al., 2015, 2016). The event files were later used for epoch extraction of the EEG data.

EEG data were recorded continuously with Ag/AgCl electrodes mounted on a 32-channel (Romberg stance and stepping task) and 64-channel (compensatory balance task) electrode cap (Neuroscan, El Paso, TX, USA) based on the international 10-20 lead system. The 32-channel electrode cap was connected to a NuAmps amplifier whereas the 64-channel cap was connected to a SynAmps2 amplifier (Neuroscan, El Paso, TX, USA). However, for this study, we analyzed the EEG data from only 30 channels. To monitor vertical and horizontal eye movements, electrooculography signals were also recorded simultaneously using four surface electrodes (VEOU, VEOL, HEOR, and HEOL) situated above and below the left eye and both outer canthi. All channels were referenced to linked mastoids (A1 and A2). The impedances of all electrodes were maintained below 5 kΩs throughout the recording period. EEG signals were amplified, sampled at 1000 Hz, filtered online (band pass: DC-300 Hz), and stored for offline analysis.

Preprocessing of EEG data was carried out using custom-made scripts in EEGLAB (Delorme and Makeig, 2004) running in MATLAB (The Mathworks, MA, USA). EEG signals were band pass filtered in the 1-30 Hz range for reactive balance control tasks and 0.05-30 Hz for the predictive balance control task (Varghese et al., 2016). Linear finite impulse response

filters were applied forward and then backward, eliminating the phase delays by digital filters on the signal (Delorme and Makeig, 2004). The filtered signals were then segmented into baseline corrected epochs time-locked to perturbation onset for the reactive-external, peak ML COP displacement for the reactive-internal, and APA onset for the predictive-balance control task. The epoch length, baseline period, and ERP period extracted for each balance task are summarized in Table 6.1. Baseline intervals (prior to the onset of perturbation or cue to move) were used to compare patterns and amplitudes of connectivity against event-related intervals.

Table 6.1: Length of epochs and time-window of baseline and ERPs.

Balance Task	Total epoch	Baseline Period	ERP Period
Reactive-internal (Natural instability-evoked N1)	-2000 to 500 ms	-2000 to -1700 ms	0 to 250 ms
Reactive-external (Perturbation-evoked N1)	-600 to +500 ms	-600 to -300 ms	0 to 200 ms
Predictive (APA-related ERP)	-1500 to 1000 ms	-1200 to -900 ms	-800 to 200 ms

The perturbation-evoked N1 (identified as the largest negative component between the 0 ms and 200 ms after the perturbation onset), natural instability-evoked N1 (largest negative component in a time-window of 0 ms to 250 ms prior to the peak ML COP displacement), and APA-related ERPs (negativity between -800 ms prior to and 200 ms after APA onset) were obtained by averaging the EEG epochs of the reactive-external, reactive-internal, and predictive balance control tasks, respectively (Varghese et al., 2014, 2015,2016). ICA was performed on epoched EEG data to remove eye blinks, eye movements, whole-body movements, muscle

artifacts, heart signals, and line noise artifacts (Bell and Sejnowski, 1995; Jung et al., 1998). One of the major artifacts encountered in balance studies is the movement artifact; however, ICA has been widely used to remove movement artifacts (Thompson et al., 2008; Varghese et al., 2016). Identification and rejection of artifact ICs were based on the visual inspection of topographic maps, power spectra, and time domain activity of each IC (Delorme and Makeig, 2004). ICA-pruned EEG data was once again visually inspected to further remove epochs contaminated by gross movements that were not removed by ICA noise reduction. EEG data of two subjects was discarded for the reactive-external task due to excessive artifacts in the EEG data that masked the perturbation-evoked N1. To exclude any bias from unequal number of participants, EEG data of only 12 participants per balance task was included for further analysis. For APA-related ERPs, the data of the two participants was excluded as there were less than 20 usable trials after noise reduction. On average, 35 artifact-free trials were selected for each subject for the perturbation-evoked N1 and APA-related ERPs whereas approximately 70 artifact-free trials were selected for the natural instability-evoked N1 (Stavrinou et al., 2007). Finally, the data were resampled to 512 Hz for functional connectivity analysis. The signal processing work flow from data acquisition to statistical analyses is depicted in Figure 6.1.

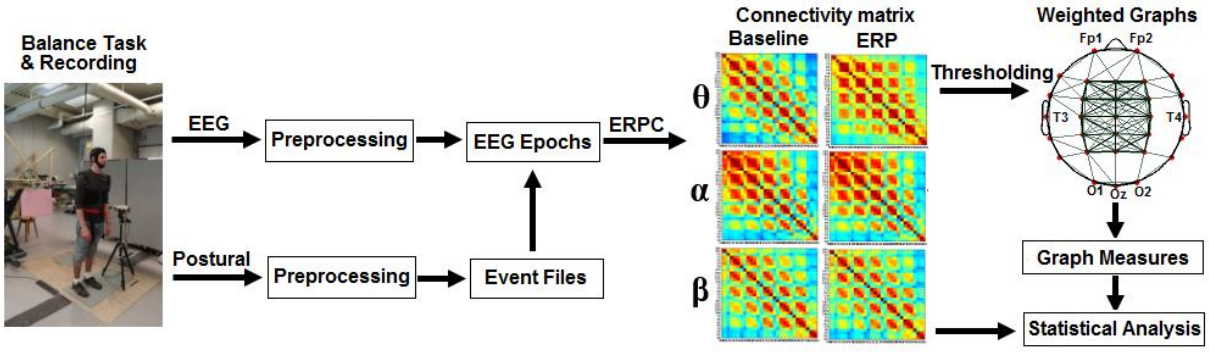

Figure 6.1: Analysis Pipeline. EEG and postural data were acquired during reactive and predictive balance control tasks and preprocessed. Postural data were used to generate event files

containing the latencies of balance control events which were then used to epoch EEG data. Functional connectivity matrices were generated for theta, alpha, and beta frequency bands using event-related phase coherence. Each connectivity matrix was thresholded to generate an undirected, weighted graph. Graph measures were extracted from each graph and tested statistically.

6.3.4 Functional Connectivity Analysis

Functional connectivity between all pairwise combinations of EEG electrodes was computed using ERPC. Coherence between two EEG signals is the spectral cross-correlation normalized by their individual auto spectra (Andrew and Pfurtscheller, 1996). ERPC computes the coherence value at a specific frequency and time-point by unit normalizing the magnitude of the spectral estimate of each trial in the two electrodes prior to the calculation of coherence and then averaging the single-trial phase differences between the two electrodes across all trials (Delorme and Makeig, 2004; Roach and Mathalon, 2008). Thus, ERPC takes into account only the relative phase of the two spectral estimates at each trial and provides a measure of phase consistency of EEG signals between two electrodes (Delorme and Makeig, 2004). ERPC between two EEG signals, *x* and *y*, at a given frequency *f* and time *t* is defined as:

$$ERPC_{x,y}(f,t) = \frac{1}{N}\sum_{k=1}^{N}\frac{X_k(f,t)Y_k(f,t)^*}{|X_k(f,t)Y_k(f,t)|}$$

where *n* is the total number of trials, $X_k(f,t)$ and $Y_k(f,t)$ are the spectral estimates of *x* and *y* at trial *k* and $Y_k(f,t)^*$ is the complex conjugate of $Y_k(f,t)$ (Delorme and Makeig, 2004). ERPC ranges from 0 to 1 with a value of 1 indicating oscillations in two channels are occurring synchronously at a particular frequency (Delorme and Makeig, 2004; Perfetti et al., 2011).

To compute the spectral estimates of *x* and *y*, we used Hanning-tapered short-time FFT and the length of the epochs chosen in the balance tasks enabled to extract spectral estimates for 200 time points and linearly spaced frequencies from 1-30 Hz for each trial. It has been proposed

that each frequency band is associated with distinct cognitive functions; hence we performed the connectivity analysis separately for theta, alpha, and beta frequency bands which have been shown to be modulated during balance control (Basar et al., 2001, Slobounov et al., 2008, Varghese et al., 2014, Van Diessen et al., 2015). For every subject, task, and frequency band, two 30×30 functional connectivity matrices were obtained: a baseline matrix and an ERP matrix containing the mean phase coherence values of each frequency band during baseline and ERP time-window, respectively.

6.3.5 Graph Theoretical Analysis

The main objective of this study was to examine functional networks during reactive and predictive balance control. Graph theory was applied to derive the functional networks using EEGNET software running in MATLAB (Hassan et al., 2015). Functional connectivity matrices of each participant were converted into undirected, weighted graphs. The nodes/vertices of the graphs represented EEG electrodes and their location in the graph were derived from the coordinates in the international 10-20 EEG electrode placement system. The edges/lines connecting the nodes were weighted by the corresponding ERPC values. Graph theory provides an abstract representation of a real-world system's elements and their interactions (Bullmore and Sporns, 2009). However, since there exists a connection between almost every pair of nodes in the graph, the connectivity matrix of each participant was thresholded to filter out weak and non-significant connections as they might represent spurious connections and may mask the topology of strong and significant connections (Rubinov and Sporns, 2010). Each matrix was thresholded in such a way that the density (D), defined as the fraction of existing edges to possible edges, was equal for each graph. This thresholding resulted in an equal number of edges in the graph for all participants and for all task conditions which allowed comparison of graph measures between

balance tasks while controlling the effects of graph density on network topology (Bernhardt et al., 2016). Since there is no specific basis for selecting a threshold, a spectrum of threshold values is likely necessary. In the present study, three threshold values were chosen resulting in a graph density of 0.86, 0.55, and 0.35.

The thresholded graphs were characterized with three graph measures computed using standard formulas for the weighted and undirected graphs implemented in the Brain Connectivity Toolbox (Rubinov and Sporns, 2010). The path length L_{ij} between node *i* and node *j* is the minimum number of edges to be traversed to form a connection between two nodes (Watts and Strogatz, 1998). For weighted graphs, the weighted path length between two nodes was derived via a mapping from weight (*Wij*) to length ($L_{ij} = 1/W_{ij}$). Characteristic path length (CPL), a measure of functional integration, is the mean shortest path length between all pairs of nodes in the graph and is defined as:

$$CPL = \frac{1}{n}\sum_{i\in N} \frac{\sum_{j\in N, j\neq i} {d_{ij}}^{w}}{n-1}$$

where *N* is the set of all nodes in the graph, *n* is the number of nodes, and dij^{w} is the weighted distance matrix which contains the shortest path length between all pairs of nodes (Rubinov and Sporns, 2010). CPL is calculated as the global average of distance matrix excluding disconnected nodes and distances on the main diagonal of the matrix (Rubinov and Sporns, 2010).

Transitivity (T), a measure of functional segregation, is the ratio of 'triangles to triplets' in the graph and is defined as:

$$T = \frac{\sum_{i\in N} 2{t_i}^{w}}{\sum_{i\in N} k_i(k_i-1)}$$

where t_i^{w} is the number of weighted triangles around a node *i* and k_i is the weighted node degree defined as the number of weighted edges connected to node *i* (Newman, 2003; Rubinov and

Sporns, 2010). Transitivity (a classical version of the clustering coefficient) measures the mean of the fraction of triangles around each individual node in the graph and is normalized collectively (Rubinov and Sporns, 2010). It is therefore not influenced by nodes with low degree which is a major limitation of the clustering coefficient (Rubinov and Sporns, 2010).

Modularity (Q), a measure of functional segregation, is a statistic that quantifies the degree to which a graph can be decomposed into distinct non-overlapping modules with maximum edges within a module and minimum edges between modules and is defined as:

$$Q = \frac{1}{S^w} \sum_{i,j \in N} \left\{ Wij - \frac{{k_i}^w {k_j}^w}{S^w} \right\} \delta_{m_i, m_j}$$

where m_i and m_j are the modules containing node i and node j, respectively, S^w is the sum of all weights in the graph, and $\delta_{mi,mj} = 1$ if $m_i = m_j$ and 0 elsewise (Newman, 2006; Rubinov and Sporns, 2010).

In addition to these three graph measures, connectivity strength of each unthresholded weighted graph was computed, defined as the average over weights of all edges in a graph (Bola and Sabel, 2015). The graph measures were extracted separately for each of the threshold values.

6.3.6 Statistical Analysis

In the present study, we sought to characterize the functional networks during reactive and predictive balance control which were constructed using ERPC and GTA. To characterize the event-related changes in network topology, the connectivity pattern, strength, and graph measures were compared during ERPs against baseline (pre-perturbation/pre-movement onset). In addition, the connectivity pattern and strength were compared between reactive-internal (natural instability-evoked N1) and reactive-external (perturbation-evoked N1) as well as between reactive and predictive (APA-related ERP) balance control. The Mantel test was used

for assessing similarity in the spatial pattern of connectivity between baseline and ERP and between ERPs. Mantel tests are often used to test the significance of association between the two square, symmetric similarity (or distance) matrices by measuring the pairwise relationship of matrix elements (Mantel, 1967; Nummenmaa et al., 2012; Omidvarnia et al., 2014). Student's t-tests (paired and independent sample) were used to compare the connectivity strength between baseline and ERP and between ERPs. Separate two-way repeated measures analysis of variances (ANOVAs) were performed for each frequency band (theta, alpha, beta) and graph measure (dependent variable) with threshold values (0.86, 0.55, 0.35) and time-window (baseline, ERP) as the two within factors. Likewise, separate two-way repeated measures ANOVAs for each frequency band and graph measure were conducted with ERPs (perturbation-evoked N1, natural instability-evoked N1, APA-related ERP) as between factors and threshold values as the within factor. The Ryan-Joiner test and Mauchly's sphericity test were used to assess normality and sphericity assumptions, respectively. Greenhouse-Geisser corrections were performed for the violation of sphericity assumption. The alpha level was set at 0.05 for all statistical analyses.

6.4 Results

6.4.1 ERP and Functional Connectivity Matrix

In this study, EEG functional connectivity was investigated during the perturbation-evoked N1, natural instability-evoked N1, and APA-related ERP (Fig. 6.2). Scalp maps of ERPs revealed widespread activation in the fronto-centro-parietal areas (Fig. 6.3A). Strikingly, functional connectivity matrices generated for baseline and ERPs in theta (Fig. 6.3B), alpha (Fig. 6.4), and beta (Fig. 6.5) frequency bands showed a similar pattern of functional connectivity during baseline and ERPs for all frequency bands.

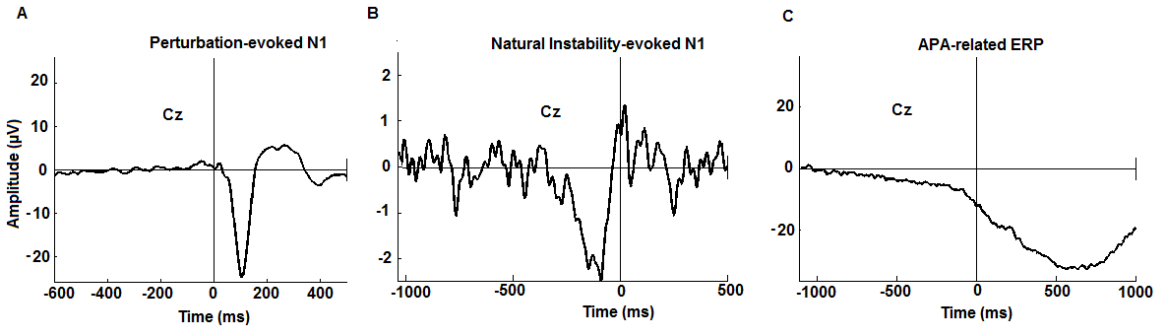

Figure 6.2: Grand-averaged (n = 12) APA and CPA-related ERPs at Cz electrode.
(A) Perturbation-evoked N1, (B) natural instability-evoked N1, and (C) APA-related ERP.

Global assessment of matrix similarity using the Mantel test revealed that the overall pattern was similar across baseline and the perturbation-evoked N1 (theta: Mantel statistics 0.96, $p < 0.01$; alpha: Mantel statistics 0.97, $p < 0.01$; beta: Mantel statistics 0.99, $p < 0.01$), baseline and the natural instability-evoked N1 (Mantel statistics 0.99, $p < 0.01$ for theta, alpha, and beta bands), as well as baseline and the APA-related ERP (Mantel statistics 0.99, $p < 0.01$ for theta, alpha, and beta bands). These observations led to a speculation that there exists a balance control network which is active while standing still (baseline period) as well as during balance control events. In addition, the overall pattern was stable between the natural instability-evoked N1 and perturbation-evoked N1 (theta: Mantel statistics 0.92, $p < 0.01$; alpha: Mantel statistics 0.87, $p < 0.01$; beta: Mantel statistics 0.89, $p < 0.01$) and between the perturbation-evoked N1 and APA-related ERP (Mantel statistics 0.91, $p < 0.01$ for theta, alpha, and beta bands). Thus, a similar pattern of connectivity was observed in all frequency bands during reactive-internal, reactive-external, and predictive balance control.

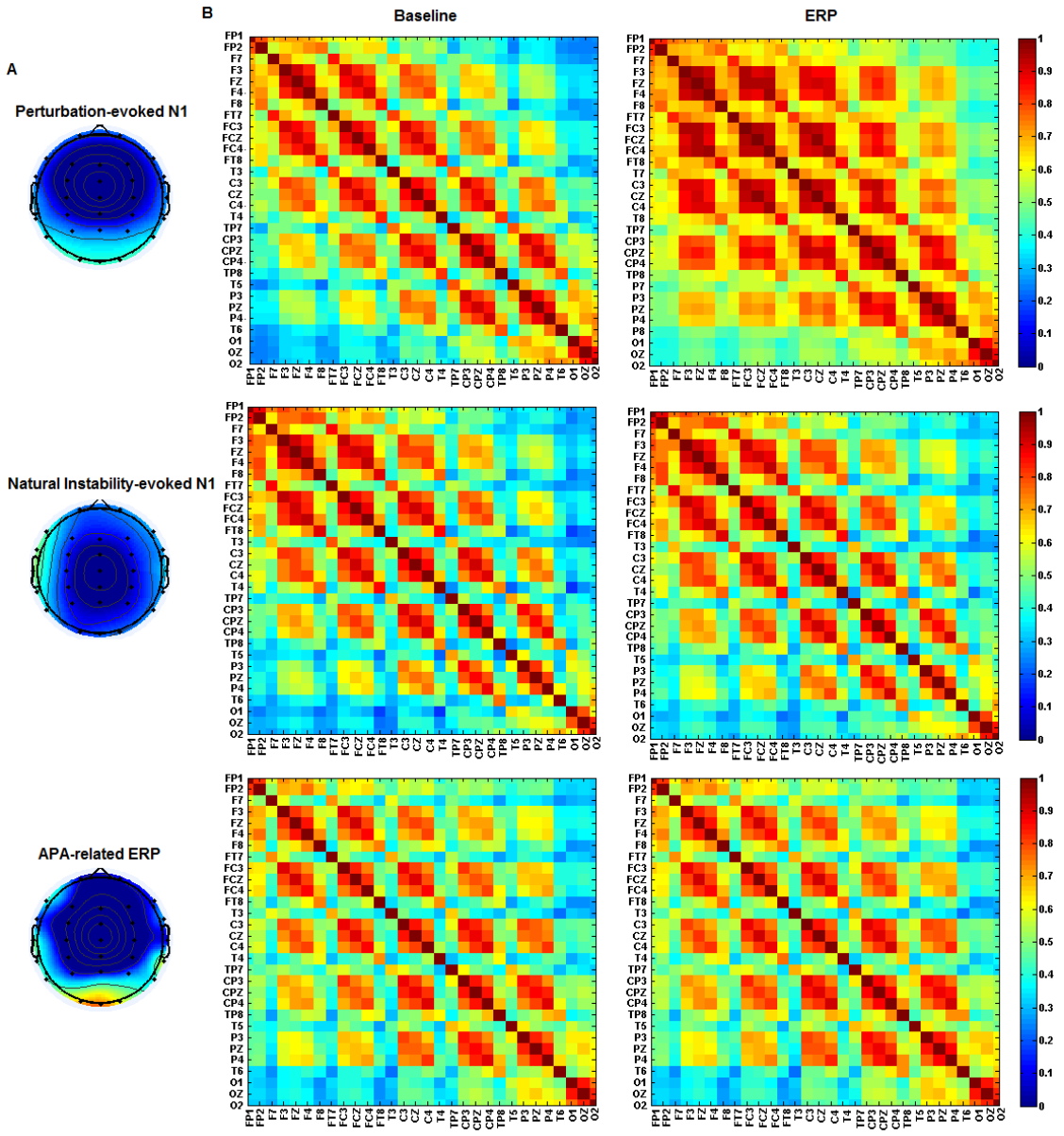

Figure 6.3: ERP-scalp maps and connectivity matrices at theta band. (A) Topographic voltage maps of grand averaged (*n* = 12) perturbation-evoked N1, natural instability-evoked N1, and APA-related ERP. (B) Grand-averaged (*n* = 12) connectivity matrices for baseline (the first column) and ERPs (the second column) at the theta frequency band (4-7 Hz). The connectivity matrix is a 30×30 square, symmetric matrix, where the x-axis and y-axis denote 30 EEG channels. Each element in the connectivity matrix represented the grand-averaged (*n* = 12) ERPC value between two channels in the theta band. ERPC values range from 0 to 1, with a value of 1 in the main diagonal.

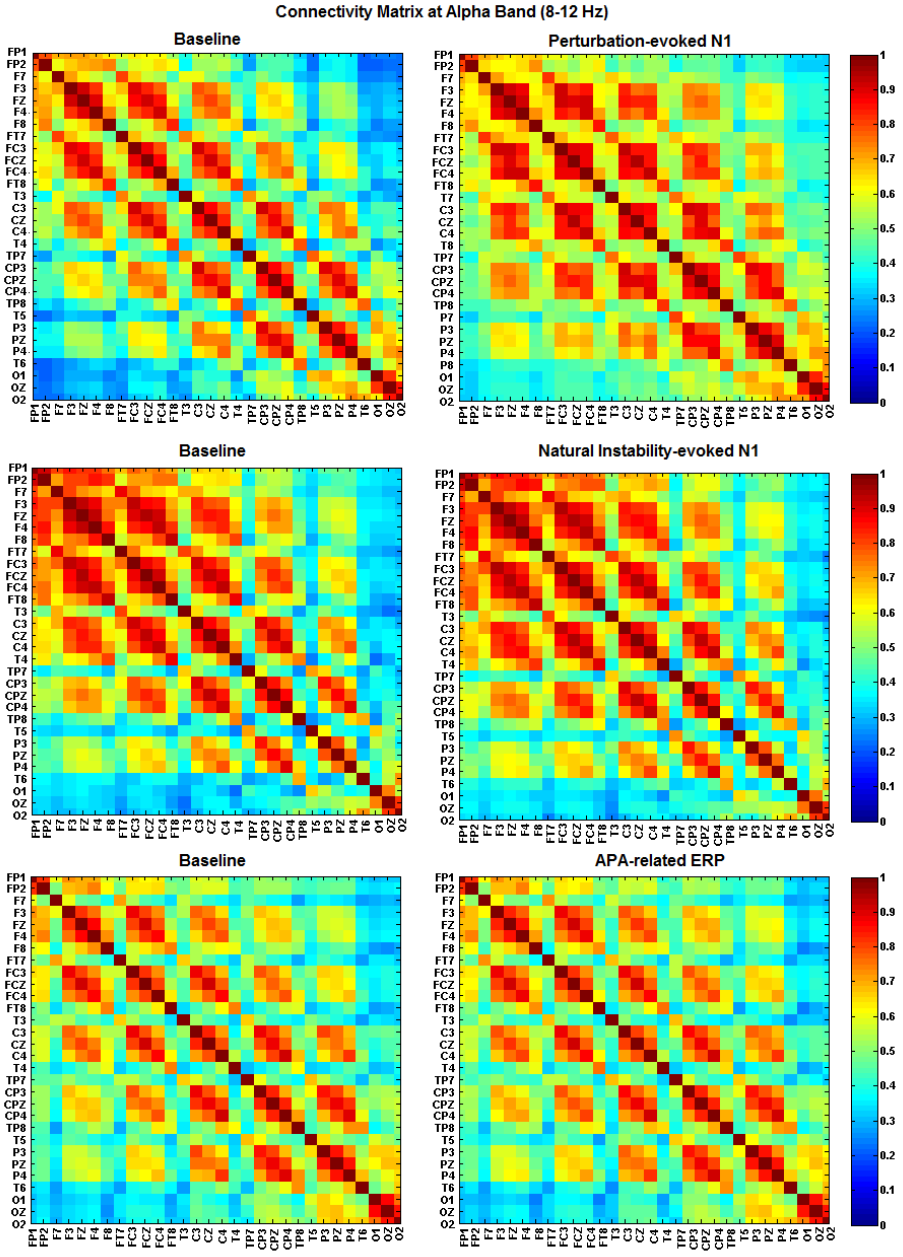

Figure 6.4: Connectivity matrices at alpha band. Grand-averaged (n = 12) connectivity matrices for baseline (the first column) and ERPs (the second column) at the alpha frequency band (8-12 Hz). The connectivity matrix is a 30×30 square, symmetric matrix, where the x-axis and y-axis denote 30 EEG channels. Each element in the connectivity matrix represented the grand-averaged (n = 12) ERPC value between two channels in the alpha band. ERPC values range from 0 to 1, with a value of 1 in the main diagonal.

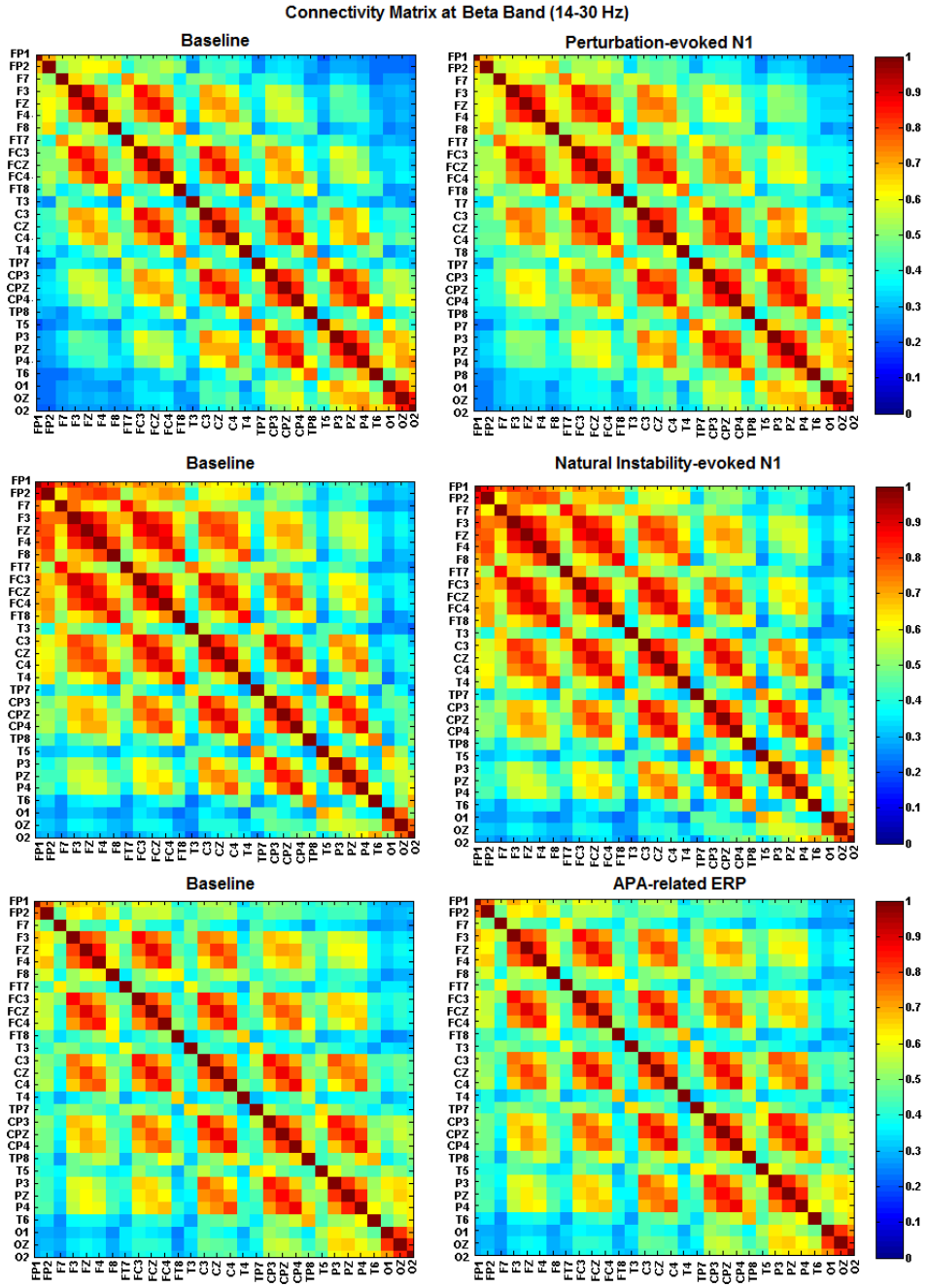

Figure 6.5: Connectivity matrices at beta band. Grand-averaged (n = 12) connectivity matrices for baseline (the first column) and ERPs (the second column) at the beta frequency band (14-30 Hz). The connectivity matrix is a 30×30 square, symmetric matrix, where the x-axis and y-axis denote 30 EEG channels. Each element in the connectivity matrix represented the grand-averaged (n = 12) ERPC value between two channels in the beta band. ERPC values range from 0 to 1, with a value of 1 in the main diagonal.

6.4.2 Graph Theoretical Analysis

To explore the functional networks underlying balance control, each connectivity matrix was thresholded to generate an undirected weighted graph. Figure 6.6A shows the grand-averaged (n = 12) weighted graphs of baseline and the perturbation-evoked N1 in the theta frequency band for three density-based threshold values (graph density = 0.86, 0.55, 0.35). While the nodes of the graph denote the EEG electrodes, the edges/lines denote the functional connection between two electrodes. The thickness/weights of the edges denote the corresponding ERPC values. It can be seen that the functional connections between fronto-centro-parietal areas increased during the perturbation-evoked N1 as indicated by the increased number and weight of edges compared to baseline. A similar trend was seen for the natural instability-evoked N1 (Fig. 6.8A) and the APA-related ERP (Fig. 6.10A) in the theta frequency band. However, such a trend was less prominent in alpha (Fig. 6.7A) and beta bands (Fig. 6.9A) for all the ERPs. To characterize the strength of connections, the connectivity strength of unthresholded weighted graphs was computed and compared between baseline and ERPs (Table 6.2). It was found that the connectivity strength increased significantly ($P < 0.05$) during the perturbation-evoked N1 compared to that of baseline values in theta, alpha, and beta frequency bands. However, the increase in connectivity strength was not statistically significant for the natural instability-evoked N1 and APA-related ERP in all frequency bands except for the APA-related ERP in the theta band ($P = 0.04$). In addition, there was a significant ($P < 0.05$) increase in connectivity strength during the perturbation-evoked N1 compared to the natural instability-evoked N1 and APA-related ERP in the theta band. However, this increase was not statistically significant in alpha and beta frequency bands.

Finally, we extracted three weighted graph measures (characteristic path length, transitivity, and modularity) from each thresholded graph and compared between baseline and ERPs. Mean values of graph measures as a function of threshold are shown in Figs. 6.6B, 6.7 B, 6.8B, 6.9B, and 6.10B. In general, compared to baseline, there were trends for increased transitivity, decreased modularity, and either a decrease or no change in characteristic path length during ERPs for all threshold values. These trends were confirmed by statistical analysis of graph measures. The repeated measures ANOVA revealed that the main effects found in the study are independent of threshold values. For the perturbation-evoked N1, there was a significant increase in transitivity in theta ($F(2,11) = 29.64$; $P < 0.01$), alpha ($F(2,11) = 11.18$; $P < 0.01$), and beta ($F(2,11) = 6.49$; $P = 0.03$) frequency bands relative to baseline. In addition, there was a significant decrease in modularity in theta ($F(2,11) = 7.18$; $P = 0.02$), and beta ($F(2,11) = 7.18$; $P = 0.04$) frequency bands. The decrease in modularity in the alpha band was not statistically significant. Similarly, there was a trend (not significant) for increased transitivity and decreased modularity during the natural instability-evoked N1 and APA-related ERP in theta and alpha bands. However, all the graph measures seem to be unaffected in the beta band during the natural instability-evoked N1 and APA-related ERP. Likewise, the characteristic path length seemed to be almost unchanged or slightly decreased during ERPs relative to baseline. There was no statistical difference in graph measures between the ERPs. However, there were trends for increased transitivity and decreased modularity during the perturbation-evoked N1 compared to the natural instability-evoked N1 and APA-related ERP in the theta band. In summary, balance control events were related to rapid and transient reorganization of the network's topology, mainly in theta and alpha bands, as reflected in the changes of graph measures during ERPs relative to baseline.

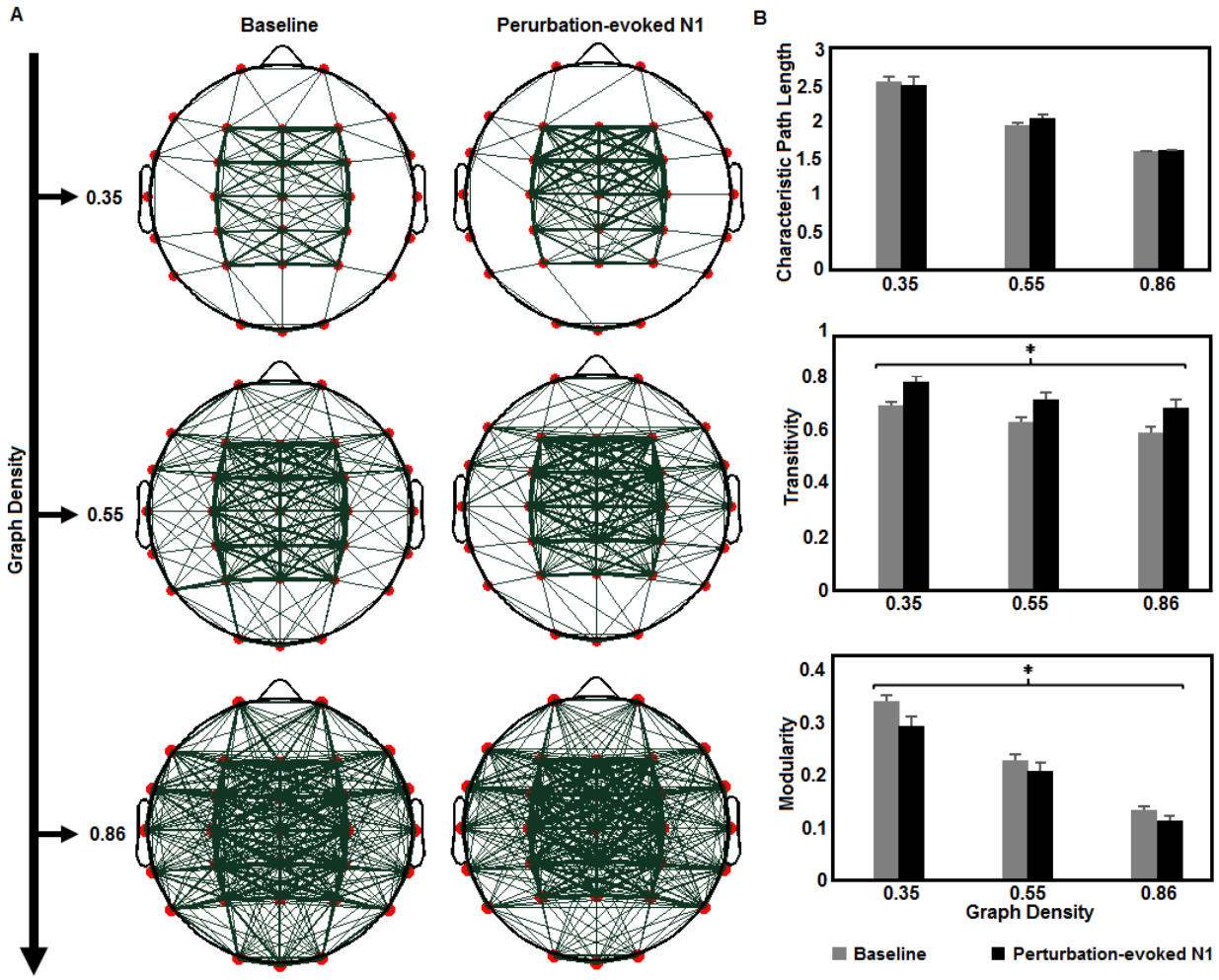

Figure 6.6. Theta-band networks and graph measures of the perturbation-evoked N1 (A) Graph representation of grand-averaged thresholded (graph density = 0.86, 0.55, 0.35) connectivity matrices of baseline and the perturbation-evoked N1 in the theta frequency band. Nodes of the graph denote EEG electrodes in the international 10-20 system and thickness of edges denote ERPC values between two electrodes. (B) Mean and standard error of characteristic path length, transitivity, and modularity of baseline and the perturbation-evoked N1 as a function of threshold. Asterisk indicates a significant difference ($P < 0.01$) in graph measures.

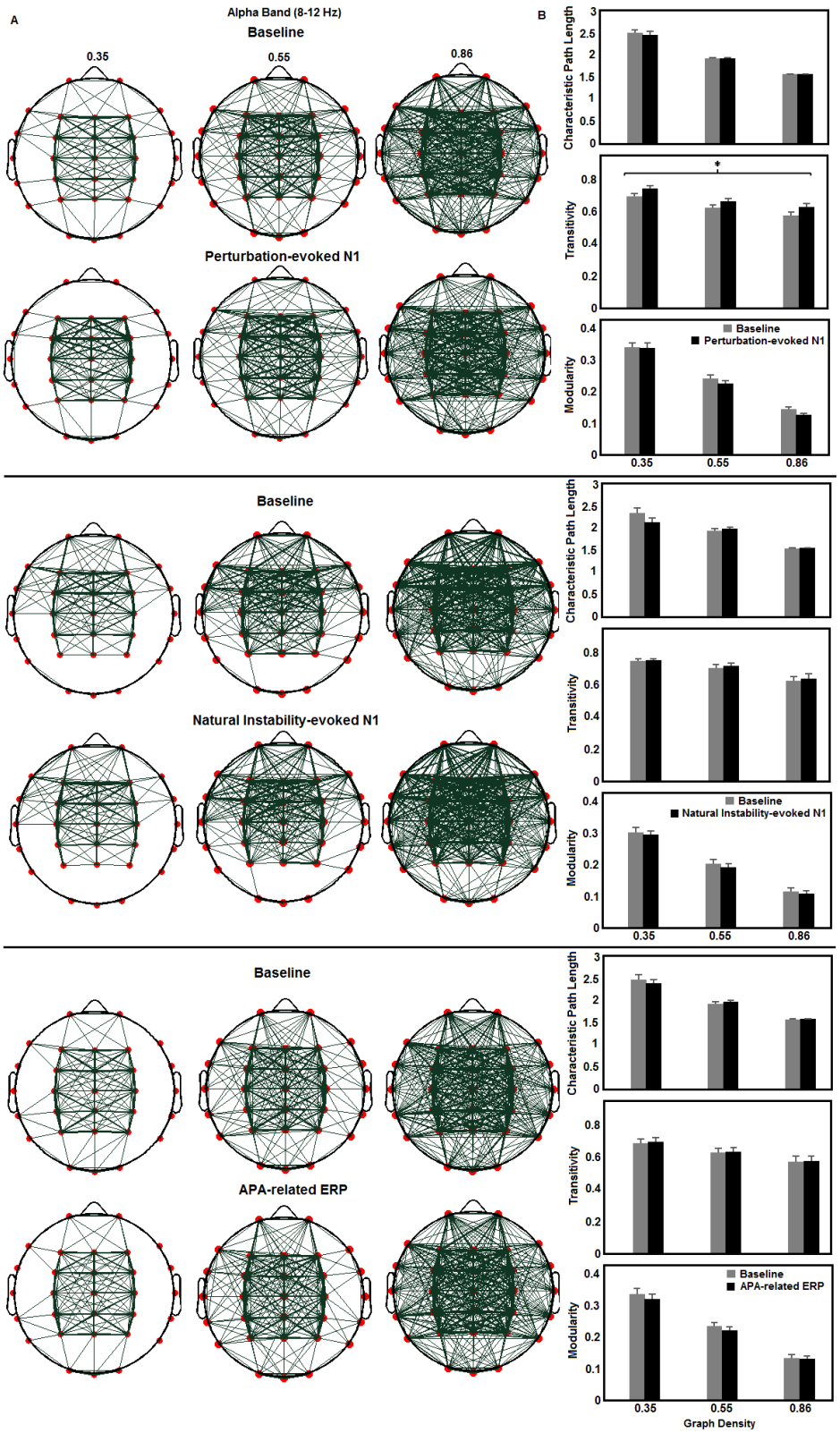

Figure 6.7: Alpha-band networks and graph measures. (A) Graph representation of grand-averaged thresholded (graph density = 0.86, 0.55, 0.35) connectivity matrices of baseline and

ERPs in the alpha frequency band. Nodes of the graph denote EEG electrodes in the international 10-20 system and thickness of edges denote ERPC values between two electrodes. (B) Mean and standard error of characteristic path length, transitivity, and modularity of baseline and ERPs as a function of threshold. Asterisk indicates a significant difference ($P < 0.01$) in graph measures.

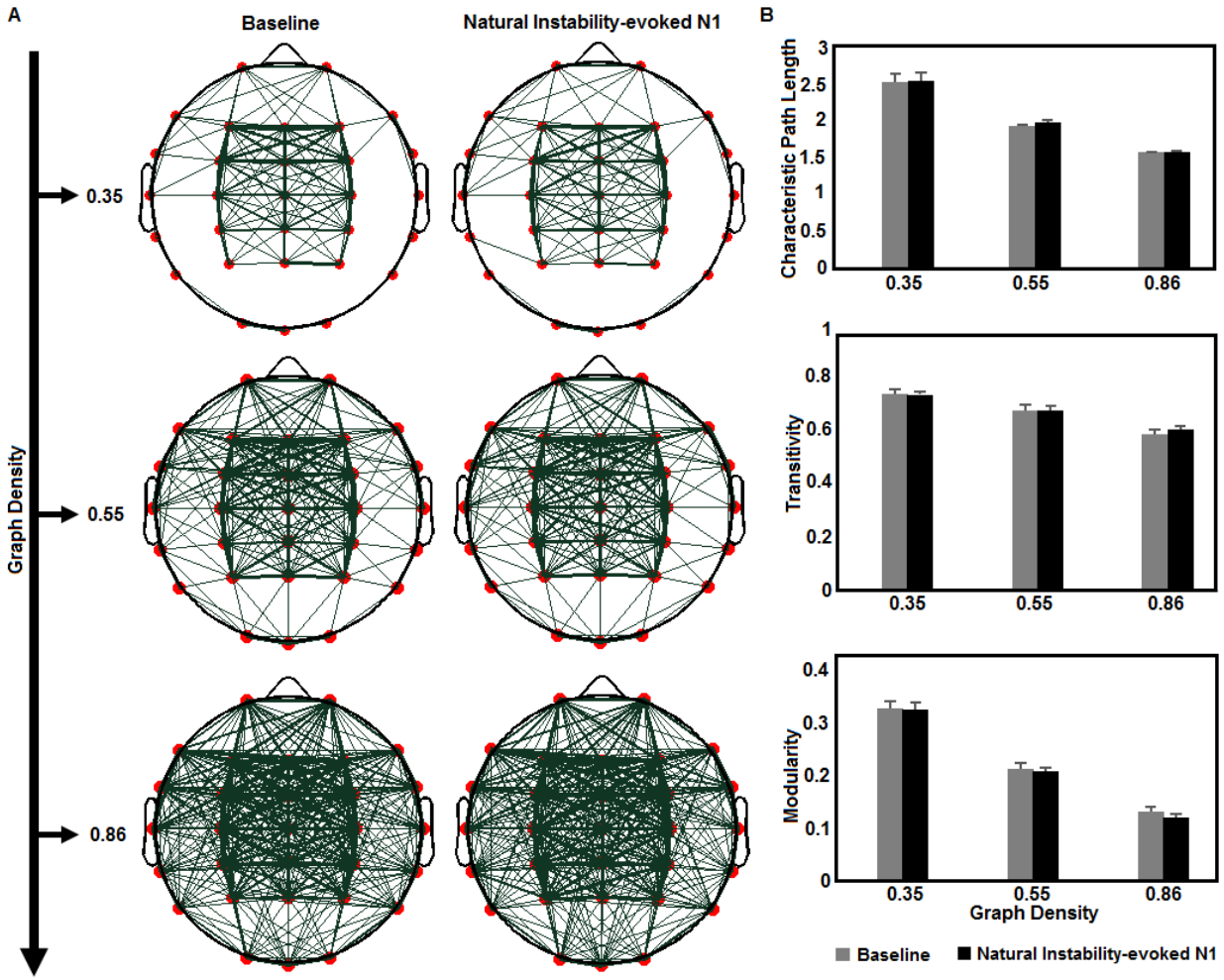

Figure 6.8. Theta-band networks and graph measures of the natural instability-evoked N1 (A) Graph representation of grand-averaged thresholded (graph density = 0.86, 0.55, 0.35) connectivity matrices of baseline and the natural instability-evoked N1 in the theta frequency band. Nodes of the graph denote EEG electrodes in the international 10-20 system and thickness of edges denote ERPC values between two electrodes. (B) Mean and standard error of characteristic path length, transitivity, and modularity of baseline and the natural instability-evoked N1 as a function of threshold.

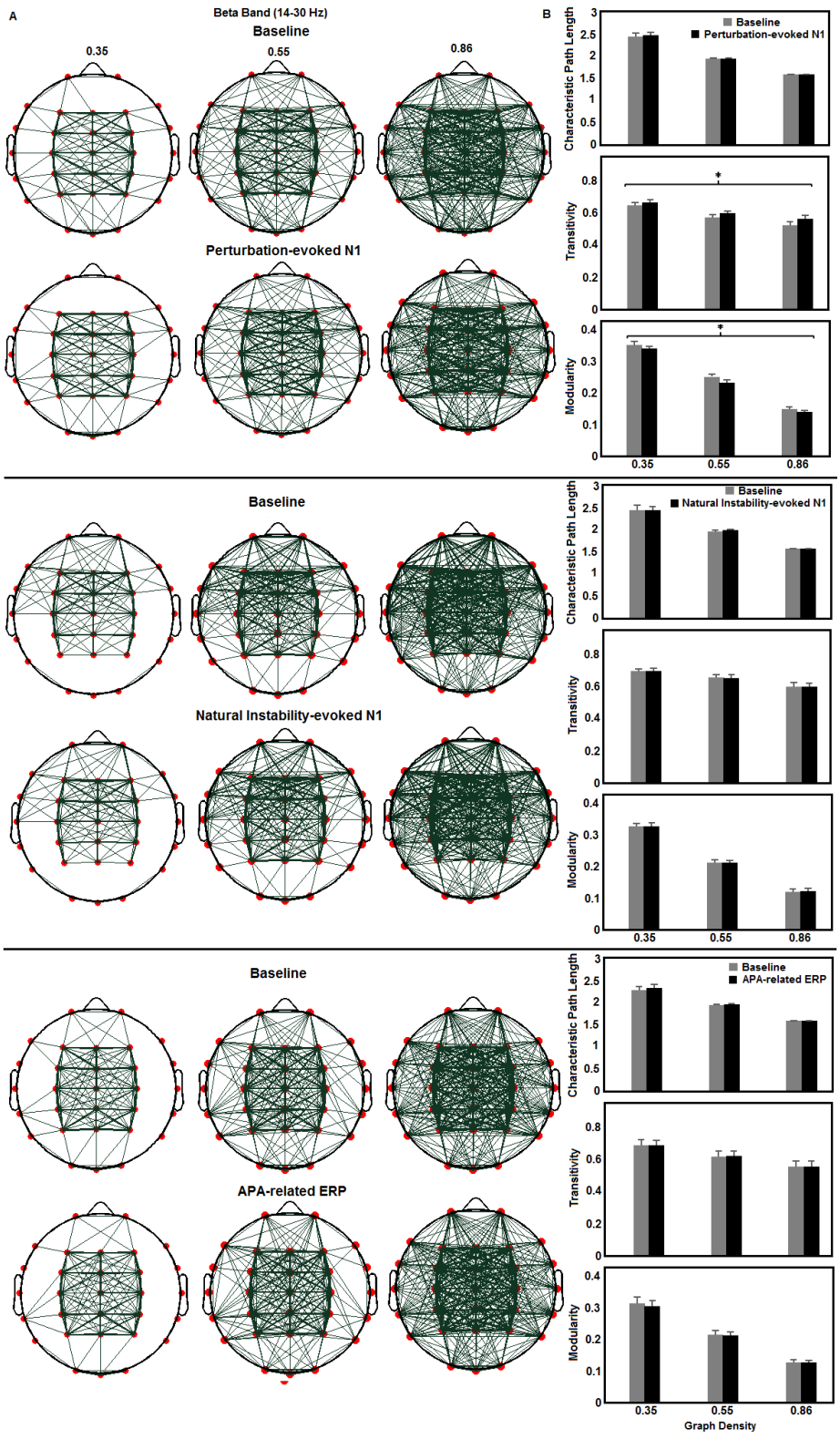

Figure 6.9: Beta-band networks and graph measures. (A) Graph representation of grand-averaged thresholded (graph density = 0.86, 0.55, 0.35) connectivity matrices of baseline and ERPs in the

beta frequency band. Nodes of the graph denote EEG electrodes in the international 10-20 system and thickness of edges denote ERPC values between two electrodes. (B) Mean and standard error of characteristic path length, transitivity, and modularity of baseline and ERPs as a function of threshold. Asterisk indicates a significant difference ($P < 0.01$) in graph measures.

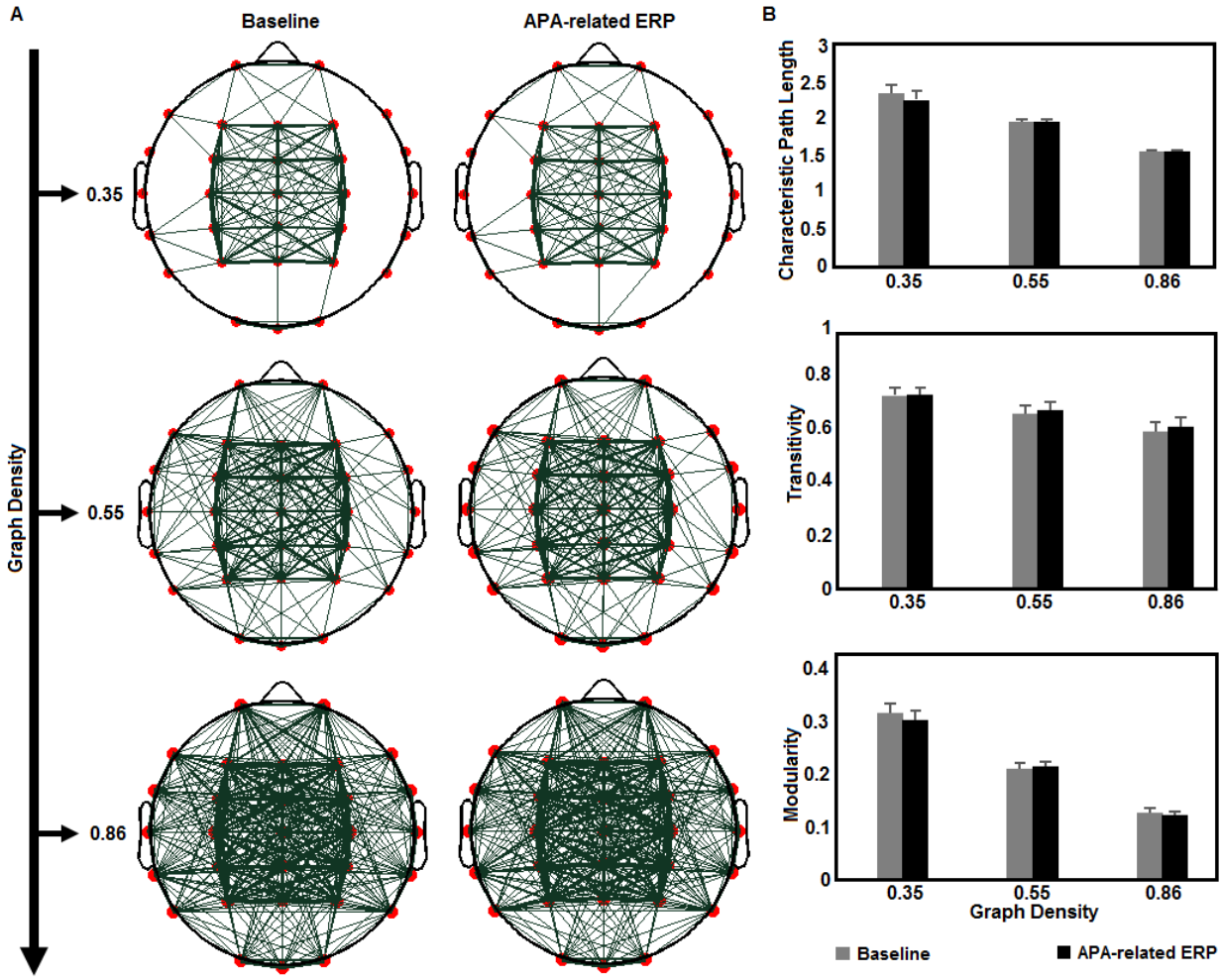

Figure 6.10: Theta-band networks and graph measures of the APA-related ERP. (A) Graph representation of grand-averaged thresholded (graph density = 0.86, 0.55, 0.35) connectivity matrices of baseline and the APA-related ERP in the theta frequency band. Nodes of the graph denote EEG electrodes in the international 10-20 system and thickness of edges denote event-related phase coherence values between two electrodes. (B) Mean and standard error of characteristic path length, transitivity, and modularity of baseline and the APA-related ERP as a function of threshold.

Table 6.2: Mean (n = 12) and standard deviation values of connectivity strength of baseline and ERPs and their corresponding two-tailed t values and P values (paired t test, dF =11, $t_{critical}$ = 2.2) indicating the differences between baseline and ERP connectivity strength when no thresholding was applied on the weighted graph.

	Connectivity Strength					
	Baseline	SD	ERP	SD	t Stat	*P* value
Perturbation-evoked N1_Theta	0.555	0.078	0.652	0.117	-3.774	0.003
Natural instability-evoked N1_Theta	0.529	0.057	0.553	0.045	-1.516	0.158
APA-related ERP_Theta	0.540	0.112	0.559	0.108	-2.328	0.040
Perturbation-evoked N1_Alpha	0.533	0.076	0.596	0.083	-3.802	0.003
Natural instability-evoked N1_Alpha	0.560	0.064	0.574	0.077	-1.878	0.087
APA-related ERP_Alpha	0.538	0.104	0.539	0.105	-0.187	0.855
Perturbation-evoked N1_Beta	0.491	0.075	0.531	0.076	-2.812	0.017
Natural instability-evoked N1_Beta	0.539	0.086	0.539	0.077	-0.092	0.928
APA-related ERP_Beta	0.518	0.116	0.521	0.111	-0.581	0.573

6.5 Discussion

To our knowledge, the present study is the first to report the functional networks associated with human bipedal balance control events. ERPC and GTA were used to reveal functional interactions between cortical areas. As predicted, the present study supports the hypothesis and found that similar patterns of functional connectivity, but different connectivity strengths exist between reactive and predictive balance control as well as between reactive-internal and reactive-external. Similar patterns of connectivity but a significant increase in connectivity strength were found during the perturbation-evoked N1 compared to the APA-related ERP.

Likewise, we observed a similar pattern of connectivity, but a significant increase in connectivity strength during the perturbation-evoked N1 compared to the natural instability-evoked N1. One surprising outcome of this work was the absence of difference in the pattern of connectivity between baseline and ERPs. In spite of the significant amplitude of ERPs associated with perturbation-evoked reactions and the large pre-movement activity associated with predictive control, the pattern of connectivity was similar to baseline activity. This raises, in part, a question about the pattern of connectivity during the baseline period. This interval does not constitute a true 'rest' interval since it occurs during intervals when individuals are standing and either anticipating a forthcoming instability or a cue to move. As a result, this interval is characterized by ongoing static balance control as well as some degree of preparatory or expectancy activity. Collectively, this work supports the model of a complex network of cortical activity that is associated with both voluntarily initiated balance reactions as well as the most automatic naturally occurring reactions such as those that occur when trying to stand still.

Although there was a similar pattern of connectivity between baseline and ERPs, there was however, an increase in the strength of connectivity during ERPs in theta, alpha, and beta frequency bands compared to the resting state for all postural task conditions. The latter does continue to reinforce evidence for cortical activity linked to events related to the control of predictive and/or reactive balance control. GTA revealed that this increased connectivity strength corresponds to increased transitivity and decreased modularity, specifically in theta and alpha bands. Increased transitivity indicates a greater number of connections and increased connection strength suggests increased weight between connections (Rubinov and Sporns, 2010). However, the characteristic path length was relatively unchanged during ERPs. Since characteristic path length is influenced by long-range connections, the present results suggest that there might be no

alterations in the long-range connections (e.g. occipital-frontal) during ERPs compared to the baseline balance control network (Varela et al., 2001; Rubinov and Sporns, 2010). This is also evident by little change in the beta band in most of the graph measures between baseline and ERPs as beta frequencies are suggested to mediate long-range cortico-cortical information transfer (Schnitzler and Gross, 2005). Instead, the increased number of connections might indicate the formation of new short-range connections between neighbouring areas (e.g. frontal-central, central-parietal) (Varela et al., 2001). This is also evident in the decreased modularity during ERPs. In addition, our study provides direct support of the previously proposed network topological 'fingerprint' of cognition in which the baseline network is characterized by modular structure with high clustering within modules and transient reorganization of the network occurs during cognition as reflected by decreased modularity and increased clustering between modules in cognitive networks (Bola and Sabel, 2015). The present results suggest that the balance control is also a cognitive act as opposed to the traditional belief of being automatically maintained by subcortical circuits and increased cognitive demand and neural integration is required during balance control events as reflected by increased transitivity and decreased modularity during ERPs. This is in line with previous dual-task studies demonstrating that the concurrent performance of cognitive and balance recovery tasks results in interference effects (see Maki and McIlroy, 2007 for review).

In the current study, we investigated ERPC in theta, alpha, and beta frequency bands. These frequency bands were shown to be modulated during reactive and predictive balance events (Slobounov et al., 2008; Varghese et al., 2014, 2016). Coherence in specific frequency bands is thought to be related to distinct cognitive functions. Increased fronto-parietal theta coherence was associated with increased cognitive demands such as attention and working

memory (Sauseng et al., 2005). Increased alpha and beta coherences between fronto-central areas were found during movement preparation and execution (Leocani et al., 1997). Oscillatory synchronization in distinct frequency bands below the gamma band has been proposed to be the mechanism underlying the emergence of functional motor networks between cortical and subcortical areas in various motor tasks (Schnitzler and Gross, 2005). Therefore, phase coherence in different frequency bands observed in our study might reflect distinct cognitive processes underlying balance control. It has been reported that the perturbation-evoked N1 is the result of phase-locking of theta, alpha, and beta frequency bands (Varghese et al, 2014). The present results extend this finding and suggest that phase-locking of theta, alpha, and beta frequency bands between neural assemblies distributed across the cortex might have contributed to the balance-related ERPs. While the current study explored connectivity between signals in different electrode locations rather than anatomical regions, phase synchronization was found between frontal, central, parietal areas during balance-related ERPs. Inferred from the previous balance studies, it is likely that these cortical areas might include primary sensory and motor cortices, SMA, PMC, cingulate cortex, PFC (dorsolateral PFC and frontal eye field), temporal cortex, posterior parietal cortex, primary visual cortex, and visual association cortex (Nieoullon and Gahery, 1978; Gurfinkel and Elner 1988; Birjukova et al., 1989; Viallet et al., 1992; Massion et al., 1999; Ouchi et al., 1999; Perennou et al., 2000; Solopova et al., 2003; Beloozerova et al., 2005; MacKinnon et al., 2007; Kazennikov et al., 2008; Mihara et al., 2008; Yakovenko and Drew, 2009; Jacobs et al., 2009; Slobounov et al., 2009; Chang et al., 2010, Marlin et al., 2014).

Given the consistency of the pattern of connectivity and ERPC in different frequency bands this leads to speculation about a ‘balance control network’ engaged when standing still (baseline) and under more dynamic conditions (reactive and predictive balance control events).

Previous studies have shown functional networks (e.g. face network) and phase synchronization mechanisms underlying cognitive acts such as face perception (Rodriguez et al., 1999; Wang et al., 2016) and visual discrimination tasks (Bola and Sabel, 2015). In the present study, phase synchronization (measured using ERPC) was also found between frontal, central, and parietal areas indicating a potential mechanism for functional integration to maintain stability. Alternatively, it has been suggested that cognitive processes merely change the weights or local features of the resting-state networks (Dosenbach et al., 2010). As such, instead of a 'balance control network', the widespread cortical functional connectivity found in this study during baseline might be one or a combination of the resting-state functional brain networks found in a human mature brain such as default-mode network, sensorimotor network, and fronto-parietal network (Dosenbach et al., 2010; Rosazza and Minati, 2011). In addition, the altered network topology, as evidenced by increased transitivity and decreased modularity, observed during ERPs might be the task-related (balance control) reorganization of these intrinsic networks (Bola and Sabel, 2015).

Regardless of the specificity of the underlying network, the question that remains is what is the specific role of this cortical network in balance control? One might argue for two possible general roles: 1) active contribution to the detection and reaction to postural instability and generation of predictive postural responses or 2) activation that is more generically related to event detection reflecting activity linked to preparedness, rather than movement execution. There has been some specific suggestion that the perturbation-evoked N1 represents the sensory processing of postural instability (Dietz et al., 1984), error detection (Adkin et al., 2006), afferent input in primary sensory areas and cortico-cortical transfer of afferent input to the frontal motor areas (Dimitrov et al., 1996). Such speculation, and the associated autonomic activation that is

temporally coupled to such reactions (Sibley et al., 2009), leads to some speculation of a more generic role in detecting postural instability. In such a model, the cortical activity may serve to redirect cortical resources (e.g. attention) and modulate subcortical networks responsible for the control of the evoked responses and subsequent behavior.

While it is not possible to exclude the potential role of the cortex in detecting postural instability, the accumulated pieces of evidence might seem to suggest the activity is linked to the actual control of responses. Previous studies have proposed different roles for subcortical and cortical structures in balance control. It is suggested that the basic postural networks for APAs and CPAs are located in the spinal cord and brain stem, whereas the cerebellum and basal ganglia are involved in adaptive control and acquisition of APAs and CPAs (Nashner et al., 1979; Massion, 1992; Horak and Diener, 1994; Massion et al., 1999; Timmann and Horak, 2001). However, these structures appear to not be involved in the generation and triggering/initiation of APAs and CPAs as evidenced by similar temporal characteristics of postural adjustments observed in cerebellar and parkinsonian patients compared to that of normal subjects (Horak et al., 1992; Timmann and Horak, 2001). Single neuron recordings in the motor cortex of rabbits and cats revealed strong activation during postural corrections and APAs that precede a reaching movement, suggesting a potential role for the motor cortex in generating APAs and CPAs (Beloozerova et al., 2003; Yakovenko and Drew, 2009). Lesion studies in humans have shown impaired APAs associated with rapid arm movements in SMA patients and proposed that the SMA generates an APA, whereas M1, basal ganglia, and the brain stem execute the APA (Gurfinkel and Elner, 1988). In addition to the SMA, M1, PMC, and polymodal sensory cortex were also shown to be involved in the generation, triggering, and timing of postural adjustments (Chang et al., 2010; Viallet et al., 1992; Perennou et al., 2000; MacKinnon

et al., 2007; Jacobs et al., 2009). In addition, transient inhibition of cortical motor regions using continuous theta burst stimulation led to an attenuation of compensatory arm response suggesting a motor cortical contribution to CPAs (Bolton et al., 2011). Furthermore, theta frequency bands were related to monitoring postural instability, whereas alpha and beta frequency bands were proposed to be related to the generation and execution of postural responses (Slobounov et al., 2008, 2009). Collectivity, this work leads one to favour a view that cortical activity is a direct contributor to the sensorimotor transformation that underpins reactive and predictive balance control. Cortical information flow in a sensorimotor activity is suggested to flow from primary sensory areas to unimodal and multimodal sensory association areas to the motor association areas and finally end in M1 generating the specific motor output for the detected sensory input (Rizzolatti et al., 1998). Inferred from the above mentioned studies and balance control being a complex sensorimotor task, it is likely that the role of functional cortical networks observed in the present study might be anticipating or detecting postural instability, sensory processing of postural instability, planning, generating, and initiating postural adjustments to maintain balance.

6.5.1 Methodological considerations and Limitations

In this study, weighted graphs were analyzed as opposed to binary graphs which were used in most connectivity studies. The weighted graphs contain information about connectivity strength enabling weak and non-significant links to be filtered out to focus on the strong and significant connections (Rubinov and Sporns, 2010). Although EEG offers excellent temporal resolution enabling the examination of transient changes in cognitive networks, it is often limited by volume conduction. It is possible that the phase coherence observed in this study might be due to spurious synchronization due to volume conduction (Rodriguez et al., 1999). However, this possibility was ruled out for the following two reasons. Firstly, it has been shown that

volume conduction decays rapidly with separation of electrodes greater than 2 cm (Menon et al., 1996; Rodriguez et al., 1999). The EEG electrodes used in the present study have a diameter of 1 cm and the inter-electrode distance was greater than 2 cm for each electrode pair. Secondly, ERPC considers only the phase information, hence it is less prone to volume conduction from a common source that mostly affects the amplitude dynamics. Another issue to consider is the phase distortion. By using zero-phase lag band pass filtering, common referencing, and sensor-space rather than source-space, the original phase difference of the EEG time series was preserved (Thatcher, 2012). In addition, artifact removal using ICA has ensured that the phase coherence results are not from non-neural sources and comparison with baseline ensured that the increased coherence during ERPs are related to specific balance control events.

In the present study, only 30 channels were included for analysis, even though 64 channels were collected for the reactive-external experiment which enabled the comparisons to be made between graph measures and connectivity matrices of reactive and predictive balance control. ERPC computes the phase consistency of each epoch and then averages across all trials, thereby increasing the stability of phase coherence values (Van Diessen et al., 2015). In addition, the individual average of ERPC values were used to construct connectivity matrices which were then used for graph theoretical and statistical analysis. Using the same number of participants (n =12) excluded any bias in statistical analysis due to unequal number of participants. While the number of trials per participant for the perturbation-evoked N1 and APA-related ERPs were similar (35 trials), approximately 70 artifact-free trials were selected for the natural instability-evoked N1. The smaller amplitude of the natural instability-evoked N1 required a sufficiently greater number of trials to extract the ERPs. Previous studies have compared unequal number of trials to examine the cortical connectivity during real (220 trials) and imagined (120 trials) finger

movements and found similar connectivity patterns (Stavrinou et al., 2007). Hence, the statistical results obtained in this study using individual average values are likely not biased by the unequal number of trials although this has not been specifically tested.

6.6 Conclusions

In the present study, it was shown that functional connectivity exists during bipedal balance control in the theta, alpha, and beta frequency bands. It is proposed that a balance control network exists while standing (baseline period) and frequency-specific reorganization occurs during balance control events (ERPs). This reorganization was characterized by increased connectivity strength, increased transitivity, and decreased modularity. A similar pattern of connectivity was also found between reactive and predictive, reactive-internal and reactive-external balance control events. It is suggested that this balance network is involved in detecting postural instability, planning, generating, and executing postural responses to maintain bipedal balance. The present results open a window to extend the assessment of balance impairments from conventional behavioral and ERP analysis to a quantifiable assessment of functional networks that reveal the neural integration of various cortical areas to maintain stability.

Chapter 7

General Discussion

7.1 Overview of findings

The overarching goal of this thesis was to extend the understanding of the activity of the cerebral cortex associated with human bipedal balance control. Traditionally, balance control was thought to be mediated by subcortical structures based on animal studies (Sherrington, 1910; Magnus, 1926). However, research from the past few decades in humans and animals using single neuron recordings, dual-task and attention studies, lesion studies, EEG, TMS, fNIRS, and PET studies have shown potential cortical involvement in both reactive and predictive balance control (for review see Jacobs and Horak, 2007; Maki and McIlroy, 2007). However, the specific role of the cortex in balance control remains unclear. In addition, there is scarce research exploring cortical activations and functional interactions between different cortical areas during reactive and predictive balance control that reveal a cortical network involvement in balance control. Hence, the two overarching goals of this thesis were to examine a potential network involvement and its generalizability to different types of balance tasks. This was investigated specifically in young healthy adults during three different balance tasks: standing still, feet-in-place balance reactions, and voluntary stepping. Study 1 explored the frequency characteristics and mechanisms underlying the generation of the perturbation-evoked N1. It was found that the perturbation-evoked N1 is at least partly due to the phase reset of ongoing delta, theta, alpha and beta frequencies. It is suggested that different frequencies represent the activity of different neural assemblies distributed across brain regions with specific cognitive functions (Başar-Eroglu et al., 1992). Therefore, the partial phase-reset model of the perturbation-evoked N1 provided indirect evidence of a network involved in the response to perturbations requiring a balance reaction.

Study 2 investigated the cortical activity linked to 'automatic' balance reactions that occur continuously when one is standing still and its dependence on the amplitude of these balance reactions. It was observed that an evoked N1 potential (the natural instability-evoked N1) exists prior to the onset of 'automatic' balance reactions that occur during standing still and peak amplitude and spectral power of the natural instability-evoked N1 increased as postural challenges and demand for reactive control increased. The timing, scalp distribution, and frequency modulations during this N1 parallel to that of the perturbation-evoked N1 suggesting the involvement and generalizability of a cortical network to the most automatic balance reactions occurring during standing still at least in more demanding tasks (narrow stance) when the reliance on reactive control is higher. Study 3 examined the cortical activations related to the preparation and execution of APAs preceding a step and whether the activation is dependent on the context of control. It was found that there were specific MRPs related to APAs that preceded a step. The specific MRPs related to the APA and FO in study 3 suggest that APAs and focal tasks are organized independently as separate postural and motor commands supporting the 'parallel mode' of postural control and movement and are coordinated either subcortically or cortically (Massion, 1992). In addition, comparable MRPs between the APA and lateral weight shift in study 3 revealed parallels in cortical activation regardless of the context of control. The scalp distribution and frequency modulations during APA-related MRPs parallel to that of the perturbation-evoked N1 suggesting the involvement and generalizability of the cortical network to predictive balance control. Thus, the results of the first three studies provided indirect support for the involvement of a cortical network and its potential generalizability across different balance tasks. Study 4 relied on the use of connectivity analysis in an attempt to provide more direct evidence for the cortical network involvement and its generalizability. Specifically, study

4 investigated functional connectivity examining whether similar patterns and strengths of connections exist between task conditions. A functional network was characterized during bipedal balance control in theta, alpha, and beta frequency bands. A comparable pattern of connectivity existed between reactive and predictive, reactive-internal and reactive-external balance control with different connectivity strengths. This suggests the generalizability of this functional network across different balance tasks. Moreover, a similar pattern of connectivity during baseline and ERPs led to speculation that a 'balance control network' might exist while standing (baseline period) and that frequency-specific reorganization occurs during balance control events (ERPs). The latter is assumed based on the task-related differences in connectivity strength, transitivity and modularity. Inferred from previous studies, this balance control network might be involved in anticipating/detecting postural instability, planning, generating, and executing anticipatory and compensatory postural responses.

In summary, the findings of this thesis extend the existing body of literature regarding the cortical control of balance and suggest that, rather than a single cortical area, it is possible that a distributed cortical network is involved in balance control. The results of the four studies revealed modulation and existence of functional networks in specific frequency bands. The perturbation-evoked N1 was composed of frequencies from the delta to beta range. The natural instability-evoked N1 was associated with modulations in the delta to gamma range. APA-related ERPs exhibited ERD/ERS of alpha, beta, and gamma frequencies. Finally, in study 4 there was evidence of functional networks in theta, alpha, and beta frequencies. Modulations of various frequencies during reactive and predictive balance control may reflect the role of multiple cognitive functions performed by the cortex. It has been suggested that delta frequencies are related to signal matching, decision making, and surprise, whereas theta frequencies reflect

sensorimotor integration, focused attention, and signal detection (Basar et al., 1992, 2001). Alpha and beta frequencies are believed to correspond to intra- and inter-cortical information transfer during movement preparation and execution (Rizzolatti et al., 1998). Gamma frequencies reflect focused cortical arousal accompanying both motor and cognitive tasks and represent a physiological correlate of selective attention (Basar et al., 1992, 2001). If these assumptions are true, it is likely that postural perturbations or volitional movements induce synchronized activation of different neuronal assemblies in the fronto-central-parietal areas. The integrated activity of these neural assemblies, in turn, signal either anticipation or detection of postural instability, perform cortical information processing to generate and execute complex postural control strategies to maintain balance. Thus, the results of this thesis reinforce the view that cortical networks likely play an important role in the control of stability.

7.2 Contributions to the existing literature

The findings of this thesis contribute to filling gaps in the existing literature regarding cortical involvement during reactive and predictive balance control. For instance, only the time domain information of PEPs has been available thus far. Study 1 of this thesis revealed the frequency characteristics of the perturbation-evoked N1 and also proposed the mechanisms underlying the genesis of the N1. While previous studies have shown modulation of different frequency bands (theta, alpha, beta) during reactive and predictive balance control as evidence for cortical involvement, the findings of study 1 revealed that phase-locking of these frequencies gave rise to the perturbation-evoked N1 (Del Percio et al., 2007; Sipp et al., 2013; Slobounov et al., 2005; 2008; 2009). Another major contribution of this thesis to the existing literature is the natural instability-evoked N1 found in study 2 that parallels the perturbation-evoked N1 in study 1. While previous studies have shown frequency modulations while standing (Del Percio et al.,

2007; Slobounov et al., 2009), this is the first study to reveal an ERP related to reactive balance control events occurring during standing still. It has been suggested that standing still is composed of both open-loop and closed-loop postural control mechanisms (Collins and De Luca, 1993). The results of study 2 suggest that if standing still is composed of a series of discrete balance reactions to naturally-occurring time-varying instabilities, then the cortex has a similar role in reactive balance control as it does for maintaining stability during unexpected external perturbations (study 1). This is evident by similar temporal and topographic characteristics of the perturbation-evoked N1 and natural instability-evoked N1. While study 1 and 2 contributed to the understanding of cortical involvement in reactive balance control, study 3 demonstrated cortical activations related to predictive balance control. Previous literature has shown APA-related ERPs and frequency modulations during upper limb movements (Yoshida et al., 2008; Barlaam et al., 2011; Ng et al., 2011). However, APA-related ERPs and frequency modulations for lower limb movements are reported less frequently. Since lower limb movements specifically affect stability by altering the BOS, it is of particular importance to understand the neural control of APAs during lower limb movements. The results of study 3 revealed that there exist specific ERPs related to the preparation and execution of APAs that occur prior to stepping and are associated with frequency modulations in specific frequency bands. In addition, study 3 also found parallels in cortical activation regardless of the context of control (postural component vs. focal component).

To our knowledge, all of the research studies (except the review studies) completed so far in balance control have examined cortical involvement focusing on a specific cortical area such as the M1, SMA, PPC, PFC and PMC. However, study 4 of this thesis is the first of this kind to examine cortical interactions during reactive and predictive balance control using functional

connectivity. The results of study 4 extend the existing body of literature and suggest that rather than a single cortical area, as reported in previous studies, it is likely that a distributed cortical network is involved in balance control and the neural interactions between these areas give rise to complex postural strategies to regain balance. This is evident through the increased number of functional connections and increased connectivity strength during ERPs. Altogether, the findings of this thesis addressed certain gaps in the existing body of literature regarding the cortical control of balance and suggest that the cortex is actively involved in maintaining stability as evidenced by the ERPs time-locked to the moments of instability. However, given the limited spatial resolution of EEG, further studies are required to reveal the specific role of each cortical region in reactive and predictive balance control. Nevertheless, based on the present findings and inferred from the existing literature using single neuron recordings, lesion studies, and non-invasive technologies, it is likely that the role of the cortex might be the generation and initiation of APAs and CPAs (Horak et al., 1992; Viallet et al., 1992; Perennou et al., 2000; Timmann and Horak, 2001; Beloozerova et al., 2003; MacKinnon et al., 2007; Jacobs et al., 2009; Yakovenko and Drew, 2009; Chang et al., 2010). In summary, the findings of this thesis work extended the understanding of the cortical control of human bipedal balance and in turn could lead to future work exploring the mechanisms underlying disordered balance control associated with neurological injury and aging.

7.3 Limitations

The four studies of this thesis used EEG to capture brain signals and characterize cortical activations during reactive and predictive balance control. While EEG offers excellent temporal resolution (< 1 ms) compared to other non-invasive neural imaging techniques, it is often limited by poor spatial resolution (1-10 cm) (Sakkalis, 2011). In addition, due to volume conduction of

the brain tissue, EEG signals measured from a specific electrode site might not solely represent the local neural activity underlying the electrode (Horwitz, 2003; Van Diessen et al., 2015). One possible solution to this problem is the source reconstruction from EEG signals. However, current source reconstruction techniques offer limited resolution without prior constraints and assumptions and also do not completely overcome the problems of volume conduction and field spread (Van Diessen et al., 2015). Another major limitation of using EEG in balance studies is the non-neural artifacts due to eye blinks, eye movements, whole-body movements, line noise, EMG, ECG, sweat, and detachment of electrodes (Thompson et al., 2008). These artifacts might obscure the balance-related neural signal. However, ICA has been shown to be a promising tool for removing these artifacts and ICA was used in all four studies prior to further analysis. The functional connectivity explored in study 4 is based on EEG signals and hence no clear conclusions can be derived about the structural/anatomical connectivity which is usually explored using diffusion-weighted MRI (Sakkalis, 2011). Due to the limited spatial resolution of EEG, the specific role of each cortical region in balance control cannot be concluded from the present findings. In order to reveal the specific role of each cortical area, there is a need for the application of additional neural techniques or a combination of techniques such as PET, TMS, fNIRS, fMRI (of motor imagery of balance tasks) or single neuron studies in animals. In addition to these technical limitations, the studies of this thesis were conducted on young healthy adults and hence the findings of this thesis cannot be generalized to other populations such as older adults and balance-impaired patients. Future studies in these populations are required to generalize these findings.

The similar pattern of connectivity between baseline and ERPs in study 4 led to speculation of the existence of a ‘balance control network’ while standing still (baseline) and

during ERPs. However, this study did not provide direct evidence for the existence of such a network as there was no control condition of a non-balance task (eg. sitting or lying). Subsequent studies will need to use an appropriate task comparison to establish the potential involvement of balance-specific networks versus more general sensorimotor and/or attentional networks.

7.4 Future directions

The studies of this thesis examined cortical activations and connectivity during reactive and predictive balance control in young healthy adults. However, there is still scarce research regarding the mechanisms underlying impaired balance control associated with aging and various neural diseases. Hence an important piece of future work should be the examination of frequency characteristics of the perturbation-evoked N1 and evidence of the natural instability-evoked N1 and APA-related ERPs in older adults and balance-impaired patients in comparison to that of healthy controls to see whether there are any alterations in the amplitude of ERPs or frequency characteristics that might reflect their impaired balance. Another potential area of future research is to examine functional connectivity of ERPs in these populations. It has been shown that various neurological diseases such as epilepsy, Alzheimer's disease, schizophrenia, and autism are characterized by altered brain connectivity compared to healthy subjects (for review see Sakkalis, 2011). Thus, brain connectivity techniques are potential clinical tools for evaluating cortical dysfunctions. As such, a major focus of future work is to examine functional connectivity in older adults and balance-impaired patients during reactive and predictive balance control tasks.

Study 4 of this thesis examined only functional connectivity which did not provide any information about the anatomical connectivity and direction of cortical information flow

(Horwitz, 2003). Hence, further studies examining effective connectivity are required to reveal the direction of information flow during balance control. In addition, the nonlinear functional connectivity techniques (e.g. phase locking value) have to be used to capture nonlinear interactions, which could not be revealed by linear techniques such as ERPC (Sakkalis, 2011). The findings of study 4 led to speculation of the existence of a 'balance control network' while standing still (baseline) and during reactive and predictive balance control events (ERPs). However, this study did not provide direct evidence which could be investigated in future studies by comparing the functional connectivity of baseline and ERP periods to that of a sitting condition where there is no requirement of balance control. Apart from time domain and frequency domain analyses of EEG signals, future studies should employ EEG source localization techniques (e.g. BESA, LORETA) as well as other neurotechniques such as PET, TMS, and fNIRS to probe the cortical contributions to balance control.

Future studies should more directly address the specific role of this cortical activity. In spite of this growing understanding of the cortical activity that is temporally coupled with both reactive and predictive balance control, there remains little direct insight into the purpose of this activity. While it is likely that improved localization and understanding of the specific nature of connectivity (e.g. direction) could inform about the potential regions involved, novel behavioral studies would need to be developed to help reveal the role. For instance, inhibiting or disrupting specific cortical areas using TMS or stimulating cortical areas using transcranial direct current stimulation and examining the amplitudes and timings of both muscle activations patterns and cortical activations (ERPs) during APAs and CPAs. Alternatively, lesion studies could provide insight into the purpose of these cortical activations. By examining the balance-related ERPs and postural responses from cortical stroke patients during APAs and CPAs could reveal the

potential role of these cortical activations in balance control. In summary, there remains much to be learned about the role of the cortex in human bipedal balance control and causes of impaired balance control which could be investigated by combining existing knowledge as well as applying new biomechanical and neural techniques.

7.5 Implications

The findings of this thesis extended understanding of the cortical control of balance by revealing the cortical activations and connectivity temporally coupled with reactive and predictive balance control. First, this work adds to the growing evidence of the distributed nature of the CNS control of human stability control. In addition, the work highlights a cortical network, rather than single diploes (e.g. Marlin et al., 2014), which reinforces a complex role for the cortex in the control of balance rather than as part of an alerting or event detection network. These findings, in turn, may have potential functional and clinical implications in identifying causes of instability associated with aging and various neurological disorders. Specifically, the amplitude and timing of ERPs related to APAs and CPAs can be used as a diagnostic tool to assess impaired balance in older adults and balance-impaired patients. Evidence of reduced and delayed perturbation-evoked N1 responses in older adults has revealed the potential benefits of electrophysiological markers to augment behavior measures (Duckrow et al., 1999). It is possible that building on the functional connectivity work towards the development of a more refined model of the cortical network could be used to explore predictors of balance control challenges in those with cortical lesions (e.g. stroke, multiple sclerosis, traumatic brain injury) or age-related changes in cortical state (e.g. white matter disease). In the long term, extending from this work to advance a more detailed model of the cortical network of activity, along with the clear utility of behavioral measures, may be used to help guide understanding of the next generation of diagnostic criteria

and even personalized therapeutic approaches. In summary, understanding the neural control of human bipedal balance could help identify the causes of balance impairments associated with various neurological disorders and develop diagnostic and therapeutic tools, in turn reducing injuries due to falls and subsequently decreasing health care costs and improving the quality of life.

7.6 Conclusions

This thesis examined cortical activations and functional connectivity associated with reactive and predictive balance control in young healthy adults during three balance tasks: standing still, compensatory feet-in-place reactions, and voluntary stepping. We observed cortical activations in time and frequency domains and a similar pattern of connectivity during reactive and predictive balance control. The findings of this thesis reinforce the view that cortical networks likely play an important role in the control of stability. The insights provided in this thesis extend our understanding of the cortical control of human bipedal balance with potential future work in balance-impaired individuals to identify the causes of instability. This knowledge can be used to further develop a more precise and robust model of the CNS control of human balance that in turn could aid development of future diagnostic measures to assess balance disorders.

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