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## Cortical Oscillations During a Lateral Balance Perturbation While Walking

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# CORTICAL OSCILLATIONS DURING A LATERAL BALANCE PERTURBATION WHILE WALKING

by

Joseph J. Lee, B.S.

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

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#### ABSTRACT CORTICAL OSCILLATIONS DURING A LATERAL BALANCE PERTURBATION WHILE WALKING

Joseph J. Lee, B.S.

Marquette University, 2016

The role of sensory systems in the cortical control of dynamic balance was examined using electroencephalography (EEG) recordings during balance perturbations while walking. Specifically, we examined the impact of sensory deficits on cortical oscillations using vibratory stimuli to suppress sensory feedback and by comparing cortical oscillations during balance perturbations while walking in people with sensory deficits associated with cervical myelopathy and neurologically intact controls. Balance during walking provides a rich framework for investigating cortical control using EEG during a functionally relevant task. While this approach is promising, substantial technical challenges remain in recording and processing EEG in the noisy, artifact laden environment associated with walking. We therefore first investigated the role of sensory attenuation in healthy, adult controls within the framework of a simple, motor task. We then examined the effectiveness of using independent component analysis and additional machine learning techniques such as clustering and linear classifiers for differentiating noise from actual brain activity in EEG signals during walking. Finally, we examined a more complicated experimental framework using a custom cable-servomotor system to deliver a lateral pull to the waist of participants with cervical myelopathy while walking and measured their cortical activity using high density EEG.

We observed that the attenuation of sensory input in healthy controls induced a similar change in beta band modulation as found previously in spinal cord injury for simple movements of the ankle. During walking, large increases in theta band power throughout the cortex were observed to modulate with lateral balance perturbations. Theta band modulations in the frontal areas of the cortex were significantly delayed in time and displayed a more spatially lateralized cortical localization for participants with cervical myelopathy compared to age-matched, healthy controls. The timing of these theta power modulations were significantly correlated with the initiation of a widening step width correction in response to the balance perturbation. Our results support a link between the modulation of cortical oscillations and sensorimotor integration in simple and complex motor paradigms.

#### ACKNOWLEDGEMENTS

Joseph J. Lee, B.S.

Show me Your ways, O Lord; Teach me Your paths. Lead me in Your truth and teach me, For You are the God of my salvation; On You I wait all the day. -Psalm 25: 4 & 5

So this particular path ended up being a little longer, involved a little more waiting, than I first anticipated but His grace proved sufficient for every trial.

I'd like to thank,

My advisor Brian for his steadfast support, guidance and his example of "just doing the right thing and sorting the rest out later,"

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Dylan Snyder and Ryan McKindles for their help with countless EEG setups,

All the volunteers who let us take a peak into their brains,

And finally, my family and friends - thank you so much for keeping me in your thoughts and prayers while I took the scenic route in life, sometimes also referred to as grad school.

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### Chapter 1: Introduction and Background

#### **1.1 INTRODUCTION**

Cortical oscillations serve an important role in the neural control of balance during walking. The intuitive ease with which we normally walk is underlain by complex interactions between automated patterns from the spine and the active supraspinal integration of sensory afferents used for motor planning and execution. Innate limb mechanics combined with rhythmic firing from the spinal cord provide an elegant mechanism for bipedal locomotion, yet taken alone, fail to explain our ability to navigate around the dynamic and often unexpected conditions of the surrounding environment. The necessity for this direct input from the cortex during walking is made especially evident after disruptions to supraspinal contributions such as in patients with myelopathy, commonly found to present with significant gait deficits. Characterizing brain activity during a lateral balance perturbation would provide valuable insight in how and why the brain utilizes sensory feedback while walking.

We examined the impact of sensory deficits on cortical oscillations using electroencephalography to measure brain activity in both simple volitional movements and the framework of a complex, lateral balance control task during walking. Sensory information was manipulated using vibratory stimuli and through the recruitment of participants with cervical myelopathy, commonly observed to suffer reduced proprioceptive feedback (Clarke and Robinson 1956). This chapter will provide an

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overview on the neural control of walking and balance within the context of functional neuroimaging and pathology of the spinal cord.

#### **1.2 CONTROL OF MOVEMENT**

#### 1.2.1 Control of Volitional Movement

The control of volitional movement in the neocortex occurs in several interconnected regions ranging from the various facets of the motor cortex surrounding the central gyrus to areas of the parietal cortex. To what degree and the exact method of how these areas cooperate is a complex question. One of the traditional frameworks of cortical motor control is the concept of a motor map linking areas of the primary motor cortex to the control of specific parts of the body (Jasper and Penfield 1949). While a rough medial lateral representation (cortical homunculus) has been observed, it is generally acknowledged that there is no concise and orderly delineation of M1 regions mapping specific parts of the body (Schieber et al. 2001; Lotze et al. 2000; Indovina and Sanes 2001). Instead, a diffuse pattern of neuronal activity in several different brain regions has been observed with single unit recordings to possibly encode a wide variety of factors including velocity, direction, force and joint angles (Scott and Kalaska 1995; Georgopoulos et al. 1992; Georgopoulos et al. 1982; Reina, Moran, and Schwartz 2001).

Cortical motor control is not an isolated system however, limited to a one-way transfer of motor commands to the periphery but a dynamic one, constantly receiving sensory feedback. A diverse array of inputs such as visual and proprioceptive receptors provides the information needed for adaptive movement in changing environments (Dietz, Quintern, and Sillem 1987; Patla 1997; Paulus, Straube, and Brandt 1984). The introduction of noise and delayed sensory feedback to this system leads to the need for some form of predictive capability within the brain. A popular hypothesis for a forward model involves the creation of an efference copy, replicating efferent motor commands, to use as an internal model to first predict and then compare to actual sensory feedback (Gauthier and Robinson 1975; Feinberg 1978; Bridgeman 1995).

Errors from this comparison can be used to further refine outbound motor commands more efficiently than relying on delayed feedback alone (Shadmehr, Smith, and Krakauer 2010).

#### 1.2.2 Control of Walking and Balance

Walking in humans comprises a series of elegant solutions to a complex problem, consolidating several different mechanism of passive and active control. Innate properties of bipedal limb dynamics modeled as an inverted pendulum can alone account for a stable and self-sufficient gait (Collins, Wisse, and Ruina 2001; McGeer 1990; Kuo 1999). When combined with rhythmical firing patterns from central pattern generators in the spinal cord, these autonomous subcortical structures form the basis for the cyclical stepping that encompasses walking (Brown 1914; Whelan 1996; Delcomyn 1980; Dimitrijevic, Gerasimenko, and Pinter 1998). Proprioceptive inputs directly modulate these spinal patterns in reflexive pathways for rapid corrections (van Wezel et al. 2000; Valero-Cabré, Forés, and Navarro 2004; Zehr and Stein 1999). Concurrently, the supraspinal integration of sensory afferents provides feedback for adapting to the dynamic conditions of the immediate environment (Dietz 1992; Pearson 2004). Somatosensory, visual and vestibular afferents are all integrated in the cortex for the prediction, planning and assessment of motor responses to external perturbations (J. V. Jacobs and Horak 2007; Adkin et al. 2006; Dietz, Quintern, and Sillem 1987). Maintaining stability in response to medial lateral perturbations in particular, have been theorized to require greater active cortical control (Bauby and Kuo 2000).

#### 1.2.3 Electroencephalography and Motor Control

Electroencephalography is a functional imaging technique that measures at the most basic level, neuronal current flow generated by excitatory postsynaptic potentials (Murakami and Okada 2006). Due to their electromagnetic sensitivities, EEG tends to be more sensitive to radial sources primarily from gyri, with contributions from sulci. Large populations of synchronous neuron activations, typically macrocolumns consisting of thousands of pyramidal neurons, are needed before the corresponding voltage potential across the scalp can be measured by an EEG electrode (Misulis and Head 2003; Hari and Salmelin 1997). The measurement of a direct analogue to neuron activation, in contrast to hemodynamic responses, allows for millisecond temporal resolution, far superior than other imaging modalities such as functional Magnetic Resonance Imaging or Positron Emission Topography (Logothetis 2003; Logothetis 2002). Spatial resolution is limited however, in light of the ambiguities in solving an inherently underdetermined system and the relatively smaller number of measurement points available (Michel et al. 2004).

EEG-based research into motor control does not offer the spatial resolution of single unit recordings and must therefore be approached from a different tack. At the most basic level, motor evoked potentials from individual EEG channels have provided information on the time course of activation over rough areas of the brain such as the sensorimotor cortex - although interpreting the significance of changes in characteristics such as peak amplitude and slopes can be nebulous (Toro et al. 1994; Shibasaki et al. 1980). Advances in source localization, particularly in new methods for solving the inverse problem, have allowed for more accurate localization of neuronal activation patterns on the cortex (Baillet 2011; Grech et al. 2008). Time-frequency analysis offers insight into oscillations of specific frequency bands and their dynamic distribution of power during a motor task (Pfurtscheller, Stancák, and Neuper 1996; Pfurtscheller and Lopes da Silva 1999; Kilavik et al. 2013). A promising avenue of current research is the use of connectivity measures such as phase coherence to not only measure oscillations in a given region, but to identify interactions between different brain regions (Siegel, Donner, and Engel 2012; Stam et al. 2009).

Recording EEG while walking presents several challenging problems related to noise in both the technical implementation and the interpretation of results. Motion artifact tied to electrode movement leads to changes in impedance and other electromagnetic properties unavoidably correlated in time to gait events such as heel strike (Castermans et al. 2014). Myogenic contamination from the neck and face is highly variable due to differences in muscle location, activation timing, and differing levels of fatigue (Misulis and Head 2003; Metting van Rijn, Peper, and Grimbergen 1990; McMenamin et al. 2010). Currently, this noise has been attenuated primarily through a combination of advances in EEG hardware with the use of active electrodes that amplify signals directly at the scalp to minimize line noise and motion artifact, in addition to the application of various blind source separation algorithms in offline processing (Gwin et al. 2011; Snyder et al. 2015; Wagner et al. 2012).

#### **1.3 SENSORY MANIPULATION**

#### 1.3.1 Cervical Myelopathy

Myelopathy is the broad, overarching term for disorders of the spinal cord. Cervical myelopathy typically refers to spondylosis, a chronic degeneration of the spine, rather than the acute trauma associated with spinal cord injury (SCI). Several factors likely contribute to the pathophysiology of cervical myelopathy, including stenosis resulting from ossification of spinal ligaments, congenital susceptibilities, and repetitive injuries to the cervical area of the spine (Baptiste and Fehlings 2006; C.-J. Chen et al. 2003; Firooznia et al. 1982). This degeneration leads to a wide range of sensory and motor deficits, including the loss of joint position sense, two point discrimination and impairment of lower limb vibration perception (Clarke and Robinson 1956; Salvi, Jones, and Weigert 2006). Advances in non-invasive imaging modalities such as fMRI, PET, and EEG have allowed for the study of motor control in human SCI. Broad generalizations of SCI literature are difficult due to the variation in motor paradigms, imaging techniques, degree and time of injury. Roughly categorized, the current state of art has focused on differences of activation magnitude, spatial representation, and neural synchrony. Significant increases in activation magnitude have been found during motor tasks in the M1, S1, supplementary motor area (SMA), premotor area (PMA), and parietal cortex (Curt et al. 2002; Bruehlmeier et al. 1998; Alkadhi et al. 2004). Several contradictory studies have observed no change or even reduced activations compared to controls during movement (Cramer et al. 2005; Castro, Díaz, and van Boxtel 2007; Halder et al. 2006). Spatially, the two most prominent trends that have been observed are a posterior shift in motor representation and a tendency for cortical activations to be displaced towards the deafferented limb representation (Lotze, Laubis-Herrmann, and Topka 2006; Green et al. 1998).

Synchronous activity in the human brain has been observed across a wide range of frequencies and structural regions (Buzsáki 2004). Neural oscillations found in the beta frequency range (15-30Hz) of electroencephalography (EEG) signals demonstrate a distinctive trend over motor areas during movement commands. Specifically, neurons of the motor cortices desynchronize, defined as an event--related decrease in spectral power, during movement initiation and are subsequently followed by a significant resynchronization (Pfurtscheller 1992; Pfurtscheller and Lopes da Silva 1999). These oscillatory signals are theorized to mediate coordination of different local networks spatially distributed across the brain (Schnitzler and Gross 2005; Kopell et al. 2000). In human spinal cord injury (SCI), this event related desynchronization (ERD) has been found to be amplified, along with an attenuation of the event related resynchronization (ERS) when compared to controls (Gourab and Schmit 2010).

#### 1.3.3 Muscle and Tendon Vibration

Proprioceptive feedback to alpha motor neurons are channeled primarily through excitatory Ia afferents from the muscle spindle sensitive to muscle length and inhibitory Ib afferents from the golgi tendon organs sensitive to muscle tension (Houk, Rymer, and Crago 2013). Prolonged vibration has been observed to reduce feedback from Ia afferents due to a heighted discharge threshold, presynaptic inhibition, and neurotransmitter exhaustion (Shinohara 2005). This attenuation of Ia afferents reduces activity of the motor unit pool and thereby reduces maximum voluntary contraction force (Yoshitake et al. 2004). In contrast, brief vibration has been found to increase Ia excitatory input to  $\alpha$  motor neurons (Roll, Vedel, and Ribot 1989). Covibration of tendon flexor and extensors has been shown to evoke an interesting phenomenon of illusory movement (Kavounoudias et al. 2008). The sensation of movement in a particular direction was created solely through vibrating the correct combination of antagonistic muscles and tendons at a differential frequency. Cortically, neuronal activation from vibration has been observed to be diffuse across several regions of the brain including

somatosensory and thalamic regions (Coghill et al. 1994; Tobimatsu, Zhang, and Kato 1999).

#### **1.4 SPECIFIC AIMS**

# 1.4.1 Aim 1: Attenuation of sensory feedback produces changes in patterns of movement related brain activity

We propose to alter brain signals in neurologically intact (NI) subjects by attenuating proprioceptive feedback in a simple motor paradigm. Specifically, we will utilize prolonged vibration of a tendon or muscle spindle, which has been previously demonstrated to depress Ia afferents. Electroencephalography will assess cortical activation patterns of neurologically intact (NI) controls during ankle dorsiflexion. Frequency analysis will center on event related desynchronization/resynchronization (ERD/ERS), a measure of neuronal synchrony associated with motor commands. Source localization of the EEG signals will offer information on primary motor (M1) and somatosensory (S1) cortical activity across the time domain. We hypothesize that after sensory attenuation, brain activity patterns in NI subjects will resemble those observed in SCI subjects with reduced proprioceptive feedback due to their impairment under normal conditions (i.e. no vibration). 1.4.2 Aim 2: Brain activity modulates with lateral balance perturbations while walking.

Balance during walking provides a rich framework for investigating cortical control using EEG during a functionally relevant task compared to simple, isolated movements of the foot. Brain activity was recorded using EEG while participants were walking on a treadmill and delivered a medial-lateral pull to the waist using a custom cable servomotor setup. Significant challenges remain however in both the technical implementation and interpretation of EEG signals recorded in the noisy environment inherent to walking. We evaluated the feasibility of using independent component analysis and additional machine learning techniques such as clustering and linear classifiers for differentiating noise from actual brain activity in EEG signals during walking. We hypothesized that cortical oscillations, shown in previous studies to be strongly associated with motor control, would shift in magnitude and spatial orientation as a function of sensory integration and motor planning and serve as a reference for interpreting possible gait related brain activity.

# 1.4.3 Aim 3: Sensory deficits in myelopathy participants will lead to a shift in magnitude and phasing of balance related cortical oscillations while walking

Walking while facing an imminent loss of balance requires a complex integration of several sensory afferents, in addition to the planning and anticipation of a timely executed motor plan. We believe that the lower limb sensory deficits presenting in individuals with myelopathy may provide a framework to address the role of cortical oscillations observed in walking after a lateral balance perturbation. Using a custom cable-servomotor system, we delivered a lateral pull to the waist of participants with cervical myelopathy during walking and measured cortical activity using high density electroencephalography. We hypothesized that reduced sensory feedback in a challenging, whole body motor task such as maintaining stability in gait would exhibit similar changes in magnitude and spatial localization of cortical oscillations previously observed after an attenuation of proprioceptive feedback in rudimentary motor paradigms isolated to single limbs.

# Chapter 2: Attenuation of sensory feedback produces changes in patterns of movement related brain activity

#### 2.1 INTRODUCTION

Disruption of sensory inputs may alter cortical rhythms and drive welldocumented but poorly understood oscillatory changes found in motor commands. Neural oscillations have long been theorized to facilitate coordination and communication between different cortical regions (Schnitzler and Gross 2005). Beta band activity (15-30 Hz) in particular has been strongly associated with motor control (Kilavik et al. 2013). These neural oscillations in the beta frequencies shift in magnitude and spatial orientation after spinal cord injury (SCI), possibly in response to sensory deficits (Kokotilo, Eng, and Curt 2009). We hypothesized that sensory attenuation in healthy, adult controls could thereby induce a comparable shift in cortical oscillations within the framework of a simple, motor task.

Synchronous activity in the human brain has been observed across a wide range of frequencies and structural regions (Buzsáki 2004; Feige, Aertsen, and Kristeva-Feige 2000; Gerloff et al. 1998). Neural oscillations found in the beta frequency range (15-30Hz) of electroencephalography (EEG) signals demonstrate a distinctive trend over motor areas during movement commands. Specifically, neurons of the motor cortices desynchronize, defined as an event--related decrease (ERD) in spectral power, during movement initiation and are subsequently followed by a significant resynchronization (Pfurtscheller and Lopes da Silva 1999). These beta band oscillations have been implicated in numerous cortical roles, from a broad association with motor commands to specific functions ranging from the processing of sensory inputs to cortical anticipation of future events (van Ede et al. 2011; Zhang et al. 2008; Reyns et al. 2008). While there is no definite consensus on a comprehensive framework for these modulations, there is a growing agreement towards the role of oscillatory signals in mediating the coordination of different local networks spatially distributed across the brain (Laughlin and Sejnowski 2003; Müller-Putz et al. 2007; Caplan et al. 2003).

In human incomplete spinal cord injury, event related resynchronization (ERS) has been found to be attenuated, along with an amplification of the ERD when compared to controls (Gourab and Schmit 2010). Significant increases in activation magnitude were found during motor tasks in sensorimotor areas while several contradictory studies have observed no change or even reduced activations compared to controls during movement (Alkadhi et al., 2005; Hotz-Boendermaker et al., 2008, Castro et al., 2007; Halder et al., 2006). Spatially, prominent trends have been observed in posterior shifts of motor representation and a tendency for cortical activations to be displaced towards the deafferented limb representation (Cramer et al., 2005; Green et al., 1998; Lotze et al., 2006). Similar disruptions in cortical activity have also been reported in patients with various forms of sensory deafferentation (Kristeva et al. 2006; Reyns et al. 2008; Cassim et al. 2001). The large body of changes in brain activity reported after changes in afferent feedback suggests that there is a link between the processing of sensory information and modulation of cortical oscillations.

The objective of this study was to investigate the effects of attenuated proprioceptive feedback on EEG signals of healthy control subjects during a simple ankle

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motor task using prolonged tendon and muscle vibration, previously demonstrated to depress Ia afferents (Shinohara 2005). We hypothesized that the attenuation of sensory input would induce a similar change in beta band modulation as found in SCI, consisting of an attenuation of ERS, magnified ERD and a posterior spatial shift of activity.

#### 2.2 METHODS

#### 2.2.1 Experimental Protocol

Ten healthy, neurologically intact volunteers participated in this study (5 men, 5 women, age range: 20-35 years). Participants came to a university laboratory and performed a series of simple movements of the ankle during EEG recordings of brain activity. Vibration and electrical stimulation were applied during the protocol at targeted times. Written informed consent was obtained from all participants and the study protocol was approved by the Marquette University Institutional Review Board.

The targeted movements consisted of a brisk dorsiflexion of the right ankle after a visual cue, while seated in a comfortable position. Four different types of conditions were randomly interleaved across 5 blocks and consisted of the following: 1) no vibration before the visually cued ankle dorsiflexion, 2) 10 s  $\pm$  1 s prolonged vibration of the tibialis anterior (TA) before the visually cued ankle dorsiflexion, 3) electrical stimulation (e-stim) of the TA, and 4) 10 s  $\pm$  1 s vibration of the TA followed by e-stim. There were a total of 50 instances of each condition, separated by a 10 s  $\pm$  1 s interval where the subject was instructed to remain at rest. E-stim consisted of a 2 Hz stimulus, 2.5 s

duration, (stimulator model D67A, Digitimer Ltd., Letchworth Garden City, UK) applied to the common peroneal nerve were it crosses the head of the fibula. A bar electrode with two 1 cm diameter contacts (2.5 cm between electrodes) was used to deliver a stimulus at 90% of motor threshold, identified by visual observation of twitch contraction prior to beginning the test protocol. The e-stim was used to produce an evoked potential, in order to obtain a measure of the cortical response to the ascending sensory signal. Vibration was applied to the TA at 70 Hz using a custom vibrator consisting of an eccentric mass placed on a motor shaft. The vibrator was strapped over the middle of the tibialis anterior using a cohesive bandage. Vibration was applied to condition the sensory afferents of the muscle (Ribot-Ciscar, 1998) so that they would be less responsive during the movement.

#### 2.2.2 Data Acquisition

Signals from a 64 channel, active electrode EEG cap (ActiCap, Brainproducts), using a modified 10-20 convention and FCz reference, were sampled at 2000 Hz and bandpass filtered between 1 and 500 Hz (Synamps 2 amplifier, Compumedics Neuroscan). Electrode impedance was maintained below 20 k $\Omega$  using high viscosity electrolyte gel (SuperVisc, Brainproducts). Electromyography (EMG) recordings were taken from the TA and the medial gastrocnemius (MG) muscles using wireless electrodes (Trigno, Delsys), sampled at 2000 Hz and bandpass filtered between 10-350 Hz.

#### 2.2.3 Data Analysis

Offline data analysis was conducted using the Fieldtrip and EEGLab toolboxes, Brainstorm (Tadel et al. 2011), and custom scripts (Matlab, Mathworks). EEG data were re-referenced from the FCz electrode to a whole head average reference and epoched by movement onset as defined by TA EMG (5 s before event or vibration and 5 s after) or estim pulse (500 ms before event and 500 ms after). Epochs with gross artifacts were removed according to a z-score threshold above 2 standard deviations of the mean (mean 4.5/50 epochs across all subjects), while blink artifacts were removed through independent component analysis using the extended runica (Makeig, 1996) and ADJUST algorithms for determining artifact related components (Mognon, 2010).

Brain signals associated with dorsiflexion movement were characterized by eventrelated desynchronization (ERD) followed by event-related synchronization (ERS) of the beta frequency band (13-35 Hz). A beta band time frequency (TF) decomposition of the Cz electrode was calculated using Morlet wavelets. The TF decompositions were smoothed over time using a Savitzky–Golay smoothing filter ( $2^{nd}$  order polynomial), averaged across epochs and referenced to a baseline rest period before onset of vibration or visual cue as a percent change in power. Local ERD and ERS minima and maxima means of individual subject's TF decompositions were identified using a custom Matlab masking algorithm identifying regions of interest consisting of >75% maximum power or <50% minimum power. Minimum (ERD) and maximum (ERS) TF power values between the no vibration and prolonged vibration conditions were then compared using a paired t-test ( $\alpha = 0.05$ ). Phasing differences across trials may have underlined changes observed in the evoked potential following prolonged vibration. In order to better characterize the effect of vibration on cortical activity, phase coherence of the E-stim conditions (no vibration/prolonged vibration before E-stim) was calculated using an intertrial coherence (ITC) method (Tallon-Baudry et al., 1996):

$$\text{ITC} = \left| \frac{\sum \frac{X}{\sqrt[2]{X * \overline{X}}}}{\sqrt[2]{n_{\text{trials}}}} \right| \le 1$$

where X = Fourier power spectrum (real and imaginary values).

Maximum ITC values between the no vibration and prolonged vibration conditions were compared using a paired t-test (2 tailed,  $\alpha = 0.05$ ) to evaluate the difference in latencies of evoked potentials across trials.

Possible differences in the motor characteristics of ankle dorsiflexion following prolonged vibration were quantified using EMG of the TA and MG. EMG data was rectified and the root mean square (RMS) was calculated using a sliding window with 50% overlap. Muscle activation was enveloped using a Hilbert and z-transform to find EMG amplitudes and latencies. Differences in amplitudes and latencies for the TA/MG EMG between the no vibration and prolonged vibration conditions were assessed using a paired t-test ( $\alpha = 0.05$ ).

The spatial topography of beta band modulations and evoked potentials on the cortex were characterized using the Brainstorm toolbox. Source localizations of

ensemble averaged EEG signals onto a common cortical surface (*MNI*/Colin27 *brain*, 1 *mm resolution*) were prepared using a boundary element method forward model (OpenMEEG) and a whitened, minimum-norm inverse solution (Baillet et al., 2001). Sources for individual subjects were z-score normalized to a baseline at rest for group averages. Cortical sources for the e-stim conditions with and without prolonged vibration were cross-correlated for each vertex of the *MNI*/Colin27 *brain* mesh to localize evoked potential phasing differences found previously with ITC. The mean norm of the cross-correlated e-stim values were calculated from 3 cortical regions of interest (ROI) located in the left hemisphere: frontal (caudal middle and superior frontal gyri), sensorimotor (precentral, postcentral and paracentral gyri) and parietal (inferior and superior parietal gyri), using a gyral based Desikan-Killiany cortical atlas (Desikan et al., 2006).

#### 2.3 RESULTS

Prolonged tibialis anterior vibration muted the ERD and ERS signals associated with dorsiflexion movements. Maximum beta band synchrony (ERS) of the group-averaged Cz electrode was significantly attenuated from  $138\pm51\%$  to  $93.8\pm52\%$  (% $\Delta$  in power from baseline rest, p=0.0199) after prolonged vibration compared to ankle dorsiflexion without vibration (Figure 1). Maximum desynchrony (ERD) of beta band power at movement onset was also observed to be attenuated from  $34.1\pm15\%$  to  $22.1\pm13\%$  (% $\Delta$  in power from baseline rest, p=0.0557) after prolonged vibration.



Figure 1. Group averaged time frequency decomposition of the Cz electrode, normalized to percent change from baseline rest, of ankle dorsiflexion (A), and ankle dorsiflexion after sensory attenuation through prolonged vibration (B). Dashed line represents movement onset as defined by TA EMG. Maximum and minimum power values of the TF decomposition, identified as the mean power of ROI's consisting of either >75% of maximum power or <50% of minimum power, were used in a paired t-test to determine significance, while error bars denote standard deviation (C).

Despite the changes in the brain signals, the motor output was similar for the vibration and no vibration tests. The corresponding motor output, as measured by EMG of the TA and MG presented in Figure 2, was not statistically different in mean or variance (t-test/F-test) after vibration in either latency (TA paired t-test/F-test: p=0.88/0.26) or amplitude (TA: p=0.31/0.27) across subjects. Thus, there were no apparent differences in the motor output for the vibration and no vibration conditions.



Figure 2. Latency of movement onset after the visual cue as defined by TA and MG EMG (left). EMG amplitude of TA and MG during movement (right).

There were slight changes in the localization of modeled cortical current sources with tibialis anterior vibration. Cortical sources of ankle dorsiflexion during movement initiation were localized to frontal, medial motor and sensorimotor areas associated with motor planning, execution and control of the leg (Figure 3A). These cortical sources shifted posteriorly into medial, superior parietal areas during beta band
resynchronization, shown at the time point corresponding to maximum power in Figure
3B. After prolonged vibration, cortical sources were observed to shift posteriorly during movement initiation, while largely confined to the same regions during resynchronization (Figure 3B).



Figure 3. Source localization of ankle dorsiflexion during movement onset (A), maximum TF power (B), in addition to movement onset (C) and maximum TF power (D) after prolonged vibration.

Evoked potentials using electrical stimulation of the TA were measured to characterize the effect of prolonged vibration on cortical activity. Group ensemble averaged EEG signals from over the Cz electrode during the e-stim conditions showed several positive and negative peaks following stimulation (Figure 4A). A strong phasing of the estim evoked response across trials was observed in the ITC (maximum value: 0.46) corresponding with the N80 peak (Figure 4B) and was attenuated (paired t-test: p=0.052) following prolonged vibration (maximum value: 0.35) (Figure 4C). Spatial localization of the phasing between the e-stim evoked response with and without prolonged vibration showed that components of the evoked response phase lagged the evoked response after prolonged vibration in the frontal and sensorimotor areas by approximately 30 ms (Figure 4D).



Figure 4. Grand average (Cz electrode) of the e-stim evoked response with and without prolonged vibration (A), intertrial coherence of the e-stim evoked response (B) intertrial coherence of the e-stim evoked response after prolonged vibration (C), and grand average cross correlation map across regions of interest (D).

#### 2.4 DISCUSSION

Acute changes in patterns of movement related brain activity were observed following attenuation of sensory feedback in young, healthy controls. We measured a significantly decreased beta power ERS (increasing power) associated with simple ankle dorsiflexion after prolonged vibration of the TA. These beta band power shifts in premotor and sensorimotor cortical oscillations were not accompanied by a change in the timing or magnitude of ankle dorsiflexion as measured by EMG. Prolonged TA vibration decreased the inter-trial coherence of evoked potentials indicating that sensory feedback was disrupted from increased variance in the timing of afferent sensory information processed by the cortex. Our findings provide evidence towards beta band oscillations holding a significant role in the integration of sensory input with cortical motor commands.

Beta band oscillations we measured from our participants were observed to modulate with basic, cued ankle dorsiflexion much as expected. The pronounced rebound in beta power following a discrete movement characterizing ERS (along with its preceding ERD counterpart) is distinctive in the noisy and often ambiguous nature of EEG measurements (Pfurtscheller 1992). From upper and lower limb movements to active, passive, and imagined activations, the distinct reproducibility with which ERS has been observed across a wide variety of motor paradigms encourages the idea that this prominent feature of motor commands must be of some cortical importance (Müller-Putz et al. 2007; Demandt et al. 2012). Proposed theories are numerous, including the inhibition of motor networks to maintain certain motor states (Pfurtscheller, Stancák, and Neuper 1996; Gilbertson et al. 2005), resetting the sensorimotor network in preparation for further sensory inputs (Zhang et al. 2008; Gaetz and Cheyne 2006), and even the modulation of attention or correctness of movement (van Ede et al. 2011; Koelewijn et al. 2008).

The transient nature of the sensory attenuation used in our study and its acute effect on beta ERS for healthy, young controls may suggest that these oscillations are changing within the confines of a normal, fully functioning mechanism for sensorimotor integration rather than permanent changes in brain structure and connectivity from neural plasticity. Attenuated beta ERS in motor commands have been reported in several chronic conditions linked to somatosensory deficits such as incomplete spinal cord injury, neuropathy, amyotrophic lateral sclerosis, and as a result of normal aging (Bizovičar et al. 2014; Gourab and Schmit 2010; Labyt et al. 2006; Reyns et al. 2008). Long term sensory deafferentation from these conditions may imply a structural reorganization of cortical sensorimotor networks (Feige, Aertsen, and Kristeva-Feige 2000). However, the prolonged vibration we used to attenuate proprioceptive feedback was interleaved with "normal" ankle movements, providing a transitory disruption of proprioceptive input, yet still leading to a decrease in the beta power ERS observed in healthy, young adults. Similar decreases in motor beta oscillations were found after an ischaemic nerve block was used to temporarily deafferent healthy controls (Cassim et al. 2001). A simple increase in cortical baseline from prolonged vibration would not account for the measured decrease in ERD. Instead, the immediate modulation of beta power ERS after sensory attenuation in otherwise normal subjects and the return back to normal magnitudes of beta power during trials without the vibratory stimulus, may support the

idea that these oscillatory signals play an active role in mediating the coordination of sensorimotor networks.

Specifically, this increase in cortical beta power may reflect the processing of proprioceptive feedback in relation to the execution of a motor command. Beta power modulations have previously been associated with proprioceptive afferents (Gaetz and Cheyne 2006; Alegre et al. 2002; Keinrath et al. 2006). In addition, these oscillations have been theorized to underlay the comparison of motor predictions with their respective motor outcomes (Arnal and Giraud 2012; Koelewijn et al. 2008; Kristeva et al. 2006). Holding an active role in mediating motor plans corresponds to previous observations of beta band cortical activity having direct, functional links to movement in both passive measurements of EMG coherence and slowing of voluntary movement after direct cortical stimulation at these frequency ranges using transcranial magnetic stimulation (Kristeva, Patino, and Omlor 2007; Pogosyan et al. 2009). The short latency and continuous feedback of proprioceptive afferents would provide an effective error signal that could generalize across a wide variety of conditions.

Proprioceptive feedback to alpha motor neurons are channeled primarily through excitatory Ia afferents from muscle spindles sensitive to muscle length (Houk, Rymer, and Crago 2013). Vibratory evoked potentials have been traced to regions in the somatosensory cortex, while oscillations reflecting the frequency of vibration have been observed in the prefrontal cortex (Romo et al. 1999; Spitzer, Wacker, and Blankenburg 2010; Tobimatsu et al. 2000; Tobimatsu, Zhang, and Kato 1999). Prolonged vibration has been observed to reduce feedback from Ia afferents resulting from a number of subcortical factors including heighted discharge threshold, presynaptic inhibition, and
neurotransmitter exhaustion (Curtis and Eccles 1960; Hayward et al. 1986; Hultborn et al. 1987). Cortically, we were able to measure the inter-trial coherence of normally strongly phase locked e-stim evoked potentials from the Cz electrode to decrease following prolonged vibration. The decreased coherence was not a result of an attenuation in amplitude but because of a phase shift in certain components of the evoked potential occurring earlier in the premotor and sensorimotor cortex. This may suggest that prolonged vibration attenuates Ia afferent sensory feedback cortically by increasing the variance of feedback over a period of time rather than a simple reduction of firing rate or amplitude.

Cortical beta band modulations have been well characterized to modulate with motor commands. We observed that attenuation of sensory feedback in young, healthy controls leads to a corresponding decrease in beta band synchronization magnitude. This acute, yet temporary change in beta oscillations suggests that these modulations are a mechanism for sensorimotor integration, rather than a mere byproduct of cortical activity.

# Chapter 3: Brain activity modulates with lateral balance perturbations while walking

# **3.1 INTRODUCTION**

Cortical oscillations likely mediate the control of human walking during balance perturbations to gait (Nielsen and Sinkjaer 2002). The rhythmical component of walking has conventionally been attributed to the spinal cord, with supraspinal structures largely relegated to an unclear, ancillary role (Whelan 1996), although rhythmic EEG measurements have been made during pedaling (Jain et al. 2013) and stepping on a treadmill (Gwin et al. 2011). In contrast, the control of balance during walking invokes networks throughout the nervous system, including the cerebral cortex, providing a means for investigating cortical activity during a functionally relevant task (Dijkstra, Schoner, and Gielen 1994; Kavounoudias et al. 1999; Johansson, Magnusson, and Fransson 1995; Horak 2006). While technical aspects of recording and processing EEG in a noisy walking environment remain challenging, having a recurring, discrete event with known associations to cortical activity in the form of a balance perturbation may help further refine EEG techniques. In the current study, we developed a novel technique for assessing EEG during a balance perturbation to treadmill stepping and characterized the cortical response in young healthy adults.

A large portion of the control of walking has traditionally been attributed to spinal networks. Evidence ranging from the iconic experiments in the decerebrate cat to treadmill stepping in humans with chronic spinal cord injury have illustrated the idea that basic motor patterns underlying gait can be produced by central pattern generators within spinal circuits (Brown 1914; Stuart and Hultborn 2008; Calancie et al. 1994). Realistic walking conditions however, necessitate a complex interaction of visual, somatosensory, and vestibular feedback mediated by the cortex for maintaining balance in both baseline walking and in response to unexpected perturbations (Armstrong and Marple-Horvat 1996; Peterka 2002; T. H. Petersen et al. 2012). Lateral stability in particular, requires active control of gait and posture in response to dynamic sensory feedback from the ever changing walking environment (Bauby and Kuo 2000). Thus, supraspinal structures that integrate sensory information for motor planning are also likely to be involved in functional walking. The cerebral cortex, in particular, might be instrumental in this component of walking.

Several challenges persist in measuring cortical activity with EEG in the noisy environment inextricably tied to walking. Myogenic contamination from the face and neck is both unavoidable and highly variable in presentation, influenced by a number of factors including muscle location, size, and fatigue (Misulis and Head 2003; Metting van Rijn, Peper, and Grimbergen 1990; McMenamin et al. 2010). Motion artifact stemming from the movement of EEG electrodes and sensor leads results in changes to impedance and other electromagnetic properties that are problematically time-locked with gait events such as heel strike (Castermans et al. 2014). Noise has been mitigated using several signal processing techniques such as independent component analysis (ICA) or by structuring experimental paradigms that integrate walking with cognitive tasks that have well characterized cortical activity (Gwin et al. 2011; Wagner et al. 2016). Refined techniques are needed to obtain accurate measures of brain activity during walking. The objective of this study was to examine the effect of a balance perturbation on cortical movement-related oscillations during walking. The perturbation provided a framework for testing cortical control of walking, with expected brain activity due to processing of multimodal sensory feedback and motor planning to maintain balance. Brain activity was measured using EEG while participants walked on a treadmill and a medial-lateral pull was applied to the waist using a custom cable servomotor setup. We hypothesized that cortical oscillations, shown in previous studies to be strongly associated with motor control, would shift in magnitude and spatial orientation in response to the perturbation. The results were interpreted in the context of brain control of dynamic balance.

### 3.2 METHODS

#### 3.2.1 Experimental Protocol

Ten young, healthy, neurologically intact volunteers able to walk on a treadmill participated in this study (5 men, 5 women, age range: 21-31 years). Participants were secured in a fall arrest harness and given time to acclimate to moving on an instrumented treadmill (Bertec, Columbus, Ohio). Brain activity was then recorded using electroencephalography (EEG) while participants walked on a treadmill and were given a side to side balance perturbation to the waist (Figure 1.). The experimental protocol was approved by the Marquette University Institutional Review Board and written informed consent was obtained from all participants. There were 60 balance perturbation trials, each starting with a period of standing at rest for 10 s, until a visual cue notified the start of the instrumented treadmill (Bertec, Columbus, Ohio) up to a self-selected comfortable walking speed ( $0.94 \pm 0.13$  m/s). A balance perturbation composed of a medial to lateral pull normalized to 7.5% of bodyweight was delivered to the subject's waist using a custom cable servomotor setup. The balance perturbation was timed to a randomly determined right heel strike (RHS) from 6 to 10 RHS after the start of the trial (implemented in LabVIEW, National Instruments, Austin, TX). Heel strikes were tracked in real time using dynamic center of pressure measurements obtained from the treadmill force plates (Walker 2013). Another visual cue 5 RHS after the perturbation signaled the stop of the treadmill and the end of the trial.



Figure 1. Instrumented treadmill and cable servomotor setup (A) and the wall projection shown to participants for the laser head tracking trial (B).

# 3.2.2 Data Acquisition

EEG signals were recorded using a 64 channel active electrode cap setup (Acticap, Brainproducts Munich, Germany) arranged in the modified 10-20 convention, sampled at 1000 Hz with a FCz reference (Synamps 2 amplifier, Compumedics Neuroscan Victoria, Australia) and filtered (bandpassed between 0.3 to 200 Hz and notch filtered at 60 Hz to remove line noise). Electrode impedance was held below 20 k $\Omega$ using high viscosity electrolyte gel (SuperVisc, Brainproducts). EMG signals were recorded using wireless electrodes (Trigno, Delysys Natick, MA) from the tibialis anterior (TA) and medial gastrocnemius (MG), sampled at 1000 Hz and bandpass filtered between 10-350 Hz. Kinematic data was recorded from the lower extremities at 200 Hz with an eight camera Vicon Mx motion capture system using reflective markers arranged according to the Plug-in-Gait model (Davis et al. 1991). Additional markers were used to monitor the trajectory of the head. EMG, kinematic, and force plate data from the instrumented treadmill were collected using Vicon Nexus software.

#### 3.2.3 Data Preprocessing

EEG data was preprocessed and analyzed using custom Matlab scripts (Matlab, Mathworks), in addition to the Fieldtrip, Brainstorm, and EEGLAB toolboxes (Oostenveld et al. 2011; Tadel et al. 2011; Delorme and Makeig 2004). Extremely noisy trials and channels were rejected according to measures of variance and z-score above a 2 standard deviation threshold. EEG signals were re-referenced to a whole head average reference, bandpass filtered from 1 to 100 Hz (6<sup>th</sup> order Butterworth), and epoched to the beginning of standing at rest and 5 RHS after the balance perturbation of each trial.

# 3.2.4 Artifact Characterization and Removal

Three conditions focusing on different prospective sources of noise were conducted for each subject before the main balance perturbation protocol: 1) motion artifact was accentuated by instructing participants to forcibly stomp their feet while walking  $(50 \pm 10.4 \text{ percent}$  increase in vertical ground reaction forces compared to normal walking, paired t-test: p = 0.0003), 2) exaggerated EMG activity of the face and neck was examined through a head tracking task where the participant was asked to concurrently track a randomized target projected in their forward field of view using a head mounted laser (Figure 1B), 3) followed lastly by a normal baseline walking condition. Independent component analysis (ICA) using the AMICA algorithm (Delorme et al. 2012) was then used to separate EEG channels within subjects into maximally independent components (IC) under the assumption that sources of artifact and true cortical activity were linearly mixed.

Consistent features in IC power spectrum, dipole location and scalp topography were observed across subjects and conditions. Power spectrums estimated using a Welch's periodogram included characteristics plausibly associated with artifacts, such as disproportionately elevated power in higher frequency bands suggesting EMG contamination from the neck/face, in addition to spectrums exhibiting large peaks at gait stepping frequencies and their corresponding harmonics (Figure 2A). These features were quantified by measuring the slope of the power spectrum and using a peak finding algorithm, respectively (2A). Several IC's presented improbable sources in the periphery or even outside of the cortex itself after single dipole locations were fitted using a 3-shell overlapping spheres forward model, ICBM152 brain atlas (Fonov et al. 2009), and Fieldtrip's DIPOLE\_FIT function (2B). Fitting a single dipole to IC's comprised of multiple sources may erroneously localize to a plausible region of the cortex. Dipoles inaccurately spatially averaged between multiple sources of activity were visually identifiable as a spread of local minima and maxima in the IC's scalp topography (Figure 2C). These topography maps were quantified by taking the standard deviation of the projected topography's derivative, which provided a simple approximation of the smoothness of the topography's surface.



Figure 2. Select independent components representative of consistent observations across subjects, and their corresponding features in A) power spectrum, with peaks and slope denoted in red, B) dipole location in Talairach coordinates marked in green, and C) scalp topography (Subject 1 - IC's 2, 10 and 36, hypothesized to correlate with motion artifact, EMG contamination, and true cortical activity are shown from left to right).

We hypothesized that these features could be used to separate IC's into groups associated with different aspects of noise such as motion artifact and EMG contamination. Independent components from the walking, stomping, and baseline conditions were clustered into groups according to the features we quantified in power spectrum, dipole location, and scalp topography using a k-means algorithm (Appendix A.1) implemented with the Scikit-learn Python library (Pedregosa et al. 2012). K-means clustering inherently divides datasets into unlabeled groups which must be independently categorized. The ground truth of each unlabeled cluster group was then estimated by computing the linear partial correlation (Pearson) between IC's and a new, separate set of features emphasizing motion artifact and EMG contamination. Specifically, a group's relation to motion artifact was assessed through correlation of head kinematics (head markers centroid position, velocity and acceleration) and ground reaction forces recorded from the instrumented treadmill (force and moments in the x, y and z directions), while their relationship to EMG artifact was evaluated through the correlation of peripherally located EEG channels under the assumption that electrodes such as TP9/TP10 (positioned over the mastoids) would likely contain higher EMG activity from the eyes, face, and neck (Figure 3) (Kline et al. 2015; O'Regan and Marnane 2013).



Figure 3. Electrode montage (modified 10-20 convention), with the peripheral electrodes Fp1/Fp2, FT9/FT10, TP9/TP10, PO9/PO10 used for EMG noise correlations denoted in orange.

The k-means clustering algorithm consistently separated IC's into significantly different groups favoring motion artifact correlations, EMG correlations, or neither source of noise – implying actual brain activity (Figure 4A). Partial correlations of the ICA components and artifact features were fitted to a repeated measures model using the cluster groups as predictor variables. Repeated measures MANOVA was applied separately for each cluster and multiple comparisons correction (Tukey-Kramer) was performed to determine how they significantly differed within and across the stomping, tracking and baseline walking conditions (Appendix A.2). A greater proportion of these IC's were found to correlate with motion artifact features in the stomping task, while a larger segment of IC's correlated with EMG features in the tracking task (Figure 4). Cluster groups were labeled and combined into brain activity, motion artifact, or EMG noise as determined from the partial correlations (Figure B). Independent components of

the main balance perturbation trials were then classified as belonging to brain activity, motion artifact, or EMG noise using a linear support vector machine (SVM) trained according to support vectors comprised of the initial, now clustered and labeled, set of power spectrum, dipole location, and topography features (Figure C and Appendix A.3).



Figure 4. Labeling of cluster groups from the Track, Stomp and Baseline pre-trials was determined by the partial correlations (strength denoted by greyscale) found between IC's (rows) and motion/EMG artifact features (columns) across all subjects. Cluster groups have been ordered and labeled by correlation similarity for ease of comparison.



#### A. Cluster IC features from pre-trials





C. Classify main balance trials with trained SVM



Figure 5. A select number of IC features from the stomping pretrial are visualized above, consisting of the power spectrum slope, scalp topography smoothness, and whether the IC dipole was localized inside the boundaries of a common cortex surface (15,000 vertices mesh, non-linear ICBM152 brain atlas). These features, in addition to others not visualized here, were clustered using the k-means algorithm, with the different groups

denoted by color (A). The ground truth (i.e. were any of these groups related to motion artifact, EMG noise, or real brain activity) of these cluster groups were then determined through the analysis of various partial correlations between IC's and measures such as head motion and ground reaction forces from the instrumented treadmill (B). Cluster groups found to be correlated with noise or probable brain activity were used to create support vectors to train a linear SVM. Finally, the trained SVM was used to classify IC's from the main, balance control trials as motion artifact, EMG noise, or brain activity (C).

#### 3.2.5 Data Analysis

Independent components classified as brain activity, motion artifact, and EMG artifact were grouped together and separately localized back onto the cortical source space using a constrained, minimum norm inverse solution, a boundary element method forward model (OpenMEEG), and a common cortical surface (15,000 vertices mesh, non-linear ICBM152 brain atlas). Three regions of interest (ROI) were selected based on combined segmentations from the ICBM152 atlas: frontal (rostral middle, superior, and caudal middle frontal regions), sensorimotor (M1S1) (precentral, postcentral and paracentral regions), and parietal (superior and inferior parietal, supramarginal, and precuneus regions). Time frequency decompositions of these ROI's were calculated using Mortlet wavelets (1 Hz central frequency, 2s full width half maximum), time warped to gait events (consisting of the following events: right heel strike (RHS), right toe off (RTO), left heel strike (LHS), left toe off (LTO), start and end of the balance perturbation), and smoothed in time using a Savitzky–Golay smoothing filter, before

being averaged across epochs. The time frequency spatial topography of the full cortical surface (i.e. each of the 15000 vertices) was calculated across epochs for the theta (5-7 Hz), alpha (8-12 Hz) and beta bands (15-30 Hz) using averaged time bins (100 evenly spaced bins between the start and end of the balance perturbation) to cut down on otherwise unwieldy file sizes (>1TB/subject). Power values of the ROI's and the individual vertices of the spatial topography were referenced to the baseline period of standing as a percent change in power.

#### 3.3 RESULTS

#### 3.3.1 Motion and EMG Artifact

Independent components were classified across subjects by SVM, with a majority of components assigned as EMG noise (69%), compared to 8% for motion artifact and the remaining 23% of components classified as real brain sources (Figure 6). The uniform distribution of classified components across subjects suggests that there was no subject specific bias.



Figure 6. The number of independent components classified as motion artifact, EMG noise, or real brain activity across all 10 subjects (distribution between individual subjects denoted by color).

EMG noise primarily consisted of higher frequency content in the gamma band (Figure 7) located posteriorly in the cortex (+49.7% increase in average parietal gamma power compared to brain activity, ANOVA: p=0.039). Motion artifact contained extremely high power content in lower frequencies throughout the cortex (+3006% increase in average theta power over all ROI's compared to brain activity, ANOVA: p=0.0025), tightly time-locked to heel strike in the theta, alpha and beta bands (10). The timing of motion artifact theta and alpha band peak power was found to be significantly

different from brain activity (ANOVA, theta: p = 0.022 and alpha: p = 0.0031) in the sensorimotor and parietal areas (Figure 8).



Figure 7. Motion and EMG group ensemble average of the frontal, sensorimotor, and parietal ROI's time frequency decompositions, normalized to percent change from baseline rest. Solid line represents the start and end of the balance perturbation, while the dotted lines represent right and left heel strike.



Figure 8. Motion artifact time series of the averaged theta, alpha and beta power for the frontal, sensorimotor and parietal ROI's. Box plots of the peak maximum and minimum timings across all subjects are displayed below each time series with median, averages and outliers denoted by lines, diamonds and crosses. The maximum and minimum ranges from the real brain activity time series box plots when available (no comparable maximum beta and minimum theta activity was observed) are indicated in light and dark grey, respectively.

#### 3.3.2 Brain Signals

Consistent patterns of brain activity were observed to be associated with the onset of the balance perturbation while walking. Specifically, balance perturbations during walking were associated with cortical power modulations in the theta, alpha and beta bands (Figure9). Theta band power increased greatly in the frontal, sensorimotor and parietal ROI's following the medial-lateral pull to the waist (a respective 88.6 ± 60.2%,  $164 \pm 141\%$ , and  $129 \pm 126\%$  increase in peak power compared to standing at rest, t-test: p<0.01), while a consistent pattern of desynchronization (decreasing power) was observed in the alpha and beta bands following heel strike.



Figure 9. Group ensemble average of the frontal, sensorimotor (M1S1), and parietal ROI's time-frequency decompositions, normalized to percent change from baseline rest. The solid line represents the start and end of the balance perturbation, while the dotted lines represent right (darker grey) and left (lighter grey) heel strike.

Timing and localization of theta, alpha and beta frequencies were characterized for the perturbation (Figure 10). The elevated theta band power observed during the balance perturbation appeared to begin in the parietal and sensorimotor areas before peaking in the frontal motor planning regions (Figure 6:  $3.19 \pm 0.15$ s,  $3.23 \pm 0.14$ s, and  $3.32 \pm 0.11$ s respectively), however neither the timing nor magnitude between regions were found to be significantly different (ANOVA, timing: p = 0.16 and magnitude: p = 0.35). Beta band desynchronizations were found to regularly follow toe off events in the gait cycle, while alpha band activity mirrored the timing of theta band resynchronizations and beta band desynchronizations (ANOVA, resync: p = 0.13 and desync: p=0.79). Both the theta and alpha band resynchronizations following the pull localized bilaterally across the entire cortex, while alpha band desynchronizations displayed laterality towards the right hemisphere compared to the bilateral localization in the beta band (Figure 11).



Figure 10. Time series of the averaged theta, alpha and beta bands for the frontal, sensorimotor and parietal ROI's. Box plots of the peak theta maximum, beta minimum, and alpha maximum/minimum timings for individual subjects are shown below each time series with median, averages and outliers denoted by lines, diamonds and crosses, respectively. Solid lines represent the start and end of the balance perturbation, while dotted and dashed lines represent heel strike and toe off gait events.



Figure 11. Time frequency spatial topography of the group ensemble averaged theta, alpha and beta bands at the 3.1 and 3.6 s time bins - masked to show only the activations for the frontal, sensorimotor and parietal ROI's.

# **3.4 DISCUSSION**

Significant theta band power modulations were observed bilaterally throughout the cortex following the start of the balance perturbation. This increase in theta power began in the parietal region of the cortex before moving anteriorly to the sensorimotor and frontal areas, however the timing was not found to be significantly different. A widespread beta band desynchronization, i.e. a decrease in power compared to standing baseline, was observed to modulate with gait cycle events, with timing consistently trailing toe-off. These power modulations were different in timing and magnitude when compared to motion and EMG artifact. Differences between the motion and EMG artifact themselves were also identified, with a consistent large magnitude motion artifact, suggesting great care be taken in deliberately removing motion-related noise from EEG recordings during walking.

The apparent "parietal first" timing of the theta modulation observed in this study is consistent with the role of the parietal cortex in integrating vestibular, proprioceptive, and visual sensory afferents before committing information anteriorly to the frontal and sensorimotor regions (Andersen et al. 1997). The parietal cortex is strongly associated with sensorimotor integration, translating perception into action through the coordination of different areas of the brain (Gottlieb 2007). These regions of the cortex then influence the motor response to a loss of stability, whether through the direct selection of optimal motor plans or more indirect changes to the general readiness of certain neuronal ensembles in preparation for a balance perturbation (J. V. Jacobs and Horak 2007; De Waele et al. 2001). The coarse spatial resolution of EEG, in addition to the smoothing applied to the time frequency decompositions may explain the lack of statistical significance we observed in this posterior to anterior theta timing.

We postulate that vestibular afferents, which would be especially pronounced during an unstable balance event, likely contribute to the cortex-wide spread of theta band power after the balance perturbation. In animals, there is a strong link between theta oscillations and the hippocampus - notably, peripheral vestibular lesions in rats have been shown to attenuate the power of these oscillations (Buzsáki 2002; Russell et al. 2006). Broad regions of the human cortex spanning the frontal, sensorimotor and parietal areas receive vestibular input, based on brain imaging in conjunction with electrical or caloric vestibular stimulation (Brandt, Dieterich, and Danek 1994; Fasold et al. 2002; Kahane et al. 2003; De Waele et al. 2001; Blanke et al. 2000). Similar modulations in cortical theta power have also been measured by EEG when stepping off a balance beam after a loss of balance, which would elicit comparable changes in sensory afferents (Sipp et al. 2013).

The large, widespread increase in theta band power may therefore reflect cortical processing of the abrupt change in sensory feedback, such as vestibular input, caused by the balance perturbation (Nielsen and Sinkjaer 2002). Although the exact timing of the pull to the waist was randomized across a period of several gait cycles, participants were aware that a perturbation would eventually occur, resulting in an anticipation of the pull in the latter portion of the experiment, which has been associated with slow brain potentials in other test paradigms (van Boxtel and Brunia 1994). Elevated cortical theta power has previously been observed in a complementary range of tasks including working memory, attention, and learning -- favoring complex sensorimotor integration paradigms and increasing notably with rising cognitive demands (Bland and Oddie 2001; Schacter 1977; Cruikshank et al. 2012; Klimesch 1999). This range of low frequency oscillations has also been measured by ECoG, and strongly correlates with higher frequency gamma power in the 80 to 150 Hz range throughout the human cortex, suggesting a potential source in the coordination of different areas of the brain (Canolty et al. 2006). Specifically, this coupling of theta - gamma frequency bands may modulate cortical excitability states, allowing slow, theta band oscillations a framework to rapidly

heighten the readiness of far flung local neuronal ensembles in response to external perturbations (Schroeder and Lakatos 2009; Schnitzler and Gross 2005).

This idea of large scale networks unifying the activity of disparate cortical regions is a compelling one and has been dedicated a substantial amount of research, particularly the concept of phase synchronization in different frequency bands providing a mechanism for linking nodes in a hypothetical cortical network (Varela et al. 2001). Large scale gamma synchronizations related to selective attention have been measured 240-380 ms after experimental cues, similar in timescale to the cortical activity we observed in response to the balance perturbation (Doesburg et al. 2008; Fell et al. 2003). Increased high gamma activity in general has been previously reported during walking, particularly in sensorimotor areas (Seeber et al. 2014; Seeber et al. 2015). Direct mapping of these connectivity networks as graphs have been observed to display "small world" network structures specific to theta and gamma band frequencies, more efficient than purely random pairings of graph nodes, and possibly giving rise to a functional structure for advance cognitive tasks such as maintaining balance in novel environments (Stam 2004; Fries 2009).

Direct measurement of high gamma power oscillations by EEG during walking remains complicated however by signal attenuation and myogenic contamination from the face and neck, which produces noise at high gamma frequencies. The majority of independent components across all subjects were consistently classified as EMG noise, indicating a wide variability of these artifacts, likely resulting from the continuous activation of different facial and neck muscles during gait (Seeber et al. 2015; McMenamin et al. 2010). Perhaps due to this intrinsic variability however, the averaged contribution of EMG artifact components did not appear to be strongly time locked to gait events and remained confined to high frequency ranges, simplifying the interpretation of lower frequency modulations. In contrast, the motion artifact group, which was correlated to head kinematics and force plate events, comprised a far smaller proportion of independent components, yet contained large power magnitudes. The phasing with heel strike in low frequencies implies that mechanical artifacts resulting from stepping and head motion are highly stereotyped across gait cycles. EEG recordings from cortically inert participants wearing a silicone cap have also been shown to exhibit similar frequency modulations tied to gait events (Kline et al. 2015). The high power of motion-based noise highlights the importance of adequately removing and interpreting results in light of these mechanical artifacts.

Several sophisticated processing techniques have previously been utilized to minimize noise in EEG signals of walking, primarily variations of blind source separation such as ICA or principle component analysis (PCA) used in the sliding windows of artifact subspace reconstruction (ASR) (Wagner et al. 2012; Bulea et al. 2015). Our results may provide some insight into the effectiveness of ICA in separating noise from brain activity, which has remained uncertain (Snyder et al. 2015). Specifically, the timing of the increasing theta power modulations after the balance perturbation revealed a much wider inter subject variability than the near identical groupings of the motion artifact theta modulations across subjects, which also trailed each heel strike, rather than solely the balance perturbation. In higher frequencies such as the beta band, we observed the widely reported desynchronization consistently modulating with the gait cycle (Gwin et al. 2011; Seeber et al. 2014). These differences in timing and magnitude across frequencies between independent components classified as brain activity versus artifact suggests that ICA may provide an effective method for differentiating noise in walking EEG signals.

The control of balance during walking has been theorized to require active cortical control. We observed theta band oscillations to modulate with balance perturbations consistent with this idea of supraspinal involvement. These modulations were observed to be significantly different in timing, frequency and magnitude compared to motion artifact and EMG noise, which we differentiated and classified using a combination of ICA, clustering, and SVM's. We believe that these techniques may further refine current methods used for the attenuation of noise recorded from EEG while walking.

# Chapter 4: Sensory deficits in myelopathy participants will lead to a shift in magnitude and phasing of balance related cortical oscillations while walking

# **4.1 INTRODUCTION**

In this study, we examined the impact of sensory loss on cortical oscillations underlying dynamic balance perturbations. To test the effects of sensory deficits on changes in cortical signals, we measured electroencephalography (EEG) during a balance perturbation to walking in people with cervical myelopathy, who have both sensory loss and deficits in dynamic balance control (Clarke and Robinson 1956). Increases in the theta band power of EEG have previously been measured following a loss of balance in healthy individuals (Hülsdünker et al. 2015; Sipp et al. 2013). The exact role of these low frequency oscillations, such as whether this widespread cortical activity is indicative of a motor control response or perhaps weighted towards integration of the various sensory afferents comprising a balance event, remains unclear. Exploring how and where these oscillations shift following altered sensory feedback in people with myelopathy may further discern the role of cortical theta modulations in postural control and their interplay with the more autonomous, sub-cortical structures typically associated with normal gait.

Balance-specific cortical oscillations have been observed to be widely distributed throughout the cortex. Frontal regions have been associated with a generalized cortical reaction to unexpected changes in sensory signals, often in conjunction with different aspects of attention, learning and error feedback (George Mochizuki et al. 2009; Mihara et al. 2008; Adkin et al. 2006). Posteriorly, the parietal cortex has been theorized to be involved in sensorimotor integration, and is likely to be important in balance perturbations considering the vestibular, proprioceptive and visual feedback (Gottlieb 2007; Andersen et al. 1997; Klimesch 1999). Theta band activity in particular, modulates with the loss of balance for both standing and walking. (Hülsdünker et al. 2015; Sipp et al. 2013). The broad distribution of cortical regions involved in dynamic balance and the association with theta power fluctuations has resulted in conjecture on the exact nature of these oscillations and their role in dynamic balance control.

Simple volitional movements have well characterized cortical patterns of activity consisting of power modulations in specific frequency bands. Beta band power corresponding with basic movements for example, has been thoroughly described in the sensorimotor cortex as a series of desynchronization (reduced power) and resynchronizations (increased power) (Cassim et al. 2001; Kilavik et al. 2013; Pfurtscheller, Stancák, and Neuper 1996; Pfurtscheller and Lopes da Silva 1999). These beta band oscillations decrease in magnitude following the attenuation of sensory feedback, from both acute, transient changes using vibration and chronic reduction in sensation resulting from spinal cord injury (Gourab and Schmit 2010; Müller-Putz et al. 2007). Changes in cortical beta band oscillations following altered sensory feedback may also translate to more complicated motor tasks such as maintaining balance after a perturbation while walking.

Walking while facing an imminent loss of balance requires a complex integration of several sensory afferents, in addition to the planning and anticipation of a motor plan. We believe that the lower limb sensory deficits presenting in individuals with myelopathy may provide a framework to address the role of cortical oscillations observed in walking after a lateral balance perturbation. Using a custom cable-servomotor system, we delivered a lateral pull to the waist of participants with cervical myelopathy during walking and measured cortical activity using high density EEG. We hypothesized that reduced sensory feedback in a challenging, whole body motor task such as maintaining stability in gait would exhibit similar changes in cortical oscillations previously observed in simpler motor paradigms isolated to single limbs.

#### 4.2 METHODS

### 4.2.1 Experimental Protocol

Ten cervical myelopathy subjects (4 males and 6 females, mean age 51.6  $\pm$  13.8), all post-surgery and capable of independently walking on a treadmill, and 10 healthy, age matched controls were recruited for this study (5 males and 5 females, mean age 50.2  $\pm$  12.3). Walking function was evaluated using a 10 meter walk test (myelopathy: 1.35  $\pm$  0.23 m/s, control: 1.43  $\pm$  0.22 m/s). Participants began each trial standing at rest for 10 s, until a visual cue notified the start of the treadmill up to a self-selected comfortable walking speed. On average, myelopathy participants chose a treadmill walking pace 50.5% slower than their over ground walking speed (0.66  $\pm$  0.17 m/s). The walking speed for controls was matched to their respective, age matched myelopathy participant (mean: 53% slower than their over ground walking speed).

A balance perturbation timed to a random left heel strike 6 to 10 steps after the start of the trial normalized to 5% of bodyweight was delivered to the subject's waist using a custom cable servomotor setup (Walker 2013). This balance perturbation was designed to accentuate center of mass sway by pulling the subject laterally away from the midline during left and right heel strike (i.e. laterally towards the left after LHS and towards the right after RHS) for one gait cycle. A visual cue after the perturbation signaled the stop of the treadmill and the end of the trial.

#### 4.2.2 Data Acquisition

Electroencephalography signals recorded from a 64 channel active electrode cap setup (Acticap, Brainproducts: Fs = 1000 Hz, FCz reference) were bandpass filtered between 0.3 and 200 Hz, and notch filtered at 60 Hz to attenuate line noise (Synamps 2 amplifier, Compumedics Neuroscan). EEG electrodes were arranged in a modified 10-20 convention and impedances kept below 20 k $\Omega$  using high viscosity electrolyte gel (SuperVisc, Brainproducts). Electromyography (EMG) signals were measured from the tibialis anterior (TA) and medial gastrocnemius (MG), in addition to force plate measurements sampled at 1000 Hz from the instrumented treadmill (Bertec, Columbus, Ohio) and kinematic data from an eight camera Vicon motion capture system.

Data were preprocessed and analyzed using custom Matlab scripts (Matlab, Mathworks) and the Fieldtrip, EEGLAB, and Brainstorm toolboxes (Oostenveld et al. 2011; Delorme and Makeig 2004; Tadel et al. 2011). Independent component analysis (AMICA: Delorme et al. 2012) was applied to the EEG signals to remove blink, EMG and motion artifact after classification using k-means clustering and a linear, support vector machine (refer to Aim 2 methods). Independent components classified as brain signals were localized back together into cortical source space using a boundary element method forward model (OpenMEEG) and a constrained, minimum norm inverse solution. Three cortical regions of interest (ROI) were selected based on combined segmentations from the ICBM152 atlas: frontal (rostral middle, superior, and caudal middle frontal regions), sensorimotor (M1S1) (precentral, postcentral and paracentral regions), and parietal (superior and inferior parietal, supramarginal, and precuneus regions). Time frequency decompositions of these ROI's were calculated using Morlet wavelets (1 Hz central frequency, 2s full width half maximum), time warped to gait events and smoothed in time, before being averaged across epochs. The spatial topography of the full cortical surface (i.e. each of the 15000 vertices) was calculated across frequency bands for the theta (5-7 Hz), alpha (8-12 Hz) and beta bands (15-30 Hz) using averaged time bins to cut down on otherwise unwieldy file sizes (>1TB/subject). Power values were then referenced to the baseline period of standing rest as a percent change in power. Multiple linear regression of the timing of theta (5-7 Hz), alpha (8-12 Hz), and beta (15-25 Hz) power maximum/minimum peaks after the balance perturbation were performed to
examine their correlation to different kinematic measures such as time to step width correction after perturbation.

#### 4.2.4 Kinematic Analysis

Center of mass (CoM) in the medial-lateral direction was calculated using numerical double integration of ground reaction forces (GRF) using the trapezoidal method (King and Zatsiorsky 1997). Double integration of GRF's has long been considered the gold standard in calculating CoM measurements but is often deferred in favor of a body segment model using motion capture due to limitations in capture volume from floor mounted force plates in a traditional gait lab and the difficulty of accurately estimating integration constants (Gutierrez-Farewik, Bartonek, and Saraste 2006). These limitations were ameliorated through the use of an instrumented treadmill offering force plate data for the entire length of the trial, in addition to providing known velocities. The integration interval consisted of the medial-lateral zero crossings of the center of pressure (CoP), under the assumption that CoP = CoM when the horizontal GRF is equal to zero. Integration constants were back calculated from the difference between the experimentally recorded CoP and estimated CoM, which were further verified with the known velocity of the treadmill. The initial velocity constant was assumed to be zero since each trial began at standing rest. The effect of the medial-lateral pull on calculated ground reaction forces was corrected by subtracting the force profile measured from load cells instrumenting the cables at the participant's waist. Finally, double integration center of mass calculations were validated with CoM measurements extrapolated from

the pelvis centroid trajectory determined by motion capture markers and the Vicon Plugin-Gait model (mean correlation:  $0.94 \pm 0.05$ , p < 0.0001).

$$CoM_{velocity} = \int GRF_x(t)dt \tag{1}$$

$$CoM_{position} = \int CoM_{velocity}(t) dt$$
 (2)

Where the integration constant,  $v_0$ , was initially set to 0.

Dynamic balance was characterized by estimating the margin of stability (MoS). This measure provides a simple estimate of stability while walking by examining center of mass in relation to base of support (BoS) over time (A L Hof, Gazendam, and Sinke 2005). Specifically, the dynamic center of mass was extrapolated from CoM position along with its associated velocity component, scaled to pendulum (i.e. leg) length, and compared to the base of support determined from the CoP (Figure 1). Situations where this extrapolated center of mass (XCoM) strays from the base of support may reflect periods of instability while walking (At L Hof 2008).

$$MoS = Min(BoS - (CoM + v/\omega_0)) \qquad \omega_0 = \sqrt{\frac{g}{l}} \qquad (3)$$

Where v = CoM velocity, g = gravitational constant, and l = leg length



Figure 1. Example single trial (Myelopathy Subject 1) demonstrating the calculation of margin of stability (MoS) from the extrapolated center of mass and base of support.

# **4.3 RESULTS**

Theta band power in the 5-7 Hz range was observed to modulate with the balance perturbation through an increase in power over the entire cortex for the frontal, sensorimotor and parietal regions of interest (Figure - Control:  $81.3 \pm 99.3$ ,  $82.9 \pm 91.6$ ,  $78.2 \pm 70.5$ , t-test p <=0.041. Myelopathy:  $89.9 \pm 89.1$ ,  $98.8 \pm 69.6$ ,  $89.9 \pm 65.3$ , t-test p <= 0.011). This large increase in theta power following the balance perturbation was delayed in the frontal cortical areas of myelopathy subjects (Control:  $0.37 \pm 0.27$  s,

Myelopathy  $1.27 \pm 0.44$  s, 2 sample t-test p = 0.00003). Spatially, this delayed frontal theta power was lateralized to the right hemisphere in myelopathy participants compared to the more bilateral distribution observed in healthy controls (Figure 2).



Figure 2. Group ensemble average of the time frequency decompositions from the frontal, sensorimotor and parietal regions of interest. Solid lines represent the start and end of the balance perturbation, while dashed lines denote heel strikes from the gait cycle.



Figure 3. Group ensemble time frequency spatial topographies of the control and myelopathy during their respective theta band maximums.

The myelopathy group was observed to walk with a larger baseline step width compared to controls (Control:  $171 \pm 21$  mm, Myelopathy:  $211 \pm 48$  mm, 2 sample t-test p = 0.028). Their base of support remained consistently greater than controls on average, only reaching parity during the actual step correction, where participants generally widened their step width in response to the balance perturbation (Figure ). This step width correction occurred earlier in controls, typically immediately after the start of the perturbation, while myelopathy participants widened their step width after the end of the

perturbation (Control:  $3.7 \pm 0.25$  s, Myelopathy:  $4.1 \pm 0.27$  s, 2 sample t-test p = 0.0071). The minimum margin of stability after the balance perturbation generally occurred earlier in controls, reflecting the trends seen in step width (Control:  $4.47 \pm 0.18$  s, Myelopathy  $4.69 \pm 0.25$  s, t-test p = 0.043).



Figure 4. The group ensemble base of support (mm) over the course of the balance perturbation trial is shown in orange for myelopathy participants and blue for controls. The percent change in step width and margin of stability from baseline walking are

shown below. Solid lines indicate the start and end of the balance perturbation, while dashed lines represent heel strike gait events.

A small, yet significant minority of trials in both groups consisted of a narrowing of step width in response to the balance perturbation (Figure ). A greater proportion of trials in the myelopathy group compared to controls were comprised of this decrease in base of support (Controls: 28% trials, Myelopathy: 40% trials), however individual participants varied greatly in their ratio of widening versus narrowing step width after the balance perturbation (Range: 3% - 90% narrowing SW trials). Controls modulated their center of mass with their base of support, while the myelopathy group's center of mass remained consistent regardless of their step width (XCoM widen versus narrow correlation, Controls:  $\rho = 0.77$ , Myelopathy:  $\rho = 0.92$ , p < 0.00001). Minimum margin of stability was delayed in time when step width narrowed in controls (wide/narrow minimum MoS  $4.39 \pm 0.2$  s/  $4.75 \pm 0.2$  s, t-test p = 0.0013), while a greater magnitude but no significant difference in timing of minimum MoS was observed in the myelopathy group (wide/narrow minimum MoS mean:  $-67.1 \pm 20\% / -100.1 \pm 28\%$  change from baseline, t-test p = 0.0087).



Figure 5. Group ensemble base of support (mm) split into trials where step width either widened or narrowed in response to the balance perturbation. The percent change in step width and margin of stability from baseline walking are also shown. Solid lines indicate

the start and end of the balance perturbation, while dashed lines represent heel strike gait events.

Time frequency decompositions controlling for step width response remained largely similar with the exception of frontal cortical areas in the myelopathy group (Figure ). Theta power modulations in myelopathy participants were observed to largely be limited to trials with a widening step width in the frontal cortex. No correlation in narrowing step width trials was observed between the timing of the step width correction and the timing of theta power peaks in the sensorimotor and parietal ROI's. A weak, yet significant positive correlation was found in these widening step width trials between the timing of theta band power peaks across all ROI's and the start of the step width correction in response to the balance perturbation (Figure ).



Figure 6. Group ensemble average of the time frequency decompositions from the frontal, sensorimotor and parietal regions of interest divided into trials where participants widened or narrowed their step width in response to the balance perturbation. Solid lines represent the start and end of the balance perturbation, while dashed lines denote heel strikes from the gait cycle.



Figure 7. Correlations from multiple linear regression of the timing of theta band modulation peaks in the frontal, sensorimotor and parietal regions of interest and the timing of step width corrections for trials with a widening base of support in response to the balance perturbation.

#### 4.4 DISCUSSION

Large increases in theta band power throughout the cortex modulated with lateral balance perturbations during walking. Theta band modulations in the frontal areas of the cortex were significantly delayed in time and displayed a more spatially lateralized cortical localization for participants with cervical myelopathy compared to age and speed matched, healthy controls. Participants generally responded to the lateral pull to the waist by either widening or narrowing their step width. The timing of these theta power modulations were significantly correlated with the initiation of a widening step width correction in response to the balance perturbation. We believe these results support a link between the modulation of low frequency cortical oscillations and sensorimotor integration.

The increase in theta power, which correlated with the onset of step width corrections, may represent the cortical integration of sensory signals used to determine a motor response for the lateral pull to the waist. Maintaining lateral stability has been theorized to require greater active cortical control when compared to simple, forward gait, which has been observed to retain stabilizing properties from the bipedal motion of the limbs themselves (Bauby and Kuo 2000; Slobounov et al. 2008). This reactive motor response to proprioceptive, visual, and vestibular feedback during an ongoing balance event could hypothetically range from direct central input to indirect mediation of reflexes in the leg and trunk (Nielsen and Sinkjaer 2002). Previous studies have found the excitability of these reflex pathways in the legs to modulate with transcranial magnetic stimulation at latencies consistent with cortical involvement, in addition to

direct measurements of cortical theta modulations associated with loss of balance using EEG (Yang and Stein 1990; N. Petersen et al. 1998; Sipp et al. 2013; Dietz, Quintern, and Sillem 1987).

The delayed frontal theta power modulations we observed in our myelopathy group may derive from reduced proprioceptive feedback, commonly presenting as a loss of joint position sense, two point discrimination and impairment of lower limb vibration perception in cervical myelopathy (Clarke and Robinson 1956). Normally, prolonged downward gaze while walking for healthy, young controls has been shown to be unnecessary during an unexpected balance perturbation to acquire sufficient visuospatial information for maintaining balance (Zettel et al. 2005). A reduction in proprioceptive feedback however, may motivate a greater reliance on longer latency visual feedback, collaborated by previous observations of myelopathy subjects displaying greater instability in walking after reducing visual information by darkening the surrounding room (Drew et al. 2008; Dvorak, Sutter, and Herdmann 2003). Spatially, a visual processing bias may also explain the shift in balance related theta power localization we found from bilateral, medial areas near the sensorimotor cortex to more lateralized, posterior regions of the brain such as the occipito parietal cortex in participants with myelopathy (Patla 1997). Similar reorganizations of cortical activity have been recorded after incomplete spinal cord injury, including posterior shifts in motor activations and a broader, diffuse topography of motor related beta oscillations (Gourab and Schmit 2010; Raineteau and Schwab 2001; Kokotilo, Eng, and Curt 2009).

Less precise foot placement, which could reasonably be assumed after reduced proprioceptive feedback, has been shown to lead to a wider step width in gait (At L. Hof

et al. 2007). Our myelopathy subjects also had a corresponding delay in minimum margin of stability, suggesting that the delayed timing of cortical theta oscillations may have resulted from a later loss in balance due to a widened baseline step width. The significantly greater pre-perturbation step width we observed in myelopathy participants compared to controls may be a compensatory motor strategy to minimize deficits in sensory information by prolonging the window where a motor correction to a perturbation could still successfully prevent a fall. Delayed somatosensory evoked potentials in the leg area of the motor cortex have been measured, even in myelopathy patients with no clinical signs of lower limb weakness (Masur et al. 1989). A general widening of baseline step width would provide greater leeway in keeping their center of mass within the base of support during a lateral perturbation, regardless of any shortfalls in motor weakness or sensory feedback (A L Hof, Gazendam, and Sinke 2005). Comparable gait abnormalities in step width have previously been found in patients with cervical myelopathy and several other populations with neurological impairments resulting in motor and sensory deficits such as stroke and multiple sclerosis (Kuhtz-Buschbeck et al. 1999; Sosnoff, Sandroff, and Motl 2012; G. Chen et al. 2005).

In general, participants were observed to either widen or narrow their step width in response to the lateral balance perturbation, favoring the former. Trials consisting of a widening base of support tended to initiate a step width correction before the start of the balance perturbation, implying a degree of anticipation. Although the exact heel strike coupled to the lateral pull was randomized from trial to trial, participants could still heighten vigilance and plan for the perturbation in advance, which modulates cortical activity in preparation for anticipated instability (Jesse V. Jacobs et al. 2008; G. Mochizuki et al. 2010). The markedly wider baseline step width in participants with myelopathy was in contrast to their tendency to narrow their step width following the pull to the waist in a larger percentage of trials compared to controls. Narrowing the base of support would require compensating proximal adjustments such as with the trunk, consistent with changes in XCoM in controls but not in our myelopathy subjects (Bloem et al. 2000; Horak 2006). Notably, decreased medial lateral trunk variability has been linked to deficits in balance control for older adults (Moe-Nilssen and Helbostad 2005).

The failure of cortical theta activity to modulate with the balance perturbation in narrowing step width trials for our myelopathy participants provides evidence that these theta oscillations serve a role in successfully executing an optimal motor response to losses in stability. The inability of our myelopathy participants to adjust their XCoM with the direction of their step width correction was also accompanied by the absence of an anticipatory stepping correction preceding the balance perturbation and a greater loss of stability according to MoS, suggesting that the narrowing of step width in myelopathy participants was not an alternative motor strategy but an inaccurate estimation of perturbation timing. Similarly, narrow step width and decreased step width variability has previously been associated with the likelihood of falling (Owings and Grabiner 2004; Brach et al. 2005; Guimaraes and Isaacs 1980). A mistiming of the perturbation would explain the suboptimal loss in balance found in these narrowing step width trials comprised of both a larger magnitude in MoS as well as a delayed return to baseline MoS. Our results support the hypothesis that active cortical control is a necessary part of maintaining lateral balance during walking.

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In all likelihood, it is a combination of factors reflecting the multifaceted requirements of stable walking rather than a singular difference in stepping characteristics that explains the changes in cortical oscillations we observed in myelopathy participants. The fear of falling itself for example, has been linked to wider step width during baseline gait, and the older age of our participants would be expected to contribute to balance deficits as well (Maki and McIlroy 2007; Woollacott and Tang 1997). Although we found no significant differences in walking speed from the 10 meter walk test, the wider baseline step width in our myelopathy participants would come at a substantially increased mechanical and metabolic cost (Donelan, Kram, and Kuo 2001). Current standardized functional assessments of myelopathy such as the Nurick scale and Japanese Orthopaedic Association (mJOA) scoring system involve coarse, qualitative measures of sensory and motor deficits. Further research into more quantitative measures of function in myelopathy patients is needed to reveal the differences we observed in step width variability and suboptimal losses of balance (Salvi, Jones, and Weigert 2006). The delay in theta modulation timing and changes in cortical localization we observed in myelopathy volunteers for instance may possibly be used as a functional balance metric. Training paradigms utilizing a similar lateral perturbation may reveal whether these changes can be normalized as patients acclimatize to the balance task or if these cortical differences are symptomatic of permanent underlying changes in cortical structure.

# Chapter 5: Integration of Results

## 5.1 SUMMARY

Changes in patterns of movement related brain activity were observed following attenuation of sensory feedback in simple, volitional movements and within the framework of a dynamic balance control task during walking. We measured a significantly decreased beta power ERS (increasing power) associated with simple ankle dorsiflexion after prolonged vibration of the TA. Significant theta band power modulations were observed bilaterally throughout the cortex following the start of lateral balance perturbations during walking. These power modulations were different in timing and magnitude when compared to spectrograms comprised of independent components classified as motion and EMG artifact. Furthermore, differences between the motion and EMG artifact themselves were determined, with the consistent yet extreme magnitude of motion artifact time frequency content suggesting great care be taken in deliberately removing motion related noise from walking recordings. Balance related theta band modulations in the frontal areas of the cortex were significantly delayed in time and displayed a more spatially lateralized cortical localization for participants with cervical myelopathy compared to age and speed matched, healthy controls. The delayed frontal theta power modulations we observed in our myelopathy group may derive from reduced proprioceptive feedback or simply from a later loss in balance due to a widened baseline step width. We believe these results support a link between the modulation of cortical

oscillations and sensorimotor integration, in addition to providing evidence that active cortical control is a necessary part of maintaining lateral balance during walking.

# 5.2 THE CASE FOR CORTICAL OSCILLATIONS

So what do these cortical oscillations fundamentally mean?

Oscillatory activity has been found in virtually every part of the nervous system, from subcortical central pattern generators in the spine, to deep brain areas such as the thalamus (Jones 2000; Dimitrijevic, Gerasimenko, and Pinter 1998). Whether in primitive assemblies of the brainstem or the most convoluted premotor areas of the neocortex, synchronous neuronal activity at various frequencies have been well established as a routine and integral working of these structures (Bland and Oddie 2001; Maki and McIlroy 2007). Furthermore, these oscillations have been found to modulate with specific, functional actions such as the simple motor execution and more complicated responses to a balance perturbation while walking found in this dissertation, in addition to the vast amount of other experimental paradigms found in literature (Koelewijn et al. 2008; Kilavik et al. 2013; Lee 2003; Hari and Salmelin 1997).

Taken together, there is strong evidence that these phase synchronizations provide a framework for large scale communication of different areas of the brain. Theta and gamma band frequencies specifically, have been mapped to networks exhibiting properties of small world networks, a connectivity scheme much more efficient than a purely random pairing of brain regions, and possibly giving rise to a functional structure for higher cognitive tasks (Stam 2004; Fries 2009). The mechanism behind integrating different sensory modalities, motor plans and execution needed during the balance paradigm of this dissertation is likely found in these widespread cortical oscillations and their resulting modulations.

# **5.3 FUTURE STUDIES**

One of the main limitations in the use of myelopathy subjects as a model for sensory deficits is the limited nature of existing cervical myelopathy assessments. Common metrics such as the Nurick Criteria and the Japanese Orthopaedic Association score provide at best, a rough approximation of function, and are based on qualitative observations from the patient or physician (Dvorak, Sutter, and Herdmann 2003; Salvi, Jones, and Weigert 2006). The large variability of motor and sensory deficits presenting in patients with cervical myelopathy highlights both the difficulty and importance of rigorously quantifying functional deficits, especially when inferring possible sources for the changes we measured in brain activity (Clarke and Robinson 1956). Standard metrics for other neurological disorders may be adapted such as the Fugl-Meyer test for stroke or generalized measures of gait and balance such as the Dynamic Gait Index, Romberg and Berg Balance test (Bogle Thorbahn and Newton 1996; S.L. Whitney, M.T. Hudak, and G.F. Marchetti 2000; Fugl-Meyer et al. 1975).

The balance paradigm consisting of a medial-lateral pull is open to several modifications that may provide further insights into cortical balance control. Simply

adding random catch trials where no balance perturbation is applied would provide an interesting reference to further investigate motor anticipation and vigilance. Applying a continuous perturbation rather than a discrete, single pull may offer an interesting framework to observe cortical adaptations to the medial lateral pull. Any long term adaptations may be also useful in the future for training myelopathy subjects to walk with a more efficient, reduced step width than the comparatively wide baseline, step width we observed during our study.

Further possible refinements in the noise reduction techniques we applied include both the labeling of clusters and with the classifiers used to segment independent components themselves. Additional types of baseline noise characterization trials may provide a more accurate separation of feature clusters, such as the inclusion of a continuous lateral perturbation pretrial. Noise in these baseline trials may also be further isolated by having participants wear a nonconductive layer between the EEG electrodes and the scalp (Snyder et al. 2015; Kline et al. 2015). While the performance of various types of popular classifiers in small datasets is arguably indistinguishable, there may be some value in the use of transparent classifiers such as decision trees, compared to the black box nature of the SVM's we utilized (Meyer, Leisch, and Hornik 2003). With advances in both hardware and cloud storage capacities, the creation of an open access database of labeled, experimental EEG data would be cost effective, foster collaboration, and facilitate the development and reproducibility of novel methods. The same principles for classifying independent components used in this dissertation could easily be applied to a wide variety of different EEG paradigms with access to appropriate training sets. Wide enough adoption of providing open access to datasets and the resulting size of

available EEG data would also allow new, interesting avenues of study such as non-linear classification with neural networks.

Deep learning neural networks are currently a particularly promising area of machine learning, making tangible impacts in varied applications from natural language processing to artificial intelligence engines for strategy games. If oscillatory behavior, as this author believes, is indeed a fundamental mechanism for the integration of cortical networks, applying such concepts could lead to interesting implications in these neural nets composed of many hidden layers. Mimicking phase synchronizations for instance, may open new avenues to allow integration of different models, prevent overfitting, and provide a roadmap for a more universal application of neural nets.

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## **APPENDICES**

## A.1 K-means clustering

The K-means algorithm provides a straightforward, yet robust method of clustering features according to Euclidean distance. The features we defined in power spectrum, dipole location, and scalp topography (Figure 1-2) were first demeaned and scaled to unit variance (0 - 1). The initial, a priori number of clusters, k, was then chosen based on maximum silhouette score, a measure of how well separated a given number of clusters is based on their sample similarity (Figure 1A).

Silhouette Coefficient = 
$$\frac{(d_{nc} - d_{ic})}{\max(d_{ic}, d_{nc})}$$

where  $d_{ic}$  = mean intracluster distance and  $d_{nc}$  = mean nearest cluster distance

Starting from this initial cluster number k, we evaluated the correlations between ICA components and artifact features of several cluster sizes for all 3 conditions. Note how cluster sizes that are too small or large lead to cohesive groups of features being erroneously combined or split up, demonstrating the importance of independently assessing the ground truth of cluster labels. For instance, the group containing motion artifact features in the k = 5 condition divides up into multiple cluster groups combined with EMG activity in the k = 4 cluster size condition (Figure B).



Figure 1. Mean silhouette coefficients for different cluster sizes for the k-means algorithm (A), along with the clustered independent component groups and their correlations with motion/EMG artifact features when varying the number of clusters from 4 to 6 for the baseline walking condition.

## A.2 Cluster evaluation

Independent component groups clustered with the k-means algorithm were evaluated using a repeated measures MANOVA of the correlations between IC's and artifact features such as head marker velocity or ground reaction forces. Multiple comparisons of different clusters within the stomping, tracking and baseline walking conditions indicated that the k-means algorithm separated components into meaningful groups related to motion and EMG artifact (Figure 2). For example, cluster 0 was significantly different from all other clusters related to EMG or motion artifact in the stomping condition, implying real brain activity, while cluster 4, heavily correlated to motion artifact, was found to be significantly different from all other clusters in the stomping and baseline walking conditions when only using motion artifact features. Multiple comparisons of different clusters across the stomping, tracking and baseline walking conditions implied that cluster groups related to similar types of artifact were also statistically similar to one another across conditions (Figure 3). For instance, the groups related to motion artifact (S4, T4, W4) were determined to be statistically similar across conditions. These comparisons were then used to combine similar groups across conditions into groups of features related to motion artifact and EMG artifact, or real brain activity (related to neither source of noise).



Figure 2. Repeated measures MANOVA p-values for multiple comparison between the correlations (motion, EMG, and all correlations) of different cluster groups within the stomping, head tracking and baseline walking conditions.



Figure 3. Repeated measures MANOVA p-values for multiple comparison of cluster groups across the different stomping, head tracking and baseline walking conditions.

## A.3 Linear SVM classifier

A linear, support vector machine was implemented using the Sklearn Python library to classify the main balance perturbation trial IC's as motion artifact, EMG artifact, or real brain activity (Figure 4). Features previously clustered using a k-means algorithm and then combined into significant groups related to brain or artifact correlations were used as support vectors to train the SVM. We empirically found optimal parameters (error term C, gamma term for non-linear RBF kernel, etc) for the SVM using a grid search and determined that a linear SVM provided a robust classifier for EEG independent components.



Figure 4. Example of independent component classification by SVM for a single subject (Subject 1).