CORTICAL ACTIVITY OF THE SENSORIMOTOR SYSTEM IN PARTICIPANTS WITH CHRONIC ANKLE INSTABILITY

by

Christopher John Burcal

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Approved by:

_____
Dr. Tricia Hubbard-Turner

_____
Dr. Erik Wikstrom

_____
Dr. Abbey Thomas Fenwick

_____
Dr. Kenneth Bost

_____
Dr. Mark Clemens

_____
Dr. Didier Dréau

_____
Dr. Mark Faust

ABSTRACT

CHRISTOPHER JOHN BURCAL. Cortical activity of the sensorimotor system in participants with chronic ankle instability. (Under the direction of TRICIA HUBBARD-TURNER)

Patients with chronic ankle instability (CAI) exhibit a wide variety of sensorimotor deficits. These include impairments in feed-forward sensorimotor control (i.e. motor planning) as well as feed-back sensorimotor control, which pertains to refining ongoing movements. Researchers have recently begun to investigate the underlying cause of these impairments, identifying a decreased level of excitability in the primary motor cortex. However, it remains unclear if these constraints reflect large scale changes in sensorimotor control, and if they can be modified through therapeutic intervention. Therefore, our aim was to determine if impairments in feed-forward and feed-back sensorimotor control could be established in CAI patients using electroencephalography (EEG), and if these are improved through balance training. In Chapter 3, we compare EEG-derived measures of feed-forward and feed-back sensorimotor control between CAI patients and matched controls during a voluntary leaning task. In chapter 4, we assess feed-forward cortical activity during a dual-to-single-limb transition (DSLT), a task in which CAI patients have altered neuromuscular control. In chapter 5, we assess whether or not completing 4-weeks of an established balance training program can improve cortical measures of sensorimotor function in these patients. Along with traditional measures of balance, we assessed feed-forward cortical activity during a DSLT task before and after balance training. We did not identify any differences in EEG measures between CAI patients and uninjured controls during either task. Similarly, balance

training did not result in differences in feed-forward activity, however links were established between balance improvements (i.e. feed-back sensorimotor control) and feed-forward cortical activity.

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LIST OF ABBREVIATIONS

CAI	chronic ankle instability
LAS	lateral ankle sprain
EEG	electroencephalography
ERSP	event-related spectral perturbation
ERD	event-related desynchronization
ERS	event-related synchronization
BP	bereitschaftspotential
MRCP	movement-related cortical potential
ERP	event-related potential
MP	motor potential
MMP	movement monitoring potential
TMS	transcranial magnetic stimulation
IdFAI	identification of functional ankle instability
FAAM	foot and ankle ability measure
ADL	activities of daily living
SEBT	star excursion balance test
COP	center of pressure
BT	balance training
DSLT	dual-to-single limb transition
AP	anterior-posterior
ML	medial-lateral
GRF	ground reaction force
ACL	anterior cruciate ligament

ACL-R	anterior cruciate ligament reconstructed
TNS	time to new stability
Mx	anterior-posterior moment
My	medial-lateral moment

CHAPTER 1: PROPOSED RESEARCH

1.1 Background and Significance

Lateral ankle sprains represent the most common athletic injury, accounting for 15% and 20% of all injuries reported in collegiate[3] and high school sports, respectively.[4] The financial burden of these injuries are also often overlooked, and estimated to be around $2 billion in 1984 alone,[5] equating to over $4.5 billion today after a consumer price index adjustment. These injuries are often written off as innocuous and as a result receive less attention from the patient and/or healthcare provider, evidenced by the fact that less than 50% of individuals who sprain their ankle seek medical attention.[6] Conservative estimates suggest that approximately 1 out of every 3 individuals who sustain a lateral ankle sprain develop some form of chronic ankle instability (CAI),[7] a condition characterized by complaints of the ankle 'giving way' or feeling unstable.[8,9] The underlying cause of this condition is unclear, although it is believed to be due to a less than optimal healing response and/or improper post-injury adaptations following a lateral ankle sprain. Those that do not develop CAI are referred to as copers, and their inclusion in research assists greatly in describing the etiology of CAI.[10] Research has shown that CAI has a profound impact on a patients overall health and function,[11-13] as well as sensorimotor function.[11] Proper function of the sensorimotor system relies on an intact sensory and motor system but those with CAI have difficulty with sensory tasks such as kinesthesia,[14] as well as detecting both vibrotactile[15] and light touch[16] stimuli on the plantar surface of the foot relative to uninjured controls. The motor system is also impaired as spinal-level adaptations in motoneuron activation in the soleus and peroneus longus have been observed.[17] As the sensorimotor system often operates as a continuous

loop where sensory information refines motor output,[11] unreliable kinesthetic sensory information could result in misplacement of the foot. Altered motor programs could then result in a vulnerable position of the foot during gait, potentially leading to re-injury. Sensorimotor control can be divided into two subsets: feed-back and feed-forward strategies. Feed-back strategies range from simple perturbation reactions to continuously modified movements such as gait. Feed-forward strategies rely on the central nervous system (CNS) pre-planning movement.[11] Virtually all movement employs both of these strategies to accomplish the goals of the sensorimotor system, with feed-forward often preceding feed-back control.[11] Continuous tasks such as static balance and gait are often used to assess feed-back systems. Differences in kinetic and kinematic outcomes among uninjured controls, copers, and CAI participants in these tasks all provide evidence of sensorimotor dysfunction in the CAI population.[14,18-21]

Analysis of discrete tasks such as gait initiation[22] and transitioning from dual-limb to single-limb (DSLT)[1,23] have provided evidence of altered feed-forward deficits in CAI patients relative to uninjured controls, suggesting a more constrained and conservative feed-forward control mechanism. Both tasks require a stereotyped motor behavior known as an anticipatory postural adjustment (APA) that prepares the individual for a destabilizing event such as decreasing the base of support during the DSLT or the beginning of the swing phase of gait.[22,23] Additionally, Van Deun, et al.[1] reported muscle onset times to occur after the onset of movement during a DSLT, adding further evidence of feed-forward sensorimotor dysfunction in CAI patients.

Clinically, a CAI patient may experience improvements in sensorimotor function through focused therapeutic exercise prescription and balance training protocols.[24] Such protocols

are designed with an overall goal of stressing the sensorimotor system and practicing the solution of movement problems (e.g. how to optimally time and contract muscles in order to hop from one target to another while maintaining stability).[25] Central adaptations as a result of balance training are thought to decrease cortical control of movement, placing more emphasis on the more automated controllers such as the cerebellum and reticular formation (Figure 1).[26] Decreasing the cortical resources required for movement should allow for more cortical resources to be used towards ongoing working memory functions or tasks (e.g. situational awareness during sports). Dual-task investigations have shown that participants with CAI have impaired balance when completing working-memory tasks, which may indirectly suggest more cortical involvement in balance in those with CAI.[27,28] The results of balance training in a CAI population suggest that large improvements in feed-back sensorimotor control can be achieved,[24] however two key pieces of information remain unclear: 1) if feed-forward sensorimotor control is improved, and 2) if improvements are related to changes in cortical activity.

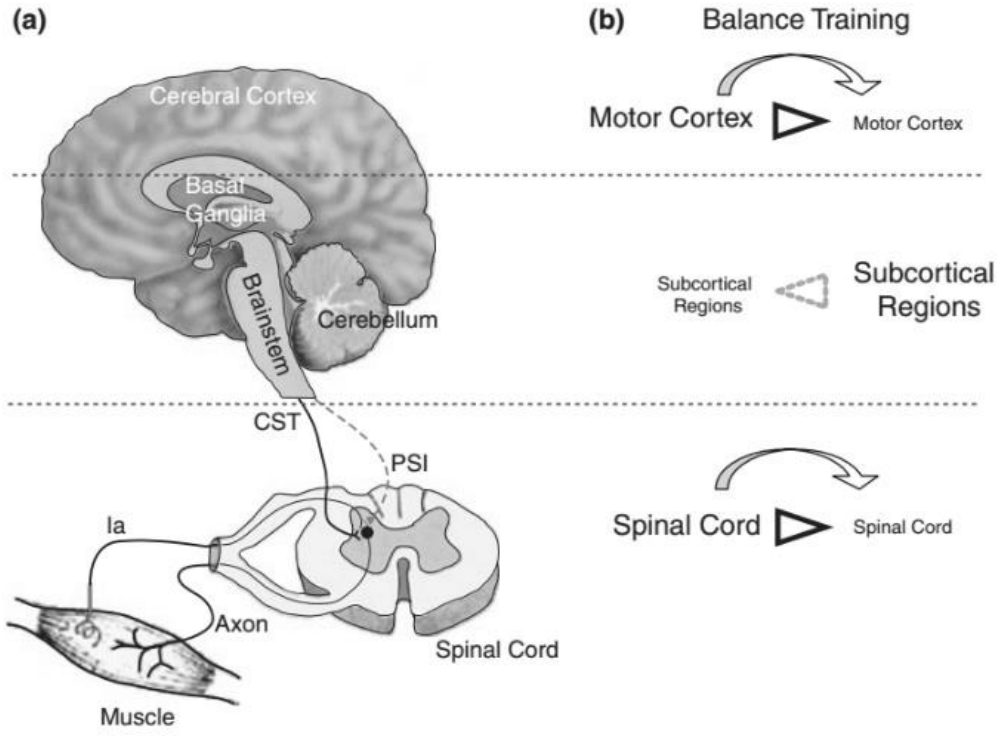

Figure 1: Summary of proposed CNS adaptations to balance training. A: Structures involved with sensorimotor control. B: After balance training the motor cortex and spinal cord have a decreased role in sensorimotor control, placing a higher emphasis on subcortical control. Adapted from Taube et al.[26]

Previous research in sensorimotor control has seen researchers draw inferences regarding the central mechanisms involved with CAI development based on peripheral sensorimotor outcomes reported in the literature. For example, Wikstrom et al.[29] and Hass et al.[22] reported altered motor control strategies in those with CAI during gait initiation and termination through center-of-pressure analysis. These investigators were the first to identify adaptations in tasks that have been associated with specific areas of the central nervous system (CNS), the supplementary motor area and pre-supplementary motor area, respectively, based on fMRI data.[30] Since then, a limited number of investigations have attempted to directly measure CNS function in those with CAI.[31-34] For example, Pietrosimone & Gribble[33] evaluated the resting motor threshold of the

motor cortex controlling the peroneus longus muscle with transcranial magnetic stimulation (TMS) and identified higher bilateral motor thresholds in those with CAI suggesting deficits in corticomotor excitability. Needle et al.[32] demonstrated increased cortical activity, as measured with electroencephalography (EEG) as ankle joint loading increased but no differences were identified among controls, copers and those with CAI. The increase in cortical activity was identified with an increase in event-related desynchronization (ERD), an outcome which presents itself as a percent change from baseline recordings within a specific frequency bandwidth during an event.[35] This ERD increase suggests an increase in the cortical activity relating to the event in question, meaning an individual requires more neural resources to process the sensory information associated with the task.[36] While these recent investigations have advanced our understanding of CNS dysfunction in those with CAI, the results are limited because both test protocols were non-weight bearing and neither captured cortical activity during a motor task (i.e. maintenance of postural control) known to be impaired in those with CAI or capable of evaluating an individual's risk of injury.

Cortical contributions to postural control have been quantified in uninjured controls using experimental protocols that incorporate both internal (e.g. forward leaning or rhythmic sway) and external postural perturbations.[2,37-41] These results indicate that the sensorimotor cortex plays a role in detecting limits of stability, as evidenced by a: 1) distinct negative deflection of EEG signals prior to the onset of oscillatory anterior-posterior sway, referred to as the motor-related cortical potential (MRCP) and 2) burst of Gamma activity (30-50 Hz) in the sensorimotor cortex prior to a compensatory posterior sway once the anterior limit of stability was reached.[41] These findings have been

suggested to be the neural correlates of anticipatory postural adjustments,[41] the phenomenon that 'primes' the individual for a postural disturbance and has been shown to be altered in those with CAI.[22,29] The MRCP is a widely studied motor potential that always precedes a self-initiated movement, characteristic of activity in the supplementary motor area and premotor cortex, areas that may be altered in those with CAI.[29,42] Increased ERD is often reported in the Alpha (8-12 Hz) and Beta (14-25 Hz) bandwidths during preparation for and execution of movement, representing feed-forward cortical control.[2,35,41,42] Decreased time-to-boundary scores in those with CAI[43] may be due to delayed recognition of an anterior limit of stability, a precursor of Gamma activity bursts, which have been linked to feed-back sensorimotor control.[2,41] Despite the obvious connections between cortical outcomes associated with the maintenance of postural control and postural control impairments in those with CAI, no research has attempted to quantify cortical activity during a weight-bearing task in those with CAI or copers. This limits our understanding of how lateral ankle sprains and CAI can alter CNS function, ultimately impeding our ability to develop effective evidence-based therapeutic interventions for the most common musculoskeletal injury sustained during sport and physical activity. This investigation represents the beginning of our understanding of the functional adaptations in the CNS as a result of a single or recurrent ankle sprain.

1.2 Specific Aims

Given the established feed-forward and feed-back sensorimotor deficits in CAI patients, I propose the following aims:

Specific Aim 1: To assess and evaluate differences in EEG measures of cortical activity during discrete tasks relating to sensorimotor control among uninjured controls, copers,

and participants with CAI. This will be accomplished by comparing EEG outcomes during two different tasks: 1) a voluntary leaning task that requires an individual to lean in one of three directions (forwards, towards injured/dominant limb, away from injured/dominant limb) and then return to starting position when the participant reaches his/her limits of stability, and 2) a transition from dual to single limb stance (DSLT). This aim was made possible through research grants awarded by the National Athletic Trainers' Association Research and Education Foundation (leaning task, see Appendix 2) and the Mid-Atlantic Athletic Trainers' Association (DSLT task, see Appendix 3).

The objectives for this aim are to:

1. Obtain EEG measures of cortical activity relating to feed-forward sensorimotor control.
2. Obtain EEG measures of cortical activity relating to feed-back sensorimotor control.
3. Compare EEG measures among groups to determine group differences.
4. Compare EEG measures within coper and CAI groups to determine if injury history, severity, and/or patient-reported outcomes are related to cortical activity.

I hypothesize that participants with CAI will display greater cortical activity relative to controls and copers during feed-forward (SA1a) and feed-back postural control (SA1b). I hypothesize that cortical activity will not differ between controls and copers (SA1c). Additionally, I hypothesize that movement toward, or a transition onto, the more severely injured limb (CAI) or injured limb (coper) will require more cortical activity than the less severely or non-injured limb (SA1d). Further, I hypothesize that patient-reported outcomes of perceived disability and injury severity will positively relate to cortical activity (SA1e).

Specific Aim 2: To evaluate the adaptations in the cortical activity of the sensorimotor system after completion of a balance training program in participants with CAI. This will be accomplished by comparing EEG measures of cortical activity before and after completion of a validated balance training protocol for CAI patients.[24] Additional measures such as instrumented force platform balance trials and clinical balance tests will be collected for validation. This aim was made possible through a research grant from the Mid-Atlantic Athletic Trainers' Association (see Appendix 3).

The objectives for this aim are to:

1. Compare baseline EEG measures to post-intervention EEG measures in participants with CAI.

2. Examine if a relationship exists between the change in EEG measures to change in sensorimotor function evaluated by clinical and instrumented analyses.

I hypothesize that cortical activity during a DSLT will decrease following balance training (SA2a). I further hypothesize that change in EEG measures will positively relate to change in clinical and instrumented balance performance (SA2b).

1.3 Experimental Design and Methods

1.3.1 Experimental Design

Two experiments were conducted, each consisting of a unique motor task that was used to evaluate the cortical contributions to sensorimotor control.

Experiment 1 utilized a cross-sectional design wherein three groups of participants (controls, copers, and CAI) were compared both within and among groups for three directions of self-initiated sway. Our independent variables are group (controls, copers, and CAI), and sway direction (anterior, medial-lateral towards and away from the

involved/matched limb [MLi and MLu, respectively]). Dependent variables include amplitude of MRCP at Cz (μV) and ERD % change at Cz and CPz (Alpha, Beta, and Gamma bands).

Experiment 2 was broken into parts 2a and 2b. Experiment 2a utilized a cross-sectional design wherein three groups of participants (controls, copers, and CAI) were compared both within and among groups during a DSLT task. Our independent variables are group (controls, copers, and CAI) and limb (transition towards the involved/dominant limb, and transition towards the uninvolved/nondominant limb [Ti and Tu, respectively]). Dependent variables included ERD% change at Cz and CPz (Alpha and Beta bands), and the time to stability during the DSLT.

Experiment 2b used a repeated measures design in the CAI group before and after completing a validated balance training protocol.[24] CAI participants from Experiment 2a completed a 4-week progression-based balance training protocol and then repeated the DSLT testing 24 hours and 7-days after completion of the balance training protocol. Independent variables were Time (pre-test [Experiment 2a], 24-hours post-completion [posttest 1], and 7-days post-completion [posttest 2]). In addition to the EEG and EMG dependent variables from Experiment 2a, time-to-boundary minima (AP and ML mean and standard deviation), and star excursion balance test (SEBT) normalized reach length in the anterior (SEBT-A), posteromedial (SEBT-PM), and posterolateral (SEBT-PL) directions were assessed over time.

1.3.2 Participants

Volunteers were recruited from the UNC Charlotte student body. A total of 60 participants were recruited for each experiment, split into three equal groups of 20.

Volunteers were recruited between the ages of 18 and 35, and represented a young adult population of all levels of physical activity. Participant demographics and injury history were been collected prior to informed consent with IRB approval (IRB Protocols 15-02-02 and 11-15-06), and informed consent was obtained once the participant reported for testing. We defined uninjured controls as individuals with no history of an ankle sprain to either ankle, a score of <11 on the Identification of Functional Ankle Instability (IdFAI) and >99% and 97% on the Foot and Ankle Ability Measure (FAAM) and FAAM-Spor t (FAAM-S), respectively.[44-46] Copers were defined as individuals with a history of unilateral ankle sprain and: a score <11 on the IdFAI, a maximum of two previous ankle sprains with at least 12 months since the most recent sprain, 0 episodes of the ankle giving way within the past 12 months, and disability scores no lower than 99% and 97% on the FAAM and FAAM-S, respectively.[10] For this investigation, patients with unilateral or bilateral CAI were enrolled. CAI was defined as those individuals who: 1) have experienced at least two lateral ankle sprains in the past; 2) have experienced at least one episode of giving way within the past 3-months; and 3) a score ≥11 on the IdFAI.[45] Individuals with bilateral CAI were still eligible; the limb with the lower FAAM and FAAM-S scores was considered the 'involved limb' for analysis (Experiment 1 and Experiment 2a) and balance training (Experiment 2b). Physical activity levels were collected using the NASA physical activity status scale;[12] these served as a demographic and all uninjured control participants were matched to CAI participants. Matching criteria included: sex, mass (kg, ±10%), height (cm, ±10%), and physical activity (identical NASA score). Previous research experience has shown that matching copers is a difficult process and would have limited our ability to obtain an n of 20. Exclusion criteria for all

groups and both investigations included known balance and vision problems, acute lower extremity and head injuries (<12 weeks prior to enrollment), chronic musculoskeletal conditions known to affect balance (e.g. ACL deficiency), history of ankle surgery to fix internal derangements, a diagnosed concussion, and any other neurologic impairments or conditions that may impact postural control or EEG signal analysis (e.g. diabetes, epilepsy).

1.3.3 Instrumentation

EEG data were collected using a NuAmps 40-channel EEG amplifier (Compumedics Neuroscan, Charlotte, NC) paired with a 40-channel QuikCap electrode placement helmet (Compumedics Neuroscan, Charlotte, NC). The QuikCap system has 40 electrodes located according to the international 10-20 system of electrode placement. Linked earlobe electrodes A1 and A2 serve as a reference to the GND (ground) electrode placed above the nasion and eye movement is monitored by X1, X2, X3, and X4. The sintered electrodes of the QuikCap were filled with an electrolyte gel that allows for a connection between the scalp and the electrode. Data from the NuAmps amplifier was sent to a workstation equipped with Curry 7 Acquisition and Signal Processing package (Compumedics Neuroscan, Charlotte, NC) and then exported for analysis in MATLAB (Mathworks Inc., Natik, MA). EEG data were amplified with a gain of 1000 set for recording range of ±55mV and recorded at 1000Hz using separate 22-bit analog-to-digital converters for each channel.[2] EMG data are collected using a 16-channel MP150 BIOPAC data acquisition system (Biopac Systems Inc., Santa Barbara, CA). Data was obtained using disposable 1 3/8in Ag/AgCl electrodes, wired to the MP150 system. Data was amplified with a gain of 1000 and recorded at 1000Hz. It was then exported to

MATLAB for synchronization and processing. Ground reaction forces (GRF) associated with the concurrent postural control task was collected using an AMTI AccuSway (AMTI Inc., Watertown, MA) force platform connected to a portable workstation via the PJB-101 (AMTI Inc., Watertown, MA) interface system. This results in 6 digitized channels (Fx, Fy, Fz, Mx, My, Mz) recorded by AMTI NetForce Software (AMTI Inc., Watertown, MA). GRF were recorded at 200Hz during both Experiment 1 and Experiment 2a/b. Force platform data was exported into MATLAB for synchronization and processing. A custom-built trigger sending a 4.8V TTL pulse simultaneously to the EEG, EMG, and force platform acquisition software, allowing for offline synchronization of data in MATLAB.

1.3.4 Data Preparation and Reduction

Eye movement and blink artifacts were removed from trials using online blink reduction tools in the Curry 7 Acquisition module. Remaining artifacts were rejected manually. A DC shift was compensated for using an online fourth-order trend correction for each channel throughout each trial (linear detrend).[2,41] EEG data was down-sampled to 200Hz using the Curry 7 Signal Processing module allowing for synchronization of the TTL pulses from our custom-built trigger device, time-locking our EEG data to the moment data shown in Figure 2. In order to prepare data for ERD analysis, three separate bandpass filters were used to isolate the Alpha (8-12 Hz), Beta (14-25 Hz), and Gamma (30-50 Hz) frequencies bandwidths. Following filtering and synchronization, manual artifact rejection ensured the appropriate number of artifact-free trials were available for grand averaging.

EMG data was exported to MATLAB and was processed using a 50Hz notch filter to remove artifact from the power source, then it was rectified, and filtered using a low-pass filter (45Hz cutoff).[1] Data was down-sampled to 200Hz to allow for synchronization with EEG and GRF data and subsequent analyses. Synchronization of each trial took place with respect to the beginning of GRF data; the custom-built trigger initiated capture of GRF data and simultaneously sent a 4.8V TTL pulse to the EEG and EMG acquisition systems.

1.3.5 Outcome Measures

The MRCP is a slowly progressing negative shift of EEG activity preceding the onset of voluntary movement, first described by Kornhuber and Deecke in 1965 (referred to as Bereitschaftspotential – readiness potential).[47] This signal is thought to result from preparatory activity in the supplementary motor area contralateral to the movement limb, as supported by significant increases in fMRI activity.[42,48] The MRCP is often split into two parts, the early and late MRCP, the former begins approximately 2 seconds before movement begins and the latter begins around 400-500 milliseconds prior to movement.[42] The MRCP is commonly used to evaluate the degree of preparedness for movement, therefore allowing a quantification of feed-forward sensorimotor control.[42] The amplitude of the MRCP has been shown to be significantly different between AP and ML sway, which may suggest different preparation strategies for these planes of movement

(Figure 2).[2] The MRCP will be present on all recorded electrode sites but is often greatest in magnitude over the region of interest Cz. Lower extremity movement will show the largest magnitude at Cz as it overlies the motor cortex dedicated to lower extremity control.[42] The MRCP was calculated as previously described.[2,41,42] In brief, the amplitude (μV) is recorded at the onset of moment shifts (Figure 2).[2,42] For example, when a negative moment is observed on the My channel of the force platform during the AP sway task, the participant has initiated a motor command to begin an anterior sway and the MRCP will be recorded. Similarly, when the Mx channel indicates a shift in the moment (positive or negative depending on a right or left directional sway), an MRCP value was recorded.[2] Based on best practice with event-related potential research, the grand average (minimum of 60 trials) was taken for each sway direction for each participant.[2,49] The amplitude, in μV, was calculated from the grand average of the Cz electrode for each condition and used as the dependent variable for our MRCP outcome measure.[2] All EEG channels in this region will exhibit the same MRCP pattern but the maximal amplitude is greatest at Cz and thus is taken from this location.

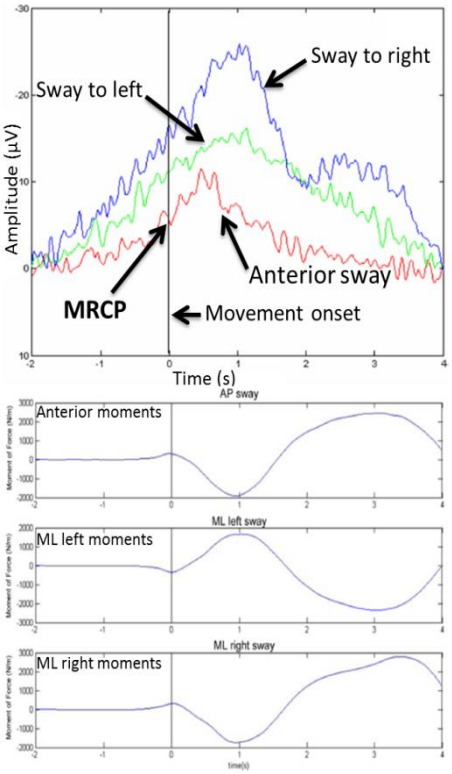

Figure 2. MRCP for each sway condition at electrode Cz (top) and moments (bottom). Adapted from Slobounov et al.[2]

A time-frequency analysis of EEG using ERD and event-related synchronization (ERS) was also performed. Electrical activity as recorded by EEG is a summative waveform sensitive to different tasks and composed of many different frequency oscillations, which represent the activity of a large number of neurons. Event-related potentials (e.g. MRCP) inform us about the magnitude of neuronal activity preceding movement, but fail to elucidate the coordination or magnitude of activity with the movement.[35] The frequency content of the EEG signal allows researchers to investigate the relative activity of an area as it relates to a task, known as ERD or ERS.[35] The frequency content of movement related EEG data is often broken into Alpha (8-12 Hz), Beta (14-25 Hz), and Gamma (30-50 Hz) bandwidths.[2,35,41] ERD is evaluated as a percent change of the power of a signal within a specified bandwidth.[35] A decreased signal power indicates a more widespread use of frequency contents and thus increased activity in a specified bandwidth relative to the baseline period.[35] To quantify ERD, the power within the given frequency band of interest in the time window after the event is represented as A and the baseline or reference period of equal duration is represented as R. ERD is then calculated as follows: ERD% = ((A – R)/R*100); the outcome being a percent change of power during the event in question.[35] ERD is typically taken from a single electrode site and requires the data to be bandpass filtered to isolate a specific bandwidth. ERD has been observed in the Alpha, Beta, and Gamma bandwidths leading up to and during voluntary movement over the sensorimotor areas of the cortex; therefore, ERD was recorded in the Alpha, Beta, and Gamma bandwidths over the Cz and CPz electrodes.[35] The event in question will consist of a 500 millisecond window that encompasses ‘A’ and a 500 millisecond window during static stance between sways or DSLT defined ‘R’ from the aforementioned ERD

equation. For Experiment 1, 'A' was taken from the maximum anterior or lateral moment (Figure 2), when the participant has reached the limits of stability and must sway back to starting position. For Experiment 2a/b, 'A' was taken from the onset of the DSLT (SP, see below, Figure 3). This analysis produced a total of 6 dependent variables per participant: Cz Alpha, Beta, and Gamma ERD, and CPz Alpha, Beta, and Gamma ERD. Muscle onset times were calculated from filtered EMG data for the following muscles bilaterally: peroneus longus, tibialis anterior, medial gastrocnemius, vastus medialis, medial hamstrings, and gluteus medius. In brief, a 25ms fixed window before the movement is compared to a 25ms moving window, an increase >2 standard deviations over the mean baseline activity is determined as the onset of EMG activity.[1] Onset is reported with respect to the starting point (SP), as described by Van Deun et al.[1] as the initial ML shift of the center-of-pressure (COP) from the starting position (Figure 3).

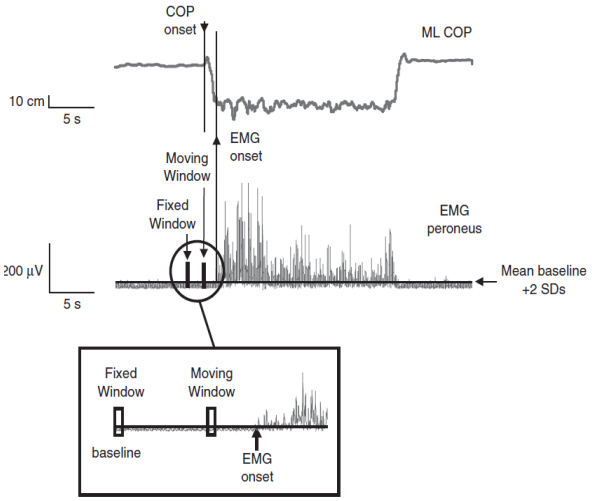

Figure 3. Overview of onset time calculations. Top: the SP in this investigation can be seen at "COP onset". Bottom: EMG onset. Adapted from Van Deun et al.[1]

Static balance trials from Experiment 2b were used to assess change in sensorimotor control following balance training. The COP data calculated from the GRF during static balance trials was transformed into time-to-boundary (TTB) data. TTB uses the coordinates of the COP to, at each data point, calculate the instantaneous velocity and direction of the COP with respect to the border of the foot (foot length and width).[50] The

result is a time-series of peaks and valleys representing the amount of time it would take, assuming the instantaneous velocity remains constant, for the COP to pass over the boundaries of the foot, indicating a loss of balance.[50] This yielded a total of 4 outcomes to be assessed, the mean and standard deviation of the TTB in both the AP and ML directions.

Change scores were calculated for Experiment 2b, and will be calculated as: baseline – posttest. These were calculated for ERD/S at Cz and CPz in Alpha, Beta and Gamma, % reach for all 3 SEBT directions, and all 4 TTB outcomes. Patient-reported outcomes such as the IdFAI and FAAM/FAAM-S were scored according to the conventions of the field and the appendices of the original papers.[46,51] The IdFAI is a summative score starting at 0, which represents no disability.[46] The FAAM and FAAM-S assign values of 4-0 to likert-style responses, with 4 representing no disability and 0 representing maximal disability; the total is then converted into a percentage disability with 100% signifying no disability.[51]

1.3.6 Participant Preparation

Once eligible for either Experiment 1 or 2a/b, a participant was provided with instructions regarding the testing procedure. Specifically, participants are to wash their hair using a shampoo the morning of testing but no conditioner or hair styling products are to be used as they negatively impact the conductivity of the electrical potentials measured through the scalp. On the day of testing, participants first provided informed consent and then completed baseline testing. Baseline testing consisted of a series of ankle injury questionnaires (IdFAI and FAAM/FAAM-S obtained during eligibility screening) and a physical exam (anterior drawer and talar tilt) as recommended by the

International Ankle Consortium.[45] To quantify participants' postural control ability relative to more traditional techniques used in the CAI literature, all participants completed 3, 10-s trials of dual and single-limb static stance on an AMTI force platform with eyes open with their hands on their hips, and contralateral knee flexed 30 degrees during single-limb trials.[20,52] While seated for EEG preparation, the scalp was abraded lightly with a comb for about 2 minutes and then prepared with a mildly abrasive conductive gel, NuPrep (Weaver and Company, Aurora, CO), to ensure low impedances. Once the scalp was prepared, the cap was placed on the participant and electrode preparation started by injecting an electrolyte gel (Compumedics Neuroscan, Charlotte, NC) into the following electrodes with a 10cc syringe outfitted with a blunt-tip needle: GND, A1, A2, X1, X2, X3, X4, FP1, FP2, F3, F4, Fz, FC3, FC4, FCz, C3, C4, Cz, CP3, CP4, CPz. Once all electrodes were filled, online impedance measurements were reviewed to ensure an optimal signal to noise ratio. Impedance was kept below 5 kOhms for all electrode sites.[2,32] Pilot testing indicated this process lasted between 20 to 30 minutes.

For Experiment 2a/b, EMG data was also collected and requires additional preparation. A trained laboratory assistant completed EEG preparation, while the primary investigator prepared the participant for EMG data collection. EMG data collection required that the skin overlying the muscle belly in question is prepared in a manner that minimizes the impedance of the signal acquired from the muscle. In order to do this, the skin overlying the muscle bellies of the following muscles: peroneus longus, tibialis anterior, medial gastrocnemius, vastus medialis oblique, the medial hamstring group (capturing signals from the semitendinosus and semimembranosus), and the gluteus medius for both the

right and left leg was shaved using a disposable razor. An additional site on the patella of the involved/dominant limb was prepared to serve as a reference, for a total of 15 sites. Then the skin was lightly abraded for a few seconds using fine sandpaper and cleaned using an ethyl-alcohol pad. Then the self-adhesive EMG electrodes were fixed to the muscle belly and evaluated using a multimeter for impedance levels and the signal was monitored using the BIOPAC software. Preparation was complete once each site displays impedance less than 5 kOhms of resistance.

1.3.7 Testing Protocol

Experiment 1 consisted of a self-initiated sway task, identical to the one described by Slobounov et al.[2] In brief, participants stood on a force platform with feet approximately shoulder-width apart and arms across their chests. Participants were then be instructed to voluntarily sway in three different directions: AP, MLi, and MLu.[2] They were instructed to sway in these directions, one at a time, until they reach their stability limits for each direction at a comfortable steady speed without moving their feet or flexing the trunk.[2] Prior to data collection, participants were be familiarized with the protocol through real-time visual feedback of their moments from the NetForce software, with verbal instructions that emphasized the production of similar amounts of movement each trial (Bottom, Figure 2).[2] Participants performed one postural sway approximately once every 10 seconds, performing 20 sways in each direction (60 total) per testing block.[2] Participants were tested over 6 blocks to ensure that at least 60 artifact-free trials were collected for each movement direction. Testing blocks were separated by at least a 5 minute break.[2] No visual feedback was provided during data collection. In experiment 1,

all three groups completed baseline testing and the Experiment 1-specific voluntary leaning task.

Experiments 2a and 2b included an additional balance task, the SEBT. The SEBT was completed in anterior, posteromedial, and posterolateral directions and took place *before* EEG and EMG preparation. Testing only these three directions is recommended because of the redundancy in information when all eight directions are tested.[53] To conduct the reach trials, the participant stood in a test grid and was instructed to reach as far as they could in the specified direction, lightly touching down the reach limb on a tape measure. Careful attention is required so that the heel does not lift from the ground providing extra distance, and that support is not provided for balance by the reaching limb. Reach distances were normalized to the subject's leg length (distance from the anterior superior iliac spine [front of pelvic bone] to the medial malleolus [bump on inside of ankle] on the same leg).[54] Participants completed three trials on each limb in each direction (18 trials total). In order to assess feed-forward sensorimotor function, participants were asked to complete a DSLT during EEG data collection.[1,23] To complete this task, the participant was asked to maintain static balance on two limbs for approximately 4 seconds with their hands on their hips, looking forward at a fixation cross on a computer monitor situated at eye-level. An arrow pointing to the right or left appeared on the screen, indicating the participant should transition to this limb, and they would transition once the visual cue is presented. The transitions occurred at a preferred speed of movement, but were limited to less than 1 second (most transitions are around 500 milliseconds). The participant must have maintained single limb balance for at least 5 seconds following the DSLT, thus completing the DSLT test trial. A total of at least 60 artifact-free trials[49] were required for

analysis, therefore the participant completed four 10-minute blocks of 60 trials, for a total of 120 DSLT per limb. All three groups completed the procedures for Experiment 2a.

In Experiment 2b, the CAI group completed a validated balance training protocol first described by McKeon et al.[24] Participants completed three 20-minute sessions a week for a total of 12 supervised training sessions over 4 weeks. The exercises aim to restore "normal" functional variability by challenging the participant's ability to maintain single limb stance through the purposeful manipulation of task and environmental constraints.[24] Progression to higher difficulty levels of each exercise are achieved independently by demonstrating movement proficiency (i.e. error free performance) as opposed to completing a specific amount of repetitions or training sessions. Table 1 illustrates the exercises and repetitions to be performed. The full protocol and progression criteria can be seen in the Appendix of the original paper.[24] Following the completion of the balance training protocol, participants with CAI repeated an identical DSLT task testing protocol with EEG and EMG data collection. Post-test assessments occurred within 24 hours and at 1-week post intervention. Baseline postural testing (static single limb balance and SEBT) were completed at these time points to confirm the previously established effectiveness of the balance training intervention.

Table 1. Description of exercises from the McKeon et al.[24] balance training protocol.

Exercise	Description
Hop to stabilization	Hop to a target position (18, 27, 36 inches [45.7, 68.6, 91.4 cm]), stabilize, hop back to the starting position, and stabilize. Hops are performed in four directions: anterior/posterior, medial/lateral, anterolateral/posteromedial, and anteromedial/posterolateral.
Hop to stabilization and reach	As above but after stabilizing, subjects will reach back to the starting and target positions during each repetition of each direction.
Unanticipated hop to stabilization	Start in the middle of a 9-marker grid (individually numbered) and hop to the randomly presented target number. Subjects can use any combination of hops they wish to reach the target.
Single limb stance balance	Complete a single limb stance exercise with eyes open.
Single limb balance with eyes closed	Complete a single limb stance exercise with eyes closed.

1.3.8 Statistical Analysis

All statistical analysis was performed using Statistical Package for the Social Sciences (version 21, IBM Corp, Armonk, NY). Effect sizes and confidence intervals were calculated using a custom Microsoft Excel 2010 script (Microsoft Corp, Redmond, WA). The a priori alpha level was set at 0.05 for all tests.

Experiment 1 was analyzed using a separate two-way analysis of variance (Group [control, coper, CAI] x Sway direction [AP, MLi, MLu]) for each EEG dependent variable (MRCP voltage, ERD/S in Alpha, Beta, Gamma at Cz and CPz); this analysis was used to test hypotheses SA1a, SA1b, and SA1d. Tukey's HSD tests were used for all post hoc analyses. One-sided independent t-tests were performed, where appropriate, to

test whether groups did not differ in EEG outcomes for hypothesis SA1c. Hedges' g effect sizes and 95% confidence intervals were also calculated to provide clinical meaningfulness. Pearson product moment correlations to test hypothesis SA1e were run among all 7 dependent variables and demographic data including clinical test results (anterior drawer and talar tilt), single limb balance outcomes (TTB), and patient-reported outcomes (IdFAI, FAAM, FAAM-S, injury demographics).

Experiment 2a was analyzed using a separate two-way analysis of variance (Group [control, coper, CAI] x Limb [Ti and Tu] for each EEG dependent variable (ERD/S in Alpha, Beta, Gamma at Cz and CPz); this analysis was used to test hypothesis SA1a and SA1d. Tukey's HSD tests were used for all post hoc analyses. One-sided independent t-tests were performed, where appropriate, to test whether groups did not differ in EEG outcomes for hypothesis SA1c. Muscle onset times are not normally distributed, and were evaluated among groups using Kruskal-Wallis H tests for each muscle, with follow-up Mann-Whitney U tests for post-hoc comparisons; Friedman tests were used within groups to evaluate the Limb main effect. Hedges' g effect sizes and 95% confidence intervals were also calculated to provide clinical meaningfulness. Pearson product moment correlations to test hypothesis SA1e were run among all 6 dependent variables and demographic data including clinical test results (anterior drawer and talar tilt), balance assessment outcomes (TTB and SEBT), and patient-reported outcomes (IdFAI, FAAM, FAAM-S, injury demographics).

Experiment 2b was analyzed using separate one-way repeated measures analysis of variance for Time (baseline [Experiment 2a], posttest 1, posttest 2) for each EEG dependent variable (ERD/S in Alpha, Beta, Gamma at Cz and CPz) to test hypothesis

SA2a, as well as balance assessment outcomes (AP/ML TTB Mean and Standard Deviation, SEBT-A/PM/PL % reach). Tukey's HSD tests were used for all post hoc analyses. Muscle onset times were compared over Time using Friedman tests for each muscle. Hedges' g effect sizes and 95% confidence intervals were calculated to provide clinical meaningfulness for the treatment effect. Pearson product moment correlations to test hypothesis SA2b were run among change scores (baseline – posttest 1) in all EEG outcomes and balance assessment outcomes.

1.3.9 Power Analysis

No previous investigation has directly captured the outcomes of interest in copers or CAI participants during weight-bearing postural tasks. All power calculations were conducted using G*Power 3.1.9.2 (Univ. Dusseldorf, Dept. of Psychology) with $\alpha = 0.05$ and β set at 0.80. Sample size estimates and power calculations for experiment 1 were determined using: differences in static dual-limb balance between controls and CAI (ML COP Velocity, effect size=0.63) indicating a sample size of n = 7 per group,[52] previous cortical activity research in CAI utilizing TMS identifying group differences with a sample size of n = 10 per group (effect size=0.89, n=6 per group),[33] and directional differences in MRCP in controls with a sample size of n = 12 per group (effect size =1.64, n=3 per group).[2] For Experiment 2a, Van Deun et al.[1] identified group differences with 10 participants per group when comparing EMG onset times during a DSLT (average effect size = 2.28), and for experiment 2b, improvements in mediolateral (ML) postural control following a balance training program were identified in participants with CAI (effect size=0.33, n=13 per group).[24] However, Needle et al.[32] failed to identify group differences in ERD with samples ranging between 6-14 per group among controls,

copers, and CAI. Thus we are confident that differences in MRCP and ERD can be identified with 15 participants per group; we plan to enroll 20 participants per group to allow for up to 25% of our participants not having usable EEG data (<60 artifact-free trials), resulting in 15 participants per group.

CHAPTER 2: EXAMINING THE RELATIONSHIP BETWEEN CHRONIC ANKLE INSTABILITY SYMPTOMS AND DUAL-TASK BALANC PERFORMANCE

2.1 Contribution to dissertation

This chapter is adapted from Burcal and Wikstrom[55]; doi:10.1123/ijatt.2016-0033. In this investigation, I examined whether or not dual-task balance performance was related to the severity of CAI symptoms. Changes in balance performance while dual-tasking can be interpreted as the relative role of cortical resources that are required to maintain single-limb balance. If balance worsens when someone is dual-tasking, using cortical resources for a cognitive task rather than balance, we are able to infer a larger cortical contribution to balance. We identified that in CAI patients there was 1) an individualized balance trade-off to dual-tasking (i.e. some got better and some got worse), and 2) a moderate relationship between injury severity, the number of episodes of the ankle giving way, and dual-task balance. These results together provide evidence that patients with worse CAI symptoms may have a greater reliance on cortical control of movement.

2.2 Introduction

Chronic ankle instability (CAI) is a musculoskeletal condition characterized by persistent symptoms following an acute lateral ankle sprain, the most common being complaints of the ankle 'rolling' or 'giving way' during activity.[8,45] Additionally, CAI patients may suffer from mechanical,[56] perceptual,[57] and/or sensorimotor alterations.[11] A meta-analysis revealed that relative to their uninjured peers, these patients have motor deficits during concentric eversion and sensorimotor deficits such as worse static balance, increased time for dynamic stabilization from a jump landing, and altered gait kinematics.[58] This poor

sensorimotor control is believed to lead to poor functional performance, which leads to reinjury and increases the constraints on the patient, leaving CAI patients within a continuum of disability.[25] Further, CAI patients with worse balance tend to have lower quality of life scores based on a variety of patient-reported outcomes (PROs).[57] Recent dual-task research suggests that poor balance may be due to an increased reliance on attentional resources in CAI patients.[28]

Dual-tasking is the simultaneous performance of a physical task (e.g. balance) and a cognitive task (e.g. counting). A large amount of literature has been dedicated towards investigating the dual-task costs pertaining to postural control in a variety of populations. By comparing balance performance between single- (e.g. balance only) and dual-task (e.g. balancing while completing a cognitive task) paradigms, one can infer the relative amount of cortical resources required to maintain static balance based on the magnitude of change between the conditions.[28,59] Research suggests that balance often improves in healthy young individuals when they complete a cognitive task while balancing.[59-61] However, researchers have shown that different populations respond to dual-tasking in different ways.[62-64] For instance, older adults had improved balance when completing a simple cognitive task, but as cognitive task difficulty increased, balance worsened.[63] There is also a detrimental effect to balance while dual-tasking in older stroke survivors, relative to both healthy old and healthy young adults.[62] Similar results are also seen in individuals with acute and subacute concussion, displaying greater cognitive and postural deficits while dual-tasking relative to controls.[64] These negative changes in balance performance are not observed in healthy individuals,[59-61] and together the evidence suggests that as constraints on the sensorimotor and central nervous system are increased,

balance worsens while performing a cognitive task. One theory to explain this dual-task interference is that when a cognitive load is placed on the patient, cortical resources normally used to control balance are diverted towards the completion of the cognitive task and balance becomes impaired.[65] Thus, dual-tasking does not negatively affect balance in healthy individuals because they do not have organismic constraints in the sensorimotor system. However, a history of brain injury (e.g. stroke or concussion) appears to impose injury-related constraints that decrease the ability to maintain balance while dual-tasking.

There is recent evidence that CAI patients have constraints in the central nervous system, which are believed to contribute to altered sensorimotor function.[31,33] It is unclear how this affects the balance of these patients while dual-tasking, as the existing literature demonstrates conflicting results.[28,66,67] A recent study found that balance was improved on the injured limb of CAI patients when performing a backwards counting task.[67] Another investigation found that balance was impaired when CAI participants were given a string of numbers to recall while balancing.[28] Others have reported that balance performance was not affected by cognitive loading in CAI patients when using three separate cognitive tasks.[66] While inconsistent results may be due to methodological differences, CAI is a heterogeneous condition, with up to seven sub-CAI populations,[68] and it is possible that the large variability in dual-task performance could be the result of individual patient constraints resulting in unique balance responses to cognitive loading.

If CAI patients have unique responses to dual-tasking, then this may represent a novel insufficiency which should be addressed in the treatment plan for the individual. The recently proposed Impairments-based treatment model proposed by Donovan and

Hertel[69] supports the need to further examine if CAI patients demonstrate unique responses to dual-tasking paradigms as this information could help clinicians develop a more comprehensive and personalized treatment plan for their CAI patients. Therefore the aim of this investigation is to determine if a relationship exists between balance performance while dual-tasking and patient-reported outcomes and injury history characteristics among CAI patients. We hypothesize that severity of CAI symptoms will positively correlate with worse balance while dual-tasking, suggesting patients with worse CAI symptoms will have a greater decrease in balance performance with the addition of a cognitive load.

2.3 Methods

2.3.1 Participants

A total of 24 participants with self-reported CAI volunteered to participate in this investigation (Table 2). Participants must have had a history of at least 2 lateral ankle sprains, at least one episode of the ankle rolling in the past 3 months, and answered yes to 4 or more questions on the Ankle Instability Instrument (AII) to be eligible.[70] This study was approved by the Institutional Review Board at UNC Charlotte.

2.3.2 Instrumentation

Balance trials were completed on an AMTI Accusway Plus force platform (AMTI; Watertown, MA) at 50 Hz. The number of ankle sprains and episodes of the ankle rolling in the past 3 months were collected with an injury history questionnaire, and 'roll' was defined as a temporary uncontrollable sensation of instability or rolling of one's ankle.[8] Patient-reported function was collected using the Foot and Ankle Ability Measure

activities of daily living (FAAM-ADL) and sports (FAAM-S) subscales[44]; these were used to determine the test limb (limb with the lower score) in the case of bilateral CAI, rather than as an inclusion criterion.

2.3.3 Tasks

Participants were asked to complete a total of 3, 10-second trials of eyes open static single limb stance during a single- (quiet stance) and dual-task condition. The dual-task condition required the participant to count backwards verbally from a randomly generated three digit number in multiples of 3. Dual-task trials began once the first subtraction of the task was verbalized, in other words if a participant was given the number 345, the trial began when the participant said "342". Participants were told to complete the counting task while maintaining balance, as more specific instructions have been shown to alter dual-task balance performance,[71] and they were instructed not to react to errors. Both conditions required hands to be placed on hips with the contralateral knee flexed approximately 30 degrees.

2.3.4 Procedures

Participants reported for a single test session, and after informed consent was obtained, anthropometric and injury demographic data were collected. Data from the force platform were used to calculate out center-of-pressure (COP) outcomes for the 10-second static balance trials in the medial-lateral (ML) and anterior-posterior (AP) planes. The COP standard deviation (ML SD, AP SD) and velocity (ML Velocity, AP Velocity) was calculated for the three trial average of each condition. A dual-task ratio was then generated as: dual-task / single-task, to represent the relative change in COP outcome as a

result of dual-tasking, with a ratio greater than one representing increased postural sway while dual-tasking, and a ratio less than one indicating decreased sway (i.e. improved balance). Since we believe that individuals respond differently to dual-tasking, a ratio was selected to reflect a relative change in balance performance rather than absolute change.

2.3.5 Statistical Analysis

Due to a non-normal distribution of dual-task ratio data, a nonparametric analysis was selected. Spearman correlations were examined between anthropometric data, injury demographics, and patient-reported outcomes and the dual-task ratios. Correlations were interpreted as weak with a correlation coefficient from 0.01 to 0.39, moderate from 0.40 to 0.69, and strong from 0.70 to 1.[16] All tests were completed in SPSS (version 21; IBM Corp, Armonk, NY). Because four dual-task ratio outcomes were correlated against patient-reported outcomes and injury characteristics, we conducted a Bonferroni adjustment (0.05 / 4) that resulted in an adjusted alpha of 0.013.

2.4 Results

Table 3 contains our correlation data, and significant dual-task ratio correlations can be seen in Figure 4 We observed significant positive correlations between the episodes of giving way in the past 3 months and the dual-task ratio for AP Velocity ($p = 0.004$, Spearman's rho = 0.567) and ML Velocity ($p = 0.004$, Spearman's rho = 0.562).

2.5 Discussion

Our hypothesis was accepted as we identified a positive relationship between the number of rolls in the past 3 months and the dual-task ratio for AP and ML Velocity. This

moderate relationship suggests that participants with a higher number of reported episodes of the ankle rolling in the past 3 months had worse balance while dual-tasking. Our data links dual-task balance performance to the severity of a hallmark symptom of CAI. Although not statistically significant, a moderate relationship was observed between the FAAM-ADL and ML Velocity ($p = 0.028$, Spearman's rho = -0.447), as was a significant moderate relationship between FAAM-ADL and number of rolls in the past 3 months ($p = 0.010$, Spearman's rho = -0.516), further linking decreased patient-reported function, the hallmark CAI symptom, and potentially dual-task balance performance. These results also provide evidence that patients with CAI respond to dual-tasking along a continuum based on their unique individual constraints, which may help explain the conflicting results found in the literature.[28,66,67]

As CAI is a highly heterogeneous population, one must consider the sample of CAI in each investigation. It is difficult to compare our results to that of Rahmana et al.[28] and Shiravi et al.[67] as limited patient-reported and injury characteristic information was provided. Both investigations required their CAI participants to have sustained one previous lateral ankle sprain and one episode of rolling. Burcal and Wikstrom[66] used CAI inclusion criteria consistent with the recommendations of the International Ankle Consortium.[45] The sample used in this investigation has similar injury demographics (Table 2) as those reported by Burcal and Wikstrom[66] including the number of ankle sprains (3.84), FAAM-ADL (92.25%), and FAAM-S (79.01%). Interestingly, the dual-task ratios in Table 2 are close to 1, suggesting that, like Burcal and Wikstrom,[66] the backwards counting task did not have a large effect on balance. The observed relationships between COP velocity and the number of rolls in the past 3 months may

possibly be due to the level of impairment or dysfunction in the sensorimotor system. Within the continuum of disability, it is thought that poor sensorimotor control eventually leads to reinjury (i.e. rolls),[25] therefore it is likely that there are greater constraints on the sensorimotor system of CAI patients that experience a higher number of rolls. Specific to dual-tasking, these CAI patients may have greater increases in the attentional costs of balance (i.e. balancing becomes less of an automatic task) which would result in greater balance impairments due to the interference caused by simultaneously processing of a cognitive task.[65]

Clinically, dual-tasking may represent a modifier for static or dynamic balance exercises. Balance training is believed to improve balance by decreasing the reliance on cortical control (i.e. attentional resources) and emphasizing more automatic structures such as the brain stem and cerebellum.[26] This is typically done by challenging the sensorimotor system via progressively more difficult tasks.[25] If some CAI patients have difficulty with dual-tasking, then by incorporating a cognitive task, the overall balance task could increase in difficulty. While speculative, the ability to maximize balance performance while dual-tasking with minimal trade-offs in either task, may represent a decreased reliance on cortical resources,[26] and potentially an increased capacity for dual-tasking. It would be hoped that these speculative improvements carry over into athletic competition, where the patient is required to complete complex motor and cognitive functions.

This investigation is not without limitations, as the test order was not randomized and all participants completed the single-task baseline balance trials prior to the dual-task balance trials. Although participants were familiarized with and practiced the cognitive task prior to testing, we cannot rule out a learning effect that may have artificially

impacted the results by lowering the dual-task ratios. The length of balance trials was also different from the existing CAI dual-task literature.[28,66,67] Because multiple trials lengths and outcome measures have been used to quantify postural control in CAI, the current results may not be representative of the results obtained with longer trial lengths and/or different outcome measures. Similarly, the ratio used to measure changes while dual-tasking may not be the best assessment technique (e.g. normalized differences may be more sensitive to dual-tasking impairments) but this remains unclear due to a lack of empirical evidence. Finally, although an acute head injury within 6 weeks of enrollment was an exclusion criterion, a history of concussion beyond this time was not controlled for and may have affected cognitive task performance. It also remains unclear whether or not a simple cognitive task such as backwards counting by 3's represents a significant enough cognitive load to replicate real-life scenarios such as reading the field of play, if other cognitive tasks would result in similar relationships, or if this differential trade-off in static balance performance would apply to dynamic tasks such as gait.

Our investigation was able to establish a link between the hallmark symptom of CAI and change in balance while dual-tasking. This relationship shows that as the number of rolls experienced by the patient increases, the disruption in balance while dual-tasking is greater, and we believe this may represent a new type of insufficiency in the CAI population. Due to the moderate nature of these relationships, and the many unanswered questions pertaining to cognitive loading and dual-tasking in patients with CAI, future research is warranted to examine the clinical feasibility of incorporating these additional task constraints to existing rehabilitation protocols.

2.6 Tables

Table 2. Participant demographics.

The means and standard deviations of the dependent variables in this investigation. The dual-task ratio represents a change from baseline, as it is the quotient of the dual-task balance trial divided by the single-task balance trial. A number greater than 1 represents more postural sway when dual-tasking relative to a single-task.

Variable	**Mean (SD)**
Sex	7 Male, 17 Female
Age (years)	21.29 (2.03)
Height (cm)	169.81 (12.89)
Mass (kg)	72.48 (22.15)
Yeses on AII	6.29 (1.52)
# of Ankle Sprains	3.88 (2.53)
# of rolls in 3 months	3.37 (2.28)
FAAM ADL (%)	85.33 (7.93)
FAAM S (%)	68.62 (12.92)
AP St Dev	0.99 (0.39)
AP Velocity	0.93 (0.28)
ML St Dev	1.00 (0.24)
AP Velocity	1.05 (0.21)

Table 3. Correlation coefficients

Spearman's rho values for each correlation to the dual-task ratio outcomes. A * indicates a statistically significant correlation ($p < 0.013$).

	AP St Dev	AP Velocity	ML St Dev	ML Velocity
Age	-0.302	-0.283	-0.105	-0.195
Height	0.074	0.081	-0.191	-0.063
Mass	-0.087	-0.18	-0.362	-0.179
Yeses on AII	0.152	0.276	0.136	0.097
# of Ankle Sprains	-0.016	0.113	0.049	-0.008
# of rolls in 3 months	0.35	0.567*	0.409	0.562*
FAAM ADL	-0.236	-0.281	-0.306	-0.447
FAAM S	0.091	-0.186	0.176	0.024

2.7 Figures

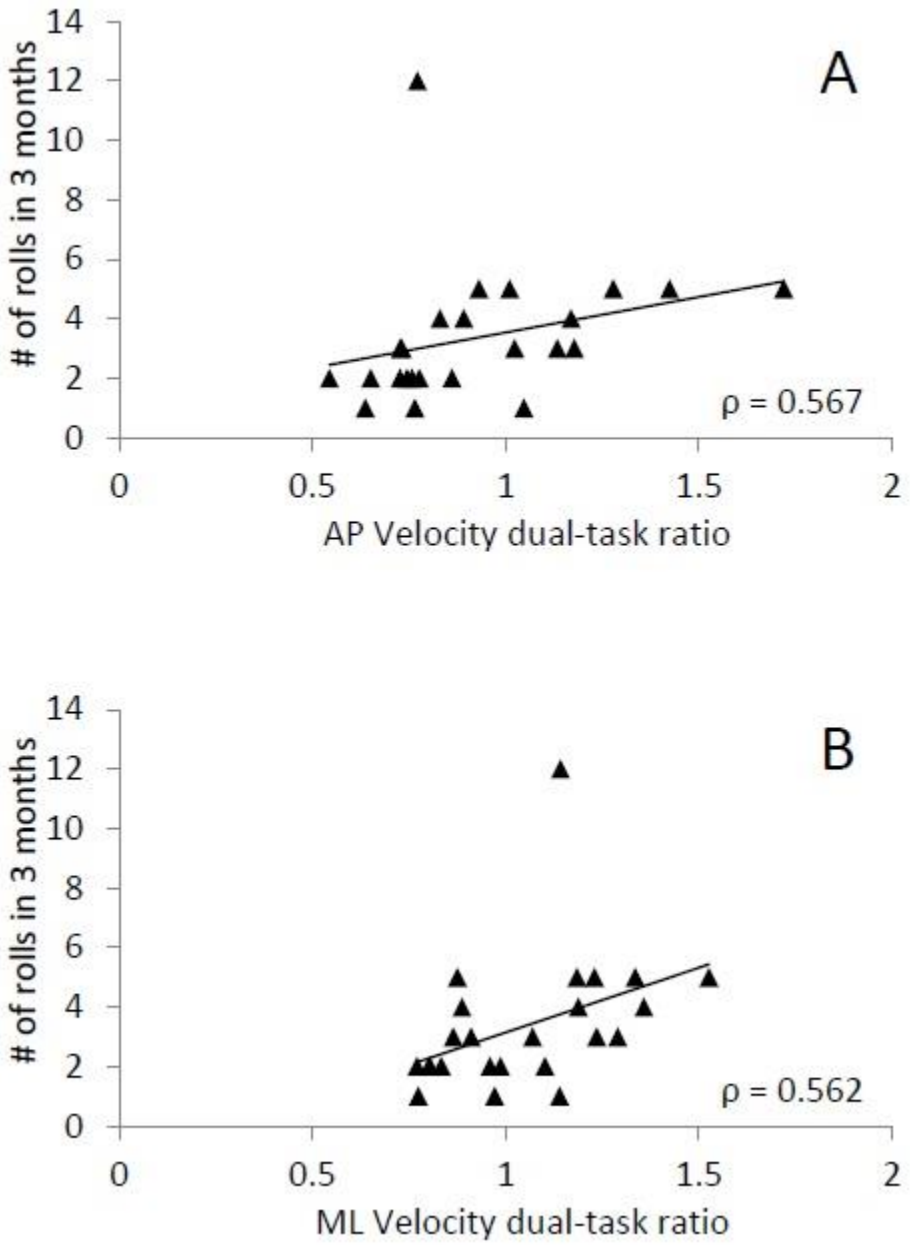

Figure 4. Correlation graphs.

The relationship between the number of rolls in the past 3 months and A: AP Velocity dual-task ratio, B: ML Velocity dual-task ratio.

CHAPTER 3: CORTICAL MEASURES OF FEED-FORWARD AND FEED-BACK SENSORIMOTOR CONTROL DO NOT DIFFER BETWEEN CHRONIC ANKLE INSTABILITY PATIENTS AND UNINJURED CONTROLS

3.1 Abstract

Patients with chronic ankle instability(CAI) are known to have a variety of sensorimotor impairments, having been identified during both feed-back (i.e. static balance) and feed-forward (i.e. gait initiation) activities. The exact neural correlates of these feed-forward and feed-back impairments have not yet been identified. Electroencephalography(EEG) can be used to assess cortical activity during sensorimotor tasks. The purpose of this investigation is to use EEG to assess feed-forward and feed-back sensorimotor activity in CAI patients relative to uninjured controls. A total of 20 CAI patients (age: 20.85±2.28yr; mass: 71.68±18.44kg; height: 174.75±7.88cm) and 20 matched controls (age: 21.70±2.62yr; mass: 68.09±15.75kg; height: 168.82±11.02cm) completed a voluntary leaning task in three directions: anterior, lateral to the involved/dominant limb, and lateral to the uninvolved/nondominant limb while cortical activity was measured using EEG. Feed-forward activity was quantified by averaging motor-related cortical potentials (MRCP) prior to movement onset and feed-back activity was quantified through event-related spectral perturbations(ERSP) in the upper alpha(10-12Hz), beta(14-25Hz), and gamma (30-50Hz) bands once an individual reached their limits of stability. Differences were assessed using 2-way (group by direction) repeated measures ANOVAs at an alpha of 0.05. No significant differences were identified in any of the EEG outcome measures between groups. A main effect of direction was identified in the MRCP ($p<0.001$) and ERSP in the beta ($p=0.018$) and gamma bands ($p<0.001$) indicating less feed-forward activity and greater feed-back activity, respectively, during leaning anteriorly relative to

laterally. Although feed-forward and feed-back impairments may be detected between group in other tasks, our results suggest this may not be due to differences in cortical activity.

3.2 Introduction

Lateral ankle sprains are one of the most common injuries in organized sports.[3,4] Recent research has suggested up to 40% of individuals develop a condition called chronic ankle instability (CAI) after an initial lateral ankle sprain.[72] This condition is primarily characterized by complaints of the ankle rolling or giving way, and some patients also present with recurrent ankle sprains and/or mechanical instability.[8] CAI has also been linked to a decrease in physical activity levels[13] and health-related quality of life scores.[57] Functionally, CAI patients exhibit sensorimotor impairments across a spectrum of tasks including static and dynamic balance,[14,73] as well as gait.[21,74] These patients are theorized to exist in a continuum of disability as a result of these deficits, where poor sensorimotor control leads to poor functional performance, increasing the risk of reinjury.

Sensorimotor control can be broken into feed-forward and feed-back control. Feed-forward control represents the planning of discrete movements or actions, such as initiating gait, or jumping. On the other hand, feed-back control utilizes afferent (i.e. sensory) information to refine ongoing movement in real-time. Feedback impairments are well described and supported by multiple meta-analyses.[14,73,75] Feed-forward deficits have also been identified in discrete tasks such as gait initiation and a dual-to-single-limb transition (DSLT). A current limitation in CAI research is that feed-forward deficits, which may represent alterations in motor planning, have been collected from peripheral instrumentation. For example, Van Deun et al.[1] found that during a DSLT, muscle onset

times occurred after the transition had begun in a CAI group whereas the control group activated muscles prior to movement. Hass et al.[22] used a force platform to investigate the center-of-pressure displacement of the anticipatory postural adjustments (APA) associated with gait initiation and found a suppressed APA in the CAI group. Together, inferences about the dysfunction of the central nervous system (CNS) have been generated using peripheral measures of the efference the CNS is creating (i.e. using electromyography to assess neuromuscular control) as opposed to directly investigating CNS function.

Pietrosimone and Gribble[33] produced the first direct evidence of CNS alterations in CAI patients by revealing that greater cortical activity was required to activate the peroneus longus muscle in both limbs relative to uninjured controls. Since then, multiple investigations have generated evidence of bilateral corticomotor alterations.[31,34,76] To date a solitary investigation utilized electroencephalography (EEG) to describe impairments in CAI patients, however, Needle et al.[32] did not identify any group differences in somatosensory cortex activation while loading the ankle joint in a non-weight bearing position. In healthy individuals, EEG has been recorded during discrete motor tasks and movement-related cortical potentials (MRCP) have been observed. One such MRCP is the bereitschaftspotential (BP) first described in 1965 by Kornhuber and Deeke.[42,47] BP is a slowly propagating negative shift of EEG activity that typically occurs about 2 seconds before movement.[42] It is believed to represent the activity within structures such as the supplementary motor area[42] that plan for movement and ultimately select the appropriate motor commands. The amplitude of the MRCP components have been shown to be affected by many factors including the perception of the movement task (e.g. level of

threat to stability, required effort), and the constraints of the task itself (e.g. force, speed).[42] The effect of movement direction was investigated by Slobounov et al.,[2] and they reported that the MRCP was greater preceding lateral leaning than that of anterior leaning, suggesting independent control for the anterior-posterior (AP) and medial-lateral (ML) components of movement preparation.

While feed-forward deficits are important to consider, feed-back deficits represent a decreased ability to utilize afferent information in an effective manner to refine movement. Feedback sensorimotor control has been quantified using EEG by creating perturbation-evoked potentials, or averaging the magnitude of the EEG activity in response to an external perturbation.[77] However, during commonly assessed measures of sensorimotor control in CAI patients (e.g. single limb balance), the postural destabilization events are internally generated. Slobounov et al.[41] reported a power increase in the gamma bandwidth between 30-40Hz when an individual was leaning anteriorly towards their limits of stability. This finding was replicated when the same group compared AP versus ML leaning, with the burst of gamma activity occurring at the limits of stability. These bursts of activity are thought to be related to sensorimotor processing, due to the high frequency and the relationship to postural events.[2,35,41]

To date, there have been no investigations measuring CNS function in CAI patients during a weight-bearing postural task. Therefore the aim of this investigation is to determine if differences in feed-forward and feed-back sensorimotor control can be identified with EEG. Specifically, we aim to compare these cortical measures between groups of CAI patients and matched uninjured controls when leaning in three directions: anterior, lateral to the involved/dominant limb, and lateral to the uninvolved/nondominant

limb. The relationship between these EEG measures and injury demographics will also be examined to see if a link exists between injury severity and cortical sensorimotor activity. Given the documented feed-forward impairments in CAI patients,[1,22,29] we hypothesize that the MRCP will be lower in CAI patients relative to uninjured controls in all 3 directions. We hypothesize that, similar to Slobounov et al.,[2] leaning in the lateral directions will reveal greater cortical activity than leaning anteriorly. We also hypothesize there will be decreased activity during the feed-back portion of the leaning task in the CAI patients, and finally, we hypothesize that the magnitude of these cortical measures will negatively relate to injury severity (i.e. less activity in a more severely injured individual).

3.3 Methods

3.3.1 Study Design

A cross-sectional design was used to compare EEG measures of sensorimotor control between CAI patients and matched uninjured controls during voluntary postural leaning in three directions: anterior, lateral towards the involved/dominant limb, and lateral towards the uninvolved/nondominant limb. Dependent variables included the amplitude of MRCP outcomes at the Cz electrode to represent feed-forward control, and event-related spectral perturbations (ERSP; upper alpha [10-12 Hz], beta [14-25 Hz], and gamma [30-50 Hz] bands) at the Cz and CPz electrodes to represent feed-back control.

3.3.2 Participants

40 individuals volunteered to participate in this investigation (Table 4). Inclusion criteria for CAI patients was consistent with the recommendations of the International Ankle Consortium,[45] defining CAI as individuals who have experienced at least one significant

lateral ankle sprain, ≥2 episodes of the ankle 'rolling' or 'giving way' within the 6 months prior to participating in the study, an Identification of Functional Ankle Instability(IdFAI) score ≥11.[45] Both unilateral and bilateral CAI patients were eligible for this investigation; if a patient had bilateral CAI, the limb with the lower FAAM-ADL and FAAM-Sport was indicated as the involved limb.[78] Uninjured controls had no history of an ankle sprain or episodes of the ankle giving way in either ankle, a score <11 on the IdFAI, and a score >99% on the FAAM-ADL and >97% on the FAAM-Sport.[45] Uninjured controls were matched to a CAI patient based on sex, mass (kg, ± 10%), height (cm, ± 10%), and physical activity (± 1 NASA Physical Activity Status Scale). Exclusion criteria for all groups were known balance and vision problems, acute lower extremity or head injury within 3 months of enrollment, a history of concussion, chronic musculoskeletal conditions known to affect balance (e.g. ACL deficiency), a history of lower extremity musculoskeletal surgery, or any other neurologic conditions that may impact postural control (e.g. diabetes) or EEG signal analysis (e.g. epilepsy). All experimental procedures performed were in accordance with the Declaration of Helsinki and were approved by the Institutional Review Board at the University of North Carolina at Charlotte (IRB 15-02-02).

3.3.3 Testing Protocol

Prior to testing the participant was given a description of the study and provided written informed consent. The voluntary leaning task is based on a one previous study that reported MRCP recordings[2,41] and required the individual to produce whole-body leaning in three directions: anteriorly (i.e. forwards), laterally to the right, or laterally to the left. Participants were familiarized with the task, leaning from even weight distribution to

their limits of stability, with their hands relaxed at their sides. Each participant performed several practice trials to learn his/her limits of stability and ensure movements were identical across trials. Each participant completed a total of 360 leaning trials, 120 per direction,[2] over a total of six 60-trial testing blocks with a 4 minute break between blocks.

3.3.4 Equipment

Ground reaction forces and moments during a trial were sampled for 8 seconds at 200Hz using an AMTI AccuSway force platform (AMTI Inc., Watertown, MA) connected to a portable laptop through the PJB-101 (AMTI Inc., Watertown, MA) interface system. Data was collected into the NetForce (Version 3.5.3, AMTI Inc., Watertown MA) software and exported to MATLAB (Mathworks, Natick, MA) for analysis.

EEG data was collected using a 32-channel Quick-Cap (Compumedics Neuroscan, Charlotte, NC) connected to a 40-channel NuAmps (Compumedics Neuroscan, Charlotte, NC) digital EEG amplifier. A custom montage was used to collect data from 14 EEG channels (FP1, FP2, F3, Fz, F4, FC3, FCz, FC4, C3, Cz, C4, CP3, CPz, CP4), four EOG channels placed above and below the left eye and lateral to each eye, and two earlobe clip electrodes (A1, A2). The linked A1/A2 earlobes served as a reference for all EEG recordings. EEG signals were amplified (gain: 19), filtered (DC-400Hz), and sampled at 1000Hz into the Curry 7 (Version 7.0.9, Compumedics Neuroscan, Charlotte, NC) software on a dedicated computer and saved for offline analysis.

Force platform and EEG data were synchronized using a custom-built trigger device. The device delivered a 4.8V TTL pulse simultaneously to the NuAmps amplifier and the PJB-101 force platform interface system. The TTL pulse created an event code in the

continuous EEG file and triggered the beginning of the trial in NetForce, creating a single file per leaning trial.

3.3.5 Data Analysis

Movement features (e.g. onset of movement or peak anterior/lateral displacement) were identified manually using a script in MATLAB 2016a. Two movement features were identified for each trial, onset (ON) and peak (PK). ON was defined as the maximal displacement of APA, and PK was the maximal anterior or lateral displacement of the GRF moments (Figure 5).[2] The time of each feature was added to the event latency in the continuous EEG file to allow for the creation of epochs.

Offline analysis of EEG data was performed in Curry 7 (Version 7.0.9, Compumedics Neuroscan, Charlotte, NC) and MATLAB 2016a. The continuous EEG file was baseline corrected and ocular artefacts were corrected in Curry 7. Further processing was performed in MATLAB using scripts written for EEGLAB version 13.6.5b.[79] The EEG data was low-pass filtered at 100 Hz and then segmented into two epochs per trial. The epoch for ON was 3500 ms in duration (-2500ms to +1000ms), and the epoch for PK was 5000 ms in duration (-4000 ms to +1000ms). Epochs were then baseline corrected (ON: -1500 ms to -1200 ms; PK: -4000 ms to -3700 ms). Epochs were then visually inspected, and those with noise or artefact were rejected. A minimum of 50 artifact-free trials per movement direction were required for computing EEG outcome measures.

Feedforward sensorimotor control was evaluated using the data from the ON epochs. These were averaged in each leaning direction and used to extract and calculate the amplitude of the MRCPs reported by Slobounov et al.[41] and were measured from the Cz electrode site. Specifically, mean negativity of three features of the MRCPs were

extracted with respect to ON: the Bereitschaftspotential (BP; -600 ms to -500 ms), the motor potential (MP; -100 ms to 0 ms), and the movement monitoring potential (MMP; 0 ms to +500 ms).[2,41] These outcomes were selected in order to reflect the early (BP) and late (MP) stages of motor planning as well as the execution of movement (MMP).[41,42] All MRCP outcomes were calculated from the averaged data at the Cz electrode, as this electrode site is located closest to the supplementary motor area (SMA) and previous researchers reported the magnitude of MRCP measures during this task being greatest at Cz.[2,41]

To assess feed-back sensorimotor control, an event-related spectral perturbation (ERSP) was calculated during -250 and +250 surrounding the PK event. This provided the change of power at each frequency within the EEG signal during this time period with respect to a reference or baseline period. The 500 ms baseline was derived from -3800 ms to -3300 ms in the epoch. This baseline was selected because the individual was maintaining dual-limb stance prior to the movement trial, therefore change in activity during PK would be additive to that required for maintenance of an upright posture. The result is a color map of signal power change at each timepoint and specified frequency (Figure 5). For this analysis, the grand average in the 500 ms time window was used in the following bands of activity: upper alpha (10-12 Hz), beta (14-25 Hz), and gamma (30-50 Hz).[2] The ERSP was calculated in each band at both the Cz and CPZ electrode sites. These sites were chosen because Cz has been reported to have the greatest ERSP response during lower extremity movements,[41,80] its proximity to SMA, and it has previously been the electrode of interest in a DSLT study.[81] Based on the layout of the 10-20 system,[82] CPz is directly

posterior to Cz, therefore it would be closer to the somatosensory cortex than Cz, allowing for a better evaluation of feed-back sensorimotor control.

3.3.6 Statistical Analysis

Each EEG dependent variable was submitted to a separate two-way (Group by Direction) ANOVA. Post-hoc analyses were addressed using Tukey's HSD tests. Between-group Hedges' g effect sizes and 95% confidence intervals were also calculated. Pearson product moment correlations were used to evaluate relationships among EEG dependent variables and demographic data including patient reported outcomes (IdFAI, FAAM-ADL, FAAM-Sport, injury demographics). Alpha was set at 0.05 for all statistical tests, and all tests were performed in SPSS (Version 23, IBM Corp, Armonk, NY).

3.4 Results

No main effects of Group or Group by Direction interactions were identified in any of the MRCP or ERSP measures at either electrode site ($p>0.05$). Between group effect sizes and 95% CIs can be seen in Tables 5, 6, and 7. Main effects of Direction were identified for both the MP ($F(2,37)=11.694$, $p>0.001$) and MMP ($F(2,37)=20.995$, $p>0.001$) variables (Figure 6), with significantly smaller magnitudes during anterior leaning than either lateral leaning (Table 5). Main effects of direction were identified in the ERSP at the Cz electrode (Table 6**)** in the gamma band ($F(2,37)=13.373$, $p>0.001$) and at the CPz electrode (Table 7**)** in the beta band ($F(2,37)=4.453$, $p=0.018$) and gamma band ($F(2,37)=20.459$, $p>0.001$). The findings in the gamma band ERSP at both the Cz and CPz electrode revealed a greater power increase, or event-related synchronization (ERS) during the anterior leaning relative to both lateral leaning conditions (Figures 7 and 8). The power decrease, or event-related desynchronization (ERD) was significantly greater

at the CPz electrode in the beta band during both lateral leans relative to the anterior leaning (Figure 8). Significant negative relationships were identified between the number of sprains on the involved limb in the CAI group and upper alpha activity at Cz ($r = -0.466$, $p = 0.038$) and CPz ($r = -0.519$, $p = 0.019$) when leaning towards the involved limb. Similar relationships were identified between the number of sprains on the uninvolved limb and upper alpha activity at the limits of stability when leaning to the involved limb at Cz ($r = -0.511$, $p = 0.021$) and CPz ($r = -0.493$, $p = 0.027$). No group differences suggests that although both groups completed the same movements, the overall cortical activity in the voltage (MRCP) and time-frequency (ERSP) domains did not differ between these two groups. An effect of direction was identified in the MRCP, with greater feed-forward activity during lateral leaning to either side, and greater gamma activity during the feed-back portion of anterior leaning.

3.5 Discussion

The purpose of this investigation was to explore whether or not differences in feed-forward and feed-back sensorimotor control are present between groups of CAI patients and matched controls with EEG instrumentation. Our primary hypothesis of group differences was rejected as there were no differences identified between the groups in the MRCP or ERSP outcome measures. Our results do, however, agree with that of Slobounov et al.[2] in regards to the MRCP and movement direction. The magnitude of the MP and the MMP were significantly lower during anterior leaning than that of lateral leaning to either side (Table 5, Figure 6). The values obtained are also similar to those first reported by Slobounov et al.,[41] with those authors reporting MRCP negativity of -12μV during anterior leaning, whereas in the present investigation we found a mean

negativity of -14±6 μV. As suggested by Slobounov et al.,[2] this direction specific change in MRCP may be due to the complexity of ML control as opposed to AP control with a larger group of muscles and synergies to be controlled in order to execute the movement. The difference between AP and ML control is apparent in Figure 6, with peak negativity occurring between +300 and +400 ms after ON during anterior leaning, and continuing to increase during lateral leaning to either side. This increase in negativity is associated with an increase in synaptic activity,[83] further supporting the idea of a more complex and energetically demanding approach to ML control compared to AP control.[2] It is worth noting that all of the trials included in this investigation represent a successful movement, therefore the movement outcome was the same in all groups. However, the MRCP is limited in that it only quantifies the magnitude of ongoing activity rather than the contents of the activity at hand (i.e. the commands being generated). The between-group point estimates do appear to suggest CAI patients have increased activity during early motor preparation, the BP, however the effect sizes cross zero. Despite this, based on our analysis of the MRCP during leaning in different directions there does not appear to be a difference in the overall feed-forward activity between CAI patients and matched controls.

There are contrasting time-frequency results between the present study and those reported by Slobounov et al.[2] These authors reported a significantly greater increase in gamma activity during ML sway relative to AP leaning.[2] However, our findings revealed a larger magnitude burst of gamma activity during anterior leaning compared to lateral leaning towards either limb. As can be seen in Figures 7 and 8, this gamma ERS occurs as the PK point is being reached and movement back to the starting point has begun. Additionally,

the magnitude and band-width within the defined gamma band (30-50 Hz) appears to be greater in the CPz electrode position. This ERS, given the proximity of the CPz site to the somatosensory cortex, supports the idea that the functional role of this gamma activity is a neural detector of postural instability.[2,41,84] While this activity has been described during movements,[2,41] it was also present when individuals were asked to visually recognize unstable postures,[84] supporting the idea that gamma enhancement has a relation to feed-back sensorimotor control. As feedback impairments are one of the most commonly described impairments in the CAI population,[14,73,75] no group differences in gamma activity during the leaning task are surprising. With the ERSP analysis, we are unable to interpret the exact content of the change in power, however it is commonly accepted to represent feed-back activity.[2,35,41,80,85,86] Meta-analysis has suggested that CAI patients weight visual information to a greater extent during feed-back motor activities,[87] likely due to inaccurate somatosensory inputs.[15,16,88] Without recording from electrodes closer to occipital sources, we are unable to perform source localization of this data or plot out precise topographies of the ERSP.

There is agreement in the literature that a power decrease, or ERD, reflects an increase in excitability or activity in the cortex.[35,80,85,86] At both the Cz (Figure 7) and CPz (Figure 8) electrodes, the uninjured control group has a more broad ERD within the higher edge of the beta band. While an increase in gamma power is thought to represent sensorimotor processing,[35] ERD in the alpha and beta bands has consistently been linked to both the planning and execution of movement.[80,85,86] The desynchronization can be interpreted as an increased independence of neural networks due to the suppression of the natural oscillatory frequencies.[36] Information theory suggests this reflects a network with a

higher capacity for information processing.[36] Figures 7 and 8 indicate that leading up to and after PK, there is a more broad-band alpha and beta ERD in the control group than the CAI group. While speculative, it is possible this represents a different strategy used by CAI patients during feed-back control due to a decreased ability to process sensory inputs. CAI patients are known to have impaired detection of light touch[16,88] and vibrotactile[15] sensory stimuli. Pfurtscheller et al.[35] report that alpha and beta can be highly subject-specific so further investigation is warranted to better understand the mechanisms of feed-back sensorimotor control in individual CAI patients.

Although our correlation analysis revealed several significant relationships between outcomes, we do not feel these support our initial hypothesis. Our data revealed significant correlations between the number of sprains on the involved, or more severely injured limb, and the alpha ERD in the Cz and CPz electrodes during sway to the involved limb. However, these correlations were driven by two outliers who reported 7 and 8 sprains on this ankle, and the relationship was not present when these individuals were removed. A similar relationship was noted between the number of sprains on the uninvolved limb and alpha ERD in the Cz and CPz electrodes during involved lateral sway, however, 9 of the CAI patients had unilateral CAI. Therefore these individuals skewed this correlation since they did not have any history of ankle sprain on the uninvolved limb.

While we are confident there are no differences between our groups in our selected outcome measures, it is possible that the selected measures are not sensitive enough to detect the proposed sensorimotor alterations associated with CAI.[11,89] For example, patients with Parkinson's disease have decreased MRCP amplitudes[42,90] and movement-

related ERSP outcomes.[91] It is possible that the sensorimotor adaptations identified through peripheral/behavioral outcomes such as EMG onset with DSLT[1] or force platform during static balance,[73,75] are better suited to identify the downstream effect of sensorimotor preparation and processing adaptations in CAI patients. We suggest future research combine these traditional outcomes in an effort to clarify if changes in external measures such as EMG can be explained by the information in the EEG signal (e.g. corticomotor coherence[92]).

This study is not without limitations, and they should be acknowledged and considered when interpreting our results. One of the largest confounding factors is that we were unable to enroll only unilateral CAI patients. While there is evidence to suggest that there is impaired sensorimotor control in the uninjured limb following lateral ankle sprain,[93] the inclusion of bilateral CAI patients may have hindered our ability to investigate whether or not unilateral or bilateral sensorimotor adaptations in the CNS can be identified in CAI patients with EEG. Lastly, the use of a broad beta bandwidth (14-25 Hz) and taking the grand mean of the power change within the 500 ms around PK in these frequencies may have limited our resolution for between-group analyses at different frequency bands, as it has been suggested that the specific frequencies that show alpha and beta ERD/ERS may differ between individuals or groups.[35]

3.6 Conclusions

The goal of this investigation was to evaluate whether or not a group of CAI patients differed in EEG-derived measures of feed-forward (MRCP) and feed-back (ERSP) sensorimotor control. Our analysis did not reveal any differences in EEG outcome measures between the groups, indicating that the same overall amount of cortical activity

is measured during the leaning movement. We did partially replicate existing findings,[2] suggesting greater feed-forward activity prior to lateral movements compared to anterior movements. Further investigations should aim to identify whether or not different movement tasks or CNS outcomes are able to identify sensorimotor deficits in CAI patients using EEG.

3.7 Tables

Table 4. Participant demographics.

Values are mean and standard deviation unless otherwise stated. NASA PASS: NASA Physical Activity Status Scale; IdFAI: Identification of Functional Ankle Instability; FAAM-ADL: Foot and Ankle Ability Measure Activities of Daily Living Scale; FAAM-Sport: Foot and Ankle Ability Measure Sport Scale.

	Uninjured Control (n = 20)	**CAI (n = 20)**
Female, no (%)	13 (65)	13 (65)
Age, yr	21.70 (2.62)	20.85 (2.28)
Height, cm	168.82 (11.02)	174.75 (7.88)
Mass, kg	68.09 (15.75)	71.68 (18.44)
NASA PASS, median (IQR)	5 (4, 6)	6 (4, 6)
IdFAI	0.00 (0.00)	17.15 (3.59)
Number of Lateral Ankle Sprains	0.00 (0.00)	2.65 (1.93)
Number of Rolls in past 6-months	0.00 (0.00)	3.85 (2.74)
FAAM-ADL, %	100.00 (0.00)	91.37 (6.18)
FAAM-Sport, %	100.00 (0.00)	82.50 (11.80)

Table 5. MRCP outcomes in μV across three different leaning directions.

The means and standard deviations of the mean negativity (μV) for each MRCP outcome in the three directions are seen above, separated by group and Direction mean with standard error. The BP, or Bereitschaftspotential, was measured as the mean negativity from -600ms to -500ms prior to movement onset. The MP, or motor potential, was measured as the mean negativity from -100ms to movement onset. The MMP, or movement monitoring potential, was measured as the mean negativity for the 500ms following movement onset. Hedges' g effect sizes were calculated as control – CAI, with positive point estimates indicating more negativity in the control group. * indicates a significant main effect of Direction ($p < 0.05$); † indicates a significant difference from the Anterior leaning direction ($p < 0.05$).

Measure	Group	Anterior	Involved	Uninvolved
BP	Control	-4.12 (3.62)	-4.02 (3.59)	-3.64 (3.52)
	CAI	-5.60 (2.94)	-4.67 (2.98)	-4.83 (3.15)
	Group Effect Size (95% CI)	-0.44 (-1.07, 0.19)	-0.19 (-0.81, 0.43)	-0.35 (-0.97, 0.27)
	Direction mean (SE)	-4.86 (0.52)	-4.35 (0.52)	-4.24 (0.53)
MP*	Control	-14.75 (5.81)	-17.39 (6.51)	-18.31 (6.62)
	CAI	-13.31 (6.18)	-16.09 (7.40)	-16.07 (6.76)
	Group Effect Size	0.23 (-0.39, 0.86)	0.18 (-0.44, 0.80)	0.33 (-0.30, 0.95)
	Direction mean (SE)	-14.03 (0.95)	-16.74 (1.10) †	-17.19 (1.06) †
MMP*	Control	-17.50 (6.83)	-22.20 (8.07)	-22.40 (7.98)
	CAI	-18.07 (8.67)	-21.99 (9.37)	-21.42 (9.28)
	Group Effect Size	-0.07 (-0.69, 0.55)	0.02 (-0.60, 0.64)	0.11 (-0.51, 0.73)
	Direction mean (SE)	-17.78 (1.23)	-22.09 (1.38) †	-21.91 (1.37) †

Table 6. ERSP outcomes in different leaning directions at the Cz electrode.

The means and standard deviations of the ERSP, in dB, in each bandwidth when the participant reached his/her limit of stability. Lower values in the upper alpha (10-12 Hz) and beta (14-25 Hz) bands indicate an increase in activity. Higher values in the gamma band (30-50 Hz) indicates an increase in activity. Between-group effect sizes are calculated as control – CAI. Due to differences between the functional significance of activity in each band, effect sizes are interpreted as a positive point estimate suggesting greater activity in the upper alpha and beta bands in the control group, and less activity with a positive point estimate in the gamma band. * indicates a significant main effect of Direction ($p < 0.05$); † indicates a significant difference from the Anterior leaning direction ($p < 0.05$).

Measure	**Group**	**Anterior**	**Involved**	**Uninvolved**
Upper Alpha	Control	-1.15 (0.99)	-1.23 (1.19)	-0.87 (0.99)
	CAI	-1.39 (1.30)	-1.17 (1.32)	-1.42 (1.09)
	Group Effect Size (95% CI)	-0.20 (-0.82, 0.42)	0.04 (-0.58, 0.66)	-0.51 (-1.14, 0.12)
	Direction mean (SE)	-1.27 (0.18)	-1.20 (0.20)	-1.15 (0.17)
Beta	Control	-0.94 (1.16)	-1.19 (1.19)	-1.09 (1.30)
	CAI	-0.68 (0.87)	-0.69 (0.84)	-0.94 (0.79)
	Group Effect Size	0.24 (-0.38, 0.87)	0.47 (-0.16, 1.10)	0.14 (-0.48, 0.76)
	Direction mean (SE)	-0.81 (0.16)	-0.94 (0.16)	-1.02 (0.17)
Gamma*	Control	0.59 (1.21)	0.09 (0.82)	-0.04 (0.90)
	CAI	0.60 (0.92)	0.24 (0.76)	0.10 (0.72)
	Group Effect Size	0.01 (-0.61, 0.63)	0.18 (-0.44, 0.80)	0.17 (-0.45, 0.79)
	Direction mean (SE)	0.60 (0.17)	0.16 (0.13) †	0.03 (0.13) †

Table 7. ERSP outcomes in different leaning directions at the CPz electrode.

The means and standard deviations of the ERSP, in dB, in each bandwidth when the participant reached his/her limit of stability. Lower values in the upper alpha (10-12 Hz) and beta (14-25 Hz) bands indicate an increase in activity. Higher values in the gamma band (30-50 Hz) indicates an increase in activity. Between-group effect sizes are calculated as control – CAI. Due to differences between the functional significance of activity in each band, effect sizes are interpreted as a positive point estimate suggesting greater activity in the upper alpha and beta bands in the control group, and less activity with a positive point estimate in the gamma band. * indicates a significant main effect of Direction ($p < 0.05$); † indicates a significant difference from the Anterior leaning direction ($p < 0.05$).

Measure	**Group**	**Anterior**	**Involved**	**Uninvolved**
Upper Alpha	Control	-1.59 (1.20)	-1.76 (1.33)	-1.45 (1.00)
	CAI	-1.75 (1.61)	-1.94 (1.63)	-1.93 (1.34)
	Group Effect Size (95% CI)	-0.11 (-0.73, 0.51)	-0.12 (-0.74, 0.50)	-0.40 (-1.03, 0.22)
	Direction mean (SE)	-1.67 (0.22)	-1.85 (0.24)	-1.69 (0.19)
Beta*	Control	-0.94 (1.01)	-1.20 (0.92)	-1.13 (0.85)
	CAI	-0.74 (1.06)	-1.03 (0.98)	-1.18 (0.88)
	Group Effect Size	0.19 (-0.43, 0.81)	0.18 (-0.44, 0.80)	-0.06 (-0.68, 0.56)
	Direction mean (SE)	-0.84 (0.16)	-1.11 (0.15) †	-1.16 (0.14)
Gamma*	Control	1.01 (1.23)	0.25 (0.73)	0.14 (0.81)
	CAI	1.09 (1.08)	0.32 (0.80)	0.23 (0.69)
	Group Effect Size	0.07 (-0.55, 0.69)	0.09 (-0.53, 0.71)	0.13 (-0.49, 0.75)
	Direction mean (SE)	1.05 (0.18)	0.29 (0.12) †	0.19 (0.12) †

3.8 Figures

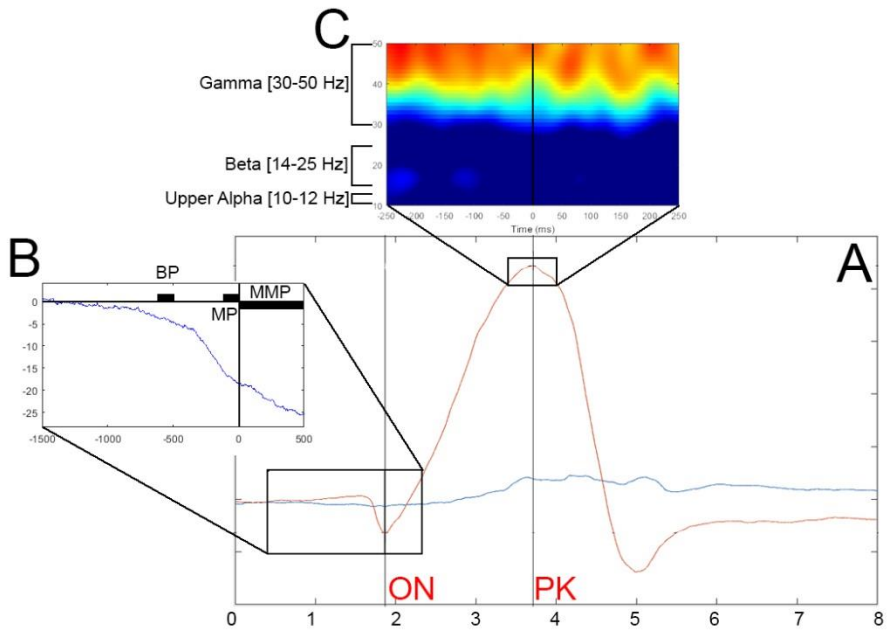

Figure 5. Overview of outcome measures and events relating to voluntary leaning.

An example of the progression of the My (medial-lateral moment) output is seen in A. ON, labelled in red, is the time used for the onset of movement at the maximal displacement of the anticipatory postural adjustment. PK is identified as the maximum lateral (or anterior) point during the leaning task. B represents the relationship between the movement itself and the motor-related cortical potentials measured in this investigation. The mean values of BP: bereitschaftspotential, was measured from -600 to -500 ms prior to movement, MP: motor potential, was measured from -100 to ON, and MMP: movement monitoring potential, was measured from ON to 500ms after ON. C represents an exemplar ERSP that is calculated during the time window from -250ms prior to and +250ms after PK. The ERSP is a colormap, with more red colors indicating a power increase and more blue colors representing a power decrease. The three bands analyzed are also depicted: upper alpha (10-12 Hz), beta (14-25 Hz), and gamma (30-50 Hz).

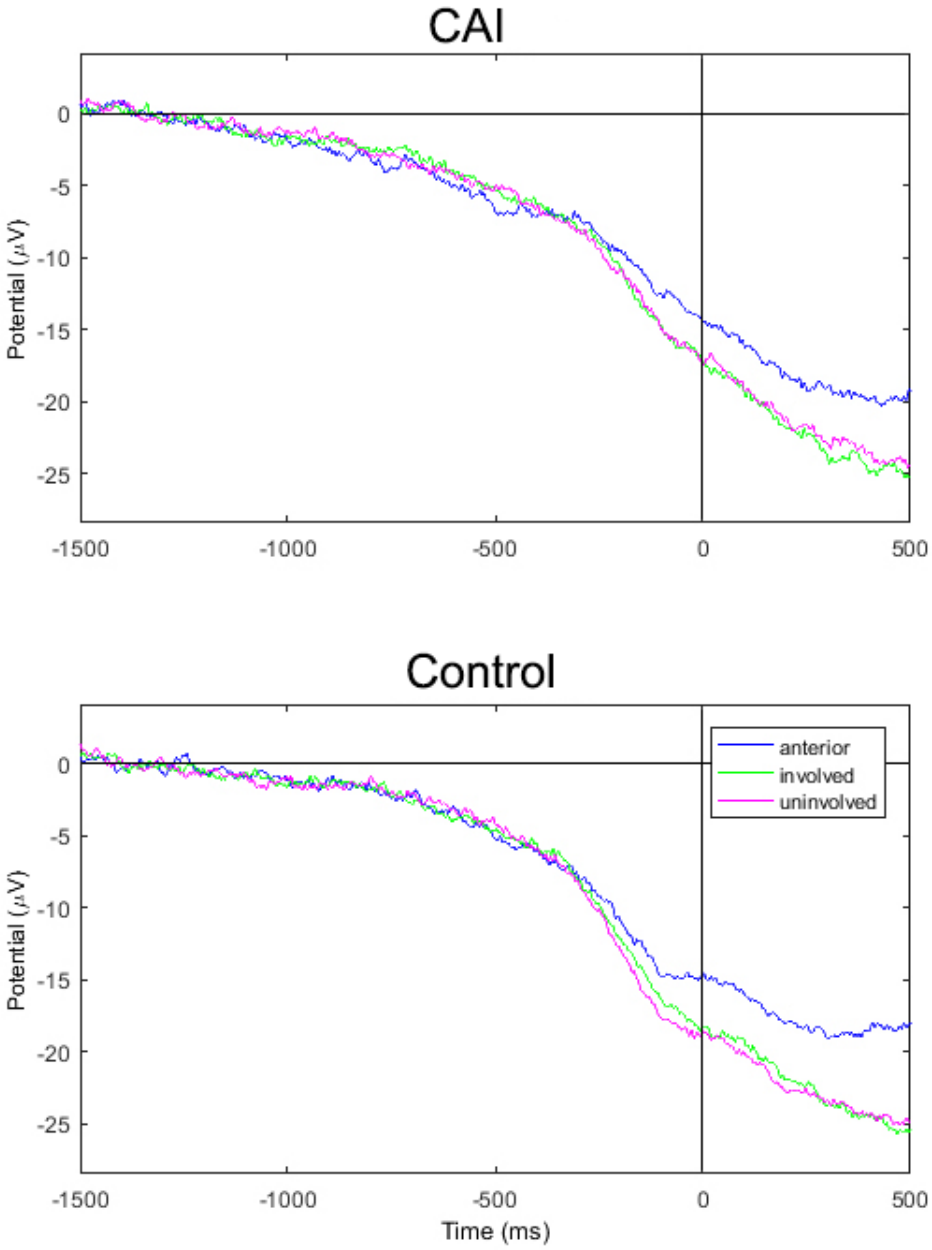

Figure 6. MRCP waveforms compared across leaning directions.

The slowly evolving waveform from which the MRCP outcomes were calculated can be seen above. Units are in µV, with more negative values indicating greater activity. The difference between lateral leaning and anterior leaning is very apparent beginning approximately 100ms prior to movement onset.

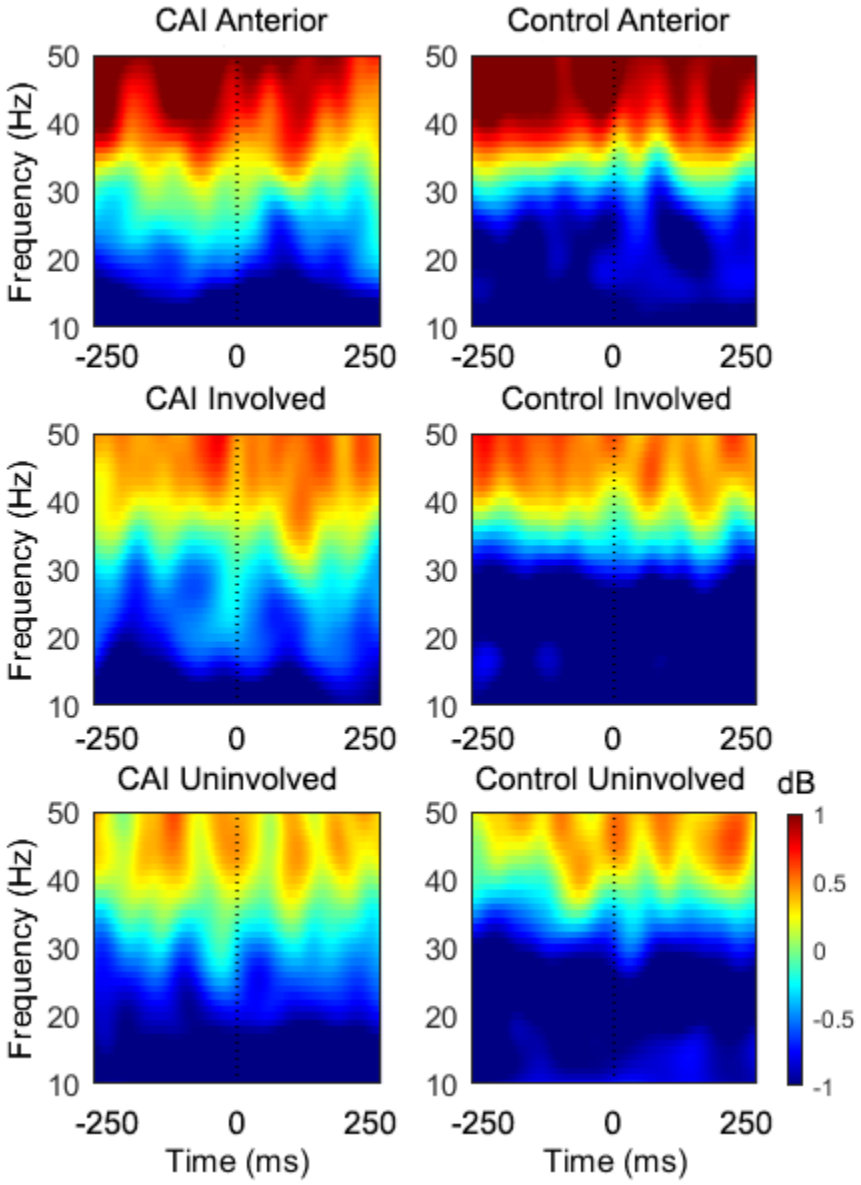

Figure 7. ERSP, in dB, at the Cz electrode during voluntary leaning in three different directions.

The ERSP, or event-related spectral perturbation, reveals the change in power in a given frequency band at a given time with respect to a baseline period. The scale on the bottom right hand side of the figure indicates how to interpret different colors. Red colors indicate a power increase, and blue colors indicate a power decrease. In the lower frequencies, below 30Hz, more blue colors indicate greater activity. Red colors indicate greater activity in frequencies > 30 Hz.

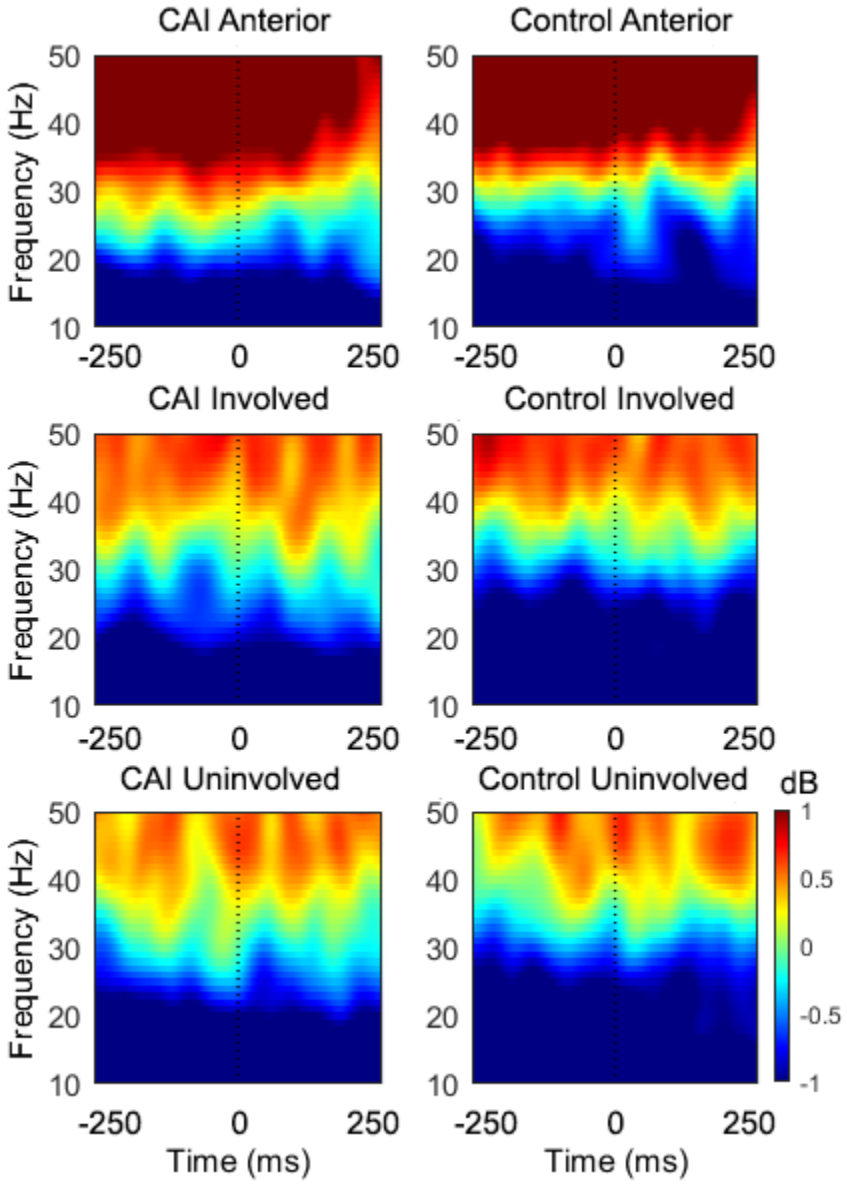

Figure 8. ERSP, in dB, at the CPz electrode during voluntary leaning in three different directions.

The ERSP, or event-related spectral perturbation, reveals the change in power in a given frequency band at a given time with respect to a baseline period. The scale on the bottom right hand side of the figure indicates how to interpret different colors. Red colors indicate a power increase, and blue colors indicate a power decrease. In the lower frequencies, below 30Hz, more blue colors indicate greater activity. Red colors indicate greater activity in frequencies > 30 Hz. Compared to the magnitudes (colors) of activity in Figure 7, feed-back sensorimotor activity appears to be greater at the CPz electrode than the Cz electrode.

CHAPTER 4: FEED-FORWARD SENSORIMOTOR CONTROL DURING A LATERAL STEPPING TASK IN CHRONIC ANKLE INSTABILITY PATIENTS

4.1 Abstract

Chronic ankle instability (CAI) patients are known to have impaired feed-forward control assessed during discrete tasks such as gait initiation, gait termination, and dual-to-single-limb transitions (DSLT). Despite this evidence, no investigations have looked at cortical activity during weight-bearing tasks. Therefore the purpose of this investigation was to evaluate feed-forward cortical activity during a DSLT in CAI patients relative to controls. Cortical activity was measured using electroencephalography (EEG) from 20 CAI patients (age: 20.55±2.44yr; mass: 70.31±16.89kg; height: 171.00±7.83cm) and 20 matched, uninjured controls (age: 21.20±2.73yr; mass: 68.08kg; height: 168.74cm). Participants performed a total of 120 DSLT trials to each limb. Feed-forward cortical activity was assessed with an event-related spectral perturbation (ERSP), revealing the log change in power in the upper alpha (10-12Hz), beta (14-25Hz), and gamma (30-50Hz) bands. The grand average of the ERSP was taken in the 500ms prior to DSLT onset in each band. Patient-reported outcomes (PROs) were collected including the Foot and Ankle Ability Measure activities of daily living (FAAM-ADL) and Sports (FAAM-Sports) scales. Data were analyzed using separate repeated measures ANOVAs to assess for differences between groups and limb. Pearson product moment correlations were used to assess relationships between PROs and ERSP outcomes. No interactions or main effects of group or limb were identified in any of the ERSP outcomes ($p>0.05$). A moderate relationship was identified between the FAAM-ADL and alpha activity prior to

DSLT on the involved limb (r=-0.44, p=0.05) linking lower perceived function to decreased feed-forward activity. Despite no group differences, further research is warranted to determine if feed-back impairments in CAI patients can be linked with EEG outcomes.

4.2 Introduction

The control of upright balance and posture results from an intricate marriage and interaction of sensory and motor functions, commonly referred to as sensorimotor control. There are thought to be two broad categories of sensorimotor actions: feed-back (i.e. reaction-oriented) and feed-forward (i.e. preparation-oriented) sensorimotor control. The former relies on a constant use of afferent inputs to refine ongoing motor activities[37] where the latter operates in a predictive manner, minimizing the destabilizing effects of generated movements or predicable postural perturbations.[94] Feed-forward sensorimotor control is often tested by observing the anticipatory postural adjustments (APA) that are generated prior to voluntary movement. An APA can be observed in the center-of-pressure (COP) when an individual transitions from dual-limb to single-limb stance (DSLT). During the DSLT, the initiation of the movement is a lateral shift of the COP to the contralateral limb resulting from increased loading on this limb, before the COP shifts back to the new stance limb.[81]This feed-forward mechanism uses a controlled destabilizing event to minimize the destabilization of the transition,[94] and has been tested in healthy individuals[81] as well as those with chronic ankle instability (CAI),[1,23] and those with anterior cruciate ligament injury.[95]

CAI is a condition that occurs in approximately 40% of individuals who suffer a lateral ankle sprain.[72] It is characterized by persistent complaints and episodes of instability or the ankle 'giving way' or rolling inwards.[8,9] A broad spectrum of mechanical,[96] perceptual,[57] sensory,[16,88] and motor[14,21,73,75] impairments may also be present in these individuals with several subgroups of patients being described.[68] Feed-back deficits are well established via instrumented force platform analysis of COP measures and supported by multiple meta-analyses.[73,75] There are reports of bilateral balance deficits after lateral ankle sprain,[93] however Wikstrom et al.[97] found that these may not be present in CAI patients. Feed-forward impairments have received less attention in the literature, yet Hass et al.[22] reported a decreased COP displacement during gait initiation in CAI patients. The decreased COP displacement was only identified in the injured limb in CAI patients, as no differences were noticed in the uninjured limb. Van Deun et al.[1] assessed muscle onset times during a DSLT task and found that CAI patients had delayed muscle onset times relative to uninjured controls, providing further evidence of feed-forward dysfunction.

Feed-forward sensorimotor control is responsible for the planning and implementation of APAs. APAs are believed to be controlled by subcortical (e.g. basal ganglia, cerebellum)[94] and cortical[41,81] regions of the central nervous system (CNS) and appear to be task-specific. Measuring APAs may be particularly relevant for CAI researchers as growing evidence illustrates altered corticomotor activity in those with CAI using a variety of assessment techniques (e.g. decreased excitability of the fibularis longus and soleus using transcranial magnetic stimulation (TMS)[31,33,34,76]. Using EEG and a joint-loading paradigm[32] no differences in somatosensory activity between groups of CAI patients and healthy controls were identified. Varghese et al.[81] recently used EEG to

evaluate the cortical activity related to the APA seen during a DSLT task in healthy controls. The authors found phasic activation and deactivation in the alpha and beta bands,[81] typically associated with preparatory motor.[35,36,80,86] However, EEG has not yet been used to evaluate weight bearing sensorimotor function in CAI patients.

The aim of this investigation was to evaluate whether or not CAI patients displayed altered EEG activity during a DSLT relative to uninjured controls. Considering the reported delayed muscle onset times during this activity,[1] and decreased corticomotor excitability in CAI patients[32-34,76] we hypothesize that CAI patients will have less cortical activity compared to a group of uninjured controls. We also aim to investigate the differences in cortical activity when transitioning to the injured relative to the uninjured limb in CAI patients. Since between-limb differences have been reported during gait initiation,[22] we hypothesize activity will be lowest in the CAI patients when transitioning to their injured limb. Lastly, we aim to explore our data for relationships between injury severity and cortical activity relating to feed-forward sensorimotor control and have hypothesized that patients with worse scores on patient-reported outcomes will display lower feed-forward EEG activity.

4.3 Methods

4.3.1 Study Design

A cross-sectional design was used to compare feed-forward EEG activity prior to a DSLT between groups of CAI patients and uninjured controls. Independent variables included Group and Limb (involved/dominant, uninvolved/nondominant). Dependent variables included the ERSP (in dB) in the upper alpha (10-12 Hz), beta (14-25 Hz), and gamma

(30-50 Hz) bands at the Cz (premotor and primary motor cortex) and CPz (primary somatosensory and posterior parietal cortex) electrodes.

4.3.2 Participants

Participant demographics can be seen in Table 8. CAI inclusion criteria were consistent with recommendations by the International Ankle Consortium; CAI patients must have experienced at least one significant lateral ankle sprain, ≥2 episodes of the ankle 'rolling' or 'giving way' within the 6 months prior to participating in the study, an Identification of Functional Ankle Instability(IdFAI) score ≥11.[45] If a patient had bilateral CAI, the limb with the lower Foot and Ankle Ability Measure activities of daily living (FAAM-ADL) and sports (FAAM-Sport) score was indicated as the involved limb.[78] Uninjured controls had no history of an ankle sprain or episodes of the ankle giving way in either ankle, a score <11 on the IdFAI, and a score >99% on the FAAM-ADL and >97% on the FAAM-Sport.[45] Uninjured controls were matched to a CAI patient based on sex, mass(kg, ± 10%), height(cm, ± 10%), and physical activity(± 1 NASA Physical Activity Status Scale). Exclusion criteria for all groups were known balance and vision problems, acute lower extremity or head injury within 3 months of enrollment, a history of concussion, chronic musculoskeletal conditions known to affect balance(e.g. ACL deficiency), a history of lower extremity musculoskeletal surgery, or any other neurologic conditions that may impact postural control(e.g. diabetes) or EEG signal analysis(e.g. epilepsy). All experimental procedures performed were in accordance with the Declaration of Helsinki and were approved by the Institutional Review Board at the University of North Carolina at Charlotte (IRB 11-15-06).

4.3.3 Testing Protocol

Upon arriving for the testing session, participants were given a description of the study and then provided written informed consent. Four patient-reported outcome measures (PROs) were collected: FAAM-ADL, the FAAM-Sport, the 11-item Tampa Scale of Kinesiophobia (TSK11), and the Fear Avoidance Beliefs Questionnaire physical activity subscale (FABQ). Participants were familiarized with the movement task. In brief, the participant would stand on the force platform with their feet shoulder-width apart and their arms relaxed hanging at the side. Upon verbal cue of either "right" or "left" the participant would transition from dual-limb support to standing and maintaining balance on either the right or left leg, respectively. Each trial was 8-seconds induration, and the verbal cue was given between 1 and 2 seconds after the beginning of the trial. Instructions were given for the participant to focus on an even weight distribution prior to each new trial. A total of 120 trials were collected on each limb, for a total of 240 trials, which occurred in a random order. Testing was broken into four blocks of 60 trials, with a 4 minute seated break between blocks.

4.3.4 Equipment

Force platform data were collected using an AMTI Accusway force platform (AMTI Inc., Watertown, MA) connected to a portable laptop using a PJB-101 (AMTI Inc., Watertown MA) interface. Data was sampled at 200 Hz and recorded using the NetForce software (Version 3.5.3, AMTI Inc., Watertown, MA).

EEG data was collected using a 32-channel Quick-Cap (Compumedics Neuroscan, Charlotte, NC) connected to a 40-channel NuAmps (Compumedics Neuroscan, Charlotte,

NC) digital EEG amplifier. EEG signals were amplified (gain: 19), filtered (DC-400Hz), and sampled at 1000Hz into the Curry 7 (Version 7.0.9, Compumedics Neuroscan, Charlotte, NC) software on a dedicated computer and saved for offline analysis. A custom montage was used to collect data from 14 EEG channels (FP1, FP2, F3, Fz, F4, FC3, FCz, FC4, C3, Cz, C4, CP3, CPz, CP4), four EOG channels placed above and below the left eye and lateral to each eye, and two earlobe clip electrodes (A1, A2). The linked A1/A2 earlobes served as a reference for all EEG recordings. Impedance was kept below 5 kOhms throughout testing.

Force platform and EEG data were synchronized using a custom-built trigger device. The device delivered a 4.8V TTL pulse simultaneously to the NuAmps amplifier and the PJB-101 force platform interface system. The TTL pulse created an event code in the continuous EEG file and triggered the beginning of the trial in NetForce, creating a single file per leaning trial.

4.3.5 Data Analysis

The onset of the DSLT, defined as the beginning of the APA, or lateral excursion of the COP[1,23,81] was visually identified in each trial (Figure 9). The latency of the onset of the APA (ON), was added to the latency of the EEG trigger event so that data could be segmented.

EEG data were processed offline in Curry 7 and using scripts in EEGLAB version 13.6.5b[79] within MATLAB 2016a (Mathworks Inc., Natik, MA). Curry 7 was used for baseline and ocular artifact correction and then data was exported in to MATLAB for further processing. The data were low-pass filtered at 100Hz to remove trigger artifact

and then segmented into 3s long epochs around ON (-1500 ms to +1500 ms). Epochs were baseline corrected (-1200 ms to -1000ms)[81] and visually inspected, with noisy trials and trials with significant movement artifact being rejected. A minimum of 40 trials were used for analysis for each condition.[81]

The EEG signal is a complex signal comprised of many frequency components at a given time. An ERSP analysis computes the change in power at each frequency with respect to an event. The ERSP was calculated using the newtimef function in EEGLAB v13.6.5b, which calculates the average event-related power change in a logarithmic scale (dB) with respect to the average pre-event spectral power as a baseline. The ERSP was grand averaged across the 500ms window in three bands of activity: upper alpha (10-12Hz), beta (14-25 Hz), and gamma (30-50Hz). All three bands were selected due to their role in sensorimotor processing and movement preparation.[2,35,36,81] A decrease in upper alpha and beta power represent an increase in cortical excitability and increases in gamma power are believed to represent rapid sensorimotor processing.[35,36] The ERSP was calculated in all three bands at the Cz and CPz electrode sites. The Cz electrode side was chosen for consistency with a previous DSLT investigation,[81] as its location is closest to the supplementary motor cortex and primary motor cortex overlying the lower extremity muscles within the 10-20 system.[82] CPz was selected as it is just posterior to Cz, therefore it would allow monitoring of activity closer to the somatosensory cortex, and it’s contributions to feed-forward control.

4.3.6 Statistical Analysis

Separate 2-way (Group [control, CAI] by Limb [involved/dominant, uninvolved/nondominant]) repeated measures ANOVAs were used for all 6 EEG dependent variables. Tukey's HSD post-hoc tests were used to evaluate direction of differences. Group differences in PROs were assessed using independent samples t-tests. Linear relationships between feed-forward cortical activity, PROs, and injury demographics measures were assessed using Pearson product moment correlations. These were only run on dependent variables in the CAI group, due to the homogeneity of these outcomes in the control group. Hedges' g effect sizes and 95% confidence intervals were calculated for between group (CAI – control) and between-limb (involved/dominant – uninvolved/nondominant) comparisons. All tests were performed in SPSS (Version 23, IBM Corp, Armonk, NY) at an alpha of 0.05.

4.4 Results

A summary of our EEG outcomes can be seen in Tables 9 and 10. No main effects of Group, Limb, or Group * Limb interactions were identified in any of the 6 EEG outcomes ($p > 0.05$). The ERSP plots at the Cz and CPz electrodes can be seen in Figures 10 and 11, respectively. Between-group effect sizes were small, and all of the 95% confidence intervals crossed zero. As expected, given our inclusion criteria the CAI patients had significantly worse scores on all PROs on both limbs ($p<0.05$). Two significant correlations were identified: a moderate negative relationship between the FAAM-ADL and upper alpha activity prior to transitioning to the involved limb at CPz ($r=-0.444$, $p=0.05$), and a moderate negative relationship between the number of rolls on

the uninvolved limb and beta activity at Cz prior to transitioning to the uninvolved limb (r=-0.501, p=0.025). Only 6 out of 20 CAI patients in this sample indicated one or more rolls to the uninvolved limb in the past 6 months, therefore this finding was driven by the uneven distribution of this outcome variable.

4.5 Discussion

Our initial hypothesis that feed-forward cortical activity would be decreased in the CAI group relative to the uninjured controls was rejected as we failed to identify any significant group differences (Tables 9 and 10). We did identify significantly worse scores on two PROs evaluating health-related quality of life, the FABQ and TSK-11, in the CAI patients relative to uninjured controls. This finding agrees with the results of previous investigations reporting significantly worse, or decreased health-related quality of life, in CAI patients compared to uninjured controls.[57] We do not feel our correlations fully support our secondary hypothesis that a relationship between PROs and EEG outcome measures would be present. A relationship between patient-reported function as measured by the FAAM-ADL and the upper alpha activity at CPz prior to DSLT towards the injured limb can be seen in Figure 12. Interestingly, it appears that patients with worse perception of functions during activities of daily living have less suppression of upper alpha activity prior to movement. Upper alpha suppression, or event-related desynchronization (ERD), is commonly reported prior to movement in healthy individuals[35,85] therefore we feel this partially supports the idea that patients with worse symptoms of CAI have negative alterations in feed-forward sensorimotor control.

The hypothesis that between-limb differences would be present was also rejected, as we did not identify any significant differences between limbs in the CAI group. As seen in Tables 9 and 10, all of the between-limb effect sizes crossed zero, suggesting there are no differences in feed-forward sensorimotor control measured by EEG between limbs in CAI patients. A confounding factor in this analysis is that we did not include only unilateral CAI patients in this investigation. Nine CAI patients had bilateral CAI and 11 had unilateral CAI. In a secondary analysis, we dichotomized these groups into unilateral and bilateral CAI to compare feed-forward activity between limbs with paired-samples t-tests. No differences between limbs were identified in the bilateral CAI group ($p>0.05$). However, significantly more ERD was identified at the Cz electrode in the upper alpha band prior to DSLT towards the involved limb in unilateral CAI patients. This finding suggests there may be limb-specific adaptations to feed-forward sensorimotor control. This is supported by Hass et al.[22] who reported impaired gait initiation COP displacement to the involved limb only. However, the small sample size for this secondary analysis warrants caution with the interpretation and further investigation to better examine the between-limb differences in unilateral and bilateral CAI patients.

A lack of group differences may be due to the manner in which the ERSP was quantified, but our results agree with the existing literature. Needle et al.[32] did not report significant differences between CAI patients and uninjured controls during ankle joint loading. The authors reported a desynchronization of activity (i.e. increased cortical activation) in the upper alpha band in the somatosensory cortex as the traction force on the joint increased[32] in both groups. While this result may suggest there are no differences in cortical function, it is important to understand how ERSP was quantified in these investigations. The

present investigation used the grand average of the ERSP within a 500ms epoch prior to movement onset in three distinct bands of activity. Needle et al.[32] reported the peak value in a band of activity. It is possible that no group differences were identified by Needle et al.[32] or the present investigation because the ERSP was quantified with a single number. Almost all between group effect sizes have point estimates favoring greater activity in the control group apart from the gamma bandwidth towards the involved limb in both electrodes (Tables 9 and 10). Although small in magnitude there appears to be greater low frequency (10-12 Hz) activity in the control group relative to the CAI group. It is possible that this may represent intact sensorimotor processing[86] as part of motor preparation, where this isn't as pronounced in the CAI group. Taken together with the correlation between this measure at the CPz electrode and the FAAM-ADL (Figure 12), it is possible that utilizing a more sensitive analysis could reveal group differences. EEG is a complex signal comprised of multiple frequencies within a given time period. Therefore, it is possible that using a single number to quantify a changing signal has limited these two investigations in explaining sensorimotor dysfunction in CAI patients. Therefore, we suggest future studies use smaller time windows, as well as applying advanced techniques such as permutation-based statistics to analyze their results.[98]

Hiller et al.[68] suggest there are up to 7 subgroups of CAI patients, each presenting with different impairments and symptoms, therefore some CAI patients may have altered feed-forward control whereas others may not. Mixed results in the CAI dual-task literature further support the heterogeneity of sensorimotor alterations. These studies compare balance-only conditions to balance while dual-tasking, or performing a cognitive task while balancing, and generate inferences about the relative attention required to maintain

balance.[28,55,65-67] There is evidence to suggest that balance may get worse while dual-tasking,[28] although two recent studies have shown that balance may actually improve in CAI patients while dual-tasking.[66,67] Burcal and Wikstrom[55] investigated the direction of dual-task effect (i.e. did balance improve or get worse while dual-tasking) to see if it was related to injury severity in CAI patients. The authors found a link between worse balance while dual-tasking and an increased number of episodes of the ankle giving way, interpreted as patients with more severe symptoms requiring more attentive resources to maintain single-limb balance.[55] Given the high variability in the present study in our EEG outcome measures and the link between patient-reported function and feed-forward cortical activity (Figure 12), it remains a possibility that the heterogeneity within our CAI sample could have masked differences. We recommend that efforts are made in future investigations to stratify CAI patients into a single subgroup[68] to better assess for sensorimotor impairments.

This study is not without limitations, and the testing block design significantly limited our ability to compare results with the existing DSLT EEG literature.[81] Varghese et al.[81] evaluated the ERSP among differing conditions, but each test block consisted of 10 trials of the same movement condition. The randomized trial design used in the current investigation may better reflect a contingent negative variation (CNV) study design, in which an imperative stimulus dictates the correct response. In this study, this would be indicated by which limb to transition onto. Despite these differences, very similar patterns of alpha and beta power modulation have been reported in movement-related CNV studies.[99-101] Another limitation is the potential of movement artifacts in our averaged EEG data. One of the significant sources of artifact in movement-related EEG

studies are due to the slight impedance changes that can occur during movement.[102] While others have used independent component analysis (ICA) to identify these artifacts and remove them from the data[81,102,103] our limited EEG electrode montage limited our ability to conduct an appropriate ICA-based artifact correction. However, special effort was made to reject trials with obvious movement artifact, and the upper alpha band was chosen to prevent contamination of the data with these artifacts, which were measured to occur at less than 10Hz in our raw data. Lastly, as discussed in the prior paragraph, a convenience sample was used for CAI patients and we enrolled individuals with both bilateral and unilateral CAI, due to the exploratory nature of this investigation. The inclusion of CAI patients with bilateral CAI may have masked a between-limb difference, as supported by the significant difference noted in upper alpha activity prior to transitioning to the involved limb.

4.6 Conclusions

Our exploratory study using EEG-derived outcome measures during a DSLT did not reveal any significant between-group differences in feed-forward sensorimotor control. Overall we did not identify an effect of limb, however we did identify significantly greater ERD (i.e. more activity) in 11 patients with unilateral CAI when transitioning to their injured limb. As CNS-oriented investigations continue in those with CAI, it is important to identify those outcomes that best evaluate the cascade of sensorimotor alterations associated with this musculoskeletal condition. Therefore, future research is warranted, with appropriate measures, to examine the relationship between other established feed-back deficits and cortical activity measured by EEG.

4.7 Tables

Table 8. Participant demographics.

Values are mean and standard deviation unless otherwise stated. NASA PASS: NASA Physical Activity Status Scale; IdFAI: Identification of Functional Ankle Instability; FAAM-ADL: Foot and Ankle Ability Measure Activities of Daily Living Scale; FAAM-Sport: Foot and Ankle Ability Measure Sport Scale; TSK-11: Tampa Scale of Kinesiophobia 11-item; FABQ: Fear Avoidance Beliefs Questionnaire. * indicates a significant difference between groups ($p < 0.05$).

	Uninjured Control	**CAI**
Female, no (%)	11 (55)	11 (55)
Age, yr	21.20 (2.73)	20.55 (2.24)
Height, cm	168.74 (10.85)	171.00 (7.83)
Mass, kg	68.08 (15.41)	70.31 (16.89)
NASA PASS, median (IQR)	5 (4, 6)	6 (5, 7)
IdFAI Involved	0.00 (0.00)	19.00 (4.28)*
IdFAI Uninvolved	0.00 (0.00)	8.80 (9.12)*
Number of Ankle Sprains, Involved	0.00 (0.00)	2.70 (1.87)*
Number of Ankle Sprains, Uninvolved	0.00 (0.00)	1.15 (1.57)*
Number of Rolls in past 6-months, Involved	0.00 (0.00)	4.45 (3.03)*
Number of Rolls in past 6-months, Uninvolved	0.00 (0.00)	0.85 (1.53)*
FAAM-ADL Involved, %	100.00 (0.00)	88.64 (7.16)*
FAAM-ADL Uninvolved, %	100.00 (0.00)	97.38 (3.29)*
FAAM-Sport Involved, %	100.00 (0.00)	77.97 (12.48)*
FAAM-Sport Uninvolved, %	100.00 (0.00)	93.44 (10.68)*
TSK-11	13.55 (2.76)	19.75 (4.06)*
FABQ	0.90 (2.61)	10.25 (3.64)*

Table 9. ERSP outcomes at the Cz electrode.

The means and standard deviations of the ERSP, in dB, in each bandwidth in the 500ms prior to the DSLT onset. More negative values in the upper alpha (10-12 Hz) and beta (14-25 Hz) bands indicate higher activity. More negative values in the gamma band (30-50 Hz) indicates decreased activity. Between-group effect sizes are calculated as control – CAI. Due to differences between the functional significance of activity in each band, effect sizes are interpreted as a positive point estimate suggesting greater activity in the upper alpha and beta bands in the control group, and less activity with a positive point estimate in the gamma band. Between-limb effect sizes are calculated as involved – uninvolved, with positive effect sizes indicating greater activity preceding a transition to the involved limb.

Measure	**Group**	**Involved**	**Uninvolved**	**Limb Effect Size (95% CI)**
Upper Alpha	Control	-0.24 (0.46)	-0.20 (0.41)	0.09 (-0.53, 0.71)
	CAI	-0.18 (0.42)	-0.17 (0.41)	0.03 (-0.59, 0.64)
	Group Effect Size (95% CI)	0.12 (-0.50, 0.74)	0.06 (-0.56, 0.68)	-
	Limb mean (SE)	-0.21 (0.07)	-0.18 (0.07)	-
Beta	Control	-0.21 (0.33)	-0.32 (0.50)	-0.35 (-0.97, 0.28)
	CAI	-0.22 (0.20)	-0.25 (0.24)	-0.11 (-0.73, 0.51)
	Group Effect Size	-0.03 (-0.65, 0.59)	0.19 (-0.44, 0.81)	-
	Limb mean (SE)	-0.22 (0.04)	-0.29 (0.06)	-
Gamma	Control	-0.07 (0.19)	-0.09 (0.21)	-0.15 (-0.77, 0.47)
	CAI	-0.08 (0.13)	-0.08 (0.19)	0.02 (-0.60, 0.64)
	Group Effect Size	-0.11 (-0.73, 0.51)	0.04 (-0.58, -0.66)	-
	Direction mean (SE)	-0.08 (0.03)	-0.09 (0.03)	-

Table 10. ERSP outcomes at the CPz electrode.

The means and standard deviations of the ERSP, in dB, in each bandwidth in the 500ms prior to the DSLT onset. More negative values in the upper alpha (10-12 Hz) and beta (14-25 Hz) bands indicate higher activity. More negative values in the gamma band (30-50 Hz) indicates decreased activity. Between-group effect sizes are calculated as control – CAI. Due to differences between the functional significance of activity in each band, effect sizes are interpreted as a positive point estimate suggesting greater activity in the upper alpha and beta bands in the control group, and less activity with a positive point estimate in the gamma band. Between-limb effect sizes are calculated as involved – uninvolved, with positive effect sizes indicating greater activity preceding a transition to the involved limb.

Measure	**Group**	**Involved**	**Uninvolved**	**Limb Effect Size (95% CI)**
Upper Alpha	Control	-0.36 (0.49)	-0.39 (0.35)	-0.05 (-0.66, 0.57)
	CAI	-0.33 (0.45)	-0.26 (0.39)	0.16 (-0.46, 0.78)
	Group Effect Size (95% CI)	0.07 (-0.55, 0.69)	0.33 (-0.29, 0.96)	-
	Limb mean (SE)	-0.35 (0.08)	-0.32 (0.06)	-
Beta	Control	-0.20 (0.24)	-0.29 (0.41)	-0.35 (-0.97, 0.28)
	CAI	-0.24 (0.23)	-0.25 (0.19)	-0.06 (-0.68, 0.56)
	Group Effect Size	-0.14 (-0.76, 0.48)	0.13 (-0.49, 0.75)	-
	Limb mean (SE)	-0.22 (0.04)	-0.27 (0.05)	-
Gamma	Control	-0.07 (0.16)	-0.10 (0.15)	-0.23 (-0.85, 0.40)
	CAI	-0.11 (0.18)	-0.11 (0.15	0.00 (-0.62, 0.62)
	Group Effect Size	-0.26 (-0.88, 0.37)	-0.09 (-0.71, 0.53)	-
	Direction mean (SE)	-0.09 (0.03)	-0.10 (0.02)	-

4.8 Figures

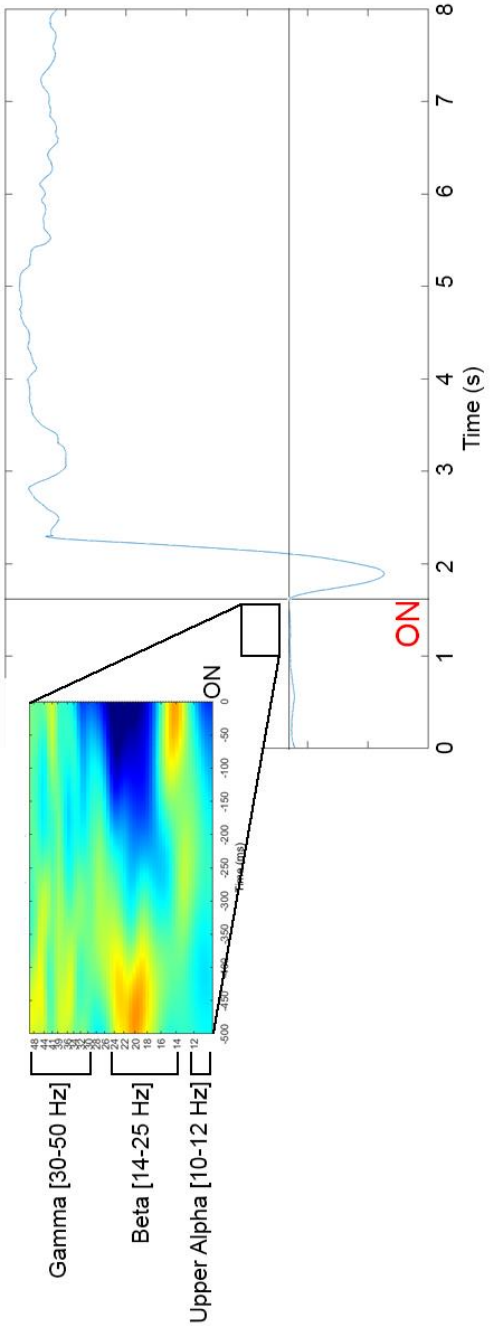

Figure 9. Onset identification and ERSP window.

The onset of movement, or ON, was visually identified at the point indicated by the vertical line. As can be seen in the upper left side, the event-related spectral perturbation was calculated within the 500 milliseconds prior to ON. The specific bands analyzed: upper alpha (10-12 Hz), beta (14-25 Hz), and gamma (30-50 Hz) are represented next to the ERSP plot.

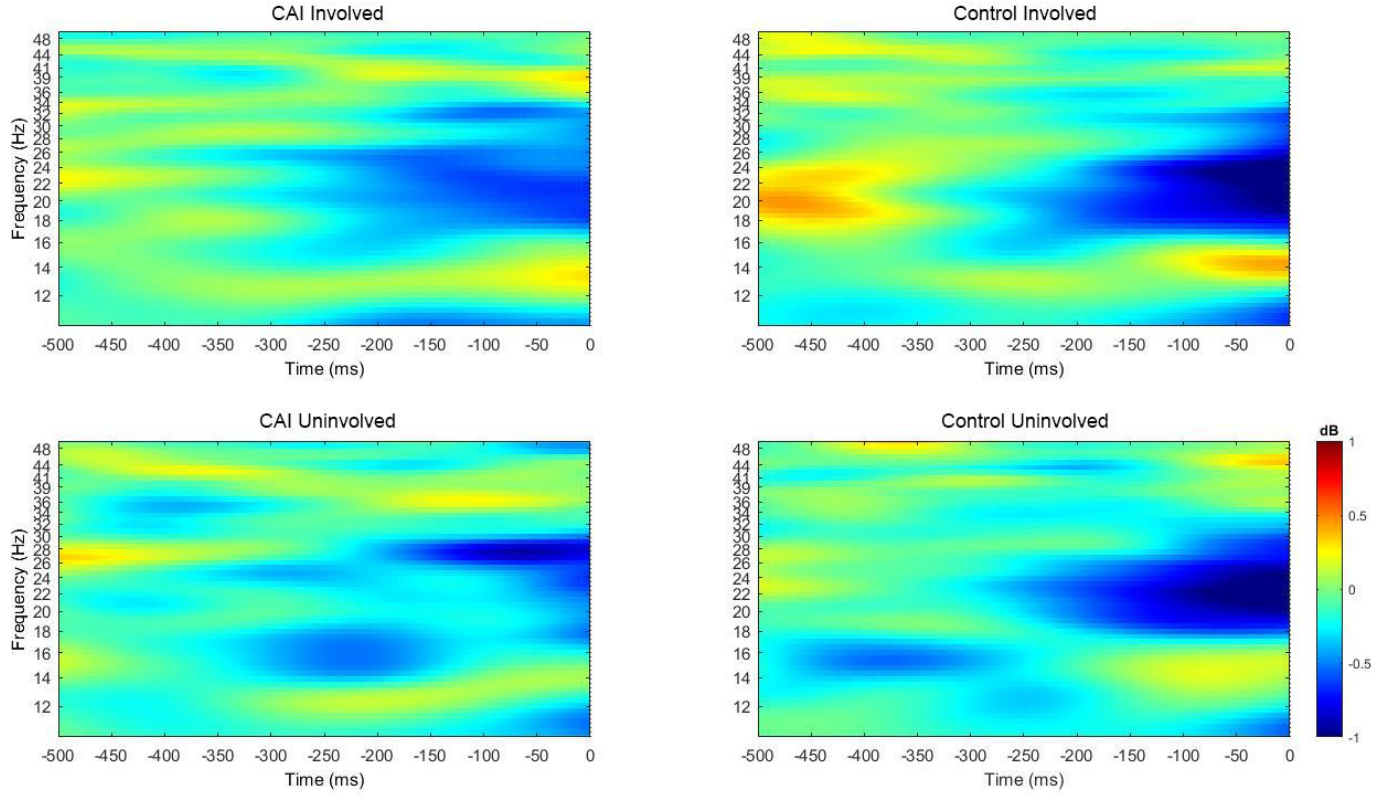

Figure 10. ERSP, in dB, prior to the DSLT movement as measured at the Cz electrode.

The bottom right corner indicates the color scale. More red colors indicate an increase in spectral power at a given frequency, and an increase in activity at frequencies > 30 Hz. More blue colors indicate a power decrease, however this represents an increase in cortical activity in frequencies < 30 Hz. As can be seen, a similar pattern of power decrease occurs in the mid-beta band beginning approximately 200ms before movement in both groups prior to DSLT onto either limb.

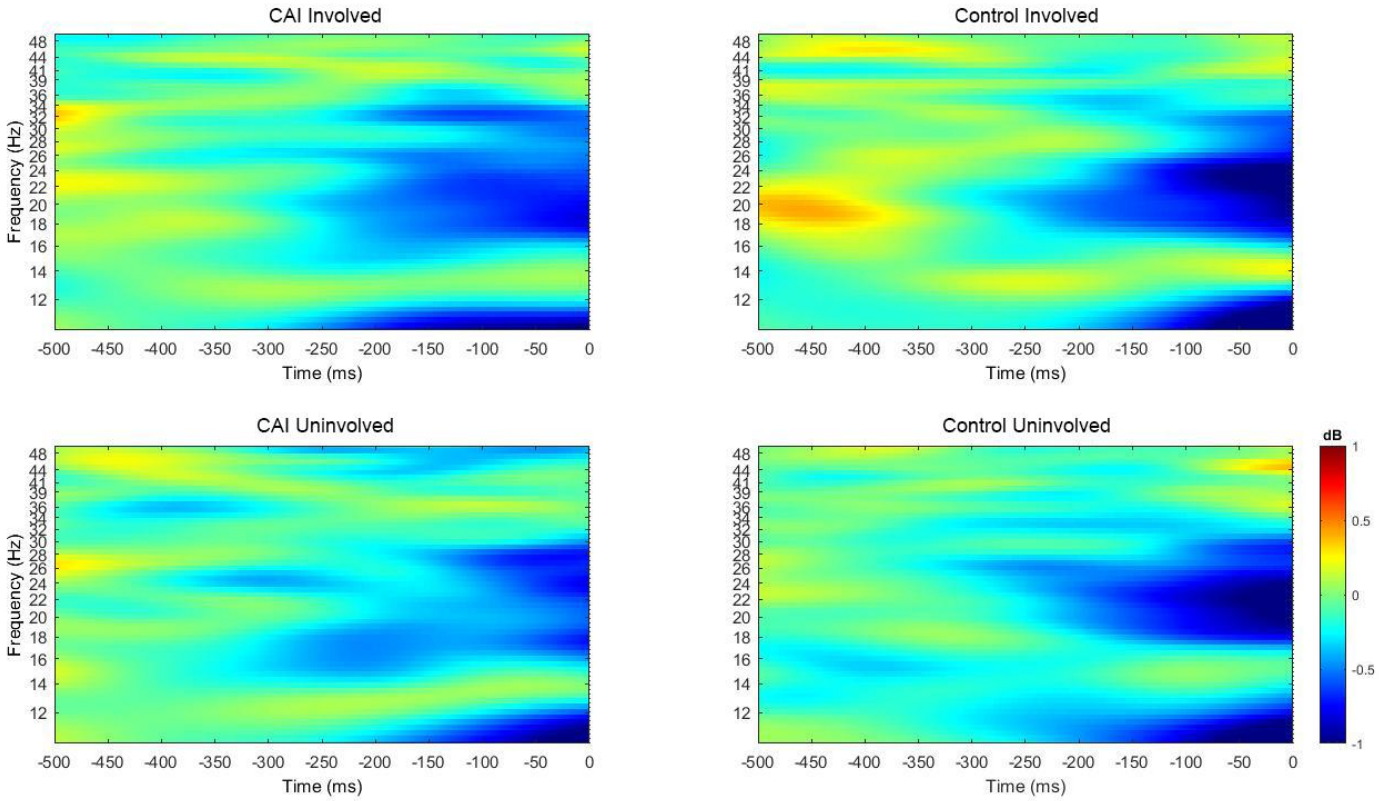

Figure 10. ERSP, in dB, prior to the DSLT movement as measured at the CPz electrode.

The bottom right corner indicates the color scale. More red colors indicate an increase in spectral power at a given frequency, and an increase in activity at frequencies > 30 Hz. More blue colors indicate a power decrease, however this represents an increase in cortical activity in frequencies < 30 Hz. As can be seen, a similar pattern of power decrease occurs in the mid-beta band beginning approximately 200ms before movement in both groups prior to DSLT onto either limb.

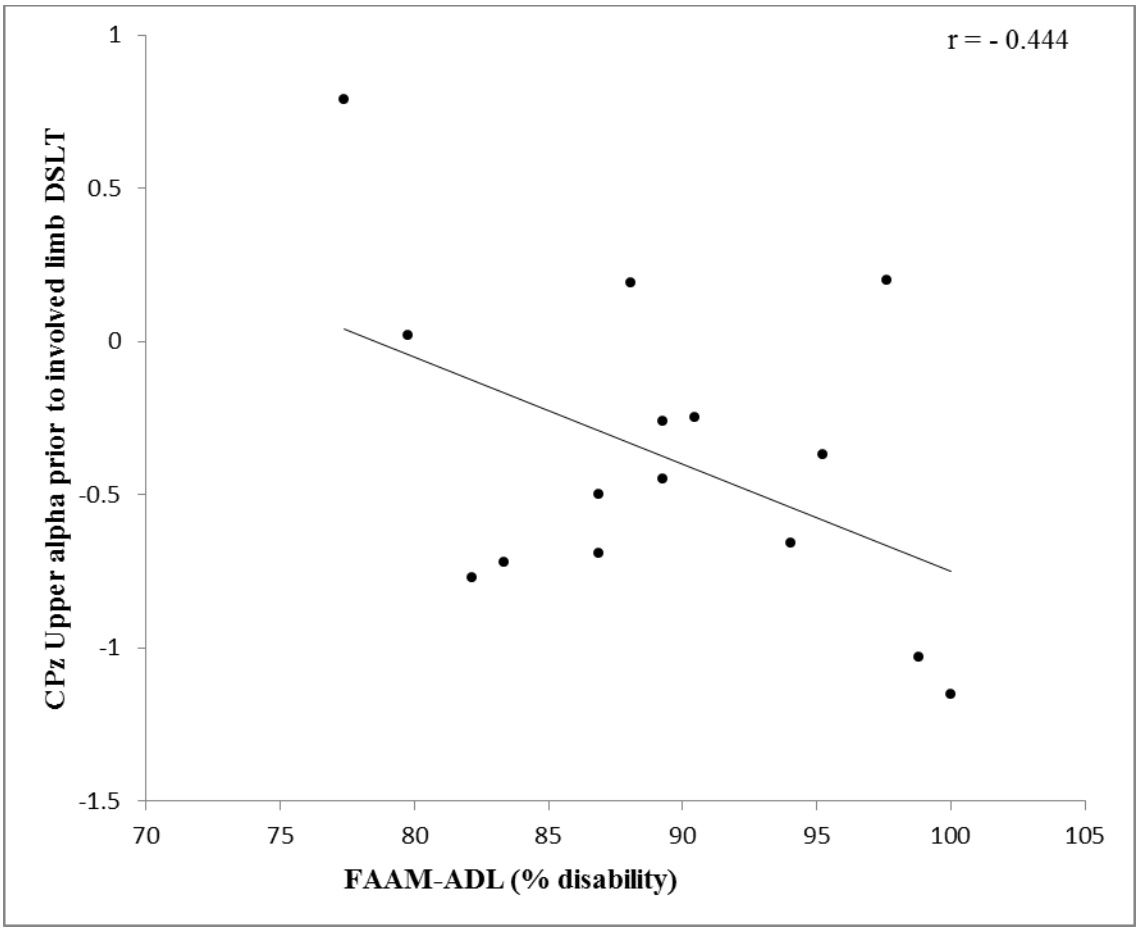

Figure 12. Correlation between FAAM-ADL and Upper Alpha activity prior to involved limb DSLT.

A significant relationship was identified in the group of CAI patients that showed a trend towards less upper alpha activity, therefore a power increase in upper alpha activity, in patients with worse perception of function during activities of daily living. Healthy individuals tend to have a power decrease, or desynchronization, prior to movement. Patients with worse perception of function may have altered feed-forward sensorimotor control.

CHAPTER 5: THE EFFECTS OF 4-WEEKS OF BALANCE TRAINING ON FEED-FORWARD SENSORIMOTOR CONTROL IN PATIENTS WITH CHRONIC ANKLE INSTABILITY: AN EEG STUDY

5.1 Abstract

Balance training is a common treatment for patients with chronic ankle instability (CAI), resulting in improved patient-reported and sensorimotor function. We currently do not know the neural mechanisms underlying these improvements. Electroencephalography (EEG) can be used to measure cortical activity during such tasks, and how it changes in response to balance training. The purpose of this investigation is to evaluate the change in feed-forward cortical activity, measured through EEG, as a result of balance training in CAI patients. Fifteen CAI patients (age: 20.80±2.37yr; mass: 70.45±19.25kg; height: 169.47±7.95cm) completed a 4-week progression-based balance training(BT) program. EEG was used to assess feed-forward cortical activity during a dual-to-single-limb transition (DSLT) prior to BT, as well as 24 hours and 7days after completing BT. Cortical activity was measured through event-related spectral perturbations (ERSP) in the upper alpha (10-12Hz), beta (14-25Hz), and gamma (30-50Hz) bands. The grand mean of the log power change, in dB, was grand averaged in each band for the 500ms prior to the DSLT. Patient-reported outcomes, Star Excursion Balance Test (SEBT) and instrumented balance trials were also collected at each time point (clinical battery). Data were analyzed using repeated measures ANOVAs. Pearson product moment correlations were run between ERSP and clinical battery outcome change scores. Alpha was set at 0.05. No significant changes in ERSP were identified after balance training ($p>0.05$). Greater improvement in SEBT anterior reach was moderately correlated with a reduction in

gamma activity (r=-0.650, p=0.009) after balance training. Future studies should aim to assess whether or not BT-induced improvements in feed-back sensorimotor control are evident using EEG.

5.2 Introduction

Epidemiological studies estimate approximately 23,000 lateral ankle sprains occur every day in the United States.[104] A long-term consequence of this injury is the development of chronic ankle instability (CAI), which is estimated to occur in about 40% of individuals.[72] The hallmark symptom of CAI is reports of recurrent ankle sprains as well as complaints of 'instability' or 'giving way',[8,9] which may significantly limit an individual's ability to remain physically active.[13] This repetitive damage to the ankle joint complex leads to a variety of sensorimotor[1,14,21,58] and mechanical[96] impairments in these patients.[25] Sensorimotor impairments are most commonly identified in the form of worsened balance in CAI patients relative to uninjured controls,[14,73,75] however there has been recent evidence to suggest impairments in feed-forward sensorimotor control (i.e. motor planning).[1,22,29] Using a model set forth by McKeon,[25] the clinician should aim to break the patient from a continuum of disability by improving sensorimotor control, in order to improve functional performance and decrease risk of reinjury.

Balance training can be used to effectively improve sensorimotor control in CAI patients,[73] and has also been shown to decrease the incidence of recurrent ankle sprains.[105] Balance training was first used by Freeman et al.[106] in 1965 and resulted in a significant reduction in complaints of instability and improved balance in 11 of 14 patients that were prescribed balance exercises. Strong, consistent evidence continues to

support the use of balance training when treating CAI patients, as evidenced by improvements in various patient-, clinician-, and laboratory-oriented outcome measures. One of the most common results in the literature is improvements in patient-reported outcomes, suggesting that patients perceive a positive change in functionality.[24,78,107] Improvements in clinician-oriented outcomes often focus on balance, with reported improvements in static[108] and dynamic balance.[24,78,107] Meta-analysis has shown that laboratory-oriented measures of static balance also significantly improve after balance training in patients with CAI.[73] As a whole, the literature suggests that balance training is an effective intervention strategy for restoring both perceptual (e.g. patient-reported function) and physical (e.g. balance and postural control) deficits associated with CAI.

Balance training in CAI patients is designed to consistently challenge the sensorimotor system to 'develop solutions' to 'motor problems' by increasing the difficulty of motor tasks.[25] This is thought to result in the body changing how it assesses and uses it's available degrees of freedom.[25,109] Effective balance results from the interaction of activity at the spinal and supraspinal level, which can further be broken into cortical and subcortical (e.g. basal ganglia, cerebellum, brainstem) regions which all have important roles in preparing for and maintaining balance (For a review, see Taube et al.[26], Visser and Bloem[110]). In order to develop more efficacious interventions a complete understanding of the treatment mechanisms and adaptations is important to refine and improve treatments such as balance training. Evidence derived from transcranial magnetic stimulation (TMS) has revealed that corticomotor excitability decreases after balance training, suggesting a smaller role of the motor cortex following balance training programs.[111] Consistent evidence also points to decreased spinal reflex excitability,[111-113]

therefore the balance training-induced improvements are assumed to result from adaptations in subcortical structures.[26]

The current literature on cortical adaptations to balance training is the result of many years of TMS research,[26] and several impairments have been identified in CAI patients using TMS. Some of these include altered cortical excitability of the fibularis longus[33,114] and soleus muscles,[34] as well as relationships between cortical excitability and patient-reported disability and balance performance.[31,76,115] This growing field of evidence suggests these patients have altered function in the motor cortex. Electroencephalography (EEG) is a tool that has recently been used to investigate CAI patients,[32] as well as the response to balance training in an elderly population.[116] EEG has recently been used to evaluate activity during feed-forward control of movement in healthy young adults by observing the time-frequency response leading up to and during a dual-to-single limb transition (DSLT).[81] This task produces an anticipatory postural adjustment (APA), a stereotyped movement generated to prepare the body for a destabilizing event (e.g. standing on one leg). They revealed a timecourse of desynchronized (i.e. increased cortical activity) low-frequency activity followed by activity believed to represent sensorimotor integration during the execution of the movement.[81] The DSLT is a task that was investigated in CAI patients by Van Deun et al.[1] who reported delayed muscle onset times, providing some of the first strong evidence of feed-forward dysfunction in this patient population.

The purpose of this investigation is to measure the cortical responses, using EEG, to balance training in CAI patients that complete a progressive[24] balance training program focused on dynamic stabilization exercises and the manipulation of task and

environmental constraints. Due to the emphasis this program places on feed-forward control, we will assess the response in EEG measures during the DSLT task previously reported in CAI[1,23] and EEG research.[81] We hypothesize that after balance training EEG activity prior to a DSLT will be decreased, indicating a decrease in cortical control of movement. Additionally, we aim to examine potential relationships between changes in EEG-based outcome measures and patient-reported disability and instrumented and non-instrumented balance outcomes. We hypothesize that those individuals with the greatest improvement in the patient-, clinician-, and laboratory-oriented outcomes will have the greatest decrease in cortical activity, suggesting a more efficient control of posture. Wikstrom and McKeon[117] recently identified that not all CAI patients respond equally to treatments, therefore due to the exploratory nature of this investigation we aimed to conduct a secondary treatment response analysis to better describe the sensorimotor adaptations attributed to balance training.

5.3 Methods

5.3.1 Study Design

A within-subjects design was used to evaluate the cortical response to balance training in CAI patients. Participants completed a DSLT to the trained limb at three time points: baseline, posttest 1 (24-48 hours after completing balance training) and posttest 2 (7 days after posttest 1). Participants completed a perceptual and balance test battery and EEG testing at each time point.

5.3.2 Participants

Fifteen CAI patients participated in this investigation (Table 11)**.** CAI was defined as individuals who have experienced at least one significant lateral ankle sprain, ≥2 episodes of the ankle 'rolling' or 'giving way' within the 6 months prior to participating in the study, an Identification of Functional Ankle Instability(IdFAI) score ≥11.[45] If a patient had bilateral CAI, the limb with the lower Foot and Ankle Ability Measure activities of daily living (FAAM-ADL) and sports (FAAM-Sport) score was used as the training limb.[78] Exclusion criteria included known balance and vision problems, acute lower extremity or head injury within 3 months of enrollment, a history of concussion, chronic musculoskeletal conditions known to affect balance(e.g. ACL deficiency), a history of lower extremity musculoskeletal surgery, or any other neurologic conditions that may impact postural control(e.g. diabetes) or EEG signal analysis(e.g. epilepsy). All experimental procedures performed were in accordance with the Declaration of Helsinki and were approved by the Institutional Review Board at the University of North Carolina at Charlotte (IRB 11-15-06).

5.3.3 Perceptual and Balance Testing

At the baseline session, participants were given a description of the study and then provided written informed consent. Perceptual, patient-reported outcomes (PROs) included the FAAM-ADL, the FAAM-Sport, the 11-item Tampa Scale of Kinesiophobia (TSK11), and the Fear Avoidance Beliefs Questionnaire physical activity subscale (FABQ). Following this, participants completed a balance assessment which included static balance trials on the force platform and the Star Excursion Balance Test (SEBT).

Static balance trials were collected on a force platform in three conditions: dual-limb stance, eyes open single-limb, eyes closed single-limb. Participants completed three, 10-second trials that were averaged for each condition. The SEBT was collected according to recommendations by Gribble et al.,[54] with participants informed to complete each trial with their hands on their hips, maintaining support limb contact with the ground at all time, and not to bear weight on the reaching limb. Reach distance was normalized to leg length, measured from the anterior superior iliac spine to the medial malleolus. SEBT was performed in the anterior (SEBT-A), posteromedial (SEBT-PM), and posterolateral (SEBT-PL) directions. Participants completed 4 practice trials before the average of three test trials were used for analysis. All test trials were performed on the training limb.

5.3.4 DSLT Task

Participants completed a total of 120 DSLT trials.[81] With their hands relaxed and hanging by the side, a participant would stand within a box drawn on the force platform approximately shoulder-width apart and upon a verbal cue the individual would transition to single-limb balance and maintain it for approximately 5 seconds. An individual trial was 8-seconds in duration, and the verbal cue was delivered between 1 and 2 seconds after the beginning of the trial. Participants were given instructions to ensure even weight distribution between legs and not react until the verbal cue. Testing occurred over 2 testing blocks with a 4 minute seated break between blocks.

5.3.5 Balance Training

Participants were enrolled in a 4-week balance training program developed by McKeon et al.[24] This program consists of 12, 20-minute sessions over a 4-week period comprised of

5 exercises (Table 12). The program is designed to continually challenge the sensorimotor system by manipulating task (e.g. hop distance) and environmental (e.g. support surface) constraints. Participants would progress to a new level of difficulty only after they show proficient (i.e. error-free) movement for each direction of each exercise for every repetition of that exercise. Progression was determined independently and happened from session-to-session as opposed to within a session. A full description of the exercises and progression criteria can be seen in the appendices of the original report.[24]

5.3.6 Equipment

Force platform data were collected using an AMTI Accusway force platform (AMTI Inc., Watertown, MA) connected to a laptop using a PJB-101 (AMTI Inc., Watertown MA) interface. Data for static balance trials was recorded with the BalanceClinic software (Version 1.4.2, AMTI Inc., Watertown, MA) at 50 Hz, and data for DSLT trials was sampled at 200 Hz using the NetForce software (Version 3.5.3, AMTI Inc., Watertown, MA).

EEG data was collected using a 32-channel Quick-Cap (Compumedics Neuroscan, Charlotte, NC) connected to a 40-channel NuAmps (Compumedics Neuroscan, Charlotte, NC) digital EEG amplifier. A custom montage was used to collect data from 14 EEG channels (FP1, FP2, F3, Fz, F4, FC3, FCz, FC4, C3, Cz, C4, CP3, CPz, CP4), four EOG channels placed above and below the left eye and lateral to each eye and earlobe clip electrodes (A1, A2). The linked A1/A2 earlobes served as a reference for all EEG recordings. Impedance was kept below 5 kOhms throughout testing. EEG signals were amplified (gain: 19), filtered (DC-400Hz), and sampled at 1000Hz into the Curry 7

(Version 7.0.9, Compumedics Neuroscan, Charlotte, NC) software on a dedicated computer and saved for offline analysis.

Force platform and EEG data were synchronized using a custom-built trigger device. The device delivered a 4.8V TTL pulse simultaneously to the NuAmps amplifier and the PJB-101 force platform interface system. The TTL pulse created an event code in the continuous EEG file and triggered the beginning of the trial in NetForce, creating a single file per leaning trial.

5.3.7 Data Analysis

Static balance trials were analyzed using the BalanceClinic software (Version 1.4.2, AMTI Inc., Watertown, MA), and outcomes included the Path length of the center-of-pressure (COP) in cm, peak velocity (cm/s) in the anterior-posterior (AP Vel) and medial-lateral (ML Vel) planes, and the 95% confidence ellipse of the COP area (cm^2). For the DSLT trials, this investigation used a modified version of the time to new stability (TNS) originally described by Dingenen et al.[23] Due to software restrictions for external triggers, the force platform was zeroed prior to every trial, therefore without a vertical force value we were unable to calculate COP. However, with the vertical force zeroed, the force moment channels (Mx and My) reflect the change in the COP (Figure 13). The original calculation is described in detail in the original manuscript.[23] In Figure 13, the starting point of the trial, ON, is identified as the point just prior to the APA. The cumulative displacement is calculated from the crossing point (CP), when the APA crosses back over the point defined as ON, to the end of the trial. TNS is the point when the displacement becomes within 0.25 standard deviations of the cumulative displacement and remains

under this value for the remainder of the trial (Figure 13).[23] The TNS was averaged from the first 5 usable DSLT trials for each participant.

Processing of EEG data was performed in Curry 7 and MATLAB (Mathworks Inc., Natik, MA). Curry 7 was used for baseline and ocular artifact correction and then data was exported into MATLAB for further processing using scripts in EEGLAB version 13.6.5b.[79] The data were low-pass filtered at 100Hz to remove trigger artifact and then segmented into 3s long epochs around ON (-1500 ms to +1500 ms). Baseline activity (-1200 ms to -1000 ms) was subtracted from each epoch,[81] then visually inspected, with noisy trials and those with significant movement artifact being rejected. A minimum of 40 trials were used for analysis for each participant.[81]

The EEG signal is a complex signal comprised of many frequency components at a given time. An ERSP analysis computes the change in power at each frequency with respect to an event. The ERSP was calculated in the 500 ms window prior to ON, with the baseline period defined as -1200ms to -1000ms in the epoch.[81] The ERSP was grand averaged across the 500ms window in three bands of activity: upper alpha (10-12Hz), beta (14-25 Hz), and gamma (30-50Hz). All three bands were selected due to their role in sensorimotor processing and movement preparation.[2,35,36,41,81] A decrease in upper alpha and beta power represent an increase in cortical excitability and increases in gamma power are believed to represent rapid sensorimotor processing.[35,36] The ERSP was calculated in all three bands at the Cz (premotor and primary motor cortices) and CPz (primary somatosensory and posterior parietal cortices) electrode sites.

5.3.8 Statistical Analysis

EEG, PRO, SEBT, and instrumented balance outcomes were assessed using separate repeated-measures ANOVAs to assess a main effect of Time (baseline, posttest 1, posttest 2). Change scores were calculated for all dependent variables as posttest – baseline. Relationships between change scores in EEG, PRO, SEBT, and instrumented balance measures were analyzed using Pearson product moment correlations. Hedges' g effect sizes and 95% confidence intervals were calculated as posttest – baseline. Effect sizes were interpreted as weak (≤0.40), moderate (0.41-0.69), or strong (≥0.70).[118]

In order to explore the differences in cortical activity between CAI patients with a positive treatment response and those without (i.e non-responders), a modified response analysis was performed.[117] A positive treatment response was defined as a patient who exceeded the minimal detectable change (MDC) score in all 3 directions of the SEBT. Previously reported MDCs for the CAI population were used: SEBT-A (1.81%), SEBT-PM (3.16%), and SEBT-PL (5.25%).[119] Independent sample t-tests were performed on the groups of responders and non-responders on EEG, PROs, SEBT, and instrumented balance measures at baseline to see if these two groups differed. Alpha was set at 0.05 and all statistical tests were performed in SPSS (Version 23, IBM Corp, Armonk, NY).

5.4 Results

5.4.1 EEG Outcomes

We did not identify any significant differences ($p>0.05$) in any of the 6 EEG outcome measures (Table 15). All of the EEG effect sizes included 0, with differential responses in the upper alpha band compared to the beta and gamma bands. A positive point estimate

indicates a decrease in power (i.e. increased cortical activity) after balance training (Table 15, Figure 14).

5.4.2 Balance Outcomes

Means and standard deviations, change scores, and Hedges' g effect sizes can be seen for all balance measures in Table 14. A significant main effect of Time was identified in SEBT-A ($F(2,28)=29.40$, $p<0.001$), SEBT-PM ($F(2,28)=20.76$, $p<0.001$), SEBT-PL ($F(2,28)=21.21$, $p<0.001$), eyes open COP path length ($F(2,28)=5.81$, $p=0.008$) , eyes open AP Velocity ($F(2,28)=6.70$, $p=0.004$) , and eyes closed COP path length ($F(2,28)=3.53$, $p=0.043$). SEBT scores were significantly improved at both posttest sessions compared to baseline ($p<0.05$), indicating an improvement in dynamic balance. A delayed improvement effect was identified in eyes open COP path length ($p=0.015$) and AP Velocity ($p=0.009$) with significant differences noted in posttest 2 compared to baseline. No other significant main effects of Time or differences between test sessions were identified ($p>0.05$).

5.4.3 PRO Outcomes

Table 13 contains the means and standard deviations, change scores, and Hedges' g effect sizes for PROs. Significant main effects of Time were identified in FAAM-ADL ($F(2,28)=6.903$, $p=0.005$), FAAM-Sport ($F(2,28)=6.456$, $p=0.018$), and the FABQ ($F(2,28)=5.615$, $p=0.009$). FABQ scores were significantly decreased at the initial posttest from baseline ($p=0.038$). There was significant improvement in the FAAM-ADL ($p=0.019$), FAAM-Sport ($p=0.023$), and FABQ ($p=0.027$) at posttest 2 compared to baseline. Interestingly, FAAM-Sport scores were significantly higher at posttest 2

compared to posttest 1 (p=0.011). No significant differences were identified between any time points in TSK-11 scores (p>0.05).

5.4.4 Correlations

A single significant correlation between change scores was identified (Figure 15). A moderate negative relationship(r=-0.650, p=0.009) was identified between change in anterior reach on the SEBT and change in gamma (30-50 Hz) activity at the Cz electrode.

5.4.5 Response Analysis

Based on our response analysis, 8 out of 15 (53%) CAI patients had a meaningful improvement in balance. Baseline values of the two groups outcome measures can be seen in Table 16. These individuals had a significantly lower decrease in gamma power prior to DSLT movements at the baseline measurement at the Cz (p=0.019) and CPz (0.023) electrodes. No other significant differences were identified between responders and non-responders in balance or PROs (p>0.05).

5.5 Discussion

Contrary to our initial hypothesis, we did not observe any changes in cortical activity after CAI patients completed 4 weeks of balance training. The ERSP plots for the Cz and CPz electrodes can be seen in Figure 14. Overall, we did not visually identify any noticeable difference in the ERSP plots when comparing baseline to either posttest measurement of feed-forward cortical activity. We also reject our secondary hypothesis, as only a single relationship was identified between changes in cortical activity and change in balance. This relationship (Figure 15) links patients with greater improvement

in the anterior reach on the SEBT with a greater reduction in gamma activity prior to the DSLT. This effect was observed at the Cz electrode, an electrode selected for analysis due to its proximity to the supplementary motor area.

The response analysis revealed that balance training responders did not modulate gamma activity prior to the DSLT task at baseline as indicated by grand mean ERSP values closer to zero (Table 16). Gamma activity is linked to sensory integration and processing prior to and during movement,[35,36,80,86] therefore these individuals may have had less effective strategies for processing and implementing sensory information when planning movement. CAI patients are known to have impaired ability to detect both vibrotactile[15] and light touch stimuli[88] on the plantar surface of the foot, and although these have been linked to static balance impairments (i.e. feed-back sensorimotor control)[16] it remains a possibility that these impairments force a reweighting of sensory input when planning movement. An improved ability to effectively process sensory information after balance training may be supported by the correlation between greater improvement in SEBT-A reach distance and a greater reduction in gamma activity prior to movement (Figure 15) after completing balance training. Despite these findings, further research is warranted to identify the functional role of gamma suppression prior to movement in CAI patients and its relationship to sensory function and motor output due to the novel nature of this investigation.

Our PRO, SEBT, and instrumented balance results are consistent with previous investigations that have utilized the McKeon et al.[24] balance training program.[78,107] We identified significant improvement in our clinician-oriented balance measures, as both Schaefer and Sandrey[107] and Burcal et al.[78] reported significant improvement in all 3

SEBT reach directions. There was also a significant improvement in FAAM-ADL scores, similar to that reported by Schaefer and Sandrey.[107] Interestingly, a greater proportion of our additional measures showed improvement at the 1-week posttest (Tables 13 and 14). There were significant improvements in PROs (FAAM-ADL and FAAM-Sport) and instrumented balance measures (eyes-open Path length and AP Velocity) at the 1-week posttest that were not identified at the immediate posttest. This agrees with the delayed improvements in FAAM-Sport and measures of static balance reported by Burcal et al.,[78] with improvements in these outcomes being reported at the 1-week posttest but not the immediate posttest. Delayed treatment benefits are not limited to balance training, as McKeon and Wikstrom[120] found that patients reported improved FAAM-Sport scores 2-weeks and 1-month after 2-week treatments of joint mobilizations and plantar massage treatments, respectively. The underlying mechanisms of these delayed improvements are not well understood, although it may represent a time period that is required for the sensorimotor system to develop new strategies that incorporate the newly available degrees of freedom as a result of treatment.

At present there is a limited body of evidence pertaining to the effects of balance training on the central nervous system. Using EEG, Shattin et al.[116] found that using video game-based exercises, or exergaming, depressed theta activity in older adults in an RCT comparing exergaming and balance training. This group had improvements in gait parameters under dual-task conditions, thought to be attributed to the interaction between the cognitive and balance training components of the exergaming program.[116] Their balance training group showed greater improvement in gait parameters, however no significant differences were identified in the EEG analysis.[116] Our understanding of

balance training-induced adaptations in sensorimotor function have primarily come from investigations using TMS. Taube investigated a perturbation response and the plasticity of monosynaptic corticospinal projections to the soleus muscle (i.e. contributions to the long-loop reflex response).[111] They found that individuals with greater improvements in balance had a reduced excitability of these direct projections, suggesting that balance training reduces corticospinal excitability.[26,111] Although this was interpreted as a reduced role for the cerebral cortex in postural control, these authors investigated the cortical contributions to a reflex circuit within a single muscle.[111] Therefore these findings may not be pertinent when discussing feed-forward sensorimotor control. Further, TMS is often used to record the muscular response to an external stimulus by activating the motor cortex, EEG records the ongoing activity in the cerebral cortex. With these methodological and evaluation-technique differences, it is possible that our results do not contradict the literature. Future research should aim to explore alternative approaches to evaluating EEG activity, or combining EEG and TMS to provide greater insight into the adaptations resulting from balance training.

As indicated by our responder analysis, we identified that 8 out of 15 patients (53.3%) had a meaningful response to balance training. Wikstrom and McKeon[117] recently developed a clinical prediction rule to aid in identifying patients that would improve balance after STARS treatments, with significant balance improvements in 25% of patients who received stretching treatments, 45% of patients receiving ankle joint mobilizations, and 53% of patients receiving plantar massage. An impairment-based rehabilitation model was recently implemented by Donovan et al.[69] that focused on assessing patient impairments, treating these impairments, and then reassessing for

treatment efficacy. The implementation of the existing clinical prediction rules for STARS treatments, and the potential of developing one for balance training should be considered when designing a treatment plan for CAI patients.

No study is without limitations, and movement artifact is one of the major issues that can contaminate data in stepping studies.[81,102] While others have reported using an ICA-driven artifact rejection approach,[81,102,103] we were unable to employ this technique due to a limited EEG montage; so our data may have movement artifact. However, due to the speed of the movement, we feel that the activity we analyzed > 10Hz was minimally contaminated with movement artifact. Additionally, the TNS that we calculated was over a smaller period of single-limb balance, 5-6 seconds, as opposed to the 13 seconds used in the original development of this outcome measure.[23] Future investigations should aim to identify an agreeable cut-off time for single-limb balance when calculating the TNS. Lastly, the test-retest reliability of these measures have not been established, therefore future research should aim to establish the reproducibility of these outcomes to provide better context and interpretation of the results.

5.6 Conclusions

This preliminary investigation into the EEG-related cortical adaptations following balance training did not reveal any significant changes in EEG measures of feed-forward sensorimotor control following 4-weeks of balance training. However, correlation analysis revealed a relationship that suggests there may be a link between the small change observed in feed-forward cortical activity and improvement in dynamic balance. As the SEBT best represents feed-back sensorimotor control, we have established a

potential link between changes in feed-forward (i.e. motor planning) and feed-back control. With these feed-back measures consistently improving after balance training, future research is warranted to determine if EEG can be used to quantify changes in feed-back cortical activity to better explain treatment mechanisms and improve patient outcomes. Further, our response analysis showed that approximately 1 in 2 CAI patients had a meaningful response to balance training, therefore we suggest an impairments-based approach is used to treating CAI as balance training may not be effective in all CAI patients.

5.7 Tables

Table 11. Participant demographics.

Values are mean and standard deviation unless otherwise stated. NASA PASS: NASA Physical Activity Status Scale; IdFAI: Identification of Functional Ankle Instability; TSK-11: Tampa Scale for Kinesiophobia-11 item; FABQ: Fear Avoidance Beliefs Questionnaire; FAAM-ADL: Foot and Ankle Ability Measure Activities of Daily Living Scale; FAAM-Sport: Foot and Ankle Ability Measure Sport Scale.

Female, No. (%)	8 (53.33)
Age, yr	20.80 (2.37)
Height, cm	169.47 (7.95)
Mass, kg	70.45 (19.25)
NASA PASS, median (IQR)	6 (5, 7)
IdFAI	18.33 (4.47)
Number of Lateral Ankle Sprains	2.67 (2.02)
Number of Rolls in past 6-months	4.93 (3.31)
Anterior Drawer, median (IQR)	4 (3, 4)
Talar Tilt, median (IQR)	4 (4, 5)
TSK-11	19.60 (4.34)
FABQ	10.00 (3.91)
FAAM-ADL, %	88.11 (6.04)
FAAM-Sport, %	76.88 (14.11)

Table 12. Descriptions of exercises included in the McKeon et al.[24] balance training protocol.

Exercise	Description
Hop to stabilization	Hop to a target position (18, 27, 36 inches [45.7, 68.6, 91.4 cm]), stabilize, hop back to the starting position, and stabilize. Hops are performed in four directions: anterior/posterior, medial/lateral, anterolateral/posteromedial, and anteromedial/posterolateral.
Hop to stabilization and reach	As above but after stabilizing, subjects will reach back to the starting and target positions during each repetition of each direction.
Unanticipated hop to stabilization	Start in the middle of a 9-marker grid (individually numbered) and hop to the randomly presented target number. Subjects can use any combination of hops they wish to reach the target.
Single limb stance balance	Complete a single limb stance exercise with eyes open.
Single limb balance with eyes closed	Complete a single limb stance exercise with eyes closed.

Table 13. Patient-reported outcomes.

Means and standard deviations can be seen for patient-reported outcomes at each timepoint. Means and standard deviations of the change score from baseline at posttest 1 are also reported. Signs have been changed on the change scores and Hedges' g effect sizes and 95% confidence intervals so that a positive number indicates an improvement. FAAM-ADL: Foot and Ankle Ability Measure Activities of Daily Living scale; FAAM-S: Foot and Ankle Ability Measure Sports scale; TSK-11: 11-item Tampa Scale of Kinesiophobia; FABQ: Fear Avoidance Beliefs Questionnaire. * indicates a main effect of Time ($p < 0.05$); † indicates significant difference from baseline ($p < 0.05$). ‡ indicates a significant difference from posttest 1 ($p < 0.05$).

Measure	**Baseline**	**Posttest 1**	**Posttest 2**	**Posttest 1 – Baseline Change Score**	**Posttest 1 – Baseline Effect Size (95% CI)**
FAAM-ADL*	88.11 (6.04)	91.50 (5.78)	93.29 (6.75) †	3.39 (6.04)	0.79 (0.05, 1.54)
FAAM-Sport*	76.88 (14.11)	83.96 (11.74)	88.33 (8.95) †,‡	7.08 (15.47)	0.67 (-0.07, 1.40)
TSK-11	19.60 (4.34)	17.73 (2.71)	18.13 (4.93)	1.87 (3.93)	0.48 (-0.25, 1.21)
FABQ*	10.00 (3.91)	6.80 (4.06) †	6.73 (4.40) †	3.20 (4.33)	0.61 (-0.12, 1.35)

Table 14. Clinical and instrumented balance outcome measures.

Means and standard deviations can be seen of both clinical and instrumented balance outcomes at baseline, posttest 1, and posttest 2. Means and standard deviations of the change score from baseline are also reported. Signs have been changed on the absolute change score so that a positive value indicates an improvement in the outcome measure. Hedges' g effect sizes and 95% confidence intervals are also reported for the change scores, with signs changed so that a positive point estimate of g indicates an improvement following balance training. * indicates a main effect of Time ($p < 0.05$); † indicates significant difference from baseline ($p < 0.05$).

Measure	**Baseline**	**Posttest 1**	**Posttest 2**	**Posttest 1 – Baseline Change Score**	**Posttest 1 – Baseline Effect Size (95% CI)**
SEBT-A (%)*	74.71 (5.37)	80.38 (4.03) †	79.70 (4.19) †	5.66 (3.41)	1.47 (0.66, 2.27)
SEBT-PM (%)*	84.56 (9.05	92.50 (7.37) †	92.59 (7.83) †	7.94 (6.47)	1.41 (0.61,2.21)
SEBT-PL (%)*	80.98 (12.16)	90.27 (7.60) †	91.51 (7.81) †	9.29 (7.96)	0.83 (0.08, 1.58)
DL Path (cm)	11.99 (2.43)	11.33 (1.71)	11.50 (1.97)	0.67 (2.27)	0.31 (-0.41, 1.03)
DL AP Vel (cm/s)	3.22 (0.97)	2.96 (0.73)	2.95 (0.75)	0.26 (0.94)	0.23 (-0.49, 0.94)
DL ML Vel (cm/s)	3.12 (1.19)	2.91 (0.61)	2.89 (0.73)	0.22 (0.96)	0.19 (-0.52, 0.91)
DL Area (cm^2)	1.04 (0.65)	1.03 (0.38)	1.24 (0.73)	0.00 (0.59)	0.00 (-0.71, 0.72)
EO Path (cm)*	42.33 (10.89)	37.56 (9.36)	34.74 (10.10) †	4.76 (8.69)	0.50 (-0.22, 1.23)
EO AP Vel (cm/s)*	14.31 (4.36)	12.96 (3.50)	10.83 (3.70) †	1.35 (3.63)	0.33 (-0.39, 1.06)
EO ML Vel (cm/s)	11.77 (2.66)	12.75 (3.34)	11.22 (3.12)	-0.99 (2.17)	-0.24 (-0.95, 0.48)
EO Area (cm^2)	8.10 (4.51)	5.80 (2.06)	6.89 (3.17)	2.31 (4.03)	0.50 (-0.23, 1.22)
EC Path (cm)*	92.31 (21.68)	83.73 (20.71)	78.26 (23.49)	8.58 (22.63)	0.39 (-0.33, 1.11)
EC AP Vel (cm/s)	31.30 (8.36)	28.08 (7.08)	27.27 (9.50)	3.23 (8.62)	0.34 (-0.39, 1.06)
EC ML Vel (cm/s)	27.26 (6.02)	26.54 (5.42)	24.93 (7.45)	0.72 (5.38)	0.08 (-0.63, 0.80)
EC Area (cm^2)	27.25 (12.09	21.90 (6.51)	21.04 (8.13)	5.35 (10.98)	0.47 (-0.25, 1.20)
TNSP (s)	2.23 (0.22)	2.22 (0.17)	2.18 (0.13)	0.01 (0.24)	0.03 (-0.69, 0.74)

Table 15. ERSP values in dB.

Means and standard deviations can be seen of ERSP data in dB. No significant differences were identified ($p > 0.05$). The value represents the grand mean of the ERSP, in dB, from -500ms to movement onset in the following frequency bands: Upper Alpha (10-12 Hz), Beta (14-25 Hz), and Gamma (30-50 Hz). Values closer to zero indicate no change in signal power in a given frequency band. More negative values indicate event-related desynchronization, or a widespread increase in overall activity; more positive values indicate event-related synchronization, or more focal activity. Means and standard deviations of the change score from baseline at posttest 1 are also reported. Signs have been changed so that a positive value indicates an increase in cortical activity. Hedges' g effect sizes and 95% confidence intervals are also reported for change scores with the signs changes so that a positive point estimate indicates an increase in cortical activity.

Band and Electrode Site	**Baseline**	**Posttest 1**	**Posttest 2**	**Posttest 1 – Baseline Change Score**	**Posttest 1 – Baseline Effect Size (95% CI)**
Upper Alpha Cz	-0.16 (0.46)	-0.15 (0.42)	-0.15 (0.38)	-0.01 (0.62)	-0.02 (-0.74, 0.7)
Beta Cz	-0.21 (0.19)	-0.26 (0.27)	-0.16 (0.24)	0.05 (0.23)	0.21 (-0.51, 0.93)
Gamma Cz	-0.07 (0.13)	-0.09 (0.17)	-0.05 (0.15)	0.02 (0.14)	0.14 (-0.57, 0.86)
Upper Alpha CPz	-0.28 (0.46)	-0.24 (0.43)	-0.22 (0.37)	-0.05 (0.61)	-0.07 (-0.78, 0.65)
Beta CPz	-0.23 (0.23)	-0.28 (0.27)	-0.12 (0.23)	0.05 (0.29)	0.17 (-0.55, 0.88)
Gamma CPz	-0.08 (0.14)	-0.14 (0.19)	-0.08 (0.13)	0.06 (0.15)	0.36 (-0.37, 1.08)

Table 16. Baseline measures in responders and non-responders.

The means and standard deviations of patient-reported outcomes, SEBT, instrumented balance outcomes, and ERSP outcomes at baseline. IdFAI: Identification of Functional Ankle Instability; FAAM-ADL: Foot and Ankle Ability Measure Activities of Daily Living Scale; FAAM-Sport: Foot and Ankle Ability Measure Sports Scale; TSK-11: 11-item Tampa Scale of Kinesiophobia; FABQ: Fear Avoidance Beliefs Questionnaire; SEBT-A: Star Excursion Balance Test Anterior; SEBT-PM: Star Excursion Balance Test Posteromedial; SEBT-PL: Star Excursion Balance Test Posterolateral; DL: Double-limb balance; EO: Eyes-open single limb balance; EC: Eyes-closed single limb balance; AP: anterior-posterior; ML: medial-lateral; TNSP: time to new stability point. * indicates a significant difference between groups ($p < 0.05$).

Measure	**Responders (n = 8)**	**Non-responders (n = 7)**
IdFAI	17.63 (5.18)	19.14 (3.72)
Number of lateral ankle sprains	2.88 (2.48)	2.43 (1.51)
Number of rolls in past 6-months	5.00 (3.42)	4.86 (3.44)
FAAM-ADL (%)	89.28 (6.61)	86.77 (5.49)
FAAM-Sport (%)	76.96 (17.03)	76.79 (11.25)
TSK-11	17.88 (2.85)	21.57 (5.09)
FABQ	10.13 (5.00)	9.86 (2.55)
SEBT-A (%)	73.24 (4.65)	76.39 (5.99)
SEBT-PM (%)	82.13 (11.25)	87.34 (5.17)
SEBT-PL (%)	75.63 (14.11)	87.11 (5.55)
DL Path length (cm)	11.62 (2.14)	12.42 (2.84)
DL AP Velocity (cm/s)	3.34 (1.13)	3.08 (0.80)
DL ML Velocity (cm/s)	3.24 (1.53)	2.99 (0.72)
DL Area (cm^2)	0.80 (0.35)	1.30 (0.83)
EO Path length (cm)	41.58 (8.26)	43.18 (13.99)
EO AP Velocity (cm/s)	12.92 (2.72)	15.91 (5.49)
EO ML Velocity (cm/s)	11.63 (2.12)	11.93 (3.35)
EO Area (cm^2)	7.98 (2.66)	8.24 (6.25)
EC Path length (cm)	86.23 (20.32)	99.26 (22.56)
EC AP Velocity (cm/s)	30.47 (10.02)	32.26 (6.65)
EC ML Velocity (cm/s)	25.26 (6.02)	29.54 (5.57)
EC Area (cm^2)	27.29 (12.11)	27.20 (13.03)
TNSP (s)	2.15 (0.24)	2.31 (0.16)
Upper Alpha Cz (dB)	-0.22 (0.41)	-0.10 (0.53)
Beta Cz (dB)	-0.16 (0.16)	-0.26 (0.22)
Gamma Cz (dB)	**0.00 (0.05)***	-0.15 (0.14)
Upper Alpha CPz (dB)	-0.29 (0.44)	-0.27 (0.51)
Beta CPz (dB)	-0.15 (0.20)	-0.32 (0.24)
Gamma CPz (dB)	**-0.01 (0.10)***	-0.17 (0.14)

5.8 Figures

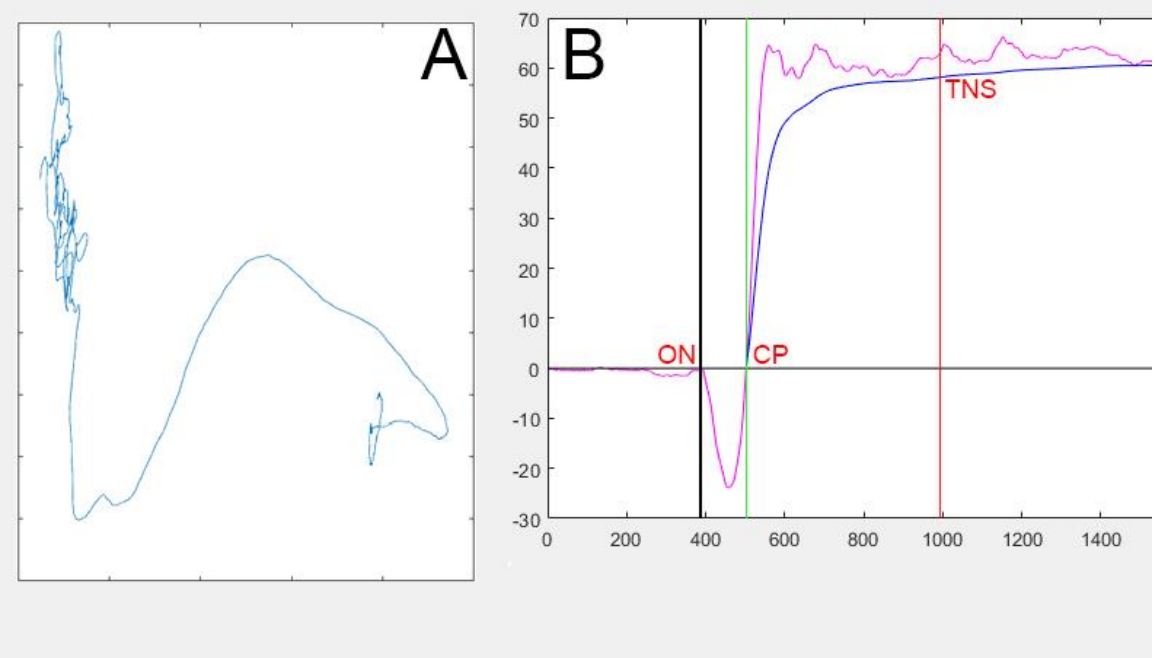

Figure 13. Example of the moment-data trace during DSLT and the calculation of TNS.

In A, the trace of the graphed Mx (anterior-posterior) and My (medial-lateral) moments can be seen. The similarity to the trace observed in COP data meant that the TNS outcome as described by Dingenen et al.[23] could be calculated. In B, movement onset, or ON, is identified when the medial-lateral moments begin shifting towards the non-stance limb. When the movement of the moments crosses past ON, a point is identified called the crossing point, or CP. The cumulative displacement from CP until the end of the trial is then calculated, and TNS is identified once the value of this displacement becomes, and stays, less than 0.25 standard deviations of this value. The full calculations can be seen in the original report.[23]

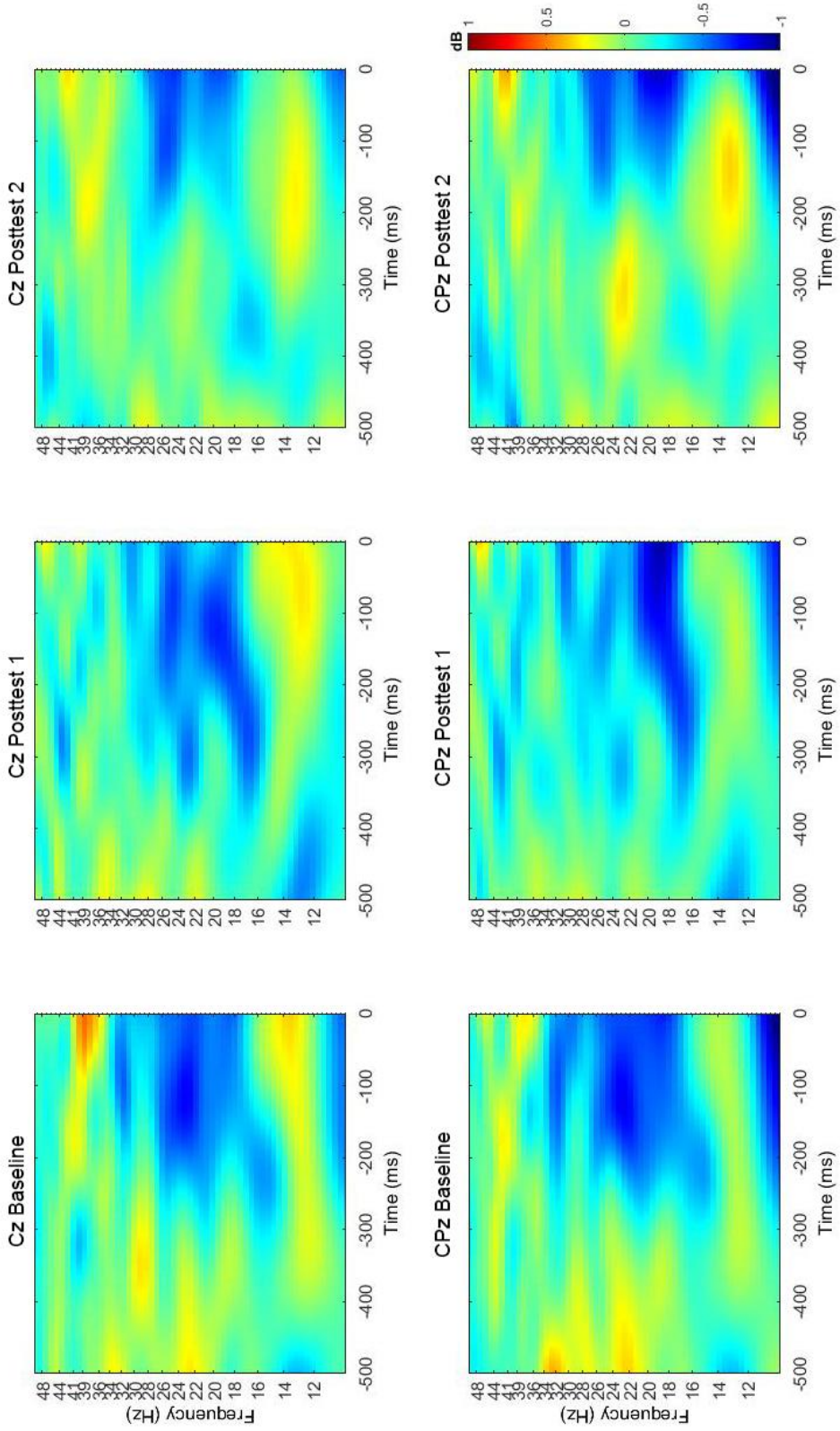

Figure 14. ERSP plots for the Cz and CPz electrodes at each time point.

As can be seen, few differences are apparent between the baseline and two posttest measurements following 4-weeks of balance training. More blue colors indicate a decrease in signal power, therefore an increase in activity in frequencies lower than 30 Hz. Yellow to red colors indicate a decrease in activity in these frequencies.

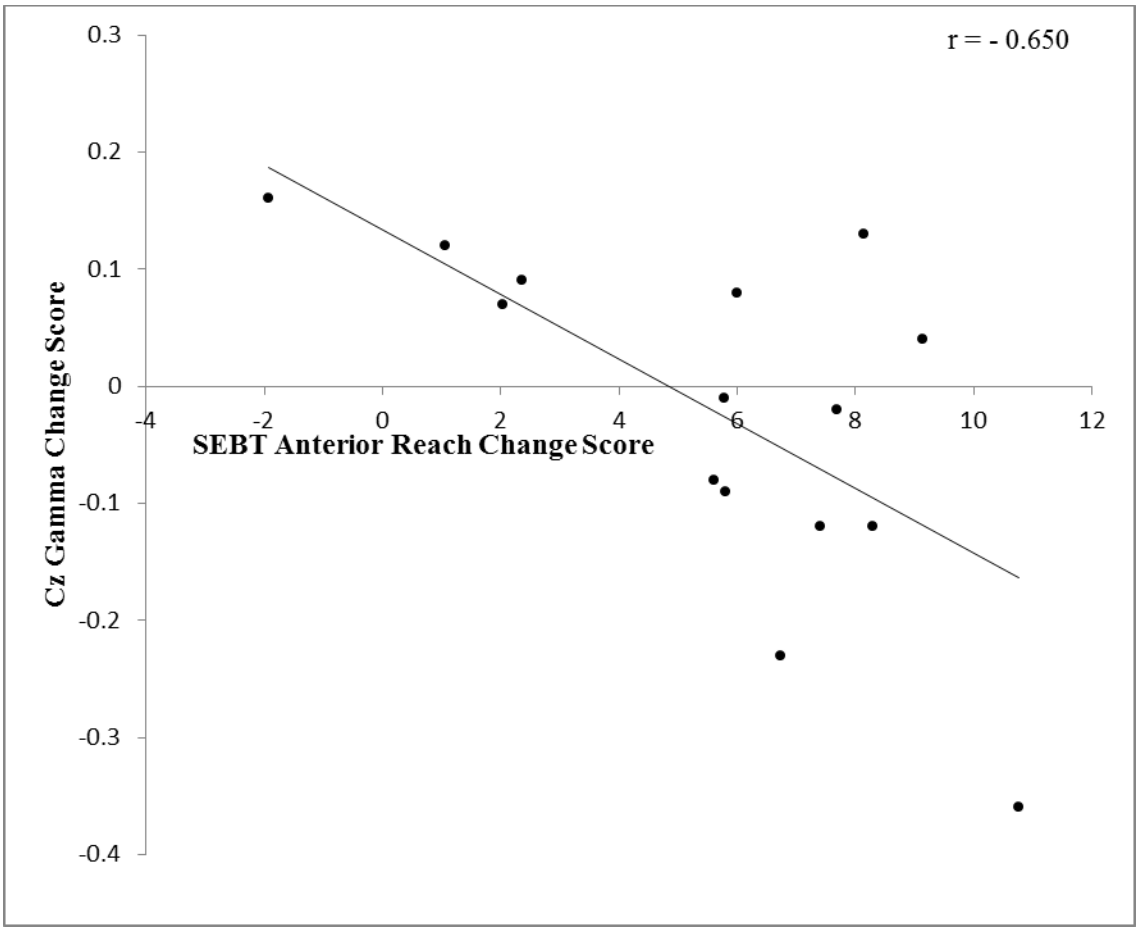

Figure 15. Correlation between change in gamma activity at Cz and SEBT-A.

A significant relationship was identified ($p = 0.009$) between change in anterior reach on the Star Excursion Balance Test (SEBT) and change in gamma activity at Cz prior to a DSLT. This relationship reveals that patients with greater improvements in feed-back sensorimotor control (e.g. SEBT-Anterior) may have a greater reduction in gamma activity, potentially due to more efficient processing of sensory information.

CHAPTER 6: DISSERTATION SUMMARY

6.1 State of CAI Research

Five decades of CAI research has resulted in a wealth of knowledge pertaining to the impairments that are associated with this chronic musculoskeletal condition. It has been well established through meta-analyses that CAI patients have multiple impairments across a broad spectrum of sensorimotor tasks.[14,68,73] The most common of which is feed-back sensorimotor control, which represents an individual's ability to gather and effectively utilize sensory information from both their internal and external environment to refine and continue an ongoing motor task. Even in a simple task such as single limb balance, CAI patients have worse balance relative to uninjured controls with their eyes open on a hard surface.[73] It is thought these impairments represent an insufficiency in the sensorimotor system being able to adapt to a reduction in the available degrees of freedom that must be controlled for movement.[25,89,109] This impaired adaptability of the sensorimotor system, relative to uninjured individuals, is highlighted by further impairments when task and environmental constraints are imposed. For instance, CAI patients have worse balance on unstable surfaces (e.g. environmental constraint),[58] and with their eyes closed on a hard surface (e.g. task constraint).[87]

There is limited evidence that CAI patients also have impaired feed-forward sensorimotor control. Feed-forward sensorimotor control consists of the processes involved in the planning and initial execution of a movement. In CAI patients, there is evidence in three tasks that feed-forward control of movement is impaired: gait initiation,[22] gait termination,[29] and DSLT.[1,23] Gait initiation and DSLT elicit a stereotyped, pre-programmed displacement of the center-of-mass called an APA.[22,23] As this task is being

executed, an individual moves opposite to the intended new stance limb, in an effort to minimize the destabilization of changing the support surface from two limbs to a single limb. CAI patients were shown to have decreased excursion during the APA, similar to that observed in aging populations,[121] when initiating gait.[22] Neuromuscular control deficits were identified during this APA when Van Deun et al.[1] identified that the onset of muscle activity in the stance limb occurred after the APA had begun in CAI patients, whereas it occurred prior to the APA in uninjured controls. Planned gait termination requires the individual to appropriately control forces through muscular activity in order to cease forward progression of gait.[29] It has been shown that the forces produced during braking were higher in CAI patients,[29] as well as decreased muscle activation during planned termination of gait.[122]

The combined evidence of feed-back[14,58,73,87] and feed-forward[1,22,23,29] impairments point towards adaptations in CNS function in CAI patients. The past 5 years has seen several researchers begin investigating these adaptations as they relate to sensorimotor function in CAI patients. Pietrosimone and Gribble[33] used transcranial magnetic stimulation (TMS) to assess the excitability of the motor cortex that activates the fibularis longus muscle (FL), a muscle that everts the ankle. They found higher resting motor thresholds in the FL, bilaterally, in unilateral CAI patients.[33] This indicates that a stronger electromagnetic stimulus was required to activate the muscles to the same output force in CAI patients relative to uninjured controls, suggesting a decrease in the excitability of this muscle. Although there are a variety of experimental setups and outcome measures that can be derived from TMS, researchers are reporting impaired excitability and negative adaptations to the corticomotor excitability for the FL[114] as well as the Soleus

muscle.[31,76] The functional implication of these findings is supported by relationships that have been identified between patient-reported function and dynamic balance.[76,115] Decreased excitability may not be applicable to all CAI patients, which are known to be a heterogeneous population,[68] as lower patient-reported function showed a quadratic relationship with high or low corticomotor excitability of the soleus muscle.[115]

Two limitations to the translation of TMS-derived measures of corticomotor impairments in CAI patients are that 1) participants are in a seated, non-weight bearing position during testing, and 2) due to time constraints with testing, typically only a single muscle is tested at a time. These two factors are important, because while effective feed-forward and feed-back sensorimotor control rely on corticomotor function, these are both complex processes involving the coordination among multiple muscles (e.g. timing, activation strengths). TMS has a very high temporal and spatial resolution, however these studies operate by generating an external stimulus and evaluating the output of the motor cortex to this external stimulus. EEG is a tool with a similarly high temporal resolution, and although it has a lower spatial resolution than TMS it can capture the internally generated time-locked responses to events. To date, a solitary investigation has measured cortical function in CAI patients using EEG. Needle et al.[32] evaluated cortical activity during a joint loading paradigm to see if there were differences in the magnitude of somatosensory activation among groups of CAI patients, ankle sprain copers, and uninjured controls. No differences were identified among groups suggesting the overall cortical activity required to detect joint motion didn't differ.[32] Despite the mounting evidence for cortical adaptations in CAI patients, no study has measured cortical activity during a weight-bearing task.

My dissertation aimed to fill this gap by evaluating both feed-forward and feed-back sensorimotor activity using EEG to see if CAI patients had altered cortical activity during weight-bearing tasks. We approached this by using previously described methods[2,41,81] and comparing cortical activity during feed-forward (MRCP prior to leaning and ERSP prior to DSLT) and feed-back (ERSP at limits of stability during leaning) activities, in groups of CAI patients and matched uninjured controls.

Once researchers and clinicians have a clear understanding of the impairments associated with their patient population, the most effective treatments can be delivered to maximize patient outcomes. A recent shift has occurred in treating CAI patients, using the Dynamic Systems Theory to develop treatments that address the complex interaction of organismic, environmental, and task constraints.[25,109,123] As outlined earlier, CAI patients have a variety of organismic constraints which may range from limited dorsiflexion,[124] increased ankle joint laxity,[96] to a broad range of sensorimotor constraints.[11] Despite these constraints, the sensorimotor system is tasked with developing an appropriate plan to control movement. However, clinical treatments can be used to address one or more of these three domains and produce beneficial results in CAI patients.

Organismic constraints in CAI patients are often modifiable through treatment. For example, strength training can be used to improve muscular strength around the ankle joint complex.[125] Smith et al.[125] found that 6-weeks of progressive strength training using therapeutic exercise bands significantly improved inversion and eversion strength. Decreased dorsiflexion range of motion[124] can be improved using either ankle joint mobilizations[126] or triceps surae stretching.[120] Clinicians can also manipulate sensory inputs through plantar massage, and improve balance in CAI patients.[120,127,128] A

randomized controlled trial compared the efficacy of three treatments for CAI patients (plantar massage, calf stretching, and ankle joint mobilizations), referred to as sensory targeted ankle rehabilitation strategies (STARS).[120] McKeon and Wikstrom[120] found that 2-weeks of any one of the STARS treatments improved patient-reported function and clinician-oriented measures of dorsiflexion range of motion and single limb balance.

Despite the ability of treatments to modify organismic constraints in a beneficial manner, it is possible that these treatments do not train the sensorimotor system's ability to adapt to changing task and environmental constraints.[25] Balance training is a common treatment to improve sensorimotor function after lateral ankle sprain, as well as in CAI patients.[73,105] A CAI-specific balance training program was developed by McKeon et al.[24] that progressively challenges the sensorimotor system by manipulating task (i.e. increasing hopping distance) and environmental (e.g. firm surface versus foam pad) constraints. Several recent investigations have tried to identify whether or not modifying organismic constraints (i.e. improve through therapeutic treatment) resulted in greater improvements than balance training alone.[69,78,107] Schaefer and Sandrey[107] combined balance training with Graston-instrument assisted soft tissue mobilization and failed to find an additive benefit of these treatments when compared to balance training alone. Similar results were reported by Burcal et al.[78] when one group of CAI patients received a 5-minute combined STARS treatment prior to each balance training session. Both of these investigations reported improvements in both groups, the balance training alone and the additive treatment group, and although effect sizes and results favored the additive treatment groups these improvements were not greater than balance training in isolation.[78,107] Recently, Donovan et al.[69] developed an impairment-based approach to

CAI rehabilitation. This approach uses patient- and clinician-oriented assessments to identify organismic constraints unique to each patient, and then to address those specific constraints during the treatment.[69] The authors found that this approach, when combined with the McKeon et al.[24] balance training program, was effective at improving both individual organismic constraints as well as sensorimotor impairments.[69]

Although there is evidence supporting the efficacy of balance training in CAI patients, at present we do not have any evidence to support the underlying of improvements in balance in this population. Currently there is limited empirical evidence to explain the underlying neural adaptations that explain the improvements in sensorimotor function.[26] Taube et al.[111] investigated the effects of 4-weeks of balance training on corticomotor excitability of the soleus muscle in healthy individuals. The authors reported decreased excitability of the cortex controlling the soleus muscle after balance training, however they identified a correlation suggesting the individuals with the greatest improvement in balance had the greatest reduction in soleus excitability.[111] These findings are not solitary, and have been replicated in healthy individuals.[112,113] In neurological populations such as stroke patients[129,130] and patients with Parkinson's disease,[131] balance training appears to decrease asymmetry between hemispheres and normalize corticomotor excitability, interpreted as a beneficial adaptation to balance training. Only one investigation to date has evaluated the change in EEG outcome measures to balance training; Schattin et al.[116] evaluated the difference between balance training and active gaming-based rehabilitation in older adults and found a power decrease in the theta band (3.5-5.5 Hz) in the active gaming rehabilitation group. A trend towards decreased activity was identified in the balance training group, supported by favoring effect sizes towards

decreased activity with the strongest beneficial effect size occurring in the upper alpha band (10-12.5 Hz).[116]

My dissertation was designed to address several gaps in the balance training and CAI literature. First, we have assessed the feed-forward cortical activity before and after participants completed a validated balance training program. This allowed us to assess any differences that occurred as a result of balance training. This also allowed us to address the lack of evidence relating to changes in feed-forward sensorimotor control after balance training, and identify potential mechanisms for patient improvement by comparing cortical measures with clinician- and laboratory-oriented measures of postural control.

6.2 Coper, Correlation, and Limb Analyses

6.2.1 Coper Results

Copers are a unique comparison group to utilize in CAI research, as they represent an optimal 'middle ground' when comparing groups of CAI patients with uninjured controls. An ankle sprain coper is an individual who has had a lateral ankle sprain (LAS), successfully recovers from this injury and does not develop CAI.[10] Wikstrom and Brown[10] hypothesize the key difference between copers and CAI patients is a successful sensorimotor reorganization after LAS. When investigating changes in the central nervous system, copers provide an excellent insight into the optimal, or successful, sensorimotor strategies after a LAS.

In regards to sensorimotor function, there are mixed results regarding whether or not copers are more similar to CAI patients or uninjured individuals. For instance, Wikstrom

et al.[20] suggest that only several instrumented measures of balance performance can successfully detect differences between copers and CAI patients. Burcal and Wikstrom[88] assessed cutaneous sensitivity on the plantar surface of the foot and found that copers, like CAI patients, had significantly decreased sensitivity in the sinus tarsi, thought to be due to the damage incurred in these sensory structures around the ankle joint as a result of the initial LAS. Despite these differences in perceptual sensitivity, it may not have an effect on cortical activity, as Needle et al.[32] did not identify differences in somatosensory cortex activity using EEG during ankle joint traction among groups of CAI patients, copers, and uninjured controls. Mixed, albeit limited, results are also present in neuromuscular alterations. Pozzi et al.[132] found increased tibialis anterior and fibularis longus activity during the SEBT in copers relative to uninjured controls. However, CNS-oriented investigations have failed to find any differences in spinal reflex[133] or corticomotor excitability[76] between copers and controls.

This is the first investigation to quantify both feed-forward and feed-back cortical activity in ankle sprain copers, and despite the very small sample size, a few noteworthy trends were identified. As can be seen in Table A1.2, there is a trend towards more feed-forward activity, measured by the bereitschaftspotential in individuals with a history of ankle sprain(s). Additionally, there was a larger decrease in gamma activity prior to transitioning onto the uninjured limb relative to the injured limb (Tables A1.7 and A1.8). Limited by a small sample size, these preliminary findings reveal that there may be alterations in feed-forward cortical activity in ankle sprain copers similar to that of unilateral CAI patients. It is unclear whether or not this represents a similarity between

the cascade of sensorimotor alterations, therefore, we suggest future investigations make efforts to include copers as an additional comparison group.

6.2.2 Correlation Results

Due to the exploratory nature of this dissertation, I opted to perform several follow-up and correlation analyses of the data. Our correlation analysis revealed several results linking injury demographics, clinical exam results, and patient-reported function to feed-forward and feed-back measures of sensorimotor control in CAI patients. Although not identified in every outcome measure, these findings provide preliminary evidence that EEG-assessed sensorimotor function is related to injury severity in CAI patients. A large number of relationships were identified between instrumented balance outcomes and cortical activity prior to and during the leaning task (Tables A1.9, A1.10, A1.11, A1.12, A1.13). Interestingly, many of these were identified in both controls and CAI patients, providing a link between a peripheral outcome of feed-back sensorimotor control and central measures of sensorimotor function. These revealed a relationship in both groups between individuals with better balance having less feed-forward and greater feed-back cortical activity. This may suggest individual differences in sensorimotor capabilities (i.e. having better balance) are related to the amount of cortical processing before and during movement.

6.2.3 Limb Results

In order to recruit as many CAI patients as possible within the given timeframe, both bilateral and unilateral CAI patients were eligible for these investigations. This has limited my ability to test the hypothesis of between-limb differences in CAI patients, as

we only identified one significant difference between limbs in any of the EEG measures. There was significantly greater event-related desynchronization (i.e. more activity) in the upper alpha band when a unilateral CAI patient was leaning towards their uninjured limb. Differences were also identified in feed-forward (DSLT) and feed-back (leaning) in the upper alpha band between the unilateral and bilateral CAI patients. As discussed in Chapter 4, compared to unilateral CAI patients, those with bilateral CAI had more feed-forward activity prior to transitioning to the uninjured limb. Additionally, bilateral CAI patients had significantly greater upper alpha activity once they reached their limits of stability while leaning towards the involved side, suggesting an increase in motor processing during this task. Interestingly, Needle et al.[32] did not identify between-limb differences in EEG-derived measures of somatosensory activity in unilateral CAI patients. These findings may represent injury-specific adaptations to feed-forward and feed-back sensorimotor control, and the differences between bilateral and unilateral CAI patients are certainly worth investigating.

6.3. Pitfalls and Alternative Approaches

6.3.1 Pitfalls and Limitations

The inclusion of bilateral CAI patients limited our ability to fully assess limb effects. Based on the first two months of participant recruitment, it was decided that bilateral CAI patients would be also enrolled so that a full group of 20 could be recruited, fulfilling the power requirements of this investigation. Given the potential for between-limb differences identified through secondary analysis, I feel this has limited the insight into whether or not adaptations were present bilaterally in feed-forward and feed-back

sensorimotor control. CAI has a high degree of heterogeneity with respect to the symptoms and impairments of each patient. Hiller et al.[68] proposed a model describing three primary groups of CAI patients (perceived instability, mechanical instability, and recurrent sprain) and the various combinations of these groups creating up to 7 unique groups. Given the high degree of variability in EEG outcome measures (e.g. standard deviations of MRCP outcomes in Table 5), it is possible that the heterogeneity in our sample masked group differences.

Given the heterogeneity of all groups in these investigations, it is possible that several factors could have influenced results. It is currently unknown whether or not sex has an impact on these cortical measures, therefore this cannot be ruled out as a confounding factor. Additionally, the BMI of the participants may have been a better criterion for matching, along with a more stringent physical activity record using a scale such as the Tegner activity level scale, or perhaps recording the preferred sports these participants specialize in. The age of the participants may have also masked the potential and hypothesized central adaptations in our CAI patients. For instance, an individual who developed CAI around 13 years of age and then was tested at 22 years of age may potentially have different sensorimotor alterations or adaptations to the CAI patient who developed the condition at 18 years old and was tested when 19 years old. Therefore the age of the participants, and the duration of time having CAI could be considered as pitfalls and an additional area for heterogeneity within CAI patients.

The bandwidths for analysis were selected in order to better place our results within the context of the literature for voluntary leaning,[2,41] DSLT,[81] and EEG research in CAI patients. However, there is often a lack of agreement in the literature when defining

bands of activity and describing the activity within each one. There is also research to suggest an individualistic nature of the beta band activity,[35] therefore it is possible a difference between groups was masked by the broad band widths used in this study (Figures 7 and 8).

An additional potential pitfall of this study design relates to the EEG methodology, and selecting a limited electrode montage that collected data from fronto-central locations. While the electrodes selected for analysis have been used previously in the literature,[2,41,81] collecting data from all of the channels in the cap would have allowed for two advantages:1) scalp topographies could be accurately represented and 2) independent component analysis (ICA) could have been used. Scalp topographies are commonly reported in EEG research and can help show the distribution of a specific waveform or spectral perturbation across the scalp (i.e. does power increase in one or both hemispheres). ICA, an advanced EEG analysis, decomposes the EEG signal into the individual components that sum to create the continuous, complex waveform. This can be used, along with the scalp topographies of the individual components to remove movement artifacts,[102,103] as well as isolating the specific movement-related EEG activity for analysis.[81] However, epochs with obvious movement artifact were removed from analysis during manual epoch rejection.

It is unfortunate we were unable to collect data pertaining to lower extremity muscle onset times during the DSLT, however we did not have the ability to test all of these muscles. The external triggering and synchronization method in the NetForce software also prevented the calculation of the center-of-pressure, limiting our ability to calculate a meaningful measure pertaining to the displacement of the APA during a DSLT trial. As a

result we do not have a good peripheral measure of feed-forward sensorimotor control to both validate our results against, nor do we have a good measure to use to examine the relationships with cortical measures of feed-forward control.

6.3.2 Alternative Approaches

Feed-back sensorimotor control was not assessed during the DSLT task. In regards to balance training, we identified significant improvements in feed-back sensorimotor control (Table 14). However, in order to calculate an ERSP, you need a time-locking event to use to properly analyze the change in activity. Slobounov et al.[40] evaluated the neural links between a COP measure of balance performance and EEG activity by performing time-frequency analysis of the COP outcome to identify moments of instability and then performing ICA and a continuous wavelet transformation to reveal power changes in the time-frequency domain.[40] This advanced technique may be applied in the future to investigations, or if possible, this dataset, to provide insight into the neural correlates of the observed improvements in a feed-back balance test (Table 14).

Using TMS has provided evidence of cortical-level adaptations to the motor cortex controlling the lower limb muscles in CAI patients.[31,33,76,114] Although it falls short in that it is not able to provide an outcome that represents the activity of the intricate sensorimotor networks within the cerebral cortex, investigations that have assessed cortical changes to balance training have used TMS.[26,111-113,129,130] A logical step and alternative approach would be to assess changes in corticomotor excitability following balance training in CAI patients to see if improvements in balance are linked to these neural adaptations.

An additional approach would be to sacrifice temporal resolution in order to utilize the superior spatial resolution of functional magnetic resonance imaging (fMRI) to evaluate the structures involved in sensorimotor control in CAI patients. There are currently no peer-reviewed publications on CAI patients using fMRI, but an unpublished thesis reported that during an ankle movement task CAI patients had greater activation in the somatosensory cortex, premotor cortex, and anterior cingulate gyrus when compared to uninjured controls.[134] In patients that have torn their anterior cruciate ligament (ACL), Kapreli et al.[135] reported increased activation in motor planning as well as sensory and visual processing regions. These findings were also replicated in ACL-reconstructed patients (ACL-R) by a recent investigation.[136] Overall these findings suggest that due to this ligamentous injury, or repair, there is a change in sensorimotor integration, weighting visual-spatial information greater than the somatosensory information when planning motion. A meta-analysis found that CAI patients displayed a similar reweighting towards visual input when comparing eyes open and eyes closed balance measures from a force platform.[87] It is possible that utilizing this approach will help by identifying structures and potentially cortical networks (through diffusion tensor imaging) that are altered in CAI patients through MRI studies. EEG-based research in CAI patients would benefit as a result, as more focused investigations could be designed to evaluate the MRI-based findings at the higher temporal resolution than EEG offers.

6.4 Future Directions

Based on the fMRI findings regarding cortical sensorimotor plasticity in ACL-R patients, a logical step is to apply similar study designs to identify impairments in the CAI population. Although EEG research[137] occurred in an ACL-R population prior to fMRI

research,[136] the findings are consistent between modalities with both producing evidence of somatosensory processing alterations. Therefore, stronger hypothesis-driven research can be conducted once both the structural and functional differences have been fully described in the CAI population. In other words, repeating the same task that may elucidate differences in fMRI activity, with EEG, may allow us to take advantage of the insight offered by the higher temporal resolution of EEG.

Balance training consistently reveals improvements in measures of feed-back sensorimotor control (Table 14).[24,78,107] With the current task, we do not have a time-locking event to use for analysis this activity. However, it may be possible through a combination of ICA and continuous wavelet transformation, as outlined by Slobounov et al.[40] The current dataset will be explored further to see if this is possible, but a future direction is to see if improvements in static and dynamic balance can be supported by changes in cortical activity during such tasks.

Based on the present results, the selected outcome measures may not have been sensitive or specific enough to detect group differences. Connectivity analyses may be able to offer additional insight into the functional relevance of these EEG measures of sensorimotor control in CAI patients. For instance, corticomuscular coherence can be assessed to identify if there is coherence (i.e. an association) between the EEG signal and muscular activity measured by EMG[138] and a link has been established between beta activity and muscular activity during static balance in healthy individuals.[92] Granger causality is another method of connectivity analysis that tests whether the variance in one signal can be predicted by variance in another signal that occurs earlier in time.[139] One application of this may be a time-varying COP-derived measure such as time-to-boundary or the

COP displacement, and the activity at the Cz electrode. Lastly, connectivity analyses can be applied between EEG electrode sites to provide insight into how oscillations differ in time and space (i.e. is time-frequency activity at one electrode related to the activity at another?). If CAI patients have similar fMRI-identified adaptations, such as an increased reliance on visual input for motor planning,[136] a connectivity analysis during an appropriate task may allow us to investigate this phenomenon with a higher temporal precision than is offered by fMRI. However, it is important to mention that these investigations benefit from using a higher-density electrode array, therefore future investigations should aim to use a minimum of 64 EEG channels in order to provide access to accurate time-frequency decomposition and signal component identification.

6.5 Conclusions

My dissertation was the first investigation to establish measures of cortical function during weight-bearing tasks in CAI patients. Specifically, both feed-forward and feed-back sensorimotor control were evaluated using EEG-derived measures of overall cortical activity. This novel approach aimed to determine if the known impairments in sensorimotor control could be explained by differences in cortical activity prior to and during two separate tasks: voluntary leaning and a dual-to-single limb transition. My results did not support my hypotheses that the amount of cortical activity relating to feed-forward and feed-back sensorimotor control would be greater in CAI patients. Interestingly, the results, and patterns of activity occurring prior to and during movement suggest that CAI patients have similar cortical activity during weight-bearing tasks. These results appear to disagree with the existing literature that has established differences in motor cortex excitability, but it may be possible that the selected measures

were not sensitive enough to detect these alterations. The EEG outcomes utilized represent the sum of the activity occurring below each electrode, therefore with this current evidence we are limited to making conclusions about the overall amount of activity during feed-forward and feed-back activity. A combined approach in the future, using functional imaging techniques (e.g. fMRI) along with EEG may provide greater insight into the theorized sensorimotor processing alterations in CAI patients.

Balance training is known to be an effective treatment in CAI patients, yet clinicians and researchers don't have empirical evidence to help explain the underlying neural mechanisms of this treatment. My dissertation was the first investigation to evaluate changes in cortical activity, assessed by EEG, in response to balance training in physically active young adults. Based on the grand average balance training did not alter feed-forward cortical activity in these patients, however, I found that balance training was only effective at improving balance in 8 out of the 15 CAI patients that received this treatment. A significant change in gamma activity, which is linked to sensory processing, was identified in the 8 patients that improved dynamic balance, therefore it is possible that the balance training had a positive effect on their ability to utilize sensory information when planning movement. Based on the low number of balance training responders, it appears that balance training is not an ideal treatment for all CAI patients, which agrees with the impairments-based approach to rehabilitation.[69]

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APPENDIX 1: COPER, CORRELATION, AND LIMB ANALYSES

A1.1 Coper Analysis

I anticipated recruiting at least 15 copers per study in order to meet power estimations, however I was unable to recruit sufficient numbers of copers to include in the manuscripts as a comparison group. I used two strategies to recruit potential participants for these investigations. I would visit a large lecture class and provide the students with a description of my studies before answering any questions they had. I then collected the email addresses of interested individuals and gave them an anonymous link to fill out my eligibility survey on Qualtrics. This survey asked basic questions such as age, height and weight, and also served to screen for my exclusion and inclusion criteria. I would also mass email a description of the study and the Qualtrics anonymous link. Throughout the course of the study I sent out several approved mass-emails, including the Department of Biological Sciences undergraduate and graduate student listservs, Department of Kinesiology undergraduate listserv, Department of Dance undergraduate listserv, and two times to the entire UNC Charlotte undergraduate student listserv.

Out of the 1,289 individuals who began the survey, 870 finished the survey completely. Out of this potential 870 individuals, I identified a total of 31 ankle sprain copers based on my inclusion criteria. I contacted these 31 individuals to inform them of their eligibility and schedule baseline testing, however only a total of 8 individuals responded to my emails and participated in these investigations; 4 of the volunteers participated in both the leaning and DSLT studies. I was able to enroll 7 copers in the leaning study and 5 copers in the DSLT study. I was able to identify 86 CAI patients that met my eligibility

and contact them, with a better response rate as I was able to enroll 20 CAI participants in each investigation. I also identified 189 eligible controls out of the 870 usable responses on the Qualtrics survey.

Based on this inability to recruit a large enough sample size of Copers in either study, I have left this data out of Chapters 3 and 4, and I will present the results here of the analyses. Independent samples t-tests were run to test for group differences, and paired samples t-tests were run to test for limb differences. All tests were run at an alpha of 0.05.

A1.1.1 Leaning Task Results

The methods and full description of this task can be seen in Chapter 3. Participant demographics can be seen in Table A1.1. No group differences ($p > 0.05$) were identified between controls and copers, or between CAI patients and copers, in either the feed-forward measures of sensorimotor control (Table A1.2) or feed-back sensorimotor control (Tables A1.3 and A1.4). I used the mean difference and 95% confidence interval around the mean difference to explore the data further, and these may suggest that copers have less of an increase in gamma activity when reaching their limits of stability than either groups. Interestingly, as can be seen in Figures A1.1 and A1.2, the copers appear to have a similar pattern of activity to that of the uninjured controls, with a more broad band of increased activity extending up to ~35 Hz.

To test whether or not there were differences between the injured and uninjured limb, I ran a paired samples t-test on the EEG outcome measures. The means and standard deviations, and between-limb Hedges' g effect sizes with 95% confidence intervals can be seen in Table A1.5. The movement monitoring potential was significantly higher in

the copers when leaning towards the involved limb compared to leaning to the uninvolved limb ($p = 0.021$). This is an interesting finding, as the movement monitoring potential is thought to represent a blend of feed-forward and feed-back activity[42], as it is calculated after movement onset.[2] No other significant between-limb differences were identified ($p > 0.05$).

A1.1.2 DSLT Task Results

The methods and description of this task can be seen in Chapter 4. Table A1.6 contains the demographics of the 3 groups. There were no significant differences identified between any of the 3 groups ($p > 0.05$) in ERSP measures at Cz (Table A1.7**)** or CPz (Table A1.8**)**. I also assessed for between-limb differences in feed-forward cortical activity, and as can be seen in Tables A1.7 and A1.8, there was significantly less gamma activity prior to transitioning to the uninvolved limb compared to the involved limb at Cz ($p = 0.015$) and CPz ($p = 0.016$). As seen in Figures A1.3 and A1.4, it appears this difference may be due to an increase (red color) between 40 and 45Hz in the 200ms prior to movement onset. Increases in gamma activity are thought to represent sensory processing prior to movement.[35,36]

A1.2 Correlation Analysis

Due to the large number of correlations performed, I opted to leave several of these comparisons out of Chapters 3 and 4. No correlations were run on the coper groups in either investigation due to the small sample sizes. In both of these studies, the linear relationships between EEG measures of either feed-forward or feed-back sensorimotor control and instrumented measures of static balance, as well as the results of the anterior

drawer and talar tilt clinical tests. Clinical tests of joint laxity were graded on a likert-style scale, with the following scores: 1) very tight, 2) tight, 3) normal, 4) loose, 5) very loose. Due to the ordinal nature of this measure, linear relationships between the anterior drawer and talar tilt scores and the EEG outcome measures were assessed using Spearman's rank-order correlations.

Instrumented balance outcomes were collected from the three trial average of 10-second static balance trials on the Accusway force platform (AMTI Inc., Watertown, MA). They were recorded at 50Hz with the BalanceClinic (Version 1.4.2, AMTI Inc., Watertown, MA) software, which was used to export the following outcomes: center-of-pressure path length (cm), peak anterior-posterior (AP) velocity (cm/s), peak medial-lateral (ML) velocity (cm/s), and the 95% confidence ellipse of the COP area (cm^2). In the leaning task study described in Chapter 3, participants completed balance trials in three conditions: dual-limb stance, single-limb stance on the involved limb, and single-limb stance on the uninvolved limb. In the DSLT study described in Chapter 4, participants completed balance trials in five conditions: dual-limb stance, eyes open single-limb stance on the involved limb, eyes open single-limb stance on the uninvolved limb, eyes closed single-limb stance on the involved limb, and eyes closed single-limb stance on the uninvolved limb. Participants in the DSLT study also completed the SEBT in the anterior (SEBT-A), posteromedial (SEBT-PM), and posterolateral (SEBT-PL) directions.

A1.2.1 Leaning Task Correlation Results

Three significant relationships were identified between the anterior drawer test results and cortical activity during a voluntary leaning task. A positive relationship was

identified between the movement monitoring potential and the anterior drawer ($\rho = 0.500$, $p = 0.025$). Moderate negative relationships were identified between the anterior drawer test results and beta activity at the Cz electrode during anterior leaning ($\rho = -0.479$, $p = 0.033$), as well as upper alpha activity during leaning to the uninvolved limb ($\rho = -0.478$, $p = 0.033$). These three relationships suggest there is lower feed-forward cortical activity and greater feed-back activity in ankles with more laxity.

In CAI patients, many significant relationships were identified between instrumented measures of balance and both feed-forward and feed-back EEG outcome measures. Table A1.9 contains the correlations for dual-limb balance, Table A1.10 contains the correlations for single-limb balance on the involved limb, and Table A1.11 contains the correlations for single-limb balance on the uninvolved limb. Relationships between cortical activity and instrumented balance measures were most frequent when assessing balance on the uninvolved limb (Table A1.11). The direction of these relationships suggest CAI patients with worse balance have decreased feed-forward cortical activity as evidenced by the relationships in uninvolved balance and MRCP outcomes (Table A1.11). The link between feed-back cortical activity (ERSP) and balance reveals an increase in feed-back activity with worse balance.

Similar relationships were also present in the control group. Table A1.12 summarizes the correlations between single-limb balance on the dominant limb and reveals several significant ($p < 0.05$) relationships between feed-forward cortical activity and ML velocity. Here, participants with lower peak ML velocity displayed lower feed-forward cortical activity. Relationships between nondominant limb balance and EEG measures in

the control group (Table A1.13) agree with the results in the CAI group, with more feedback activity being identified in participants with worse balance.

A1.2.2 DSLT Task Correlation Results

No significant relationships were identified between clinical test results and ERSP outcomes prior to the DSLT in the CAI group ($p > 0.05$). Moderate relationships were identified between beta activity prior to DSLT onto the involved limb and reach distance on the SEBT in the posterolateral direction on the involved ($r = -0.453$, $p = 0.045$) and uninvolved ($r = -0.537$, $p = 0.015$) limbs. CAI patients with higher reach distances in this direction had lower beta activity prior to movement. There was also a moderate relationship between the 95% confidence ellipse during single-limb balance on the uninvolved limb and alpha activity prior to DSLT to the involved limb ($r = -0.490$, $p = 0.028$). In the control group, two relationships were identified between peak ML velocity during single-limb balance on the dominant limb and alpha activity prior to transitioning to the nondominant limb at the Cz ($r = 0.526$, $p = 0.017$) and CPz ($r = 0.456$, $p = 0.043$) electrode sites. This relationship links participants with better balance on the dominant limb having lower activity prior to the DSLT to their nondominant limb.

A1.3 Limb Analysis

To better assess for limb differences, I dichotomized my CAI patients into unilateral and bilateral CAI to see if between-group and between-limb differences were present in these individuals. Independent samples t-tests were run to test for group differences, and paired samples t-tests were run to test for limb differences. All tests were run at an alpha of 0.05.

A1.3.1 Leaning Task Limb Results

There were no significant group differences in any of the motor-related cortical potential outcomes during voluntary leaning in any direction ($p > 0.05$). Upper alpha activity was significantly lower in unilateral CAI patients compared to bilateral CAI patients during leaning towards the involved limb ($p = 0.023$). No between-limb differences were identified in any of the outcome measures in bilateral CAI patients ($p > 0.05$). A significant difference was identified in the unilateral CAI group, with significantly greater upper alpha activity when leaning towards the uninjured limb relative to the injured limb ($p = 0.044$).

A1.3.2 DSLT Task Limb Results

Prior to a DSLT onto the uninvolved limb, bilateral CAI patients had significantly less alpha activity at the CPz electrode compared to uninjured controls ($p = 0.033$). Patients with unilateral CAI had significantly greater alpha desynchronization (i.e. more activity) than the bilateral CAI patients prior to transitioning to the uninvolved limb at the Cz ($p = 0.043$) and CPz ($p = 0.050$). No significant between-limb differences in ERSP outcomes were identified in either the unilateral or bilateral CAI subgroups ($p > 0.05$).

A1.4 Tables

Table A1.1. Participant demographics.

Values are mean and standard deviation unless otherwise stated. NASA PASS: NASA Physical Activity Status Scale; IdFAI: Identification of Functional Ankle Instability; FAAM-ADL: Foot and Ankle Ability Measure Activities of Daily Living Scale; FAAM-Sport: Foot and Ankle Ability Measure Sport Scale.

	Uninjured Control (n = 20)	Coper (n=7)	CAI (n = 20)
Female, no (%)	13 (65)	2 (29)	13 (65)
Age, yr	21.70 (2.62)	22.43 (3.10)	20.85 (2.28)
Height, cm	168.82 (11.02)	169.26 (11.15)	174.75 (7.88)
Mass, kg	68.09 (15.75)	71.54 (7.67)	71.68 (18.44)
NASA PASS, median (IQR)	5 (4, 6)	6 (4, 8)	6 (4, 6)
IdFAI	0.00 (0.00)	5.29 (1.70)	17.15 (3.59)
Number of Lateral Ankle Sprains	0.00 (0.00)	1.00 (0.00)	2.65 (1.93)
Number of Rolls in past 6-months	0.00 (0.00)	0.00 (0.00)	3.85 (2.74)
Anterior Drawer, median (IQR)	3 (3, 3)	3	3 (3, 4)
Talar Tilt, median (IQR)	3 (3, 3)	3 (3, 4)	4 (3, 4)
FAAM-ADL, %	100.00 (0.00)	100.00 (0.00)	91.37 (6.18)
FAAM-Sport, %	100.00 (0.00)	99.11 (1.52)	82.50 (11.80)

Table A1.2. MRCP outcomes in μV across three different leaning directions.

The means and standard deviations of the mean negativity (μV) for each MRCP outcome in the three directions are seen above, separated by group and Direction mean with standard error. The BP, or Bereitschaftspotential, was measured as the mean negativity from -600ms to -500ms prior to movement onset. The MP, or motor potential, was measured as the mean negativity from -100ms to movement onset. The MMP, or movement monitoring potential, was measured as the mean negativity for the 500ms following movement onset. Positive values of the mean difference indicate greater mean activity in the Coper group.

Measure	**Group**	**Anterior**	**Involved**	**Uninvolved**
BP	Control	-4.12 (3.62)	-4.02 (3.59)	-3.64 (3.52)
	Coper	-5.44 (2.43)	-5.30 (2.91)	-4.18 (1.99)
	CAI	-5.60 (2.94)	-4.67 (2.98)	-4.83 (3.15)
	Control – Coper mean difference (95% CI)	1.32 (-1.73, 4.36)	1.28 (-1.84, 4.39)	0.55 (-2.37, 3.46)
	CAI – Coper mean difference (95% CI)	-0.17 (-2.72, 2.39)	0.63 (-2.04, 3.31)	-0.65 (-3.28, 1.99)
MP	Control	-14.75 (5.81)	-17.39 (6.51)	-18.31 (6.62)
	Coper	-14.09 (1.44)	-17.09 (2.80)	-14.82 (1.90)
	CAI	-13.31 (6.18)	-16.09 (7.40)	-16.07 (6.76)
	Control – Coper mean difference (95% CI)	-0.66 (-5.29, 3.96)	-0.30 (-5.58, 4.99)	-3.48 (-8.77, 1.80)
	CAI – Coper mean difference (95% CI)	0.77 (-4.14, 5.69)	1.01 (-4.96, 6.97)	-1.24 (-6.64, 4.15)
MMP	Control	-17.50 (6.83)	-22.20 (8.07)	-22.40 (7.98)
	Coper	-15.76 (2.74)	-20.61 (2.80)	-18.20 (2.61)
	CAI	-18.07 (8.67)	-21.99 (9.37)	-21.42 (9.28)
	Control – Coper mean difference (95% CI)	-1.74 (-7.26, 3.79)	-1.59 (-8.07, 4.90)	-4.20 (-10.61)
	CAI – Coper mean difference (95% CI)	-2.31 (-9.25, 4.64)	-1.38 (-8.87, 6.11)	-3.32 (-10.64, 4.18)

Table A1.3. ERSP outcomes in different leaning directions at the Cz electrode.

The means and standard deviations of the ERSP, in dB, in each bandwidth when the participant reached his/her limit of stability. Lower values in the upper alpha (10-12 Hz) and beta (14-25 Hz) bands indicate an increase in activity. Higher values in the gamma band (30-50 Hz) indicates an increase in activity. Positive values of the mean difference indicate greater mean activity in the Coper group in the upper alpha and beta bands, and less activity in the gamma band.

Measure	**Group**	**Anterior**	**Involved**	**Uninvolved**
Upper Alpha	Control	-1.15 (0.99)	-1.23 (1.19)	-0.87 (0.99)
	Coper	-1.35 (1.02)	-1.49 (0.79)	-1.28 (1.25)
	CAI	-1.39 (1.30)	-1.17 (1.32)	-1.42 (1.09)
	Control – Coper mean difference (95% CI)	0.20 (-0.70, 1.10)	0.27 (-0.74, 1.27)	0.40 (-0.55, 1.36)
	CAI – Coper mean difference (95% CI)	-0.03 (-1.15, 1.08)	0.32 (-0.78, 1.41)	-0.14 (-1.17, 0.88)
Beta	Control	-0.94 (1.16)	-1.19 (1.19)	-1.09 (1.30)
	Coper	-0.99 (0.52)	-0.92 (0.67)	-1.15 (0.69)
	CAI	-0.68 (0.87)	-0.69 (0.84)	-0.94 (0.79)
	Control – Coper mean difference (95% CI)	0.05 (-0.89, 0.99)	-0.26 (-1.25, 0.72)	0.06 (-1.02, 1.13)
	CAI – Coper mean difference (95% CI)	0.30 (-0.42, 1.02)	0.23 (-0.49, 0.96)	0.21 (-0.48, 0.91)
Gamma	Control	0.59 (1.21)	0.09 (0.82)	-0.04 (0.90)
	Coper	0.20 (0.54)	-0.03 (0.61)	-0.36 (0.89)
	CAI	0.60 (0.92)	0.24 (0.76)	0.10 (0.72)
	Control – Coper mean difference (95% CI)	0.40 (-0.59, 1.38)	0.12 (-0.58, 0.82)	0.32 (-0.49, 1.13)
	CAI – Coper mean difference (95% CI)	0.40 (-0.36, 1.17)	0.26 (-0.40, 0.92)	0.46 (-0.23, 1.15)

Table A1.4. ERSP outcomes in different leaning directions at the CPz electrode.

The means and standard deviations of the ERSP, in dB, in each bandwidth when the participant reached his/her limit of stability. Lower values in the upper alpha (10-12 Hz) and beta (14-25 Hz) bands indicate an increase in activity. Higher values in the gamma band (30-50 Hz) indicates an increase in activity. Positive values of the mean difference indicate greater mean activity in the Coper group.

Measure	**Group**	**Anterior**	**Involved**	**Uninvolved**
Upper Alpha	Control	-1.59 (1.20)	-1.76 (1.33)	-1.45 (1.00)
	Coper	-2.06 (1.28)	-1.93 (0.79)	-2.23 (1.61)
	CAI	-1.75 (1.61)	-1.94 (1.63)	-1.93 (1.34)
	Control – Coper mean difference (95% CI)	0.47 (-0.63, 1.57)	0.17 (-0.93, 1.28)	0.78 (-0.28, 1.84)
	CAI – Coper mean difference (95% CI)	0.31 (-1.08, 1.70)	0.00 (-1.34, 1.33)	0.29 (-0.98, 1.57)
Beta	Control	-0.94 (1.01)	-1.20 (0.92)	-1.13 (0.85)
	Coper	-1.02 (0.65)	-1.09 (0.66)	-1.39 (0.94)
	CAI	-0.74 (1.06)	-1.03 (0.98)	-1.18 (0.88)
	Control – Coper mean difference (95% CI)	0.09 (-0.76, 0.94)	-0.12 (-0.90, 0.67)	0.26 (-0.53, 1.05)
	CAI – Coper mean difference (95% CI)	0.28 (-0.60, 1.17)	0.06 (-0.76, 0.89)	0.20 (-0.61, 1.02)
Gamma	Control	1.01 (1.23)	0.25 (0.73)	0.14 (0.81)
	Coper	0.70 (0.62)	0.04 (0.62)	-0.34 (0.75)
	CAI	1.09 (1.08)	0.32 (0.80)	0.23 (0.69)
	Control – Coper mean difference (95% CI)	0.31 (-0.70, 1.31)	0.21 (-0.42, 0.85)	0.47 (-0.25, 1.20)
	CAI – Coper mean difference (95% CI)	0.39 (-0.50, 1.28)	0.28 (-0.40, 0.97)	0.57 (-0.06, 1.21)

Table A1.5. Between-limb Hedges' g effect sizes for EEG outcome measures.

Means and standard deviation, and between-limb Hedges' g effect sizes for EEG outcome measures are seen above. Effect sizes were calculated as Involved limb – Uninvolved limb, with a positive point estimate indicating a more negative value when leaning towards the involved limb. This is interpreted as increased activity in the BP, MP, MMP, Upper Alpha, and Beta outcome measures. A negative point estimate indicates greater activity in the Gamma outcomes. BP: bereitschaftspotential; MP: motor potential; MMP: movement monitoring potential. A * indicates a significant difference between limbs ($p < 0.05$).

Measure	**Group**	**Involved or Dominant**	**Uninvolved or Nondominant**	**Involved – Uninvolved Effect size (95 % CI)**
BP (µV)	Control	-4.02 (3.59)	-3.64 (3.52)	0.20 (-0.42, 0.82)
	Coper	-5.30 (2.91)	-4.18 (1.99)	0.31 (-0.74, 1.37)
	CAI	-4.67 (2.98)	-4.83 (3.15)	-0.07 (-0.69, 0.55)
MP (µV)	Control	-17.39 (6.51)	-18.31 (6.62)	-0.32 (-0.95, 0.30)
	Coper	-17.09 (2.80)	-14.82 (1.90)	0.83 (-0.26, 1.93)
	CAI	-16.09 (7.40)	-16.07 (6.76)	0.01 (-0.61, 0.63)
MMP (µV)	Control	-22.20 (8.07)	-22.40 (7.98)	-0.10 (-0.72, 0.52)
	Coper	-20.61 (2.80)	**-18.20 (2.61)***	1.06 (-0.06, 2.18)
	CAI	-21.99 (9.37)	-21.42 (9.28)	0.23 (-0.39, 0.86)
Upper Alpha Cz (dB)	Control	-1.23 (1.19)	-0.87 (0.99)	0.32 (0.30, 0.95)
	Coper	-1.49 (0.79)	-1.28 (1.25)	0.29 (-0.77, 1.34)
	CAI	-1.17 (1.32)	-1.42 (1.09)	-0.25 (-0.87, 0.37)
Beta Cz (dB)	Control	-1.19 (1.19)	-1.09 (1.30)	0.15 (0.47, 0.77)
	Coper	-0.92 (0.67)	-1.15 (0.69)	-0.64 (-1.71, 0.44)
	CAI	-0.69 (0.84)	-0.94 (0.79)	-0.47 (-1.10, 0.16)
Gamma Cz (dB)	Control	0.09 (0.82)	-0.04 (0.90)	-0.20 (-0.82, 0.42)
	Coper	-0.03 (0.61)	-0.36 (0.89)	-0.36 (-1.42, 0.69)
	CAI	0.24 (0.76)	0.10 (0.72)	-0.23 (-0.86, 0.39)
Upper Alpha CPz (dB)	Control	-1.76 (1.33)	-1.45 (1.00)	0.27 (-0.35, 0.89)
	Coper	-1.93 (0.79)	-2.23 (1.61)	-0.41 (-1.47, 0.64)
	CAI	-1.94 (1.63)	-1.93 (1.34)	0.00 (-0.62, 0.62)
Beta CPz (dB)	Control	-1.20 (0.92)	-1.13 (0.85)	0.14 (-0.48, 0.77)
	Coper	-1.09 (0.66)	-1.39 (0.94)	-0.62 (-1.69, 0.46)
	CAI	-1.03 (0.98)	-1.18 (0.88)	-0.28 (-0.91, 0.34)
Gamma CPz (dB)	Control	0.25 (0.73)	0.14 (0.81)	-0.19 (-0.82, 0.43)
	Coper	0.04 (0.62)	-0.34 (0.75)	-0.37 (-1.42, 0.69)
	CAI	0.32 (0.80)	0.23 (0.69)	-0.14 (-0.76, 0.49)

Table A1.6. Participant demographics.

Values are mean and standard deviation unless otherwise stated. NASA PASS: NASA Physical Activity Status Scale; IdFAI: Identification of Functional Ankle Instability; FAAM-ADL: Foot and Ankle Ability Measure Activities of Daily Living Scale; FAAM-Sport: Foot and Ankle Ability Measure Sport Scale; TSK-11: 11-item Tampa Scale of Kinesiophobia; FABQ: Fear Avoidance Beliefs Questionnaire.

	Uninjured Control (n = 20)	**Coper (n=5)**	**CAI (n = 20)**
Female, no (%)	11 (55)	2 (40)	11 (55)
Age, yr	21.20 (2.73)	22.40 (1.67)	20.55 (2.24)
Height, cm	168.74 (10.85)	169.76 (10.35)	171.00 (7.83)
Mass, kg	68.08 (15.41)	72.52 (17.63)	70.31 (16.89)
NASA PASS, median (IQR)	5 (4, 6)	6 (2, 6)	6 (5, 7)
IdFAI, Involved	0.00 (0.00)	3.60 (1.67)	17.15 (3.59)
IdFAI, Uninvolved	0.00 (0.00	0.00 (0.00)	8.80 (9.12)
Number of Ankle Sprains, Involved	0.00 (0.00)	1.00 (0.00)	2.70 (1.87)
Number of Ankle Sprains, Uninvolved	0.00 (0.00)	0.00 (0.00)	1.15 (1.57)
Number of Rolls in past 6-months, Involved	0.00 (0.00)	0.00 (0.00	4.45 (3.03)
Number of Rolls in past 6-months, Uninvolved	0.00 (0.00)	0.00 (0.00)	0.85 (1.53)
Anterior Drawer, median (IQR)	3 (2, 3)	3 (3, 3)	3 (3, 4)
Talar Tilt, median (IQR)	3 (2, 3)	3 (3, 3)	4 (4, 4)
FAAM-ADL Involved, %	100.00 (0.00)	100.00 (0.00)	88.64 (7.16)
FAAM-ADL Uninvolved, %	100.00 (0.00)	100.00 (0.00)	97.38 (3.29)
FAAM-Sport Involved, %	100.00 (0.00)	99.38 (1.40)	77.97 (12.48)
FAAM-Sport Uninvolved, %	100.00 (0.00)	100.00 (0.00)	93.44 (10.68)
TSK-11	13.55 (2.76)	14.40 (1.52)	19.75 (4.06)
FABQ	0.90 (2.61)	0.60 (1.34)	10.25 (3.64)

Table A1.7. ERSP outcomes prior to DSLT at the Cz electrode.

The means and standard deviations of the ERSP in the 500ms prior to DSLT. Mean difference between groups are also represented with 95% confidence intervals. Positive values Lower values in the upper alpha (10-12 Hz) and beta (14-25 Hz) bands indicate an increase in activity. Higher values in the gamma band (30-50 Hz) indicates an increase in activity. Positive values of the mean difference indicate greater mean activity in the Coper group. Hedges' g effect sizes are calculated as Involved – Uninvolved, with positive point estimates indicating a more negative value on the involved limb (i.e. increased activity in upper alpha and beta, decreased activity in gamma). A * indicates a significant difference between limbs ($p < 0.05$).

Measure	**Group**	**Involved**	**Uninvolved**	**Involved – Uninvolved Effect size (95% CI)**
Upper Alpha	Control	-0.24 (0.46)	-0.20 (0.41)	0.09 (-0.53, 0.71)
	Coper	-0.15 (0.44)	0.07 (0.27)	0.46 (-0.79, 1.72)
	CAI	-0.18 (0.42)	-0.17 (0.41)	0.03 (-0.59, 0.64)
	Control – Coper mean difference (95% CI)	-0.08 (-0.56, 0.39)	-0.26 (-0.66, 0.14)	-
	CAI – Coper mean difference (95% CI)	-0.03 (-0.46, 0.41)	-0.24 (-0.64, 0.17)	-
Beta	Control	-0.21 (0.33)	-0.32 (0.50)	-0.35 (-0.97, 0.28)
	Coper	-0.27 (0.47)	-0.24 (0.31)	0.13 (-1.12, 1.37)
	CAI	-0.22 (0.20)	-0.25 (0.24)	-0.11 (-0.73, 0.51)
	Control – Coper mean difference (95% CI)	0.06 (-0.31, 0.43)	-0.09 (-0.57, 0.40)	-
	CAI – Coper mean difference (95% CI)	0.05 (-0.23, 0.33)	-0.01 (-0.28, 0.25)	-
Gamma	Control	-0.07 (0.19)	-0.09 (0.21)	-0.15 (-0.77, 0.47)
	Coper	-0.01 (0.09)	**-0.26 (0.14)***	-1.69 (-3.14, -0.25)
	CAI	-0.08 (0.13)	-0.08 (0.19)	0.02 (-0.60, 0.64)
	Control – Coper mean difference (95% CI)	-0.06 (-0.24, 0.13)	0.17 (-0.04, 0.37)	-
	CAI – Coper mean difference (95% CI)	-0.07 (-0.21, 0.06)	0.17 (-0.01, 0.36)	-

Table A1.8. ERSP outcomes prior to DSLT at the CPz electrode.

The means and standard deviations of the ERSP in the 500ms prior to DSLT. Mean difference between groups are also represented with 95% confidence intervals. Positive values Lower values in the upper alpha (10-12 Hz) and beta (14-25 Hz) bands indicate an increase in activity. Higher values in the gamma band (30-50 Hz) indicates an increase in activity. Positive values of the mean difference indicate greater mean activity in the Coper group. Hedges' g effect sizes are calculated as Involved – Uninvolved, with positive point estimates indicating a more negative value on the involved limb (i.e. increased activity in upper alpha and beta, decreased activity in gamma). A * indicates a significant difference between limbs ($p < 0.05$).

Measure	**Group**	**Involved**	**Uninvolved**	**Involved – Uninvolved Effect size (95% CI)**
Upper Alpha	Control	-0.36 (0.49)	-0.39 (0.35)	-0.05 (-0.66, 0.57)
	Coper	-0.28 (0.32)	-0.22 (0.30)	0.12 (-1.12, 1.36)
	CAI	-0.33 (0.45)	-0.26 (0.39)	0.16 (-0.46, 0.78)
	Control – Coper mean difference (95% CI)	-0.09 (-0.56, -0.39)	-0.16 (-0.52, 0.19)	-
	CAI – Coper mean difference (95% CI)	-0.05 (-0.50, 0.39)	-0.04 (-0.42, 0.35)	-
Beta	Control	-0.20 (0.24)	-0.29 (0.41)	-0.35 (-0.97, 0.28)
	Coper	-0.28 (0.41)	-0.24 (0.20)	0.12 (-1.12, 1.36)
	CAI	-0.24 (0.23)	-0.25 (0.19)	-0.06 (-0.68, 0.56)
	Control – Coper mean difference (95% CI)	0.08 (-0.21, 0.37)	-0.05 (-0.44, 0.34)	-
	CAI – Coper mean difference (95% CI)	0.05 (-0.24, 0.33)	-0.01 (-0.20, 0.19)	-
Gamma	Control	-0.07 (0.16)	-0.10 (0.15)	-0.23 (-0.85, 0.40)
	Coper	0.04 (0.12)	**-0.20 (0.09)***	-1.63 (-3.06, -0.20)
	CAI	-0.11 (0.18)	-0.11 (0.15	0.00 (-0.62, 0.62)
	Control – Coper mean difference (95% CI)	-0.11 (-0.27, 0.05)	0.11 (-0.04, 0.26)	-
	CAI – Coper mean difference (95% CI)	-0.15 (-0.33, 0.03)	0.09 (-0.05, 0.24)	-

Table A1.9. Correlations between EEG outcomes and Dual Limb balance measures in CAI patients.

Above are the Pearson correlation coefficients between EEG outcome measures during all movement conditions: MRCP (BP, MP, MMP), ERSP (Alpha, Beta, Gamma), and instrumented balance measures from dual-limb balance from the investigation described in Chapter 3. MRCP: Motor-related cortical potential; BP: bereitshaftspotential; MP: motor potential; MMP: movement monitoring potential; ERSP: event-related spectral perturbation; AP: anterior-posterior; ML: medial-lateral; COP: center-of-pressure. A * indicates a significant correlation ($p < 0.05$).

	Dual Limb Path Length	**Dual Limb AP Velocity**	**Dual Limb ML Velocity**	**Dual Limb COP Area**
BP Anterior	-0.139	-0.053	0.323	-0.271
MP Anterior	-0.227	-0.131	0.158	**-0.595***
MMP Anterior	-0.26	-0.177	0.249	**-0.467***
BP Involved	0.221	0.317	0.092	0.175
MP Involved	0.076	0.182	0.071	-0.187
MMP Involved	-0.073	0.036	0.207	-0.243
BP Uninvolved	-0.084	0.04	0.091	0.033
MP Uninvolved	0.029	0.158	0.006	-0.222
MMP Uninvolved	-0.075	0.015	0.194	-0.251
Alpha Cz Anterior	-0.372	**-0.469***	-0.034	-0.033
Beta Cz Anterior	-0.25	-0.224	-0.112	0.06
Gamma Cz Anterior	0.138	0.029	-0.065	0.346
Alpha Cz Involved	-0.255	-0.388	0.027	0.067
Beta Cz Involved	-0.175	-0.219	-0.197	0.013
Gamma Cz Involved	-0.237	-0.355	0.08	0.157
Alpha Cz Uninvolved	**-0.474***	**-0.454***	0.215	-0.072
Beta Cz Uninvolved	-0.38	-0.404	0.139	-0.102
Gamma Cz Uninvolved	-0.133	-0.298	0.079	0.113
Alpha CPz Anterior	-0.281	-0.327	-0.092	-0.072
Beta CPz Anterior	-0.141	-0.119	-0.163	0.054
Gamma CPz Anterior	0.256	0.137	-0.128	0.387
Alpha CPz Involved	-0.148	-0.24	0.003	0.072
Beta CPz Involved	-0.049	-0.078	-0.177	0.077
Gamma CPz Involved	-0.157	-0.233	0.01	0.214
Alpha CPz Uninvolved	-0.191	-0.212	-0.001	0.039
Beta CPz Uninvolved	-0.25	-0.272	0.061	-0.093
Gamma CPz Uninvolved	-0.083	-0.237	0.017	0.099

Table A1.10. Correlations between EEG outcomes and Involved limb balance measures in CAI patients.

Above are the Pearson correlation coefficients between EEG outcome measures during all movement conditions: MRCP (BP, MP, MMP), ERSP (Alpha, Beta, Gamma), and instrumented balance measures from single-limb balance on the involved limb from the investigation described in Chapter 3. MRCP: Motor-related cortical potential; BP: bereitshaftspotential; MP: motor potential; MMP: movement monitoring potential; ERSP: event-related spectral perturbation; AP: anterior-posterior; ML: medial-lateral; COP: center-of-pressure. A * indicates a significant correlation ($p < 0.05$).

	Involved Path Length	**Involved AP Velocity**	**Involved ML Velocity**	**Involved COP Area**
BP Anterior	0.298	0.05	0.027	0.171
MP Anterior	0.248	0.22	-0.021	0.027
MMP Anterior	0.135	0.284	-0.062	-0.101
BP Involved	0.217	0.055	0.087	0.148
MP Involved	0.373	0.302	-0.056	0.27
MMP Involved	0.298	0.354	-0.107	0.098
BP Uninvolved	-0.007	-0.292	0.233	0.032
MP Uninvolved	0.346	0.134	0.012	0.335
MMP Uninvolved	0.342	0.332	-0.128	0.182
Alpha Cz Anterior	-0.274	-0.313	-0.208	-0.052
Beta Cz Anterior	-0.404	**-0.567***	0.023	-0.055
Gamma Cz Anterior	-0.014	0.179	-0.255	0.083
Alpha Cz Involved	-0.322	-0.357	-0.119	-0.078
Beta Cz Involved	-0.139	-0.277	-0.176	0.031
Gamma Cz Involved	-0.4	-0.249	0.07	-0.14
Alpha Cz Uninvolved	**-0.547***	**-0.500***	0.068	-0.342
Beta Cz Uninvolved	-0.308	-0.338	0.038	-0.209
Gamma Cz Uninvolved	-0.129	0.106	-0.183	-0.165
Alpha CPz Anterior	-0.235	-0.33	-0.213	-0.075
Beta CPz Anterior	-0.258	**-0.469***	-0.1	0.007
Gamma CPz Anterior	-0.062	0.045	-0.146	0.031
Alpha CPz Involved	-0.241	-0.326	-0.166	-0.023
Beta CPz Involved	-0.066	-0.263	-0.245	0.127
Gamma CPz Involved	-0.366	-0.298	0.138	-0.124
Alpha CPz Uninvolved	-0.338	-0.393	-0.055	-0.17
Beta CPz Uninvolved	-0.229	-0.345	-0.083	-0.106
Gamma CPz Uninvolved	-0.182	0.055	-0.155	-0.173

Table A1.11. Correlations between EEG outcomes and Uninvolved limb balance measures in CAI patients.

Above are the Pearson correlation coefficients between EEG outcome measures during all movement conditions: MRCP (BP, MP, MMP), ERSP (Alpha, Beta, Gamma), and instrumented balance measures from single-limb balance on the uninvolved limb from the investigation described in Chapter 3. MRCP: Motor-related cortical potential; BP: bereitshaftspotential; MP: motor potential; MMP: movement monitoring potential; ERSP: event-related spectral perturbation; AP: anterior-posterior; ML: medial-lateral; COP: center-of-pressure. A * indicates a significant correlation ($p < 0.05$).

	Uninvolved Path Length	**Uninvolved AP Velocity**	**Uninvolved ML Velocity**	**Uninvolved COP Area**
BP Anterior	**0.491***	**0.445***	-0.363	0.306
MP Anterior	**0.483***	**0.473***	-0.258	0.316
MMP Anterior	0.311	0.388	-0.271	0.355
BP Involved	0.36	0.343	-0.228	0.34
MP Involved	**0.577***	**0.540***	-0.377	**0.545***
MMP Involved	**0.451***	**0.456***	-0.404	**0.512***
BP Uninvolved	0.13	0.089	0.036	0.132
MP Uninvolved	**0.529***	**0.452***	-0.246	0.408
MMP Uninvolved	**0.449***	**0.474***	-0.38	**0.473***
Alpha Cz Anterior	**-0.453***	**-0.542***	0.419	**-0.471***
Beta Cz Anterior	**-0.498***	**-0.611***	**0.483***	**-0.457***
Gamma Cz Anterior	-0.055	-0.15	-0.091	0.196
Alpha Cz Involved	-0.433	**-0.453***	0.397	-0.266
Beta Cz Involved	-0.317	-0.357	0.281	-0.229
Gamma Cz Involved	**-0.530***	**-0.466***	0.391	-0.156
Alpha Cz Uninvolved	**-0.659***	**-0.677***	**0.549***	**-0.508***
Beta Cz Uninvolved	-0.317	-0.412	0.254	-0.116
Gamma Cz Uninvolved	-0.202	-0.25	0.03	0.163
Alpha CPz Anterior	-0.298	-0.355	0.277	-0.316
Beta CPz Anterior	-0.345	-0.415	0.315	-0.389
Gamma CPz Anterior	-0.045	-0.082	-0.056	0.141
Alpha CPz Involved	-0.256	-0.273	0.257	-0.158
Beta CPz Involved	-0.178	-0.191	0.18	-0.194
Gamma CPz Involved	**-0.520***	-0.417	0.392	-0.254
Alpha CPz Uninvolved	-0.322	-0.359	0.322	-0.26
Beta CPz Uninvolved	-0.237	-0.312	0.213	-0.167
Gamma CPz Uninvolved	-0.313	-0.328	0.166	-0.009

Table A1.12. Correlations between EEG outcomes and Involved limb balance measures in uninjured controls.

Above are the Pearson correlation coefficients between EEG outcome measures during all movement conditions: MRCP (BP, MP, MMP), ERSP (Alpha, Beta, Gamma), and instrumented balance measures from single-limb balance on the involved limb from the investigation described in Chapter 3. MRCP: Motor-related cortical potential; BP: bereitshaftspotential; MP: motor potential; MMP: movement monitoring potential; ERSP: event-related spectral perturbation; AP: anterior-posterior; ML: medial-lateral; COP: center-of-pressure. A * indicates a significant correlation ($p < 0.05$).

	Involved Path Length	**Involved AP Velocity**	**Involved ML Velocity**	**Involved COP Area**
BP Anterior	-0.312	-0.157	0.253	-0.431
MP Anterior	-0.335	-0.103	**0.508***	-0.325
MMP Anterior	-0.205	0.001	**0.514***	-0.028
BP Involved	-0.129	-0.072	0.157	-0.335
MP Involved	-0.307	-0.241	0.42	-0.237
MMP Involved	-0.2	-0.097	**0.454***	-0.034
BP Uninvolved	-0.046	0.021	-0.019	-0.262
MP Uninvolved	-0.281	-0.188	**0.501***	-0.182
MMP Uninvolved	-0.117	-0.024	**0.462***	0.047
Alpha Cz Anterior	-0.218	-0.352	0.225	-0.148
Beta Cz Anterior	-0.017	-0.083	0.111	0.068
Gamma Cz Anterior	0.151	0.178	-0.102	0.104
Alpha Cz Involved	-0.186	-0.19	0.255	-0.186
Beta Cz Involved	-0.093	-0.089	0.148	-0.053
Gamma Cz Involved	0.086	0.132	-0.09	-0.168
Alpha Cz Uninvolved	0.065	0.038	-0.258	-0.009
Beta Cz Uninvolved	0.096	0.081	-0.099	0.073
Gamma Cz Uninvolved	0.133	0.092	-0.111	-0.023
Alpha CPz Anterior	-0.065	-0.178	0.205	-0.075
Beta CPz Anterior	-0.053	-0.137	0.16	-0.005
Gamma CPz Anterior	0.231	0.232	-0.173	0.154
Alpha CPz Involved	-0.055	-0.056	0.224	-0.076
Beta CPz Involved	-0.144	-0.099	0.25	-0.131
Gamma CPz Involved	0.113	0.161	-0.157	-0.182
Alpha CPz Uninvolved	0.082	0.067	-0.185	0.053
Beta CPz Uninvolved	0.073	0.082	-0.043	0.062
Gamma CPz Uninvolved	0.092	0.06	-0.1	-0.103

Table A1.13. Correlations between EEG outcomes and Uninvolved limb balance measures in uninjured controls.

Above are the Pearson correlation coefficients between EEG outcome measures during all movement conditions: MRCP (BP, MP, MMP), ERSP (Alpha, Beta, Gamma), and instrumented balance measures from single-limb balance on the uninvolved limb from the investigation described in Chapter 3. MRCP: Motor-related cortical potential; BP: bereitshaftspotential; MP: motor potential; MMP: movement monitoring potential; ERSP: event-related spectral perturbation; AP: anterior-posterior; ML: medial-lateral; COP: center-of-pressure. A * indicates a significant correlation ($p < 0.05$).

	Uninvolved Path Length	**Uninvolved AP Velocity**	**Uninvolved ML Velocity**	**Uninvolved COP Area**
BP Anterior	0.048	-0.109	0.143	-0.191
MP Anterior	-0.026	-0.037	0.037	-0.152
MMP Anterior	-0.069	0.043	0.036	-0.249
BP Involved	0.002	0.023	0.079	-0.103
MP Involved	-0.032	0.176	-0.034	-0.115
MMP Involved	-0.094	0.121	-0.021	-0.202
BP Uninvolved	-0.036	-0.045	0.143	-0.189
MP Uninvolved	-0.126	0.096	0.061	-0.25
MMP Uninvolved	-0.116	0.084	0.002	-0.27
Alpha Cz Anterior	**-0.455***	-0.273	0.429	**-0.640***
Beta Cz Anterior	**-0.523***	-0.239	0.433	**-0.683***
Gamma Cz Anterior	-0.108	0.051	0.121	-0.173
Alpha Cz Involved	-0.363	-0.219	0.277	**-0.476***
Beta Cz Involved	**-0.571***	-0.294	0.419	**-0.637***
Gamma Cz Involved	-0.219	-0.072	0.257	-0.282
Alpha Cz Uninvolved	-0.014	0.085	-0.114	0.028
Beta Cz Uninvolved	**-0.453***	-0.157	0.295	**-0.482***
Gamma Cz Uninvolved	-0.23	-0.002	0.187	-0.252
Alpha CPz Anterior	-0.311	-0.191	0.308	**-0.534***
Beta CPz Anterior	-0.412	-0.21	0.374	**-0.677***
Gamma CPz Anterior	0.066	0.151	-0.029	-0.044
Alpha CPz Involved	-0.14	-0.049	0.105	-0.34
Beta CPz Involved	-0.428	-0.193	0.326	**-0.588***
Gamma CPz Involved	-0.106	-0.101	0.205	-0.174
Alpha CPz Uninvolved	0.124	0.249	-0.212	0.095
Beta CPz Uninvolved	-0.351	-0.089	0.202	-0.441
Gamma CPz Uninvolved	-0.117	-0.048	0.138	-0.15

A1.5 Figures

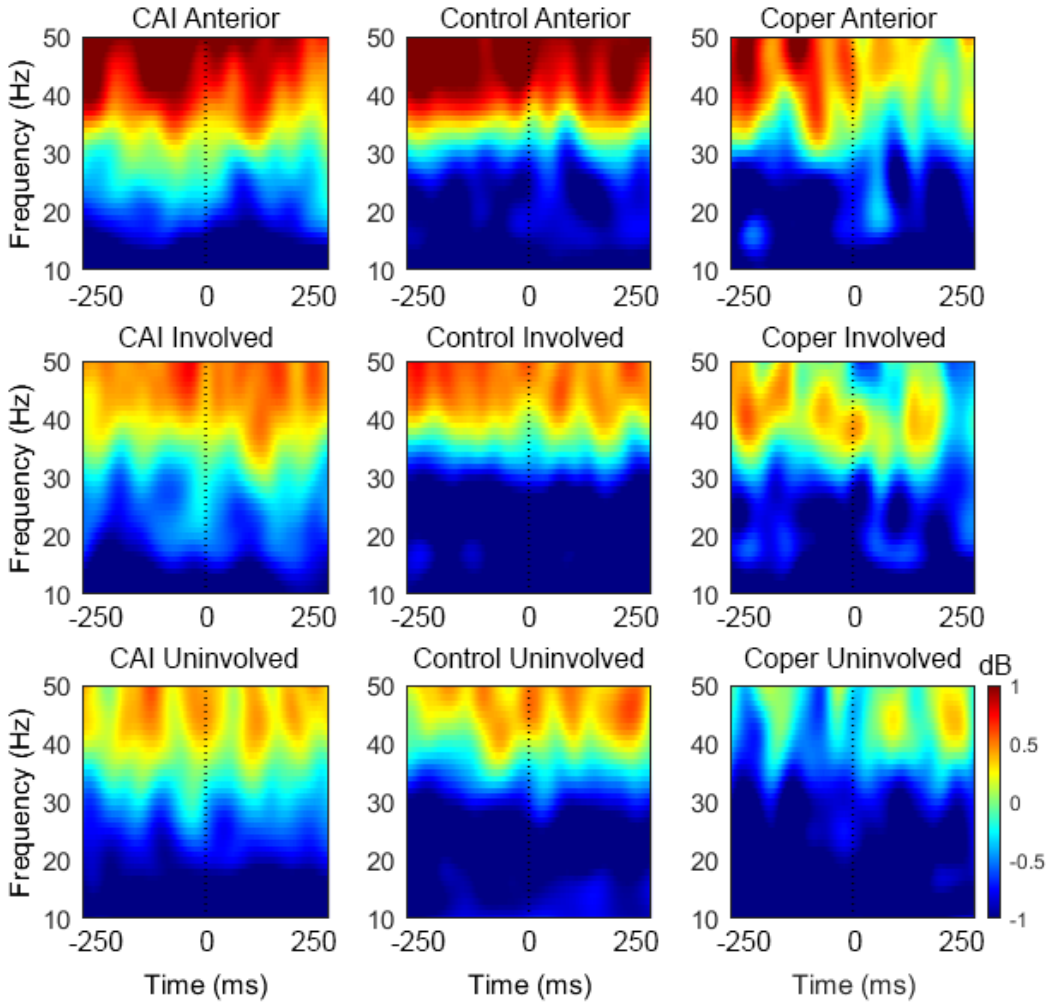

Figure A1.1. ERSP plots at Cz when an individual reaches their limits of stability across groups and conditions.

The scale at the bottom right indicates positive log-change, or increases, in spectral power with more red colors and decreased power is indicated by blue colors. These outcome measures represent feed-back activity as an individual had reached their limits of stability and had to begin sway back to their starting position to maintain stability. Although the copers were a small sample size (n = 7), their ERSP pattern appears most similar to that of the uninjured control group.

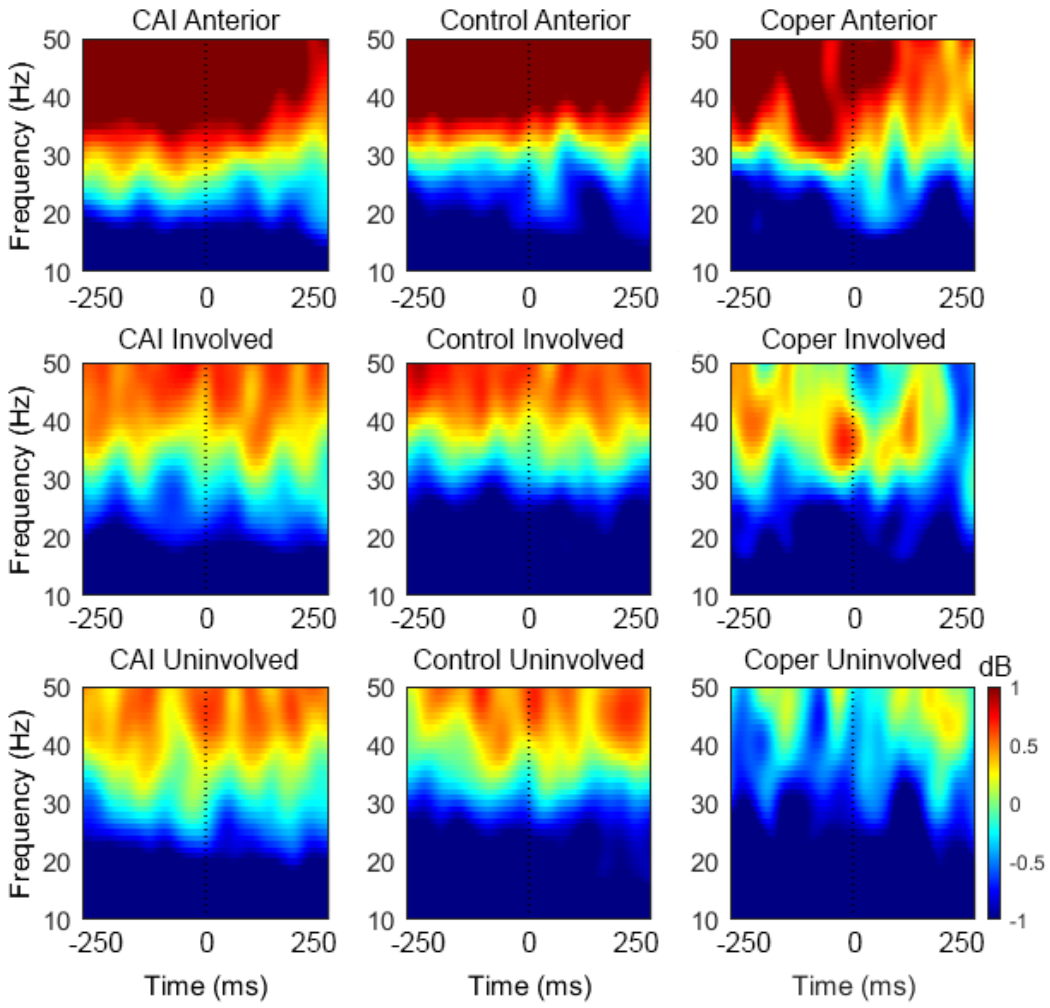

Figure A1.2. ERSP plots at CPz when an individual reaches their limits of stability across groups and conditions.

In the gamma band (30-50 Hz), more red colors indicate an increase in activity, which is linked to ongoing sensory processing. The difference in feed-back cortical activity during anterior leaning versus lateral leaning to either limb is apparent, with all three groups displaying a large power increase prior to and after reaching their limits of stability. Interestingly, the coper group (right panels) did not appear to have as much gamma activity as the control or CAI groups.

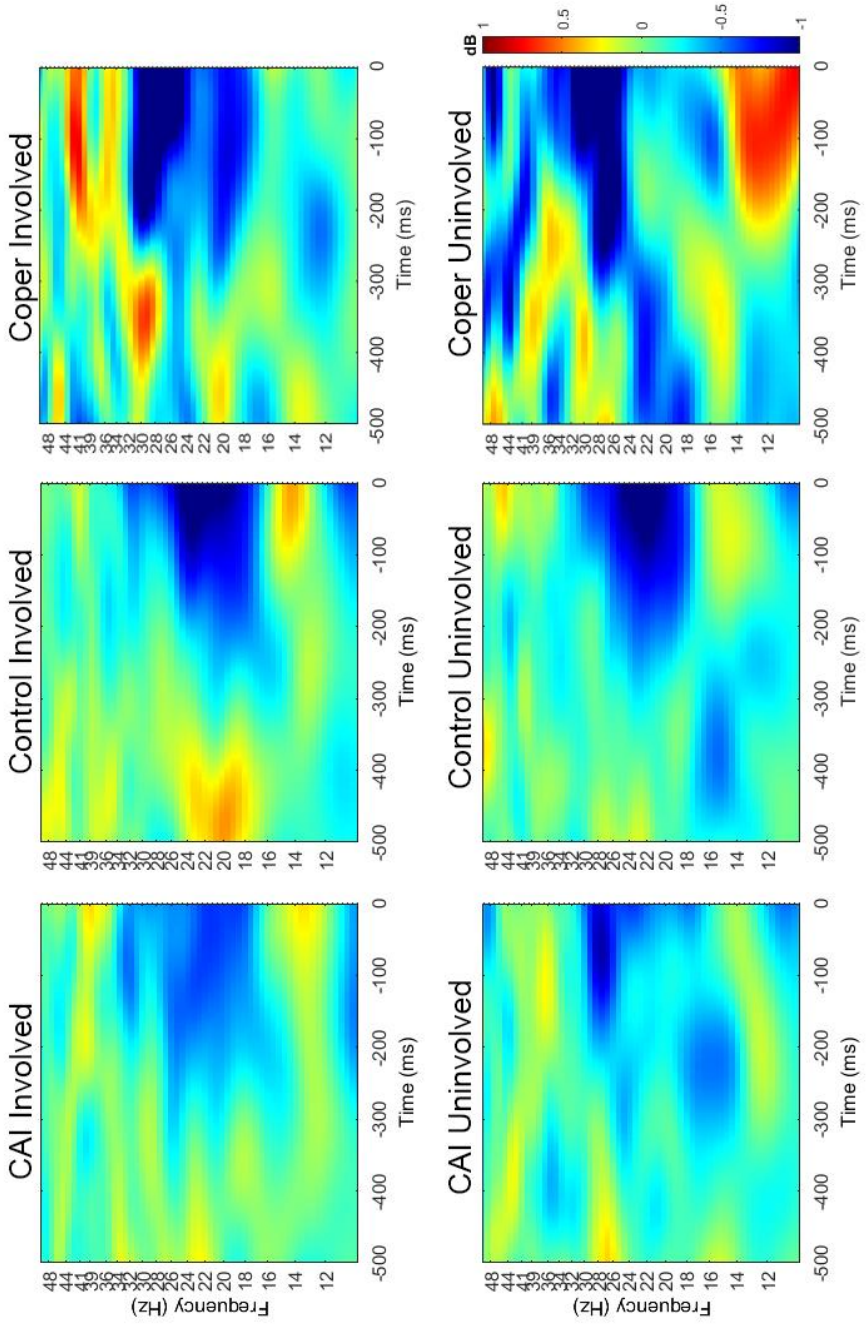

Figure A1.3. ERSP plots at Cz among groups of controls, copers, and CAI patients prior to DSLT.

The deeper blue colors in the coper group (right panels) relative to the control and CAI group suggest greater feed-forward activity just prior to the DSLT. There was a significant difference identified in gamma activity between limbs in the coper group, with the more red colors in this band (30-50 Hz) indicating greater activity prior to transitioning to the involved limb.

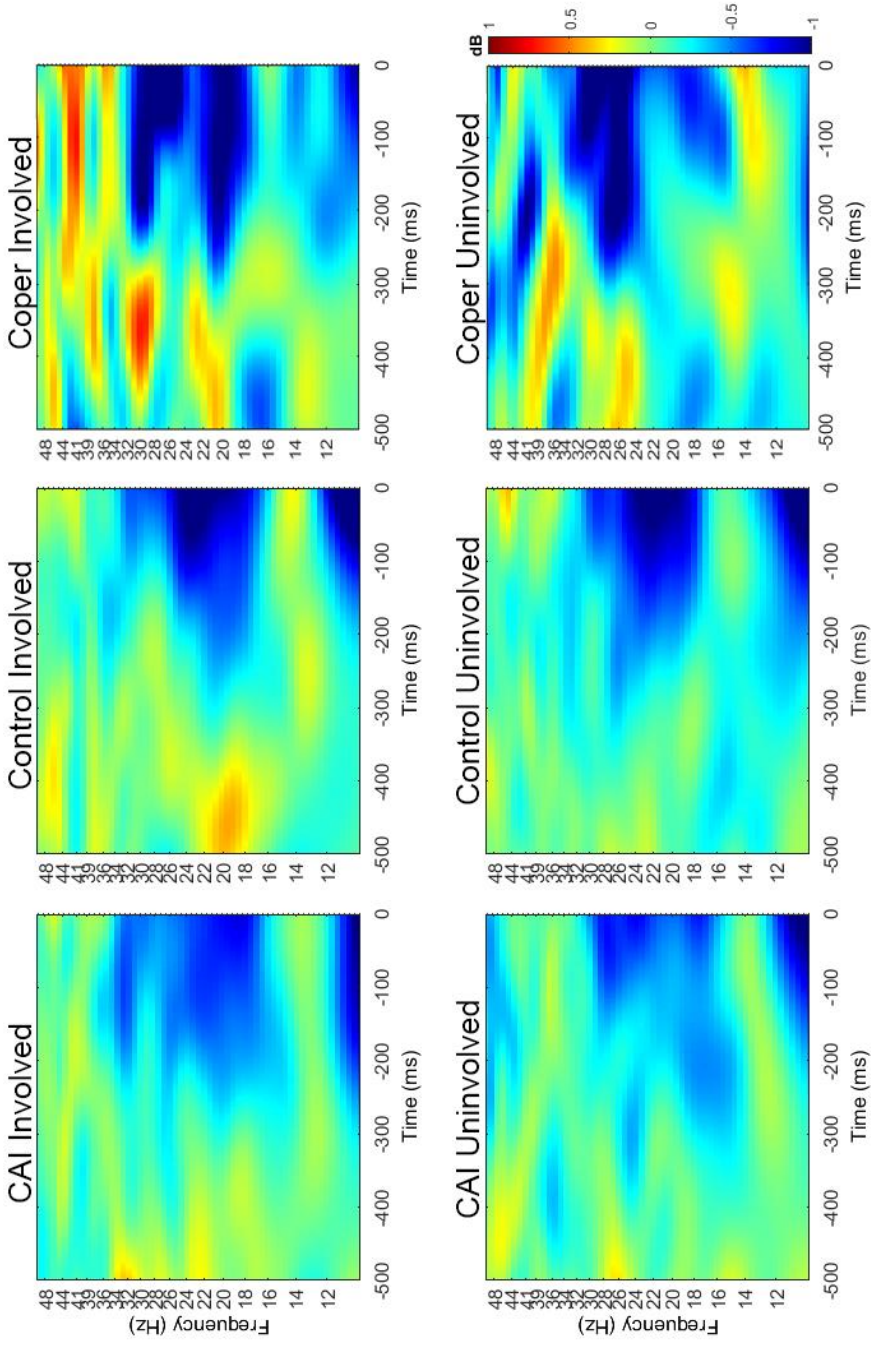

Figure A1.4. ERSP plots at CPz among groups of controls, copers, and CAI patients prior to DSLT.

A similar relationship was identified in gamma activity between limbs in the coper group (right panels). The more yellow and red colors indicate a power increase, which in the gamma band (30-50 Hz), is interpreted as greater cortical activity.

APPENDIX 2: NATIONAL ATHLETIC TRAINERS' ASSOCIATION RESEARCH AND EDUCATION FOUNDATION DOCTORAL RESEARCH GRANT

A2.1 Abstract

Postural control deficits are well documented in the chronic ankle instability (CAI) population, yet the central mechanisms of postural control in those with CAI have yet to be investigated. A more complete understanding of CAI associated dysfunction is imperative for the development and refinement of effective prevention and rehabilitation protocols. This investigation aims to explore the roles of the cerebral cortex in postural control maintenance among three groups of 20; uninjured controls, those with CAI, and those who have sprained their ankle but have not developed CAI (copers). Electroencephalography (EEG) will be used to obtain motor-related cortical potentials (MRCP) and event-related desynchronization (ERD) during a voluntary anterior-posterior and medial-lateral sway task. Medial-lateral sway will be towards and away from the involved limb. MRCP is a correlate of anticipatory postural adjustments. ERD is related to detection of stability boundaries. Separate 3x3 repeated measures ANOVAs will assess group and sway direction differences. We anticipate the MRCP will show a decreased amount of pre-movement activation in CAI relative to the controls and copers suggesting less preparation for movement. We also anticipate the ERD will reveal significantly more cortical involvement in the detection of the stability boundaries, indicating less automated strategies for postural control.

A2.2 Institutional Resources and Environment

A2.2.1 Facilities

All data collection will take place in the Neurophysiology Suite of the Biodynamics Research Lab (BioDRL-NS) housed within Cameron Building at UNC Charlotte. The equipment within this supplemental area includes: 40-channel NuAmps EEG acquisition amplifier, 2 medium 40-channel QuikCaps EEG caps, 2 large 40-channel QuikCaps EEG caps, 1 AMTI force platform, a BIOPAC EMG measurement system, a Biodex System 4 isokinetic dynamometer, and a Magstim Rapid 2 transcranial magnetic stimulation system.

Data management and processing will occur within the BioDRL-NS area. The same equipment will be at the researchers' disposal, in particular an EEG data processing workstation equipped with CURRY 7, MatLab with EEGLAB plugin, Adobe Acrobat Pro, and full Microsoft Office Professional. Additionally there is a mobile workstation that contains the Balance Clinic software for data acquisition with the AMTI force platform, Adobe Acrobat Pro, and full Microsoft Office Professional.

Support Services

The BioDRL-NS has access to academic technology services within its parent College of Health and Human Services at the University. Collaboration with an existing EEG lab in the Department of Psychology will allow for troubleshooting of EEG data collection problems, should they arise.

A2.2.2 Personnel

Erik A. Wikstrom, PhD, ATC is the principal investigator's PhD advisor. Dr. Wikstrom will oversee all areas of this project, primarily providing assistance with interpretation of findings and manuscript preparation/publication.

Abbey Thomas, PhD, ATC is a member of the PI's dissertation committee. Dr. Thomas will assist with data collection, data analysis, and interpretation.

Mark Faust, PhD is a member of the PI's dissertation committee. Dr. Faust has over 6 years of working with EEG while investigating cognitive processes. The PI has completed a laboratory rotation within Dr. Faust's lab and Dr. Faust has agreed to help troubleshoot data collection and/or analysis problems should they arise.

A2.3 Purpose and Rationale

According to the Center for Disease Control and Injury Prevention, injury associated with sport, exercise, and recreation is a leading reason for physical activity cessation. Further, physical inactivity is clearly linked to a decreased quality of life, and significant long-term negative sequelae. Lateral ankle sprains, while often considered an innocuous injury, represent a significant public health problem and financial burden on health care systems as healthcare costs for lateral ankle sprains resulted in around $2 billion in 1984, which is over $4.5 billion after a consumer price index adjustment in 2014.[5] It is estimated that approximately 25,000 lateral ankle sprains occur daily in the United States and this injury is the most common injury in collegiate athletics, representing 15% of all reported injuries.[3,4] Reported recurrence rates following an initial sprain are as high as 2 out of every 3 individuals and persistent symptoms, often termed chronic ankle instability

(CAI) such as pain and swelling are present in up to 70% of individuals who sprain their ankle.[140,141]

To date the literature has illustrated a breadth of perceptual, mechanical, and sensorimotor adaptations in those with CAI relative to uninjured controls and copers.[10] Of particular note are the postural control impairments observed across a variety of tasks and outcome measures. Decreased postural control is a risk factor for first time and recurrent lateral ankle sprains.[11,43,142] Postural control impairments are also indicative of altered motor control strategies developed from task and environmental constraints interacting with individual constraints that are sensory, perceptual, and/or motor in nature. Work from our lab and the PI's own work have demonstrated motor constraints during a single limb task[20,52,143,144] but such constraints have also been observed in double limb stance.[52,145] Most recently, unpublished work by the PI has demonstrated sensory constraints as evidenced by higher plantar cutaneous thresholds in those with CAI relative to copers and controls at multiple points on the foot/ankle complex. Further, work from our lab and my own work has confirmed that interventions targeting both sensory and motor constraints can improve postural control in those with CAI. [144,146,147] However, little is known about how those with CAI process and assign meaning to sensory information when generating motor control programs and how those processes might differ from uninjured controls or copers. Thus, a pressing need exists to better understand the perceptual processes associated with postural control in those with CAI if we are to optimize therapeutic interventions for, and prophylactic treatments to prevent, CAI.

Previous research in this field has seen researchers draw inferences regarding the central mechanisms involved with CAI development based on peripheral sensorimotor outcomes reported in the literature. For example, Wikstrom *et al*.[29] and Hass *et al*.[22] reported altered motor control strategies in those with CAI during gait initiation and termination through center-of-pressure analysis.[22,29] These investigators were the first to identify adaptations in tasks that have been associated with specific areas of the central nervous system (CNS), the supplementary motor area and pre-supplementary motor area, respectively, based on fMRI data.[30] Since then, a limited number of investigations have attempted to directly measure CNS function in those with CAI.[31-34] For example, Pietrosimone & Gribble[33] evaluated the resting motor threshold of the motor cortex controlling the peroneus longus muscle with transcranial magnetic stimulation (TMS) and identified higher bilateral motor thresholds in those with CAI suggesting deficits in corticomotor excitability. Needle *et al*.[32] demonstrated increased cortical activity, as measured with electroencephalography (EEG) as ankle joint loading increased but no differences were identified among controls, copers and those with CAI. The increase in cortical activity was identified with an increase in event-related desynchronization (ERD), an outcome which presents itself as a percent change from baseline recordings within a specific frequency bandwidth during an event. This ERD increase suggests an increase in the cortical activity relating to the event in question, meaning an individual requires more neural resources to process the sensory information associated with the task.[35] While these recent investigations have advanced our understanding of CNS dysfunction in those with CAI, the results are limited because both test protocols were non-weight bearing and neither captured cortical activity during a motor task (i.e.

maintenance of postural control) known to be impaired in those with CAI or capable of evaluating an individual's risk of injury.

Cortical contributions to postural control have been quantified in uninjured controls using experimental protocols that incorporate both internal (e.g. forward leaning or rhythmic sway) and external postural perturbations. [2,37-41] These results indicate that the sensorimotor cortex plays a role in detecting limits of stability, as evidenced by a: 1) distinct negative deflection of EEG signals prior to the onset of oscillatory anterior-posterior sway, referred to as the motor-related cortical potential (MRCP) and 2) burst of Gamma activity (30-50 Hz) in the sensorimotor cortex prior to a compensatory posterior sway once the anterior limit of stability was reached.[41] These findings have been suggested to be the neural correlates of anticipatory postural adjustments,[41] the phenomenon that 'primes' the individual for a postural disturbance and has been shown to be altered in those with CAI.[22,29] The MRCP is a widely studied motor potential that always precedes a self-initiated movement, characteristic of activity in the supplementary motor area and premotor cortex, areas that may be altered in those with CAI.[29,42] Decreased time-to-boundary scores in those with CAI[43] may be due to delayed recognition of an anterior limit of stability, a precursor of Gamma activity bursts.[41] Despite the obvious connections between cortical outcomes associated with the maintenance of postural control and postural control impairments in those with CAI, no research has attempted to quantify cortical activity during a postural control task in those with CAI or copers. This lack of empirical evidence limits our understanding of how lateral ankle sprains and CAI can alter CNS function, ultimately impeding our ability to develop effective evidence-based therapeutic interventions for the most common

musculoskeletal injury sustained during sport and physical activity. Based on these converging arguments, an opportunity exists to address a critical gap in the research and elucidate the impact of lateral ankle sprains on cortical contributions to postural control. Thus, the goal of this research proposal is to determine the differences in cortical contributions to postural control among uninjured controls, copers, and those with CAI and will be achieved by completing the following specific aims.

Aim 1: To investigate the magnitude of cortical signals relating to anticipatory postural adjustments in controls, copers, and those with CAI. Specifically, participants will voluntarily sway on a force platform in an anterior-posterior and medial-lateral orientation during a double limb stance while EEG data are concurrently captured, as previously investigated.[2] EEG outcomes will include the magnitude of MRCP associated with preparation for voluntary sway.

Hypothesis 1: We hypothesize that the magnitude of MRCP will be lower in those with CAI when compared to controls and copers. Further, we hypothesize that medial-lateral sway toward the injured limb will elicit a significantly different response in those with CAI than when the sway is toward the uninjured limb. This may potential indicate an inability to properly prepare for movement towards the chronically injured limb in those with CAI.

Aim 2: To investigate the levels of coordinated neural activity over the motor and somatosensory cortex during postural control in controls, copers, and those with CAI. Specifically, we will utilize an ERD outcome when the participant is at his/her limits of stability. ERD will be calculated from the electrode sites overlying the motor and

somatosensory cortices and will allow us to investigate the burst of gamma activity that has been identified during compensatory motion once a stability limit is reached.

Hypothesis 2: We hypothesize that we will observe higher levels of ERD in those with CAI when compared to controls and copers. This result would suggest increased cortical activity and indicate that maintaining postural control is a less automated process in those with CAI relative to copers and uninjured controls.

A2.4 Experimental Design and Methods

This study will utilize a mixed model repeated measures design wherein three groups of participants (controls, copers, and CAI) will be compared both within and among groups for three directions of self-initiated sway. Our independent variables are group (controls, copers, and CAI), and sway direction (anterior-posterior [AP], medial-lateral towards and away from the involved/matched limb [MLi and MLu, respectively]). Dependent variables will include amplitude of MRCP at Cz (μV) and ERD % change at Cz and CPz (Alpha, Beta, and Gamma bands). Rationale for the use of these specific locations (Figure 1) is reported below.

A2.4.1 Participants

Volunteers will be recruited from the UNC Charlotte student body. A total of 60 participants will be enrolled in the study and split into three equal groups of 20. We will define controls as individuals with no history of an ankle sprain to either ankle, a score <11 on the Identification of Functional Ankle Instability (IdFAI) and >99% and 97% on the Foot and Ankle Ability Measure (FAAM) and FAAM-Sport (FAAM-S) respectively.[44-46] Copers will be defined as individuals with a history of unilateral ankle injury and: a score <11 on the IdFAI, a maximum of two previous ankle sprains with at

least 12 months since the most recent sprain, 0 episodes of the ankle giving way within the past 12 months, and disability scores no lower than 99% on the FAAM and 97% on the FAAM-S.[10,45] For this investigation, patients with unilateral CAI will be enrolled. CAI will be defined as those individuals who: 1) have experienced at least two lateral ankle sprains in the past; 2) have experienced at least one episode of giving way within the past 3-months; 3) a score ≥11 on the IdFAI; 5) have self-assessed disability scores of ≤90% on the FAAM; and 6) have self-assessed disability scores ≤80% on the FAAM-S.[45] Exclusion criteria for all groups will include known balance and vision problems, acute lower extremity and head injuries (<12 weeks prior to enrollment), chronic musculoskeletal conditions known to affect balance (e.g. ACL deficiency), history of ankle surgery to fix internal derangements, a diagnosed concussion, and any other neurologic impairments or conditions that may impact postural control or EEG signal analysis.

A2.4.2 Equipment

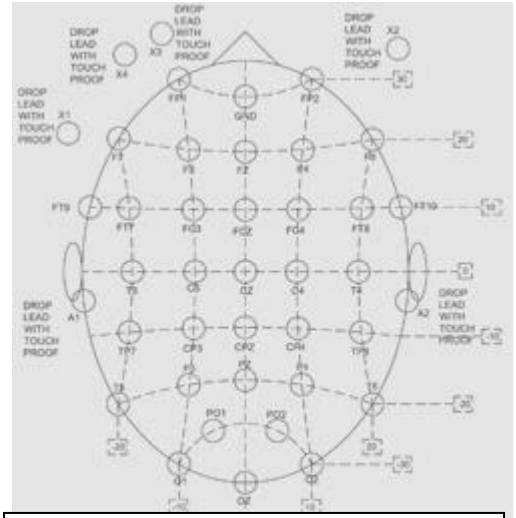

Figure A2.1 Layout of QuikCaps electrode placement (Compumedics Neuroscan, Charlotte, NC).

EEG data are to be collected using a NuAmps 40-channel EEG amplifier (Compumedics Neuroscan, Charlotte, NC) paired with a 40-channel QuikCap electrode placement helmet (Compumedics Neuroscan, Charlotte, NC). The QuikCap system has 40 electrodes located according to the international 10-20 system of electrode placement (Figure A2.1).[82] Linked earlobe electrodes A1 and A2 serve as a

reference to the GND (ground) electrode placed above the nasion and eye movement is monitored by X1, X2, X3, and X4.[148] The sintered electrodes of the QuikCap are compatible with the QuikCell system (Compumedics Neuroscan, Charlotte, NC), which utilizes a dehydrated cellulose "cell" and a conductive electrolyte solution to create contact between the electrode and the scalp. This system has been previously used in CAI research and lowers participant preparation time while maintaining an optimal signal-to-noise ratio.[32] Data from the NuAmps amplifier will be sent to a workstation equipped with Curry 7 Acquisition and Signal Processing package (Compumedics Neuroscan, Charlotte, NC). EEG data will be amplified with a gain of 1000 set for recording range of ±55mV and recorded at 1000Hz using separate 22-bit analog-to-digital converters for each channel.

Ground reaction forces (GRF) associated with the concurrent postural control task will be collected using an AMTI AccuSway (AMTI Inc., Watertown, MA) force platform connected to a portable workstation via the PJB-101 (AMTI Inc., Watertown, MA) interface system.[149] This will result in 6 digitized channels (Fx, Fy, Fz, Mx, My, Mz) recorded by AMTI Balance Clinic Software (AMTI Inc., Watertown, MA). GRF will be recorded at 200Hz. A custom-built trigger device will send a 5V TTL pulse into the PJB-101 interface system and to the NuAmps amplifier to allow for offline synchronization of EEG and GRF data using MatLab (Mathworks Inc., Natik, MA). GRF data will also undergo processing to calculate center-of-pressure outcomes (COP), providing group demographics of postural control.

A2.4.3 Data Collection Protocol

Once eligible, a participant will be provided with instructions regarding the testing procedure. Specifically, participants are to wash their hair using a shampoo the morning of testing but no conditioner or hair styling products are to be used as they negatively impact the conductivity of the electrical potentials measured through the scalp. On the day of testing, participants will first provide informed consent and then complete baseline testing. Baseline testing will consist of a series of ankle injury questionnaires and a physical exam (anterior drawer and talar tilt) as recommended by the International Ankle Consortium.[45] To quantify participants' postural control ability relative to more traditional techniques used in the CAI literature, all participants will complete 3, 10-s trials of dual and single-limb static stance on an AMTI force platform with eyes open as previously reported.[20,52] Next, participants will be seated during fitting and EEG preparation. First, the scalp will be abraded lightly for about 2 minutes and then prepared with ethyl-alcohol swabs to ensure low impedances. Once the scalp is prepared, the cap will be placed on the participant and electrode preparation will begin by injecting electrolyte fluid (Compumedics Neuroscan, Charlotte, NC) into each electrode (Figure A2.1: GND, then sintered, then reference and drop electrodes) with a 1cc syringe outfitted with a blunt-tip needle (maximum 300µL electrolyte fluid). Once all electrodes are hydrated, online impedance measurements are reviewed to ensure an optimal signal to noise ratio. Impedance will be below 5 kOhms for all electrode sites.[2,32] Pilot testing indicates this process will last from 20 to 30 minutes.

Once prepped, the self-initiated sway task, identical to the one described by Slobounov et al.[2] will be performed. In brief, participants will stand on a force platform with feet approximately shoulder-width apart and arms across their chests. Participants will then be instructed to voluntarily sway in three different directions: AP, MLi, and MLu.[2] They will be instructed to sway in these directions, one at a time, until they reach their stability limits for each direction at a comfortable steady speed without moving their feet or flexing the trunk.[2] Prior to data collection, participants will be familiarized with the protocol through real-time visual feedback of their moments from the Balance Clinic software, with verbal instructions that emphasize the production of similar amounts of movement each trial (Bottom, Figure A2.2).[2] Participants will perform one postural sway approximately once every 10 seconds, performing 60 sways in each direction (180 total) per testing block.[2] Participants will be tested over 2 blocks to ensure that at least 60 artifact-free trials are collected for each movement direction. Testing blocks will be separated by at least a 10 minute break.[2] No visual feedback will be provided during data collection, which should last approximately 70 minutes.

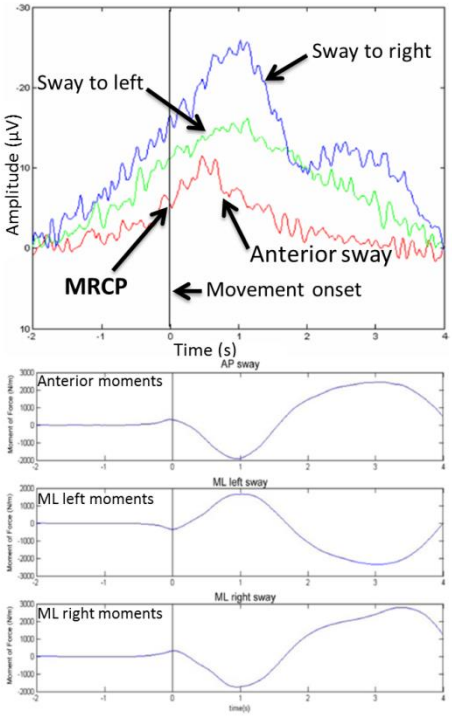

Figure A2.2. MRCP for each sway condition at electrode Cz (top) and moments (bottom). Adapted from Slobounov *et al*.[2]

Data Preparation and Reduction

Eye movement and blink artifacts will be removed from trials using online blink reduction tools in the Curry 7 Acquisition module. A DC

shift will be compensated for using an online fourth-order trend correction for each channel throughout each trial (linear detrend).[2,41] EEG data will then be down-sampled to 200Hz using the Curry 7 Signal Processing module allowing for synchronization of the TTL pulses from our custom-built trigger device, time-locking our EEG data to the moment data shown in Figure A2.2. In order to prepare data for ERD analysis, three separate bandpass filters will be used to isolate the Alpha (8-12 Hz), Beta (14-25 Hz), and Gamma (30-50 Hz) frequencies bandwidths. Following filtering and synchronization, manual artifact rejection will ensure the appropriate number of artifact-free trials are available for grand averaging.

A2.4.4 Motor-Related Cortical Potential

The MRCP is a slowly progressing negative shift of EEG activity preceding the onset of voluntary movement, first described by Kornhuber and Deecke in 1965 (referred to as Bereitschaftspotential – readiness potential).[47] This signal is thought to result from preparatory activity in the supplementary motor area contralateral to the movement limb, as supported by significant increases in fMRI activity.[42,48] The MRCP is often split into two parts, the early and late MRCP, the former begins approximately 2 seconds before movement begins and the latter begins around 400-500 milliseconds prior to movement.[42] The MRCP is commonly used to evaluate the degree of preparedness for movement, although it does still continue after the movement has begun which is related to the completion of the motor task.[42] The amplitude of the MRCP has been shown to be significantly different between AP and ML sway, which may suggest different preparation strategies for these planes of movement (Figure A2.2).[2] The MRCP will be present on all recorded electrode sites but is often greatest in magnitude over the region

of interest Cz. Lower extremity movement will show the largest magnitude at Cz as it overlies the motor cortex dedicated to lower extremity control.[42]

The MRCP will be calculated as previously described.[2,41,42] In brief, the amplitude (μV) will be recorded at the onset of moment shifts (Figure A2.2).[2,41] For example, when a negative moment is observed on the My channel of the force platform during the AP sway task, the participant has initiated a motor command to begin an anterior sway and the MRCP will be recorded. Similarly, when the Mx channel indicates a shift in the moment (positive or negative depending on a right or left directional sway), an MRCP value will be recorded.[2] Based on best practice with event-related potential research, the grand average (minimum of 60 trials) will be taken for each sway direction for each participant.[2,49] The amplitude, in μV, will be calculated from the grand average of the Cz electrode for each condition and used as the dependent variable for our MRCP outcome measures.[2] All EEG channels in this region will exhibit the same MRCP pattern but the maximal amplitude is greatest at Cz and thus will be taken from this location.

A2.4.5 Event-Related Desynchronization

A relatively recent method of analyzing EEG activity is through ERD, or conversely, event-related synchronization (ERS). Electrical activity as recorded by EEG is a summative waveform sensitive to different tasks and composed of many different frequency oscillations, which represent the activity of a large number of neurons. For example, sensory stimuli often impart a time-locked change in the electrical potential recorded from a population of neurons which is known as an event-related potential (e.g. MRCP).[49] Event-related potentials inform us about the magnitude of neuronal activity preceding movement, but fail to elucidate the coordination or magnitude of activity with

the movement.[35] The frequency content of the EEG signal allows researchers to investigate the relative activity of an area as it relates to a task, known as ERD or ERS.[35] The frequency content of movement related EEG data is often broken into Alpha (8-12 Hz), Beta (14-25 Hz), and Gamma (30-50 Hz) bandwidths.[2,35,41] ERD is evaluated as a percent change of the power of a signal within a specified bandwidth.[35] A decreased signal power indicates a more widespread use of frequency contents and thus increased activity in a specified area relative to the baseline period, in this study the approximate 10 seconds between voluntary sways.[35]

To quantify ERD, the power within the given frequency band of interest in the time window after the event is represented as A and the baseline or reference period of equal duration is represented as R. ERD is then calculated as follows: ERD% = ((A – R)/R*100); the outcome being a percent change of power during the event in question.[35] ERD is typically taken from a single electrode site and requires the data to be bandpass filtered to isolate a specific bandwidth. ERD has been observed in the Alpha, Beta, and Gamma bandwidths leading up to and during voluntary movement over the sensorimotor areas of the cortex; therefore, ERD will be recorded in the Alpha, Beta, and Gamma bandwidths over the Cz and CPz electrodes (Figure A2.1).[35] The event in question will consist of a 150 millisecond window that flanks the maximal anterior or lateral moment of the GRF (stability limits); 75 milliseconds prior and 75 milliseconds after will define A and a 150 millisecond window during static stance between movements will define R from the aforementioned ERD equation. This analysis will produce a total of 6 dependent variables per participant: Cz Alpha, Beta, and Gamma ERD, and CPz Alpha, Beta, and Gamma ERD.

A2.4.6 Statistical Analysis

To achieve Specific Aim 1: A 3x3 repeated measures ANOVA will be used to evaluate whether or not MRCP is different among groups (control, coper, and CAI) and sway direction (AP, MLi, and MLu). Tukey's HSD tests will be used for all post hoc analyses where appropriate, additionally, 95% confidence intervals and Cohen's d effect sizes will be calculated. The a priori alpha level for this test will be set at $P \leq 0.05$.

To achieve Specific Aim 2: Separate 3x3 repeated measures ANOVAs will be used to evaluate whether or not ERD outcomes are different among groups (control, coper, and CAI) and sway direction (AP, MLi, and MLu). Tukey's HSD tests will be used for all post hoc analyses where appropriate, additionally, 95% confidence intervals and Cohen's d effect sizes will be calculated. The a priori alpha level for all tests is set at $P \leq 0.05$.

Secondary Analyses: Pearson product moment correlations will be run among all 7 dependent variables and demographic data including clinical test results, double and single limb balance outcomes (e.g. COP velocity, time-to-boundary), and patient reported outcomes including IdFAI, FAAM, and FAAM-S scores. The a priori alpha level for all tests is set at $P \leq 0.05$.

A2.4.7 Power Analysis

No previous investigation has directly captured the outcomes of interest in our populations of interest. Therefore, our sample size is estimated from previous static dual-limb stance differences between controls and those with CAI.[52] Using G*Power 3.1.9.2 (Univ. Dusseldorf, Dept of Psychology), an effect size of 0.63 (ML COP velocity) and an $\alpha = 0.05$ with β set at 0.80 indicate that a total sample size ($n = 7$ per group) is needed to determine group differences.[52] We also based our sample size estimate off of previous

cortical activity research which generally uses small sample sizes but identifies group (e.g. Pietrosimone and Gribble[33]: n=10) or directional (e.g. Slobounov *et al*.[2]: n=12) differences. However, Needle *et al*.[32] failed to identify group differences in ERD with samples ranging between 6-14 among controls, copers, and CAI. Thus, we are confident that significant differences in MRCP and ERD can be identified with 15 participants per group. However, we plan to enroll 20 participants per group and allow for 25% of our participants to have unusable EEG data (less than 60 artifact free trials), which would result in 15 participants per group.

A2.5 Anticipated Outcomes

A2.5.1 Aim 1

Our primary hypothesis for Aim 1 is that individuals with CAI will display an overall lower magnitude of MRCP compared to uninjured controls and copers. The MRCP is a waveform that always precedes voluntary movement, thought to be the correlate of both anticipatory postural adjustments as well as the planning of the movement schema.[42] The magnitude of the MRCP provides insight into the degree of cortical activation as it pertains to a motor task and can be altered by factors relating to the movement (e.g. speed, intent, complexity) or the individual (e.g. injury status, perceived effort).[42] Previous research in those with CAI as it pertains to gait initiation has shown that preparatory action leading up to movement is significantly altered, suggesting that central motor pattern generators do not provide the same output as they do in uninjured individuals.[22]

We anticipate finding a difference between anterior-posterior sway and at least one of the medial-lateral sways, specifically a lower MRCP prior to anterior-posterior sway, as this

has previously been identified in healthy individuals.[2] Our secondary hypothesis within Aim 1 is that we will observe differences between the sway towards and away from the injured limb in those with CAI. This observation would provide evidence that individuals with CAI have a deficit in the cortical preparation for movement towards their injured limb, and provide a ground floor for future investigations. This may lead to a new approach in the rehabilitation of the injured ankle in athletes; if the activity leading up to movement is altered then a clinician may potentially increase the use of imagery and feedback. For example, future investigations may find that an increased emphasis on imagery in conjunction with a balance training protocol leads to a return of functional activity greater than that of established balance training protocols.

Aim 2

We hypothesized that individuals with CAI will display a greater amount of ERD as they reach their limits of stability during the voluntary sway task. ERD represents a shift of oscillatory activity within a cortical region (i.e. rather than operating at mainly the 8 Hz frequency, activity shifts to 8, 9, 10, 11, and 12 Hz),[35] indicating that an area of the brain has increased in overall activity and requires more neural resources to complete the task or event in question.[35] An increase in Gamma activity (30-50 Hz) has been identified in healthy individuals as they prepared for a compensatory movement once they reached their limits of stability; Gamma activity is indicative of high-level sensory processing and increased reliance on afferent feedback.[35,41] We expect the detection of the limits of stability to be altered in those with CAI as it has been shown that they have somatosensory deficits in a variety of mechanoreceptors.[9] ERD in the Alpha (8-12 Hz) and Beta (14-25 Hz) bandwidths has also been identified in healthy individuals during

both preparation for and the execution of movement and may be linked to activity between the supplementary motor area which plans movement and the primary motor cortex.[35] As we expect this response to be lower in magnitude through the MRCP, we expect to see the Alpha and Beta ERD to be lower in CAI compared to controls and copers.

Taken together these findings may be applied to previous investigations that look at the role of attention or working memory in those with CAI. It has been shown that individuals with CAI have worsened postural control scores while performing a cognitive task when compared to static balance.[28,143] The amount of attention required to maintain posture may be related to the automaticity of the process, with greater attention suggesting a less automatic process. Automaticity is thought to be increased as the control of posture is shifted from cortical control to midbrain or spinal levels, representing an adaptation to balance training.[26] It is our hope that these outcome measures can be used in the future to quantify the already known response of individuals with CAI to a balance training program that improves postural control.[24,144] Further, with the results of this study we hope to design a balance training protocol that emphasizes both imagery and cognitive loading (e.g serial 7's, random number generation, etc.). We feel that including a cognitive loading component to a balance training protocol will lead to greater improvements and automaticity of postural control than balance training alone.

APPENDIX 3: MID-ATLANTIC ATHLETIC TRAINERS' ASSOCIATION RESEARCH GRANT

A3.1 Research Problem

Chronic Ankle Instability (CAI) is a musculoskeletal health condition that is characterized by repetitive ankle sprains and residual impairments including sensory and motor deficits believed to disrupt the global function of the sensorimotor system.[11] A continuum of disability[25] presents itself wherein poor sensorimotor control leads to a decrease in functional performance (e.g. balance) predisposing an individual to ankle sprain, further increasing organismic constraints as evidenced by sensorimotor deficits.[11] A recent shift of emphasis towards central nervous system (CNS) dysfunction has revealed that an increased active motor threshold of the motor cortex, measured using transcranial magnetic stimulation, may be a predictor of dynamic balance performance in those with CAI.[76] Further, higher resting motor thresholds have been identified bilaterally in the peroneus longus of individuals with CAI further suggesting deficits in corticomotor excitability,[33] which may explain the significant delay in the onset of postural muscles when those with CAI transition from dual to single limb stance (DSLT).[1]

Improving sensorimotor function is an important clinical goal and balance training has been shown to be an effective intervention and prevention strategy for those with CAI by improving measures of postural control and self-reported function.[24,107] Researchers postulate that these improvements are the result of postural control becoming more automatic, suggesting a shift from cortical to subcortical (e.g. cerebellum, reticular formation) control of posture.[26] However, to date no researchers have measured cortical activity during postural control or assessed if postural control becomes more automatic

following balance training in those with CAI. This lack of empirical evidence limits our understanding of the full spectrum of CAI associated impairments and impedes our ability to optimize therapeutic interventions for those with CAI. Based on this argument, an opportunity exists to address a critical gap in the research and elucidate the impact of CAI on cortical contributions to postural control and how cortical control may be altered following a balance training protocol. Thus, the purpose of this investigation is to test the hypothesis that the reported deficits in DSLT[1] are related to altered cortical control of balance in those with CAI, and that these can be improved following balance training. To test this hypothesis we propose the following aims:

Aim 1: To assess for group differences in cortical activation during a DSLT in those with CAI compared to copers and controls.

To achieve this aim, participants will complete a DSLT task while EEG data are collected to determine the amount of cortical activity during the task. We predict that those with CAI will have altered (i.e. increased) cortical activity during the DSLT relative to copers and controls, indicating that control of the task is less automatic.

Aim 2: To determine the effect of balance training on cortical activation during a DSLT in those with CAI.

To achieve this aim, cortical control of a DSLT task will be measured before (aim 1) and after (1 and 7 days after completion) participants with CAI complete a previously established 4-week balance training protocol.[24,107] We predict that balance training will result in decreased cortical activity relative to the baseline testing in those with CAI.

A3.2 Significance of the Proposed Research:

At present, data directly measuring CNS function in those with CAI relate to motor cortex excitability[33] and joint loading paradigms in non-weight bearing positions.[32] Therefore evaluating EEG activity during a weight-bearing postural control task (DSLT) would address a critical gap in the literature. If a clinician's goal is to break the continuum of disability, elucidating the underlying mechanisms of sensorimotor deficits (i.e. the cortical alterations associated with CAI) is vital. Sensorimotor control is typically broken into feed-forward (i.e. preparing for movement) and feed-back (i.e. refining ongoing movement) strategies and both strategies are impaired in those with CAI.[1,11,22] Balance training is often used to break the disability continuum and results in static balance (feed-back) improvements but feed-forward improvements have yet to be investigated.[24,107] The proposed DSLT task stresses the feed-forward component of sensorimotor control as the movement is a preceded by an anticipatory postural adjustment similar to that of gait initiation.[1,22]

Goal-oriented movements (e.g. kicking a soccer ball) require feed-forward sensorimotor control to prepare the body for the task (kicking the ball) as well as the resulting displacement of the center of mass (stabilization). Furthermore, a case report of an accidental laboratory ankle sprain suggested inappropriate preparation for a movement as a potential cause of the injury based on the timing of kinematic discrepancies.[150] Thus, evaluating the effects of balance training on a feed-forward task and the cortical control of such a task will also address a critical gap in the literature. The ability to improve feed-forward sensorimotor control may improve outcomes associated with CAI and further reduce future injury risk. *The proposed research is significant because it will be the first*

to measure cortical activity during a weight-bearing postural control task in those with CAI. Further, this investigation will be the first to capture adaptations in the CNS following balance training in those with CAI during a both a feed-back (traditional balance trials) and feed-forward (DSLT) postural control task. Results from this investigation can be used to refine existing or develop optimal intervention and prevention programs for this ever-growing population of patients.

A3.3 Procedure

A3.3.1 Research Design

To achieve Specific Aim 1 (SA1), a cross-sectional design will be used. The independent variable for SA1 is group (controls, copers, CAI) and limb while the primary dependent variables will include event-related desynchronization (ERD) % change at the Cz and CPz electrodes (Alpha and Beta bands). To achieve Specific Aim 2 (SA2), a single group repeated measures design will be used. The independent variable for SA2 is time (baseline, post-protocol test 1, post-protocol test 2) while the primary dependent variables will be the same as described for SA1. Secondary outcomes for SA1 and SA2 will include self-reported function (FAAM, FAAM-S), traditional postural control outcomes (e.g. center of pressure), and muscle onset times (peroneus longus, tibialis anterior, medial gastrocnemius, vastus medialis, medial hamstrings, gluteus medius) during the DSLT.

A3.3.2 Sample Size and Participants

Pilot testing indicates that baseline and post-balance training testing will last approximately 90 minutes per session. No published investigations have directly captured

our cortical outcome measures in those with CAI during a weight-bearing postural control task. For SA1, Van Deun et al.[1] identified group differences in a DSLT with 10 participants per group and we will be replicating the DSLT task in the proposed investigation. Cortical activity research has also identified group differences with 10 participants per group[33] therefore we are confident 10 participants per group is sufficient to identify group differences. Similarly, a small effect size (0.33)[24] coupled with a β=0.8, α=0.05 suggests that a total of sample size of 13 participants is required to identify mediolateral (ML) postural control improvements following a balance training program (SA2). Therefore, adequate statistical power should be achieved with 13 participants per group for SA1 and 13 participants with CAI for SA 2. However, Needle et al.[32] could only use EEG data for ~75% of their participants. Therefore, we plan to enroll 20 participants per group and allow for 35% of our participants to have unusable EEG data (less than 60 artifact free trials), which would result in 13 participants per group for SA1. This conservative estimate also permits for CAI dropout during the balance training protocol (SA2) but our own experience would suggest a 5% maximum dropout rate over a 4-week balance training program. For this investigation, only those with unilateral CAI as defined by the International Ankle Consortium will be eligible to participate.[45] Copers will be defined based on the recommendations of Wikstrom and Brown.[10] Uninjured controls will be defined as individuals with no history of an ankle sprain to either ankle, and no self-reported disability. Self-reported disability will be assessed using the Identification of Functional Ankle Instability (IdFAI) and the Foot and Ankle Ability Measure (FAAM & FAAM-S) subscales. Specific inclusion criteria can be seen in Table A3.1. Exclusion criteria for all groups will include conditions affecting balance or vision,

acute (<12 weeks) lower extremity injury, history of lower extremity surgery, diagnosed concussion, or any other neurological conditions affecting EEG (e.g. epilepsy). Uninjured controls will be matched by age, sex, mass, height, and physical activity levels to each CAI participant.

Table A3.1. Specific inclusion criteria for each group. Hx: history, LAS: lateral ankle sprain.

Uninjured Control	Coper	CAI
No Hx LAS or ankle injury. <11 on IdFAI, >99% FAAM, >97% FAAM-S.[45]	Unilateral LAS. Maximum of 2 LAS with at least 12 months between sprains. <11 on IdFAI, 0 episodes of giving way, >99% FAAM, >97% FAAM-S. [10]	Unilateral CAI. Hx of ≥ 2 LAS, ≥ 1 episode of giving way in past 3 months, ≥ 11 on IdFAI, ≤ 90% FAAM, ≤ 80% FAAM-S.[45]

A3.3.3 Instrumentation

EEG data will be collected using a NuAmps 40-channel EEG amplifier (Compumedics Neuroscan, Charlotte, NC) paired with a 40-channel QuikCap electrode placement helmet (Compumedics Neuroscan, Charlotte, NC) with electrodes placed according to the international 10-20 system. Data processing will be completed with Curry 7 Acquisition and Signal Processing package (Compmedics Neuroscan, Charlotte, NC). Data will be amplified with a gain of 1000 set for a recording range of ±55 mV and recorded at 1000Hz using separate 22-bit analog-to-digital converters for each channel. EMG data will be recorded using a 16-channel MP150 BIOPAC data acquisition system (Biopac Systems Inc, Santa Barbara, CA) at 1000 Hz using a 1 3/8 in. diameter Ag/AgCl electrode. An AMTI force plate (AMTI; Watertown, MA) will be used to conduct the single limb static stance tests that will produce the COP outcomes. Force plate data will be collected at 200 Hz. Outcomes will include COP excursion, and velocity in the

anterio-posterior, mediolateral, and resultant directions during static balance trials. Unpublished data from our lab have shown this exact static balance protocol produces reliable COP excursion and COP velocity data ($ICC_{2,1}$=0.74–0.85) in those with CAI.

A3.3.4 Overview of the Methods

For SA1, potential participants will read and sign the informed consent document. The participant will then be prepared for EMG and EEG data collection. EMG preparation will be consistent with current practices. More specifically, hair will be shaved and the area lightly abraded. Electrodes will then be placed bilaterally on the peroneus longus, tibialis anterior, gastrocnemius (medial head), vastus medialis, medial hamstrings (capturing both the semimembranosus and semitendinosus), and the gluteus medius. A reference site will be placed on the patella before placements are checked for crosstalk and impedance. EEG preparation will consist of lightly abrading the scalp to ensure low impedances. The cap will then be aligned followed by injecting each electrode with approximately 100 µL (maximum 300 µL) of an electrolyte fluid using a syringe equipped with a blunt-tip needle. Once all electrodes are hydrated, online impedance measurements are reviewed to ensure an optimal signal to noise ratio. Impedance will be below 5 kOhms for all electrode sites (EMG and EEG).[32] Pilot testing indicates this entire process will last from 30 to 40 minutes. Participants will then perform a total of six 10-second traditional single limb balance trials with eyes open (3 per limb) and six 10-second single-limb balance trials with eyes closed (3 per limb) with their hands on their hips and the contralateral limb flexed to approximately 30 degrees while EEG and EMG data is collected. Next, participants will complete the DSLT task as described previously.[1] To complete this task, participants will be asked to maintain static balance

on two limbs for approximately 4 seconds, with their hands on their hips. Then participants will transition from dual-limb support to single limb support, after receiving a visual cue, and maintain single limb stance for at least 5 seconds while EEG and EMG data is collected. Transitions will occur at a preferred speed of movement, but must take less than 1-second. This will complete 1 trial. A total of at least 60 artifact-free trials will be captured for each participant in four 10-minute blocks. Each participant will complete 120 DSLT trials for each limb.

For SA2, CAI participants will return to begin the balance training program first described by McKeon et al.[24] Participants will complete three 20-minute sessions a week for a total of 12 supervised training sessions over 4 weeks. The exercises aim to restore "normal" functional variability by challenging the participant's ability to maintain single limb stance through the purposeful manipulation of task and environmental constraints.[24] Progression to higher difficulty levels of each exercise are achieved independently by demonstrating movement proficiency (i.e. error free performance) as opposed to completing a specific amount of repetitions or training sessions. Table A3.2 illustrates the exercises and repetitions to be performed. The full protocol and progression criteria can be seen in the Appendix of the original paper.[24]

Table A3.2: Description of exercises from the McKeon et al.[24] balance training protocol.

Exercise	Description
Hop to stabilization	Hop to a target position (18, 27, 36 inches), stabilize, hop back to the starting position, and stabilize. Hops are performed in four directions: anterior/posterior, medial/lateral, anterolateral/posteromedial, and anteromedial/posterolateral.
Hop to stabilization and reach	As above but after stabilizing, subjects will reach back to the starting and target positions during each repetition of each direction.
Unanticipated hop to stabilization	Start in the middle of a 9-marker grid (individually numbered) and hop to the randomly presented target number. Subjects can use any combination of hops they wish to reach the target.
Single limb stance balance	Complete a single limb stance exercise with eyes open.
Single limb balance with eyes closed	Complete a single limb stance exercise with eyes closed.

Following the completion of the balance training protocol, participants with CAI will return and repeat an identical DSLT task testing protocol with EEG and EMG data collection. Post-test assessments will occur within 24 hours and at 1-week post intervention. Traditional baseline testing and the recording of self-reported function will also be completed at these time points to confirm the previously established effectiveness of the balance training intervention.

A3.3.5 Data Management

For EEG data, eye movement and blink artifacts will be removed from trials using online blink reduction tools in the Curry 7 Acquisition module, and a DC shift will be compensated for using an online fourth-order trend correction for each channel (linear detrend). In order to prepare data for ERD analysis, two separate bandpass filters will be used to isolate the Alpha (8-12 Hz) and Beta (14-25 Hz) frequency bandwidths. An

increase in ERD in the Alpha band has been linked to increased activation in the sensorimotor cortices,[32] while Beta is linked to voluntary movement preparation and execution.[35] Manual artifact rejection will follow filtering and total trial count will be blinded to prevent rejection bias. ERD is an outcome measure that compares the power within a given frequency band against a baseline or reference period and is reported as a percent change from baseline. Electrical activity as recorded by EEG is a summative waveform sensitive to different tasks and composed of many different frequency oscillations, which represent the activity of a large number of neurons. For example, sensory stimuli often impart a time-locked change in the electrical potential recorded from a population of neurons which is known as an event-related potential. Event-related potentials inform us about the magnitude of neuronal activity preceding movement, but fail to elucidate the coordination or magnitude of overall activity during the movement. An increase in ERD suggests a more widespread use of frequency contents and therefore an increase in overall activity in a localized region relative to the baseline or reference period, so a higher ERD relates to more cortical activity.[35] The FCz, Cz, and CPz electrode positions were selected based on their proximity to the premotor cortex, motor cortex, and somatosensory cortex, respectively. Onset times for EMG will be calculated from the initial ML shift of the COP towards the swing limb, as described by Van Deun et al.[151] In brief, the COP coordinates in the ML plane will be averaged for the ~3 seconds of dual-limb support. The starting point (SP) is defined as the last frame where the COP was within the average ML position. ERD will be calculated as the 250ms prior to and after SP (500ms total), and compared against a reference period of the same duration while the participant was in dual-limb support, allowing us to capture the

planning, execution, and efference copy of the motor command. EMG data and onset times will be calculated according to Van Deun et al.[151] and will be rectified and low-pass filtered (45 Hz cutoff). A fixed, 25ms window prior to the DSLT will be compared to a 25ms moving window, and any increase in EMG activity more than 2 standard deviations above mean baseline activity will be determined as the onset time.[1] This method of determining movement onset and EMG onset have been shown to have an acceptable level of reliability and measurement agreement in both controls and those with CAI with maximum onset error of 60 and 90ms, respectively, for muscles that will be assessed in this investigation.[151]

A3.3.6 Statistical Analysis

For SA1, ERD data from each electrode (FCz, Cz, CPz) and each bandwidth (Alpha, Beta) will be submitted to a separate 3x2 ANOVA to assess the effect of Group ([control, coper, CAI] by Limb [dominant/involved, nondominant/uninvolved]). For SA2, ERD data from each electrode and bandwidth will be submitted to 1-way repeated measures ANOVAs (baseline, post-test 1, post-test 2). Post-hoc testing will be performed when appropriate to determine the location of interactions and main effects. An alpha level will be set at 0.05 for all ERD analyses, and results from each ANOVA will be analyzed and interpreted independently. EMG and all secondary outcomes (FAAM, traditional postural control outcomes) will be compared using appropriate inferential statistics and statistical significance will be determined using a traditional alpha level of 0.05. Clinical meaningfulness for all outcomes will be determined by the calculation of effect sizes and 95% confidence intervals.