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Effects of Balance Training on Spinal Reflexive Excitability Modulation, Corticospinal Excitability, and Balance Performance in Individuals with Chronic Ankle Instability

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EFFECTS OF BALANCE TRAINING ON SPINAL REFLEXIVE EXCITABILITY MODULATION, CORTICOSPINAL EXCITABILITY, AND BALANCE PERFORMANCE IN INDIVIDUALS WITH CHRONIC ANKLE INSTABILITY

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ABSTRACT

EFFECTS OF BALANCE TRAINING ON SPINAL REFLEXIVE EXCITABILITY MODULATION, CORTICOSPINAL EXCITABILITY, AND BALANCE PERFORMANCE IN INDIVIDUALS WITH CAI

Sunghoon Chung
Old Dominion University, 2024
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Chronic ankle instability (CAI) is a neurophysiologic deficit resulting in diverse sensorimotor impairments. Following acute ankle sprains, pain, mechanical instability, and joint deafferentation reduce sensory input to the central nervous system (CNS). In response, the CNS sends altered motor signals to lower extremity muscles. These CNS changes contribute to various neuromuscular impairments in CAI patients, the most common of which is reduced balance performance. Specifically, CAI patients struggle to modulate spinal reflex excitability of the soleus muscle when progressing from simpler to more complex balance tasks. This overreliance on spinal reflexes results in inconsistent activation of the ankle stabilizing muscle. To maintain balance effectively, spinal reflex excitability should be suppressed, and motor control should shift to the supraspinal center. However, CAI patients exhibited reduced supraspinal control of the soleus, as evidenced by increased cortical inhibition of the soleus muscle measured through transcranial magnetic stimulation (TMS). Thus, improving balance and restoring CNS function are among the most crucial goals for rehabilitation in individuals with CAI.

The aim of the first study was to examine the effects of a single balance training session on spinal reflexive excitability modulation, corticospinal excitability, and balance performance in

individuals with CAI. This study revealed that single-session balance training began to increase spinal reflexive excitability modulation and corticospinal excitability in people with CAI. This supports the hypothesis that balance training might be able to transfer balance control to the supraspinal level to maintain single-limb standing in those with CAI.

Although current balance training has successfully improved balance performance in CAI populations, there is still heterogeneity in training parameters. The purpose of the second study, which was a systematic review and meta-analysis, was to determine the optimal dose of balance training for individuals with CAI. This study suggested that 6 weeks, 3 sessions a week, 18 total training sessions, and equal to or less than 20 minutes as the current optimal dose of balance training for people with CAI. Providing the optimal dose can be expected to reduce the heterogeneity of balance training parameters, reducing confusion for clinicians seeking the best intervention for their patients.

Using the results of Study 2, Study 3 aimed to determine the effects of 6-week balance training on spinal reflexive excitability modulation, corticospinal excitability, and balance performance in individuals with CAI. The results of this study exhibited increased spinal reflexive excitability modulation, corticospinal excitability, and balance performance following 6-week of balance training. This suggested that balance training was effective in addressing the neurosignature, which was accompanied by improved balance performance in those with CAI. Given that these neurophysiological deficits can contribute to recurrent ankle sprains, the improved neurosignature after balance training can provide an insight into why balance training has been considered one of the most important rehabilitation protocols preventing repetitive ankle sprains with improved balance performance in those with CAI.

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NOMENCLATURE

A	Anterior
ACLR	Anterior Cruciate Ligament Reconstruction
AII	Ankle Instability Instrument
ATFL	Anterior Talofibular Ligament
BAL	Balance Training Group
BoS	Base of Support
CAI	Chronic Ankle Instability
CAIT	Cumberland Ankle Instability Tool
CFL	Calcaneofibular Ligament
CNS	Central Nervous System
COG	Center of Gravity
CON	Control Group
COP	Center of Pressure
CSP	Cortical Silent Period
EC	Eyes Closed
EMG	Electromyography
EO	Eyes Open
GABA	Gamma-aminobutryic Acid-B Receptor
H-reflex	Hoffman reflex
IdFAI	Identification of Functional Ankle Instability
LAS	Lateral Ankle Sprain
M-wave	Muscle Response

MEP	Motor Evoked Potential
MRI	Magnetic Resonance Image
PL	Posterolateral
PM	Posteromedial
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized Controlled Trial
SD	Standard Deviation
SEBT	Star Excursion Balance Test
SF-8	Short Form-8 Health Survey
SMD	Standard Mean Difference
TMS	Transcranial Magnetic Stimulation
TTB	Time-to-Boundary

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CHAPTER 1

INTRODUCTION

Ankle sprains are one of the most prevalent musculoskeletal injuries in individuals in the general population.[1] Approximately 2 million acute ankle sprains have been annually reported through the emergency department in the United States; this number is likely underestimated since many individuals with ankle sprains do not seek medical support.[2,3] Ankle sprains are often inaccurately considered trivial, but the injuries may result in residual symptoms that may lead to chronic ankle instability (CAI). CAI is marked by residual symptoms after the initial injury, such as recurrent unstable feelings of the ankle, persistent episodes of giving way, and recurrent ankle sprains.[4] Individuals with CAI may avoid participating in physical activities to reduce the frequency of these symptoms, leading to reduced health-related quality of life.[5] Furthermore, there has emerged evidence that CAI can be a risk factor for the onset of post-traumatic osteoarthritis of the ankle joints, further emphasizing the need for clinical intervention in the CAI population.[3]

The neurophysiological deficits in CAI has been well investigated following the initial injuries.[6,7] The change is initiated by pain, reduced mechanical stability, and damaged mechanoreceptors surrounding the ankle joint, all of which provide altered afferent input to the central nervous system (CNS).[8] The new afferent input can cause the CNS to produce modified efferent signals to activate lower extremity muscles.[9] Neural stimulation techniques, such as the Hoffman reflex (H-reflex) have been used to directly assess changes in the CNS by quantifying the spinal reflexive excitability using the ratio of H-reflex to muscle response (H:M ratio). One of the most consistently identified CNS changes in individuals with CAI is the reduced ability to modulate, or suppress, spinal reflex excitability of the soleus.[10] In healthy individuals, spinal reflex excitability of the soleus becomes more inhibited as postural demand is increased.[11] This normal inhibition of spinal reflexes allows supraspinal centers to control postural stability in preparation or response to perturbation.[11] Therefore, the reduced ability to modulate spinal reflexive activity of the soleus during balance activities in those with CAI, also suggests the presence of reduced supraspinal control.[10] Increased reliance on spinal reflexes can create reduced balance function when this population faces more challenging perturbations that warrant supraspinal control.[11] Given that the soleus plays a crucial role in balance,[12] improving proper spinal control of the soleus is imperative to restore balance performance in individuals with CAI.

Another method of evaluating CNS changes in individuals with CAI is using transcranial magnetic stimulation (TMS). TMS uses a pulsed magnetic field, creating an electrical current in the brain to induce the depolarization of neurons,[13] and has been employed as a non-invasive way to evaluate corticospinal excitability. When TMS is delivered to the primary motor cortex with adequate intensity, it can result in efferent excitation along the corticospinal tract causing activation of the corresponding muscles.[14] The most common outcomes that are acquired to measure corticospinal function include motor threshold, motor evoked potential (MEP), and cortical silent period (CSP). The motor threshold can be defined as the minimum intensity of stimulation needed to acquire muscle activation to a given amplitude. The resting motor threshold can be assessed as the motor threshold is measured with relaxed muscle while the active motor threshold (AMT) can be measured during voluntary muscular contraction.[15] MEP is described as the amplitude of muscle activation created by stimulation with a certain percentage of motor threshold.[14] CSP can be used to assess corticospinal inhibition regulated by the gamma-aminobutyric acid-B (GABA) receptor.[16] Using these outcomes, previous investigations observed reduced corticospinal excitability as well as increased cortical inhibition of the soleus in those with CAI.[17,18] When considered with studies regarding spinal reflex modulation, evidence suggests that the brains of individuals with CAI are unable to modulate spinal reflexes and shift control to supraspinal centers.[18] Together, this can result in reduced sensorimotor control and may help to explain consistent balance deficits within the population.

Along with the alteration of the CNS in individuals with CAI, researchers have expanded their investigations to explore whether balance training rehabilitation can prompt alterations in neural excitability because the neural alteration induced by activities allows us to determine and evaluate training protocols.[11] Specifically, it has previously been observed that H-reflex was suppressed after three days of balance training in healthy individuals.[19] On the other hand, Sefton et al. conducted 6-weeks of balance training and found the intervention increased the H-reflex in those with CAI when compared to baseline.[20] Besides population characteristics, these two studies revealed contradicting results that could be caused by the difference in the level of postural challenge during the H-reflex assessment. Trimble et al. measured H-reflex on a custom-made balance board while Sefton measured it on a stable floor, indicating that the result of H-reflex may be task dependent.[21] Therefore, investigating how H-reflex is modulated as people conduct different levels of postural tasks is warranted. From the supraspinal level perspective, patients with stroke showed increased corticospinal excitability after 3-weeks of balance training while there remains a paucity of evidence on the efficacy of balance training on neural excitability in CAI population.[22] Collectively, these results indicate that the neurosignature in the CNS could be modified if proper balance training is applied. More specifically, descending strategies for motor control in the spinal cord and brain are directly affected by balance training and coincide with balance performance improvements.[11] Although balance training has effectively modulated the neural plasticity in the CNS, there has been heterogeneity of training volumes making it difficult to determine how quickly the CNS responds to balance training. One study found suppression of the spinal reflex of the soleus and increased balance function occurred after a single session of balance training in an elderly population.[23] However, it remains unknown if neural excitability patterns exhibit similar improvements in the CAI population after a single session of balance training. Furthermore, it is crucial to study if improved neural excitability following short-term balance training can be further enhanced with the optimal dose of balance training.

The most common sensorimotor deficits in individuals with CAI is reduced balance performance assessed through the center of pressure (COP), time-to-boundary (TTB), and Star Excursion Balance Test (SEBT).[24,25] Because of this, rehabilitation typically involves balance training.[26,27] The majority of findings indicate that balance training can be effective in preventing initial and recurrent ankle sprains, as well as improving performance on balance tests.[20,28,29] Despite the successful results, heterogeneity is prevalent across previous balance training protocol parameters, including the training weeks, frequency, intensity, volume, and type of balance training exercise.[29-32] These widely varying approaches can confuse clinicians aiming to provide the optimal dose of balance training for patients with CAI.[33] In healthy populations, previous systematic reviews quantified training weeks, frequency, and volume, suggesting balance training parameters to maximize the training effects for healthy young and older adults.[34,35] Lesinski et al. presented evidence-based guidelines for the balance training protocol in healthy young adults, suggesting that 11-12 weeks of training periods, three sessions per week of training frequency, 11-15 mins of a single training session, and four exercises per training session are the balance training parameters to derive the optimal effects steady-state balance.[34] Also, an inverse U-shape relationship between training effectiveness and training period was presented, indicating the optimal effects of balance training can be achieved by the proper period of training rather than just long-term exercise.[34] To the best of our knowledge, existing research has failed to account for the inconsistency in balance training strategies for individuals with CAI. Due to the lack of evidence-based recommendations for effective balance training protocols for patients with ankle sprains, the prescription of arbitrary balance training dosages could be an inevitable tendency. A systematic review and meta-analysis of balance training protocols for individuals with CAI can provide succinct guidelines for balance training parameters that can re-establish the neurosignature and provide optimal improvements in balance performance for individuals with CAI. From the clinical perspective, reducing the heterogeneity surrounding balance protocols may allow practitioners to maximize the efficacy of their balance training and organize a proper timeline and goal setting for their patients so that they can enhance patients' adherence to rehabilitation.[36,37] Additionally, identifying if balance training with optimal parameters can improve the neurosignature can be an imperative investigation to address sensorimotor deficits represented in individuals with CAI. Based on this, there were multiple purposes to this dissertation in order to further understand the effects of balance training on neural excitability in individuals with CAI. The first purpose was to determine the effects of a single session of balance training on spinal reflex modulation, corticospinal excitability, and balance performance in individuals with CAI. The second purpose was to systematically review the literature to identify the optimal dose of balance training for individuals with CAI. The third purpose was to determine the effects of an optimally-dosed balance training intervention on spinal reflex modulation, corticospinal excitability, and balance performance in individuals with CAI.

1.1 Aims and hypothesis

Aim 1.1: To determine the effects of a single session of balance training on corticospinal excitability of the soleus in individuals with CAI.

Hypothesis 1.1.1: Balance training group (BAL) and control group (CON) will not differ in MEP, AMT, or CSP at baseline.

Hypothesis 1.1.2: BAL will have greater MEP and lower AMT and CSP at post-test compared to baseline.

Hypothesis 1.1.3: BAL will have greater MEP and lower AMT and CSP at post-test compared to CON.

Aim 1.2: To examine the effects of a single session of balance training on spinal reflexive excitability modulation of the soleus in individuals with CAI.

Hypothesis 1.2.1: BAL and CON will not differ in H:M ratio modulation at baseline.

Hypothesis 1.2.2: BAL will have greater H:M ratio modulation at post-test compared to baseline.

Hypothesis 1.2.3: BAL will have greater H:M ratio modulation at post-test compared to CON.

Aim 1.3: To identify the effects of a single session of balance training on balance performance of the soleus in individuals with CAI.

Hypothesis 1.3.1: BAL and CON will not differ in COP velocity and TTB variables at baseline.

Hypothesis 1.3.2: BAL will have lower COP velocity and greater TTB variables at post-test compared to baseline.

Hypothesis 1.3.3: BAL will have lower COP velocity and greater TTB variables at post-test compared to CON.

Aim 2: To examine the optimal dose of balance training on balance performance in individuals with CAI.

Hypothesis 2.1: A systematic review of the literature will identify the optimal dose of balance training for individuals with CAI, including the most effective period, frequency, number of total training volume, duration of a single training session, and mode of balance exercise.

Aim 3.1: To determine the effects of optimally-dosed balance training on corticospinal excitability of the soleus in individuals with CAI.

Hypothesis 3.1.1: Balance training group (BAL) and control group (CON) will not differ in MEP, AMT, or CSP at baseline.

Hypothesis 3.1.2: BAL will have greater MEP and lower AMT and CSP at post-test compared to baseline.

Hypothesis 3.1.3: BAL will have greater MEP and lower AMT and CSP at post-test compared to CON.

Aim 3.2: To examine the effects of optimally-dosed balance training on spinal reflexive excitability modulation of the soleus in individuals with CAI.

Hypothesis 3.2.1: BAL and CON will not differ in H:M ratio modulation at baseline.

Hypothesis 3.2.2: BAL will have greater H:M ratio modulation at post-test compared to baseline.

Hypothesis 3.2.3: BAL will have greater H:M ratio modulation at post-test compared to CON.

Aim 3.3: To identify the effects of optimally-dosed balance training on balance performance in individuals with CAI.

Hypothesis 3.3.1: BAL and CON will not differ in COP velocity and TTB variables at baseline.

Hypothesis 3.3.2: BAL will have lower COP velocity and greater TTB variables at post-test compared to baseline.

Hypothesis 3.3.3: BAL will have lower COP velocity and greater TTB variables at post-test compared to CON.

1.2 Operational definitions

1. Chronic Ankle Instability: A condition that describes individuals with at least one ankle sprain leading to persistent symptoms, perceived instability, episodes of "giving way", and/or recurrent ankle sprains.

2. Spinal Reflexive Excitability Modulation: An ability of the CNS to inhibit or suppress the spinal reflexive circuit to enhance the involvement of the motor cortex controlling muscles.

3. Corticospinal Excitability: An ability of the primary motor cortex within the brain and descending corticospinal pathways to control the corresponding muscles.

1.3 Assumptions

Chapter 3

1. Participants exhibited balance deficits associated with the neurosignature that was represented as reduced modulation of spinal reflexive excitability and corticospinal excitability of the soleus.
2. Baseline data of neural excitability and balance performance will not differ across participants.

Chapter 4

1. The published article provided accurate information without errors.
2. The data extracted was accurate without errors.

Chapter 5

1. Participants exhibited balance deficits associated with the neurosignature that was represented as reduced modulation of spinal reflexive excitability and corticospinal excitability of the soleus.
2. Baseline data of neural excitability and balance performance will not differ across participants.

1.4 Delimitations

Chapter 3

1. Participants aged between 18-40 year-old.
2. Participants were screened according to a guideline suggested by the International Ankle Consortium for CAI.

Chapter 4

1. Only studies investigating balance performance following balance training were included.
2. Only randomized controlled trials were included.

Chapter 5

1. Participants aged between 18-40 year-old.
2. Participants were screened according to a guideline suggested by the International Ankle Consortium for CAI.

1.5 Limitations

Chapter 3

1. Assessing neural excitability can be task-dependent, meaning that the interpretation should not be extrapolated to balance tasks other than single-limb standing.
2. Investigators were not able to control physical activity levels which could be a confounder affecting the outcomes of neural excitability and balance performance.

Chapter 4

1. Criteria employed to select studies investigating CAI varied across studies.
2. Only 8 studies reported the duration of each balance training session so meta-analysis was conducted using only 8 studies while statistical analysis for other variables was computed using 14 studies which was the final amount of the studies included in the systematic review.

Chapter 5

1. Assessing neural excitability can be task-dependent, meaning that the interpretation should not be extrapolated to balance tasks other than single-limb standing.
2. Investigators were not able to control physical activity levels which could be a confounder affecting the outcomes of neural excitability and balance performance.

CHAPTER 2

REVIEW OF THE LITERATURE

2.1 Overview of Chronic Ankle Instability

Ankle sprains are one of the most prevalent lower extremity injuries in individuals involved in competitive activities.[3] Specifically, it has been reported that over 2 million ankle sprains occurred annually, leading to roughly 3.29/1000 exposures of incidence rate.[38] Furthermore, ankle injury is associated with a heavy burden on the healthcare system by generating approximately 1.2 million visits to emergency care and $2 billion in healthcare costs annually in the United States.[2,39] Along with the financial burden with a high incidence rate, ankle sprains need to get more attention because this can influence health-related quality of life in those with CAI.[40] Gribble et al. demonstrated that the health-related quality of life, which was measured by the Short Form-8 Health Survey (SF-8) inquiring about physical and mental status, was lower in individuals with a history of ankle sprains than in healthy individuals, leading to diminished physical activity that would contribute to healthcare burden to the society.[40,41] In spite of the vicious cycle following ankle sprains, this is regarded as a trivial injury that just gets healed quickly without proper treatment, generating approximately 55% of patients with ankle sprains who do not seek medical assistance after sustaining the ankle sprains.[42] The underestimation of the ankle sprain may cause the individuals to persistently suffer from symptoms such as perceived ankle instability, episodes of ankle “giving way,” and recurrent ankle sprains, all of which are characteristics that are observed in individuals with chronic ankle instability (CAI).[43,44] Previously, it was reported that approximately 40-70% of individuals with an initial ankle sprain can have experienced the development of CAI.[45,46] The updated model suggested by Hertel et al. has well described that this lower extremity impairment is not merely structural damage but can happen due to the diverse risk factors following lateral ankle sprains.[4]

2.1.1 Updated Model of Chronic Ankle Instability

Ankle sprains are not limited to a single type but the most common type of ankle sprains that have been observed in daily and sports activities is lateral ankle sprains (LAS),[47] showing a remarkably higher incidence rate than other types of ankle sprains such as medial, high, and unknown ankle sprains.[38] LAS is referred to as inversion ankle sprains because of the mechanism of the injury. Given that the detailed mechanism of injury for the LAS consists of excessive inversion and internal rotation of the ankle joint complex, however, the inversion ankle sprain is not enough to describe the mechanism of this injury from the ankle kinematic perspective.[4] This typical mechanism generates primary tissue injury in the anterior talofibular ligament (ATFL) attached to the neck of the talus from the lateral malleolus of the fibula.[48] This anatomical characteristic contributed to exorbitant stretch or even complete tear of the ligament following the LAS. Furthermore, a higher grade in LAS involves calcaneofibular ligament (CFL) disruption as well as impairments of ATFL.[49] With the ligament damage, clinical signs and symptoms such as pain, swelling, and inflammation can be quickly observed, subsequently being followed by negative psychological and emotional responses to the injury.[4]

After the primary tissue damage, individuals with LAS are likely to go through pathomechanical impairments including pathologic laxity, arthrokinematic restrictions, or tissue adaptations, all of which are associated with structural abnormalities in the ankle joint.[4] For example, the first experience following the initial LAS would be pathologic laxity due to the disruption of ATFL and/or CFL. The damage to the two ligaments can cause the loss of integrity of the ankle joints, which were typically assessed via common clinician-oriented measures such as the anterior drawer and inversion stress tests.[50,51] In contrast, individuals with LAS or CAI can exhibit arthrokinematics or osteokinematic restrictions in their ankle joints. Previously, it has been reported that the anterior-to-posterior glide of the talus was limited due to the anterior displacement of the talus, leading to restricted dorsiflexion range of motion in people with CAI.[52] Furthermore, these mechanical restrictions can contribute to reduced flexibility of the triceps surae, which can also result in the limitations of essential ankle joint motions.[4]

Acute LAS generates damage to ankle ligaments and other tissues, which is followed by inflammatory and pain mediators. This can lead patients to exhibit sensory-perceptual and motor-behavior impairments. Sensory-perceptual impairment can be described as sensations that patients can feel following the injury.[4] This can be conscious and unconscious sensations and/or perceptions, which are related to the impairments. Among various impairments in this group, diminished somatosensory function in individuals with LAS or CAI has been well investigated. The somatosensory function is one of the peripheral sensory systems sending proprioceptive information to the central nervous system (CNS), along with the visual and vestibular systems.[53] However, it has been theorized that ankle sprains can cause disruption of ligamentous and articulus proprioceptors, leading to dysfunction in the somatosensory system.[26] This deficit can have patients represent various sensorimotor impairments such as reduced postural control, impaired muscle contraction output, and inaccurate joint position sense in individuals with CAI.[54] The sensory-perceptual impairment is also not just limited to the reduced somatosensory system because it also accompanies kinesiophobia, patient-reported instability, and health-related quality of life, which indicate that individuals with CAI and LAS shows enhanced fear of movement and reinjury during activities and diminished physical and mental health.[4]

Motor-behavior impairments in those with CAI include altered reflexes, neuromuscular inhibition, balance deficits, muscle weakness, and reduced physical activity.[4] Previous studies reported that chronically unstable ankles might be associated with alteration in spinal reflexive excitability.[10,18] Kim et al. demonstrated that there was reduced modulation of spinal reflexive excitability of ankle muscles such as the soleus and fibularis longus while individuals with CAI demanded more challenging postural conditions such as comparing prone to double-leg standing or double-limb standing to single-limb standing.[18] Furthermore, this population exhibited reduced corticospinal excitability of the soleus while maintaining quiet single-limb standing in those with CAI.[10,17,55] Collectively, these results of altered reflexes in the CNS indicate that the CNS might not be able to transfer postural control to the supraspinal level in people with CAI, suggesting that this can be one of the potential mechanisms to cause balance deficits in this population.[10] Along with the altered neural excitability in the CNS, other impairments in this group include muscle weakness in the ankle joint as well as proximal to the ankle joint.[56-58] As a consequence, individuals with CAI showed altered movement patterns such as a more inverted foot that is likely to cause LAS while walking and running.[59] These changes can be reflected in reduced physical activity for those with CAI.[60]

The updated model of CAI has been focused on the relationship between the three impairments along with environmental and personal factors, which can lead people with ankle sprains to become CAI patients or copers who fully recover from the symptoms following a history of ankle sprains.[4] Prior to the injury, our body relies on the neurosignature that is created by genetic characteristics and lived experience to achieve movement goals, leading the neurosignature to be in homeostasis.[61] However, ankle sprains disrupt the homeostasis of the neurosignature by generating inflammation and pain mediators, leading to changes in the afferent information (sensory-perceptual) and efferent outputs (motor-behavior) within the CNS.[61] The alteration of the CNS leads the brain to look up an alternative way to compensate for the deficits to achieve the movement goal, which can be described as self-organizing that is based on the persistent cyclic relationship between sensory-perceptual and motor-behavior impairments following the LAS.[4] This results in the neurosignature in a negative way in those with LAS.[4] The adjustments in balance and movement seen in individuals with CAI, leading to recurrent instances of the ankle giving way and subsequent sprains, are believed to be attributed to neurosignature adaptation or neuroplasticity.[4] Thus, addressing the neurosignature is an imperative treatment goal so that individuals with LAS become copers, which are the individuals who achieve full recovery following ankle sprains via thorough evaluation and rehabilitation.

2.2 Balance in Individuals with CAI

Balance can be defined as the ability to keep a center of gravity (COG) over the base of support (BoS) to maintain an upright posture, which can be controlled by the CNS.[62] Given that the nature of upright posture in humans causes relatively high COG and small BoS, having the COG fall out of BoS can be an inevitable problem that can threaten stability in humans.[63] Fortunately, our CNS inherently has the ability to sense the dangerous situations and address them by controlling muscular activity to prevent falling.[63]

With the basic knowledge about balance, previous studies suggested strategies to describe how we maintain the stability of our upright posture.[64,65] The ankle strategy can be described as a movement of the whole body as one segment at the ankle joint like an inverted pendulum swaying in anterior and posterior directions.[65] In other words, the torque that is produced by the anterior and posterior compartments of the ankle muscles is generated based on postural perturbations against the stability of the upright posture.[64] On the other hand, the hip strategy is characterized by a horizontal shear force at the hip joint over the BoS, which is controlled by the ventral trunk and thigh muscles with the minimum or lack of support from the ankle joint.[66] The selection of each strategy is based on the content of the environment where people are facing relating to postural control. For example, people are likely to rely on the ankle strategy as they need to respond to translation during a stance on a flat BoS, while relying on the hip strategy during a stance on a narrow surface that limits the use of the ankle strategy.[67] Likewise, individuals with CAI also use the hip strategy as compared to healthy individuals, which was considered one of the compensatory strategies to maintain balance following ankle dysfunction.[68] Beckman et al. demonstrated that people with CAI showed fast activation of gluteal muscles as compared to healthy control groups' gluteal activation.[68] They hypothesized the reduced somatosensory function after LAS leads to a diminished ability to address postural challenges at the ankle joint, causing the CNS to recruit the hip strategy to maintain balance.[68,69] However, a hip strategy may not be an effective method to compensate for the ankle strategy to maintain balance in people with CAI, as deficits in the hip joint are also consistently observed while performing balance tasks in this population.[57,70] Therefore, there is likely a need to focus on improving both ankle and hip joint function during rehabilitation to improve balance performance in individuals with CAI.

One of the predominantly reported impairments in those with CAI is reduced balance deficits.[26] To evaluate these balance deficits, a static single-leg balance test in conjunction with an instrument such as a force plate, has been thought of as the gold standard method to assess balance function.[71] The force plate provides the center of pressure (COP)-related data of participants performing diverse balance tasks on the plate.[71,72] The COP refers to the point of application of the ground reaction force vector under the foot during activities such as standing, walking, or running, suggesting how individuals distribute their body weight and adjust posture to maintain stability.[72] Through performing balance tasks on a force plate, the excursion of COP can be measured to calculate various variables such as velocity, path length, and area of the COP.[73] The excursion of COP variables has been used to determine deficits in balance performance in individuals with CAI.[71,72,74] For instance, CAI patients exhibited increased area and velocity of COP movement as compared to healthy individuals, indicating increased postural sway while conducting single-limb standing task.[71,75] However, it is unknown whether assessing balance performance via the traditional method is sensitive enough to detect balance deficits in those with CAI since there has been a lack of consistency across studies.[24,76-79] To address this, an alternative method has been proposed, which is calculating time-to-boundary (TTB) measures.[24] TTB refers to the amount of time taken for the COP excursion to reach the ends of the boundary of the BoS as the COP moves in a consistent direction with the same speed. A reduced TTB value represents a lack of postural stability, as it signifies that the individual has limited time to react, attributed to a high COP velocity and/or a position close to the stability boundary.[80] Through this measurement, individuals with CAI have shown balance control deficits, suggesting that the combination of spatial and temporal factors of the COP excursion need to be considered to detect balance deficits in those with CAI, rather than assessing them separately as the traditional measurement does.[24,81]

Static balance has also been evaluated through different visual conditions such as eyes open and eyes closed.[71] The ability to control posture is significantly influenced by visual information.[82] When participants have their eyes open, they can preferentially use visual cues as sensory feedback to sustain balance.[83] Conversely, in the eyes closed condition, reliance shifts to the somatosensory and vestibular systems for maintaining equilibrium of upright posture.[83] This hypothesis is based on sensory reweighting theory which describes that our CNS relies on sensory feedback that is subject to be recruited to maintain balance.[53] A previous meta-analysis suggested that individuals with CAI likely rely on visual feedback to maintain balance due to the fact that the CNS may try to compensate for the impaired somatosensory cues from the ankle sending postural information to the higher balance control center.[83] However, this compensatory mechanism could also influence balance deficits in people with CAI, given that the visual cue is not available to be recruited to maintain balance as visual function is distracted by other tasks besides maintaining balance.[84] Aside from this feedback perspective, feed-forward mechanisms influencing balance impairments have emerged to describe why balance deficits occur in people with CAI.[85] Briefly, individuals with CAI exhibited increased reliance on spinal reflexes rather than the brain for maintaining balance, indicating that the CNS has an altered strategy following injuries that could lead to reduced balance function.

The Star Excursion Balance Test (SEBT) along with the instrumented version (Y-Balance Test), have been commonly utilized to assess dynamic balance function in individuals with CAI.[70,86,87] The SEBT has participants perform single-limb balance while they reach their other limb as far as they can in anterior, anteromedial, anterolateral, lateral, medial, posterior, posteromedial, and posterolateral directions.[88] However, considerable redundancy in the 8 tasks let researchers simplify the task to three directions: anterior (A), posteromedial (PM), and posterolateral (PL).[25,88] Using the SEBT, dynamic balance deficits have consistently been identified in CAI populations.[70,89] A systematic review and meta-analysis determined that individuals with CAI presented less reaching distance as compared to the distance conducted by healthy individuals as well as uninjured limbs.[90] Reduced dorsiflexion and hip strength have been associated with this reduced reach distance in those with CAI.[70,91] Collectively, these findings suggest that the SEBT is a clinical test to assess sensorimotor deficits associated with CAI.[88]

2.3 The nervous system and balance performance in individuals with CAI

Proprioceptive deficits have been considered a main factor in reduced balance function in individuals with CAI.[26] Postural control requires sensory input from somatosensory, visual, and vestibular systems, which is processed by the CNS sending the motor signal down to muscles to respond to postural challenges.[26] Among the three sensory systems, the somatosensory system, also referred to as proprioception, is the nervous system that is damaged directly by lower extremity injuries such as ankle sprains or anterior cruciate ligament ruptures.[92] This peripheral nervous system involves ligamentous, articular, musculotendinous, and cutaneous mechanoreceptors which play a role in detecting sensory stimuli such as touch, pain, and pressure.[93] From the postural control perspective, somatosensory function is the ability to detect body movement and position.[26] Conversely, somatosensory dysfunction can be characterized as the inability to send the afferent input to the CNS or inaccurately perceiving where the ankle joint is in space, which is called deafferentation.[26] The deafferentation following ankle sprains may be attributed to the damage to sensory receptors originating from ligamentous and joint capsules as well as ligaments sprained.[94] Deafferentation has been assessed actively by measuring joint position sense, kinesthesia, and muscle function (i.e. reaction time or strength), indicating that individuals with CAI exhibited impaired sensorimotor function.[95,96] Assessing balance function has also been taken into account to detect proprioceptive deficits in people with CAI.[85] Previous studies have found reduced balance function in those with CAI, and have suggested that the impaired proprioceptive function disrupts afferent information that needs to be implemented by the CNS to maintain balance.[74,97,98] This was referred to as impaired feedback mechanisms since it was thought of as problems in feedback stemming from the peripheral sensory system following ankle sprains.[85] However, this concept has been challenged by studies demonstrating more widespread impairments. For example, individuals displayed bilateral sensorimotor deficits although they had unilateral CAI.[99,100] It has been also observed that CAI populations exhibited proximal joint sensorimotor deficits.[70,101] These results contradict the idea that deficits are only observed in the injured ankle joint and suggest that the impaired somatosensory function alone may not be sufficient to describe the postural control deficits in individuals with CAI. The presence of global sensorimotor dysfunction, specifically bilateral postural deficits as well as proximal adaptation, suggest that postural control problems in individuals with CAI may result not only from peripheral deficits in ankle proprioception but from central changes in motor control.[26]

TMS is a noninvasive brain stimulation technique that has been extensively utilized to evaluate corticospinal excitability and inhibition.[13] By penetrating the scalp, the magnetic field can be precisely directed to focal regions of the cortical area.[13] The specific cortical area targeted by TMS stimulation induces either excitatory or inhibitory effects, determined by the characteristics of the delivered pulse.[102] This technique also offers a nuanced and localized approach to modulating neural activity for research and clinical purposes.[103] Using this technique, three outcome measures including motor threshold, motor evoked potential (MEP), and cortical silent period (CSP), can be analyzed to assess corticospinal excitability. Motor thresholds indicates the minimum intensity of the TMS stimulation needed for MEP in a target muscle, allowing us to estimate the level of membrane excitability of corticospinal neurons innervating to a target muscle.[104] Thus, the higher motor thresholds indicate greater inhibition and less excitability, and vice versa. This is typically determined by measuring the lowest stimulation magnitude that can produce more than $50\mu V$ peak-to-peak amplitude of MEP or 2* standard deviation(SD) + averaged of the background electromyography (EMG).[105] MEP can be described as a muscle response induced by the stimulation. Once the stimulation is delivered to the proper point of the primary motor cortex corresponding to a target muscle, the MEP can be assessed.[102] The greater MEP suggests increased corticospinal excitability. CSP refers to the silent duration between the ends of the MEP and the EMG activation returned, which is generated due to the inhibitory neurotransmitter, known as γ-Aminobutyric ACID (GABA), that is released after TMS stimulation.[13] CSP can be measured by calculating 2*SD + mean of the pre-stimulus EMG signals.[106] The longer CSP suggests a longer inhibition time, which indicates reduced corticospinal excitability. Through the three outcome measures, the adaptation to cortical activation has been evaluated for people with neurological deficits and musculoskeletal injuries.[107-109]

Hoffmann-reflex (H-reflex) technique was suggested by Paul Hoffmann in 1910, which is used to measure the spinal reflex excitability by delivering electrical stimulation to the peripheral nerve innervating a target muscle.[110] This technique mimics the stretch reflex theory that is initiated by muscle spindles sensing the stretch of the muscle and exciting the Ia- afferent (Ia) pathway, which in turn leads the spinal cord to excite alpha motor neurons to contract the corresponding muscle rapidly.[111] However, the advantage of this technique is to bypass the muscle spindle to generate an action potential of the target muscle, which proceeds via the complete loop of the spinal reflex.[112] The observed action potential of the target muscle that is represented via the EMG amplitude refers to H-reflex while the EMG activation caused by a signal delivered directly via the motor pathway is called muscle response (M-wave). The spinal reflex excitability is determined using the ratio of the maximum H-reflex and M-wave.

Central motor control is a crucial part of postural control to maintain upright posture in humans.[21] The central motor control is conducted via active supraspinal and spinal adaptation depending on tasks or environment.[21] Likewise, the intricate coordination between supraspinal and spinal mechanisms is essential for effective postural control.[11] Specifically, the CNS relies on supraspinal control represented by corticospinal excitability as people face increased postural demands whereas spinal control is relatively decreased.[11] For example, the corticospinal excitability was increased during challenging standing conditions such as standing on tiptoe, leaning forwards, and standing on a free-swinging platform, indicating the CNS tries to enhance reliance on supraspinal postural control to respond to postural perturbations.[113,114] In contrast, spinal reflex excitability was reduced with increased postural demand like standing on a narrow beam and with eyes closed as compared to normal standing, which can take into account supraspinal-induced presynaptic inhibition to Ia pathway of the spinal cord corresponding to muscles associated with postural control.[115,116] However, there was evidence that the CNS also relied on spinal reflex excitability with reduced postural demand and the necessity for fast response against postural challenges.[117,118] Taken together, the interaction between supraspinal and spinal adaptations is based on postural tasks, which also suggests that neural plasticity influencing postural control can be learned via proper intervention such as balance training.[21]

Following lower extremity injuries, alteration in both supraspinal excitability and spinal excitability has been observed.[10,119] For example, the motor threshold of the motor cortex was significantly greater in the quadriceps of a limb with anterior cruciate ligament reconstruction (ACLR) while MEP was diminished.[119,120] Furthermore, people with ACLR exhibited higher bilateral spinal reflex excitability as they performed voluntary activation of the quadriceps.[121] These changes in the CNS were considered an arthrogenic inhibition that the CNS chooses to protect the knee from further injuries, which could lead to sensorimotor deficits as they are untreated.[121]Similarly, individuals with CAI showed changes in the CNS which has attributed to the neurosignature that can affect sensorimotor deficits as well as perception of ankle function and quality of life.[4] Using the TMS technique, previous studies demonstrated that individuals with CAI had lower corticospinal excitability as compared to healthy individuals or copers who had full recovery after acute ankle sprains.[10] For example, Terada et demonstrated a longer CSP of the tibialis anterior in individuals with CAI as compared to healthy individuals and copers while performing single-limb balance task, meaning that there was a longer inhibition period to the muscle in those with CAI.[55] Given that co-contraction of the tibialis anterior and soleus are crucial motor functions to maintain quiet single-limb balance, the longer inhibition to the muscle may indicate that they may not be able to use the muscle as they need to maintain the challenging balance task.[11] Along with the previous results associated with corticospinal alteration, Kim et al. demonstrated reduced ability to modulate spinal reflexive excitability in people with CAI as they changed postures from easy to hard to perform it.[18] For example, there was a reduced modulation of spinal reflexive excitability in CAI population as they switched their posture from prone to double-leg standing and from double-leg standing to single-leg standing.[18] This suggested that the CNS may not be able to suppress the spinal reflex pathways as they faced postural challenges, leading to inability to transfer the balance control to supraspinal level causing balance deficits in individuals with CAI.[18,21] That is, addressing the corticospinal adaptation following ankle sprains should be an important rehabilitation target for individuals with CAI.

2.4 Balance training and the CNS in individuals with CAI

Balance training has been considered a crucial rehabilitation strategy for individuals with lower extremity injuries or neurologic disorders.[28,122] For example, individuals with ACLR exhibited balance deficits that were restored following balance training, which also demonstrated that it was effective in preventing repetitive ankle sprains and further injuries.[28,123,124] Likewise, balance exercises for individuals with CAI consistently exhibited positive outcomes in terms of improving balance performance as well as preventing further injuries and repetitive ankle sprains.[29] Although there has been success with balance training for various populations and conditions, balance training varies between utilizing a simple ankle disc to implementing diverse exercise programs consisting of visual conditions (eyes open, eyes closed, or visual perturbation methods), static or dynamic exercises, and/or different bases of supports (stable or a foam pad).[125] In addition, training parameters for balance interventions used in previous studies have been diverse.[34,126] The heterogeneity of training parameters can bring confusion for clinicians seeking the optimal treatment plan that needs to be prescribed to patients who want to return to their lives without residual symptoms as well as with the best body health following injuries.[29] In an effort to reduce the inconsistency in training parameters, Lesinski et al. performed a systematic review and meta-analysis and suggested an inverse U-shape relationship between training parameters and balance performance, indicating that the best balance performance could be achieved via the optimal training dose rather than conducting just long-term training.[34] Given there is the heterogeneity of training parameters of balance training for those with CAI, the investigation to decrease the inconsistency is required to determine the best way to provide the best outcomes in balance performance for people with CAI.

A previous review suggested that balance training may reduce reliance on spinal excitability while it may increase cortical activities, leading to improved postural control.[21] Furthermore, once balance training is performed with a certain period of training, the balance control may transfer to the subcortical area such as the brainstem and cerebellum, meaning that the CNS learns the motor skills through the training resulting in automatic postural control.[21] For example, Schubert et al. demonstrated that corticospinal excitability of the soleus was enhanced, while spinal reflex excitability was reduced following 4-week of balance training for healthy individuals.[127] Also, Tauber et al. reported results that can support the idea that balance training can induce the activation of the motor cortex using magnetic resonance image (MRI), suggesting that there was an increased thickness in the motor cortex after a single-session of balance training.[128] This rapid change in the brain was specifically associated with muscle activation of the hip, knee, and trunk through balance tasks rather than other tasks causing the activation of the corresponding muscles.[128] On the other hand, a systematic review and meta-analysis suggested that balance training in younger adults showed a training-induced reduction in spinal reflex excitability.[129] Collectively, balance training can elicit changes in the CNS, leading to transferring the balance control to supraspinal level controlled by motor cortex in the brain.

The changes in the CNS following balance training were observed in individuals with neurological deficits such as Parkinson's disease and stroke.[22,130] For example, balance training induced an increased inhibition period of the soleus in Parkinson's disease, meaning that the balance exercises modulated the imbalance between excitation and inhibition of the motor cortex, leading to motor dysfunction like tremor.[130] On the other hand, balance training increased corticospinal excitability in individuals with stroke, leading to improved balance performance in this population.[22] These two results suggest that the neural plasticity induced by balance training can be population-dependent but lead to positive outcomes. Based on our knowledge, however, the effects of balance training on neural plasticity in individuals with musculoskeletal injuries such as ankle sprains or anterior cruciate ligament reconstruction have not been well understood. Nevertheless, patients with lower extremity injuries commonly showed undesirable alteration of the CNS, which was suggested as a risk factor causing sensorimotor deficits.[10,131] Specifically, individuals with CAI showed reduced corticospinal excitability of the soleus as well as increased reliance on spinal reflexive excitability, which was suggested as a risk factor causing reduced balance function.[10,26] Since balance training is a crucial part of rehabilitation for individuals with CAI, identifying the effects of balance training on the neurosignature that should be addressed is imperative for those with CAI to restore their balance function to prevent repetitive ankle sprains as well as improve their balance performance. Furthermore, this can help clinicians ensure why balance training needs to be involved in rehabilitation protocol for people with CAI.

CHAPTER 3

THE EFFECTS OF A SINGLE-SESSION BALANCE TRAINING ON CORTICOSPINAL EXCITABILITY, SPINAL REFLEXIVE EXCITABILITY MODULATION, AND BALANCE PERFORMANCE IN INDIVIDUALS WITH CHRONIC ANKLE INSTABILITY

3.1 Introduction

Lateral ankle sprains (LAS) are one of the most common lower extremity injuries, prevalent in both daily and sports activities.[132] Annually, over 206,000 individuals seek care in the emergency department due to injuries in the United States, resulting in approximately $12,000 of health-related costs per injury.[38,133] However, the actual occurrence of ankle sprains might be higher than the reported rate as many people who experience ankle sprains may consider these to be minor injuries.[42] Additionally, up to 70% of initial ankle sprains can develop chronic ankle instability (CAI), described as residual feelings of instability in the ankle, repetitive ankle giving way, and recurrent ankle sprains.[46] These lingering symptoms can contribute to reduced engagement in physical activities as well as diminishing health-related quality of life in those with CAI.[5] In addition, CAI has been suggested as one of the risk factors for post-traumatic osteoarthritis of the ankle joints, signifying that proper clinical intervention is necessary for people with CAI.[134]

Individuals with CAI have consistently shown sensorimotor deficits due to the altered neuroplasticity in the CNS following the initial ankle sprain.[17,18] In those with CAI, the most predominant impairment created by CNS alterations is reduced balance function.[26] Specifically, the CNS can somatosensory feedback can be altered by pain, mechanical instability, and deafferentation of the ankle joints.[26] In turn, the CNS integrates and processes the sensory input leading to modified efferent signaling delivered to the musculoskeletal system, which can affect postural control in people with CAI.[26] The neurological alteration in CAI patients has been well investigated by using the Hoffmann reflex (H-reflex) technique to test spinal-reflexive excitability.[10,18,135] The predominant difference between individuals with CAI and those without is the ability of the CNS to modulate spinal reflex excitability. individuals with CAI display reduced modulation of spinal-reflexive excitability of the soleus muscle when changing from a prone to standing position, suggesting that they might rely on spinal reflexes to maintain postural control when performing a challenging balance task.[18] Relying excessively on spinal reflex control is likely responsible for the ongoing oscillatory movement at the ankle joint, ultimately leading to a decline in balance performance.[10,21]

Co-contraction of ankle stabilizers such as the soleus and tibialis anterior is controlled by the primary motor cortex of the brain and is imperative to prevent the postural instability caused by heavy reliance on spinal reflexes.[11] The ability of the motor cortex to control the muscles has been represented as corticospinal excitability measured through transcranial magnetic stimulation (TMS).[13] Using this brain stimulation technique, individuals with CAI have exhibited reduced corticospinal excitability of the soleus.[17] This indicates the CNS of those with CAI has impaired ability to elicit proper efferent signaling resulting in dysfunction of the ankle stabilizers when attempting to maintain an upright posture.[10,21] Furthermore, the relationship between reduced corticospinal excitability and diminished ability to modulate spinal-reflexive excitability suggests that the CNS may be unable to transfer balance control from spinal to supraspinal level as there is increased postural demand in people with CAI.[10]

Improving balance function is a crucial target of rehabilitation for this population since it is associated with subsequent lower extremity injuries.[26] Various balance training protocols have been implemented, and many have exhibited effectiveness in preventing and decreasing ankle injuries as well as improving balance performance and perceived ankle function.[29,136,137] However, it is not well understood if balance training can correct the neuroplastic changes that lead to reduced balance function in individuals with CAI. In uninjured participants, previous work has identified that the neurosignature can be modified through short-term balance training. Suppression of the spinal reflex of the soleus and increased balance function occurred after a single session of balance training in an elderly population.[23] This finding suggests that a single session of balance training can begin to increase spinal reflex modulation, but it remains unknown if appropriate neural excitability patterns exhibit improvement in the CAI population after a single session of balance training. Therefore, the purpose of this study was to determine the immediate effects of a single session of balance training on soleus spinal-reflexive excitability modulation, soleus corticospinal excitability, and balance performance in individuals with CAI.

3.2 Methods

3.2.1 Study design

We used a randomized controlled trial design. The two independent variables were group (balance [BAL] and control [CON]) and time (baseline and post-training). Dependent variables involved balance function, spinal-reflexive excitability modulation, and corticospinal excitability. This study was approved by the institutional review board of the Old Dominion University.

3.2.2 Participants

A total of 30 adults (15 BAL, 15 CON) were recruited to participate in this study. We conducted an *a priori* sample size estimate using G*Power 3.1.9.7 software. With a predetermined alpha level of 0.05 and estimated power of 0.80, we estimated 12 participants in each group (24 total) were necessary to detect group differences with an effect size of at least 0.80. However, in order to ensure sufficient sampling, we increased the recruiting rate by 25%. Thus, 15 subjects in each group were recruited for the study. The sample size was estimated using the mean differences and standard deviations from spinal reflexive excitability (H:M ratio) modulation data reported by Mynark et al.[23] Participants were recruited from Old Dominion University as well as within the surrounding Norfolk community. Participants from Old Dominion University were verbally contacted during classes and by the investigators. Also, volunteers were recruited via campus flyers. All participants were between 18 to 40 years old and had CAI as defined by the International Ankle Consortium.[138] The selection criteria for CAI consisted of the followings: 1) a previous history of a significant ankle sprain that caused pain and swelling (initial ankle sprain is required to occur at least 12 months prior to study enrollment; the most recent ankle sprain must occur at least 3 months prior to study enrollment); 2) at least two recurrent episodes of "giving way," "feeling of instability," or repeated ankle sprains in the six months before the study enrollment; 3) scored ≥5 on the Ankle Instability Instrument (AII), ≥11 on the Identification of Functional Ankle Instability (IdFAI), and ≤24 on the Cumberland Ankle Instability Tool (CAIT).

Participants were excluded if they had a history of acute head or lower extremity injuries within 3 months before testing and any history of lower extremity fracture or surgery. Also, participants with contraindications for the corticospinal excitability test were excluded. A guideline represented by the National Institutes of Neurological Disorders and Stroke was utilized to screen the participants. The guideline consisted of 1) history of heart disease, stroke, cardiac pacemaker or implanted cardiac defibrillator, epilepsy or seizures, migraines or severe headaches, cancer in brain or leg muscles, diagnosed psychiatric disorder, and intracranial metallic clips; 2) currently pregnant or breastfeeding; 3) currently taking pain-relieving medication or neuroinhibiting or stimulating medication; 4) metal implants anywhere in the head, neck, or shoulders (excluding dental work); 5) personal or familial history of seizures or epilepsy; 6) ocular foreign objects or cochlear implants; 7) implanted brain stimulators, aneurysm clips, implanted medication pumps, intracardiac lines, or cardiac pacemakers; 8) history of or currently abusing illicit drugs or alcohol or currently withdrawing from any substance; 9) use of any medication that may lower seizure threshold (including, but not limited to, tricyclic antidepressants, neuroleptic agents, Baclofen, and Tramadol); and 10) history of serious intracranial pressure.[139]

3.2.3 Procedure

Informed consent documents approved by the University's institutional review board were read and signed by participants after enrollment. Then, participants were randomly assigned to BAL and CON. The randomization sequence was created by an independent investigator who prepared a sealed envelope to determine to which group the subject would be allocated. The study was conducted for two days. Participants conducted baseline measurements of corticospinal and spinal reflexive excitability with balance function on the first day. For the second day, participants performed balance training and post-training measurements to identify the immediate effect of balance training. Briefly, the testing procedures were completed in the following order: 1) corticospinal excitability (1st day); 2) spinal-reflexive excitability modulation (1st day); 3) balance testing (1st day); 4) balance training (2nd day); 5) repeat of baseline measures (2nd day).

Corticospinal excitability

Corticospinal excitability of the soleus was measured while maintaining a single-leg stance. The skin over the soleus belly was cleaned with fine sandpaper and isopropyl alcohol. Two pregelled Ag/AgCl electrodes were attached 1.75cm apart over the midline of the soleus of the testing limb.[17] A ground electrode was placed over the contralateral medial malleolus. The EMG signal was converted from analogue to digital with a 16-bit converter (MP160WSW, Biopac Systems, Inc., Goleta, CA), and then sampled at 2000 Hz and amplified at a gain of 1000 (EMG100C, Biopac Systems, Inc.).

Transcranial magnetic stimulation (TMS) was delivered to the primary motor cortex of each participant using a Magstim Super RAPID^2 PLUS^1 System (Magstim C, LTD., Wales, UK). From the stimulation, active motor threshold (AMT), motor-evoked potential (MEP), and cortical silent period (CSP) were acquired as the outcomes of interest. A swim cap was worn by participants to determine the position over the motor cortex that maximally activated the soleus of the testing limb. To identify the location, a line was drawn to bisect the hemispheres sagittally and another line was drawn to connect the external auditory meatuses. The intersection of these lines with a 1 cm by 1 cm grid allowed us to identify the appropriate location of the primary motor cortex. A Double Cone Coil (Magstim Company, Wales, UK) was positioned over the primary motor cortex's approximated representation of the soles. Then, stimulations at intensities of 40% of maximum stimulator output was provided three times to multiple points on the primary motor cortex by moving the coil systematically by 1 cm intervals. From the output of the soleus MEP, the spot that generated the highest EMG amplitudes with consistency was identified as the "hotspot". Then, the coil was fixed over the point.

The AMT was assessed via the method described in previous articles.[16,140] To acquire the AMT, the average peak amplitude of the background EMG signal was collected while participants conducted single-leg balance without magnetic stimulus. From the result, 2 standard deviations above this amplitude was set as a cut-off threshold. Lastly, AMT was defined as the lowest stimulator intensity to result in 5 out of 10 stimulations whose peak-to-peak amplitudes exceed the cut-off threshold. A higher AMT suggested reduced corticospinal excitability. Once the AMT is acquired, 100% and 120% of AMT stimulation intensities were delivered to the hotspot. Among 10 stimulations in both intensities, five MEPs of 100% (MEP_{100}) and 120% of AMT (MEP_{120}) were recorded and averaged for the final analysis. A higher MEP indicated greater corticospinal excitability. CSP of soleus was measured time from the end of MEP to a return of baseline EMG signal which was the mean EMG signal plus 2 times the standard deviation. This was assessed in both 100% and 120% of AMT (CSP_{100} & CSP_{120}). A longer CSP suggested greater corticospinal inhibition to the soleus. Like MEP, 5 CSPs were recorded during the test.

Spinal reflexive excitability modulation

Spinal reflexive excitability modulation was measured while the participants are in a prone position and a single-leg stance. As a first step, the spinal reflexive excitability during prone and single-leg balance was determined using a ratio of the Hoffmann-reflex (H-reflex) to the muscle response (M-wave) (H:M). This ratio indirectly measured the number of motor neurons that can be excited through the spinal reflex loop compared to the total available alpha motor neuron pool.

The two recording electrodes and one ground electrode used for corticospinal excitability measurements remained in the same place for spinal reflexive measurements. The EMG signal was converted from analogue to digital with a 16-bit converter (MP160WSW, Biopac Systems, Inc., Goleta, CA), and then sampled at 2000 Hz and amplified at a gain of 1000 (EMG100C, Biopac Systems, Inc.). H-reflex and M-wave were elicited by BIOPAC stimulator module (STIM100A, BIOPAC systems, Inc., Goleta CA, USA) with a 2mm shield disk stimulating electrode. The electrode was attached to the superior portion of the popliteal fossa to stimulate and deliver a series of 1-ms square-wave pulses to the tibial nerve. The stimulation was progressively increased with 0.2V until the maximal H-reflex and M-wave were obtained. Five trials of the maximal H-reflex and M-wave were recorded to calculate the H:M ratio.

The modulation of H-reflex was measured by utilizing percentage changes in H:M ratio from the prone position to single-leg balance. Five modulation trials were recorded and averaged for the final analysis. The following formula was employed to calculate the modulation of H-reflex.[141]

$$\frac{Prone - Single\ leg\ standing\ H{:}M\ Ratio}{Prone\ H{:}M\ ratio} \times 100$$

Balance function

Balance performance was measured via a force platform (AccuSway Plus, AMTI, Watertown, MA, USA) during a single-leg standing task. The force platform was connected to the Balance Clinic software (AMTI, Watertown, MA, USA) to acquire the center of pressure (COP) data. Balance function testing included two visual conditions (Eyes open vs Eyes closed) while participants maintained single-leg balance on the involved limb. Each condition was conducted for three 20-second trials. Averaged COP path length, area circle, and maximum velocity in anterior-posterior and medial-lateral directions were utilized for the final data analysis. Rest intervals of 1 minute were provided between each condition. Furthermore, subjects were protected by the primary investigator to prevent falling.

Balance training

Only the BAL group completed balance training, which consisted of two static and two dynamic balance exercises that were described in a previous article.[142] The first static balance test was the single-legged stance on a foam pad (DynaDisc, Exertools, Petaluma, CA). Participants were instructed to maintain quiet balance for three 1-minute trials. The second static balance training was conducted using a wobble board. Subjects were asked to maintain their balance with a single leg on the wobble board. Then, they slowly moved the wobble board in the anterior, posterior medial, and lateral directions without touching the ground. This procedure was conducted with 10 repetitions in each direction. For dynamic balance training, two hopping exercises were utilized. The first hopping exercise was single-leg hop training. Participants were instructed to hop as far as comfortable in the anterior direction. This training was conducted for 15 repetitions. The second hopping exercise was quadrant hop training. Subjects hopped to numbered squares clockwise and counterclockwise with their single limb. Five hops in each direction were required for the participants and two sets were conducted. To prevent fatigue, 1-minute rest was provided between each training condition and each set for the second dynamic balance training. Participants were spotted by members of the research personnel to prevent falling.

Participants conducted balance training with stroboscopic glasses (Nike SPARQ Vapor Strobes, Nike Inc, Beaverton, OR, USA). The stroboscopic glasses could provide visual perturbation with a degree between eyes open and eyes closed condition. The mechanism of the stroboscopic vision could be explained as intermittent visual perturbation by rapid cycles between opaque and transparent for 100 ms periods. The visual interruption is purported to reduce visual reliance during balance tasks. This might improve attentional ability that could help visual-motor control affecting balance function.[143] Individuals in the control group did not participate in the balance training protocol and were asked to do regular physical activity.

3.2.4 Statistical analysis

Separate 2x2 mixed-model ANOVA was used to determine the effect of group (BAL and CON) and time (baseline and post-training) on each dependent variable. When a statistically significant interaction or main effect existed, we conducted Bonferroni post hoc test for pairwise comparisons. Also, Cohen's d effect sizes (small = 0.2-0.49, moderate=0.5-0.79, large >0.8) with 95% confidence intervals were computed to determine the magnitude of significant differences.[144] All statistical significance was set a priori at $P<0.05$. All statistical analysis were performed through IBM SPSS statistics, version 24 (IBM Corporation, Armonk, NY).

3.3 Result

Table 3-1 provides demographic characteristics. Table 3-2 presents the means and standard deviation for all outcome measures.

Table 3- 1 Participant demographic

Dependent Variable	Mean (SD) BAL(n=15)	Mean (SD) CON(n=15)	P-Value
Age, y	22.00 (2.62)	23.00 (3.01)	0.35
Height, cm	170.11 (7.93)	172.11 (10.19)	0.56
Weight, kg	73.74 (19.51)	81.09 (19.61)	0.32
Previous ankle sprains, No.	3 (2.70)	3 (2.45)	1.00
AII (# of Yes)	5.33 (1.23)	5.87 (3.13)	0.30
IdFAI	15.67 (3.13)	18.33 (4.62)	0.08
CAIT	20.07 (5.12)	20.87 (3.80)	0.34

Table 3- 2 Means and standard deviations for outcome measures

	Group Mean (SD)	
Dependent Variable	Pre-test	Post-test
TMS variables		
AMT (%)		
BAL	42.13 (19.10)	40.80 (14.41)
CON	48.86 (12.13)	46.79 (16.57)
MEP_{100} (mv/mv)		
BAL	0.23 (0.11)	0.22 (0.12)
CON	0.25 (0.16)	0.25 (0.16)
MEP_{120} (mv/mv)		
BAL	0.22 (0.07)	0.22 (0.11)
CON	0.24 (0.13)	0.26 (0.17)
CSP_{100} (ms)		
BAL	61.61 (27.37)	40.58 (20.08)
CON	71.15 (45.93)	78.41 (52.68)
CSP_{120} (ms)		
BAL	80.31 (39.90)	42.43 (27.65)
CON	69.06 (44.93)	88.85 (53.88)
H-reflex variables		
H:M ratio in prone		
BAL	0.54 (0.19)	0.59 (0.18)
CON	0.64 (0.02)	0.56 (0.21)
H:M ratio in single-leg standing		
BAL	0.32 (0.11)	0.33 (0.15)
CON	0.41 (0.12)	0.41 (0.15)
H:M ratio modulation (%)		
BAL	34.05 (28.07)	43.79 (18.96)
CON	34.02 (16.15)	20.97 (34.86)
Balance function variables		
Maximum velocity in anterior to posterior direction with EO (cm/s)		
BAL	5.73 (1.29)	5.52 (1.38)
CON	5.47 (1.45)	5.16 (1.35)
Maximum velocity in anterior to posterior direction with EC (cm/s)		
BAL	12.34 (3.48)	12.17 (3.19)
CON	12.91 (3.59)	12.04 (3.19
Maximum velocity in Medial to lateral direction with EO (cm/s)		
BAL	5.29 (1.53)	4.96 (1.41)
CON	4.46 (0.95)	4.16 (0.91)
Maximum velocity in Medial to lateral direction with EC (cm/s)		
BAL	10.27 (2.40)	10.58 (3.28)
CON	11.81 (3.52)	11.02 (2.86)

3.3.1 TMS variables

AMT

According to the result, there was no significant group by time interaction ($F_{(1, 27)}$ = 0.022, P = 0.88), group main effect, ($F_{(1, 27)}$ = 1.43, P = 0.24), or time main effect ($F_{(1, 27)}$ = .465, P = 0.50) for AMT.

MEP_{100}

There was no significant group by time interaction ($F_{(1,27)}$ = 0.047, P = 0.83), group main effect, ($F_{(1, 27)}$=0.391, P=0.54), or time main effect ($F_{(1, 27)}$ = 0.117, p = 0.74) for MEP_{100}.

MEP_{120}

There was no significant group by time interaction ($F_{(1,27)}$ = 0.037, P = 0.85), group main effect, ($F_{(1, 27)}$ = 0.218, P =0.68), or time main effect ($F_{(1, 27)}$=0.439, P=0.51) for MEP_{120}

CSP_{100}

Group-by-time interaction result showed there was a significant effect, ($F_{(1, 27)}$ = 4.727, P = 0.04). A large effect size (*d*=0.95 [0.17, 1.70]) indicates that BAL's post-test CSP_{100} was significantly lower than CON.

CSP_{120}

There was a significant group by time interaction ($F_{(1,27)}$ = 16.057, P < 0.01). Cohen's *d* effect size result of the post-test presented that BAL showed significantly reduced CSP_{120} than CSP_{120} in Control with a large effect (*d* =1.10 [0.29, 1.84]).

3.3.2 H-reflex variables

H:M ratio in prone

There was no group by time interaction ($F_{(1,27)}$ = 4.228, P = 0.50), main effect of group ($F_{(1, 27)}$ = 0.403, P = 0.53), or main effect of time ($F_{(1, 27)}$ = 0.194, P = 0.66) for H:M ratio in prone.

H:M ratio in single-leg standing

There was no group by time interaction ($F_{(1, 27)}$ = 0.075, P = 0.79), main effect of group ($F_{(1, 27)}$ = 3.276, P = 0.08), or main effect of time ($F_{(1, 27)}$ = 0.236, P = 0.24) for H:M ratio in single-leg standing.

H:M ratio modulation

There was a significant group by time interaction ($F_{(1, 27)}$ = 4.763, P = 0.04). A large effect size (*d* =.81, [0.03, 1.54]) showed that BAL's post-test H:M ratio modulation was larger than CON.

3.3.3 Balance function

Maximum velocity in anterior to posterior direction with eyes open (EO)

There was no group by time interaction ($F_{(1, 27)}$ = 0.043, P = 0.74), main effect of group ($F_{(1, 27)}$ = 0.413, P = 0.53), or main effect of time ($F_{(1, 27)}$ = 2.633, P = 0.12) for Maximum velocity in anterior to posterior direction with EO.

Maximum velocity in anterior to posterior direction with eyes closed (EC)

There was no group by time interaction ($F_{(1, 27)}$ = 0.620, P = 0.44), main effect of group ($F_{(1, 27)}$ = 0.039, P = 0.85), or main effect of time ($F_{(1, 27)}$ = 1.365, P = 0.25) for Maximum velocity in anterior to posterior direction with EC.

Maximum velocity in Medial to lateral direction with EO

There was no group by time interaction ($F_{(1, 27)}$ = 0.009, P = 0.93), main effect of group ($F_{(1, 27)}$ = 3.592, P = 0.70), or main effect of time ($F_{(1, 27)}$ = 3.675, P = 0.07) for Maximum velocity in Medial to lateral direction with EO.

Maximum velocity in Medial to lateral direction with EC

There was no group by time interaction ($F_{(1, 27)}$ = 1.024, P = 0.32), main effect of group ($F_{(1, 27)}$ = 0.995, P = 0.33), or main effect of time ($F_{(1, 27)}$ = 0.195, P = 0.66) for Maximum velocity in Medial to lateral direction with EC.

3.4 Discussion

This study aimed to assess the immediate impacts of a single session of balance training on soleus spinal-reflexive excitability modulation, soleus corticospinal excitability, and balance performance in individuals with CAI. The main finding of our study was that there was increased modulation of spinal reflexive excitability after a single session of balance training in those with CAI while changing the testing position from prone to single-limb standing. This suggests that spinal reflexive excitability was suppressed with the increased postural challenge following a single bout of balance exercises. Also, there was a significantly reduced CSP after a single session of balance training, meaning that the cortical activity was increased while performing single-limb standing. Collectively, the results of this study indicate that the CNS might start to more heavily use supraspinal balance control after the intervention. However, the interpretation of the results should be very cautious due to the nature of the neural excitability measurements which are very task-dependent.

The increased modulation of spinal-reflexive excitability in the soleus indicates the CNS reduces the spinal-reflexive excitability in individuals with CAI when switching from prone to a single-limb stance after a single session of balance training. This result accords with the previous observation showing that a sole training session could cause the CNS to rely less on spinal reflexes to maintain balance in the elderly as they were required to respond to postural challenges.[23] Collectively, the two studies suggest that the CNS transfers single-limb standing balance control to supraspinal control after one bout of balance exercises.[11] The increased modulation means enhanced ability to inhibit spinal reflex, which is a pathway that the CNS uses to elicit co-contraction of the soleus and tibialis anterior, resulting in improved ankle joint stabilization.[21]

Along with increased modulation of spinal-reflexive excitability, there was significantly reduced CSP_{100} and CSP_{120} after a single session of balance training. The CNS refers to a short period of inhibition time induced by the neurotransmitter, known as gamma-aminobutyric acid (GABA), within the motor cortex leading to inhibition of the corresponding muscles.[17] In previous research, individuals with CAI displayed a longer CSP compared to healthy individuals, which was related to functional deficits like standing and gait.[10,16,145] Thus, the reduced CSP of the soleus indicates less time of inhibition to the soleus, meaning that a single session of balance training might result in increased time to activate the soleus as it was needed to maintain single-limb standing in those with CAI.[16] In other words, the shortened period of inhibition of the soleus is a favorable change in the CNS that might be associated with the improvement of balance performance in people with CAI following the intervention. However, this interpretation should be taken with caution since there was no significant improvement in AMT and MEP, which means further investigation is necessary to identify if long-term balance training has an effect on corticospinal excitability for CAI populations.

Our study revealed that there was no significant improvement in balance performance after a single session of balance training in individuals with CAI. There would be two reasons for the results. Firstly, a single session of balance training may provide insufficient load to elicit observable improvements in balance performance even though there were changes in the CNS. Previously, Lesinski et al. performed a systematic review and meta-analysis suggesting that at least 16 to 19 total training sessions were required to be performed to improve balance performance optimally in healthy young adults.[34] Likewise, healthy older adults needed at least 36 to 40 total training sessions to achieve the best balance performance via balance training.[126] On the other hand, balance training performed for 4 weeks or 6 weeks consistently showed improvement in balance performance in individuals with CAI.[29,146] Although there was no available literature suggesting the optimal training dose of balance training for people with CAI, the previous results indicate that balance training should be conducted longer than a single session to achieve observable improvement in balance performance for those with CAI. Secondly, the reduced ability of COP measurements to detect balance deficits could be the reason why we were unable to identify the improvement in balance performance following the intervention.[73] Hertel et al. demonstrated the limitation of COP measurements to detect balance impairments in CAI people, relative to utilizing time-to-boundary measurement. That is, this indicates we need further research to identify if time-to-boundary measurement can detect balance improvement in individuals with CAI following balance training.

3.5 Clinical Implications

Although balance training has provided positive effects on improving balance performance as well as preventing recurrent ankle sprains in individuals with CAI, previous research was unclear on why those interventions were successful in achieving positive outcomes.

Through this study, clinicians can ensure that balance training enables neural excitability to be changed for people with CAI. Specifically, the increased reliance on supraspinal balance control, which was accompanied by diminished dependence on spinal control, could explain why balance training has been effective for individuals with CAI in reducing the risk of repetitive ankle sprains.

3.6 Limitations

Several limitations must be acknowledged when interpreting our findings. Firstly, our study did not have control over participants' postural sway during single-leg standing. Previous research has indicated that variations in the direction of postural sway could impact neural excitability results, particularly concerning changes in muscle fiber length.[147] Therefore, differing postural sway patterns among participants in our study could have influenced the lengthening of the soleus during stimulation, potentially affecting the outcomes of TMS and H-reflex variables. Secondly, it is crucial to recognize that assessing neural excitability is task-specific. Our results should be understood within the context of the testing position adopted by our participants. In this study, TMS variables were measured while participants engaged in single-leg standing. This implies that studies employing a similar testing protocol but with participants in a seated position might exhibit distinct neural excitability characteristics. Thirdly, the duration of the effects of a single-session balance training remains uncertain. Although post-testing was conducted shortly after the balance training with a brief interval, it is unclear if the observed neural and balance performance changes would persist over a more extended period. Solidifying these changes might require more time, and there is uncertainty about whether the effects dissipate after the short intervention. Lastly, we were not able to control participants' physical activity which might affect the third limitation of our study.

3.7 Conclusion

Our research focused on assessing the immediate impacts of a single session of balance training on spinal reflex modulation, corticospinal excitability, and balance function in individuals with CAI. The primary outcome revealed an increase in spinal reflex modulation and corticospinal excitability during single-leg stance, indicating favorable adaptations for individuals with CAI. Additionally, our findings suggest that balance training has the potential to induce neural plasticity in the central nervous system of individuals with CAI. However, given the short-term nature of the intervention, it is crucial to approach the interpretation of these results with caution. Despite promising neural adaptations, the brief intervention did not lead to improvements in balance performance, indicating that a more extensive training regimen may be necessary to fully restore these attributes in individuals with CAI. Future studies should investigate the effects of a long-term balance training program on both neural excitability and balance performance in individuals with CAI.

CHAPTER 4

THE OPTIMAL DOSE OF BALANCE TRAINING FOR INDIVIDUALS WITH CHRONIC ANKLE INSTABILITY: A SYSTEMATIC REVIEW AND META-ANALYSIS

4.1 Introduction

Ankle sprains, a prevalent musculoskeletal injury in sports, pose a considerable financial burden on healthcare systems.[47] Statistics reveal that 3.29 out of every 1000 annual patient visits to US emergency departments result from ankle sprains, with each incident incurring an average charge of $1,029.[38] Beyond the high incidence and economic implications, persistent symptoms often follow ankle sprains.[42] Consequently, around 40% of individuals experiencing an ankle sprain develop chronic ankle instability (CAI), characterized by recurring sprains and a subjective sensation of the ankle giving way.[43] CAI is associated with enduring consequences such as diminished health-related quality of life, decreased physical activity levels, and the potential development of post-traumatic osteoarthritis in the ankle joint.[5,60,148]

CAI leads to various functional impairments, with reduced balance performance being a primary concern.[26] In addressing this issue, numerous balance training programs have been introduced to enhance balance function among individuals with CAI.[149-151] Prior studies highlight the effectiveness of balance training in preventing initial and recurrent ankle sprains and enhancing performance on balance tests.[20,28,29] However, determining the optimal dosage for balance training in individuals with CAI remains a challenge. Previous balance training protocols exhibit significant heterogeneity in parameters such as training periods, frequency, duration of sessions, and types of exercises. This heterogeneity makes it challenging for clinicians to identify parameters that would best optimize balance training for CAI patients.[33]

Prior systematic reviews have examined balance training protocols to determine the ideal duration, frequency, and volume for both healthy young and older adults.[34,126] According to Lesinski et al., optimal balance training parameters for maximizing effects on balance performance in healthy young adults include 11-12 weeks of training, three sessions per week, 11-15 minutes per session, and four exercises per session.[34] Their research also highlighted an inverse U-shaped relationship between training effectiveness and volume, suggesting that moderate-duration training, rather than longer durations, is more effective in improving balance performance.[34] While these findings guide balance training for the general population, there is a lack of meta-analysis focusing specifically on individuals with CAI. Therefore, this systematic review and meta-analysis aim to fill this gap by investigating the appropriate dose of balance training for enhancing static and dynamic balance performance in individuals with CAI.

4.2 Methods

4.2.1 Search Strategy

This project consisted of a systematic literature search, in accordance with guidelines suggested within the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[152] examining the effect of balance training duration and frequency on static and dynamic balance function for individuals with CAI. The primary author performed a comprehensive electronic literature search through online databases including PubMed, CINAHL, SPORTDiscus, and MEDLINE. A combination of the following keywords was employed for the literature search: (ankle instability OR ankle sprain) AND (training OR rehabilitation OR therapy OR exercise OR intervention) AND (balance OR postural control OR stability).

4.2.2 Selection criteria

After articles were returned from the online databases, the duplicated studies were identified and removed. As a second step, review studies were excluded. Then, the articles were reviewed to eliminate irrelevant studies based on title and abstract. Lastly, the remaining studies underwent a full-text review. Included studies for this systematic review were required to meet the following criteria: (1) examined participants with CAI-related characteristics such as feeling of instability, episodes of giving way, recurrent ankle sprains, and self-reported ankle dysfunction following a history of ankle sprains[44]; (2) randomized controlled trial (RCT) studies; (3) participants underwent a balance training intervention; (4) participants underwent testing of static or dynamic balance performance; (5) written in English. If the studies do not meet the inclusion criteria, they were excluded during the steps stated above. Particularly, studies with the following were excluded: (1) use of a combination of therapeutic interventions (e.g., balance and resistance training); (2) not RCTs studies; and (3) not reporting means or standard deviation to be extracted for data analysis. Two independent reviewers performed the screening process including analyzing titles, abstracts, and full texts of individual studies.

4.2.3 Assessment of methodological quality

The quality assessment was assessed based on the Downs & Black quality assessment tool. Downs & Black quality assessment tool includes 27 items that assess the study's reporting, external validity, bias, confounding, and power.[153] A score of 24-28 is "excellent" or "very low risk of bias," 19-23 is "good" or "low risk of bias", 14-18 is "fair" or "moderate risk of bias", and less than 14 is "poor" or "high risk of bias." Disagreement among the reviewers was resolved by discussion until a consensus was reached.

4.2.4 Data extraction

Two authors extracted the following information from each study: sample size, participant demographics, inclusionary criteria, independent and dependent variables, balance training parameters [training period (weeks), training frequency (sessions/week), total training sessions (weeks * sessions/week), and duration of a single training session (time)].[34] Also, the type of balance training was extracted to be classified into static, dynamic, or static plus dynamic categories. For the dependent variables, the mean and standard deviation of outcome measurement only relating to balance function were extracted. Post-testing results of balance training and control group were only extracted to determine the efficacy of balance training on individuals with CAI.

4.2.5 Statistical analysis

Within-subject (Pre-test and post-test results of only the intervention group) effects were calculated to determine the efficacy of balance training on individuals with CAI. For the meta-analysis, we used the inverse variance statistical method using Review Manager software (RevMan, Version 5.3, The Cochrane Collaboration). Specifically, we conducted standard mean difference (SMD) by calculating the mean difference in outcomes of the post-test along with 95% confidence intervals between the intervention group and control group. This statistical method was utilized to determine the optimal week, frequency, duration, and number of total sessions. Also, types of intervention such as static, dynamic, and static plus dynamic were determined via SMD calculations. We used Cohen's guidelines to interpret SMD values: small = 0.20-0.49, moderate = 0.50-0.79, and large = 0.80+.[144]

4.3 Result

4.3.1 Literature search

The results of the literature search are presented in Figure 4-1. A total of 4092 were yielded from the initial search via the four online databases described above. After the last screening procedure, 14 studies were included in this review. Table 4-1 provides information about the methodological summary of each study.

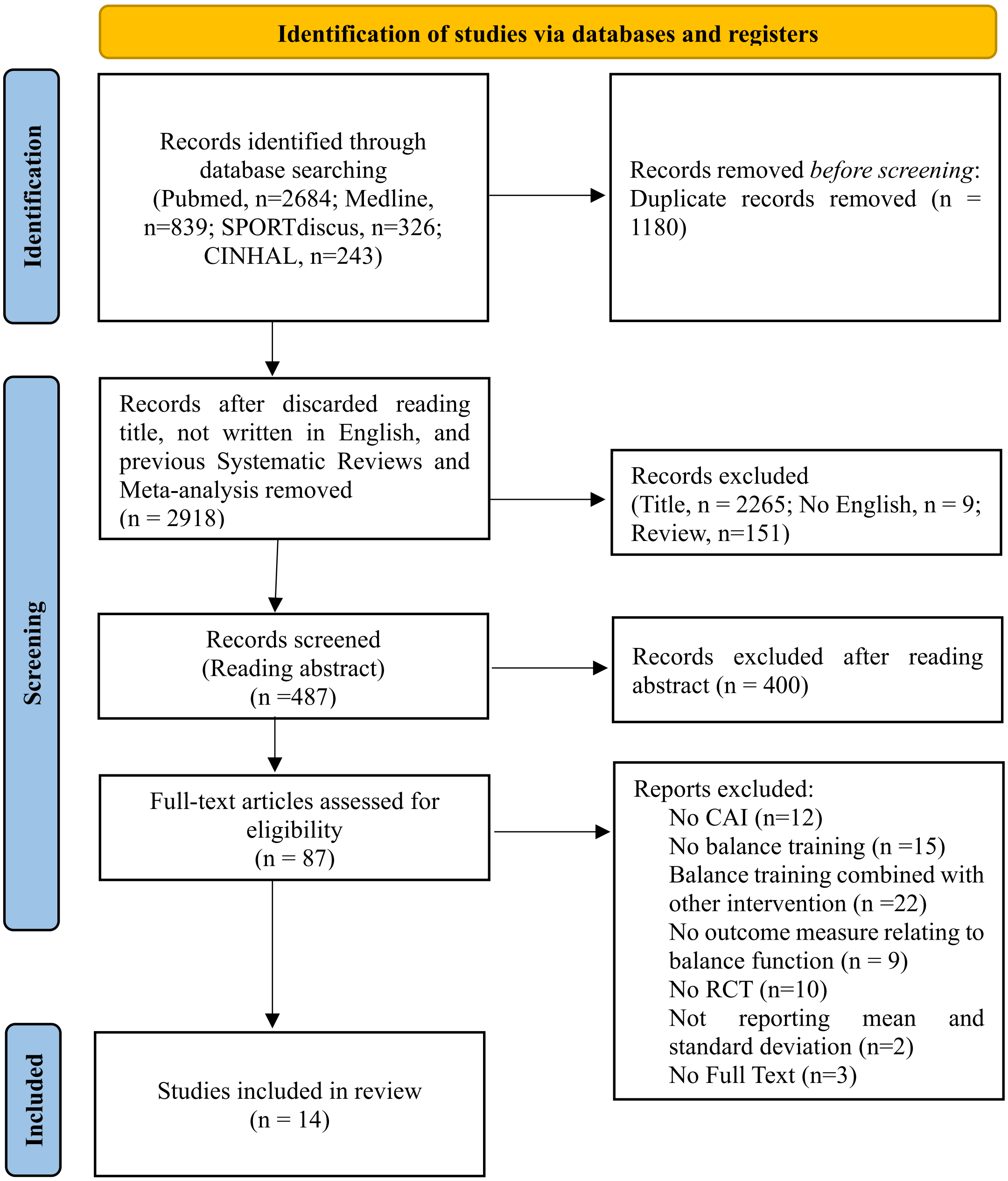

Figure 4- 1 Flow Chart

Table 4- 1 Methodological summary of the included studies

References	Subjects	Inclusion & Exclusion Criteria	Test modality
Anguish et al.[154]	*SLB* n = 9 age = 18.44±1.87 years; height = 172.50±7.43 cm; mass = 69.70 ± 10.18kg. *PHSB* n = 9 age = 18.33±1.87 years; height = 178.02±4.60 cm; mass = 81.89 ± 11.19kg.	*Inclusion Criteria* 1) a history of at least 1 ankle sprain. 2) occurring the initial ankle sprain 1 year prior to the study. 3) self-reported functional deficit detected by AII. 4) at least 2 episodes of a feeling of giving way. *Exclusion Criteria* 1) a history of lower extremity injury within 6 weeks before the study. 2) 2) a history of lower extremity surgery.	*SEBT* 1) measuring maximum reaching distance while single-leg standing. 2) assessing three directions: A, PM, PL. 3) performing three trials for each direction.
Bernier et al.[149]	n = 45 (BAL, n =17; Con, n=14; Sham, n=14); age = 22.53±3.95years; height = 172.04 ± 10.0 cm; weight = 71.72±15.7 kg. *Sham group was not involved in this study.	*Inclusion Criteria* 1) a history of at least 1 ankle sprain leading to the inability to weight bear and walk on crutches. 2) at least 2 episodes of a feeling of giving way in 12 months. 3) Pain-free at the onset of the study.	*Sway index & Equilibrium score* 1) Single-limb stance on a stable and tilting force plate for 20 s 2) 4 conditions: - Stable platform with EO - Stable platform with EC - Tilting platform with EO - Tilting platform with EC 3) 2 trials for each condition 4) Sway index: the value of the standard deviation of the distance while swaying. 5) Equilibrium Score: actual sway in 4 directions in relation to the theoretical limit.

Table 4- 1 Continued

Burcal et al.[30]	*BAL* n = 12 age = 21.17±1.64years; height = 170.82±15.09 cm; mass = 74.04 ± 24.76kg. *BAL with STARS* n = 12 age = 21.42±2.43years; height = 168.80±10.85 cm; mass = 71.93 ± 20.23kg. *BAL with STARS group was not involved in this study.	*Inclusion Criteria* 1) self-reporting at least 90 mins of exercises per week. 2) a history of at least 2 ankle sprains. 3) occurring the initial ankle sprain 1 year prior to the study. 4) self-reported functional deficit detected by AII and FAAM-ADL & S. 5) at least 1 episode of a feeling of giving way. *Exclusion Criteria* 1) a history of lower extremity and head injuries within 6 weeks before the study. 2) a history of lower extremity surgery. 3) balance and visual problems. 4) chronic musculoskeletal deficits affecting balance.	*SEBT* 1) measuring maximum reaching distance while single-leg standing. 2) assessing three directions: A, PM, PL. 3) performing three trials for each direction. *Postural sway measured by TTB* 1) Single-limb stance on a stable force plate for 10 s. 2) 3 trials. 3) EO and EC. 4) TTBs for outcome measures.
Conceição et al.[155]	*BAL* n = 22 age = 24.00±4.00 years; height = 173.00±9.80 cm; mass = 71.64 ± 11.98 kg. *Control* n = 22 age = 22.00±3.00 years; height = 171.00±9.70 cm; mass = 70.00 ± 11.03kg.	*Inclusion Criteria* 1) self-reporting at least 30 mins of exercise per day for 3 days a week. 2) a history of at least 2 ankle sprains. 3) at least one ankle sprain within 6 months before the study. 4) self-reported functional deficit detected by CAIT. 5) at least 1 episode of a feeling of giving way. *Exclusion Criteria* 1) acute injuries with S/Sx. 2) history of the lower extremity that can affect complete activities in the study. 3) history of fracture.	*COP displacement* 1) Assessing static balance with EO and EC - Single-limb stance while focusing on a mark on the wall located 4 m away (EO). - performing 5, 10 s 2) Assessing dynamic balance performance while kicking a ball - Measure COP displacements before limb motion, before kicking, and after kicking. - Performing 5 kicks 3) Outcome measures - COP area in A/P and M/L directions for static balance performance. - COP ranges in A/P and M/L directions for dynamic balance performance.

Table 4- 1 Continued

Cruz-Diaz et al.[31]	*BAL* n = 35 age = 31.89±7.91 years; height = 1.71±0.08 m; mass = 66.42 ± 11.75 kg. *Control* n = 35 age = 28.83±7.91 years; height = 1.71±0.09m; mass = 69.34 ± 10.73kg.	*Inclusion Criteria* 1) at least one ankle sprain within 6 months before the study. 2) self-reported functional deficit detected by CAIT. 3) at least 1 episode of a feeling of giving way. 4) no history of lower extremity injuries or neuromuscular deficits. *Exclusion Criteria* 1) missing 2 training sessions during 6-week of intervention.	*SEBT* 1) measuring maximum reaching distance while single-leg standing. 2) assessing three directions: A, PM, PL. 3) performing three trials for each direction.
Elsotohy et al.[156]	*BAL* n = 11 age = 20.70±1.15 years; height = 164.00±6.86 cm; mass = 67.80 ± 13.95 kg. *Control* n = 10 age = 21.45±2.11 years; height = 161.00±3.54 cm; mass = 74.63 ± 13.55kg. *Cross-education* n = 11 age = 20.72±1.60 years; height = 161.27±5.62 cm; mass = 65.54 ± 9.74kg. *Cross-education group was not included in this study.	*Inclusion Criteria* 1) history of at least 1 ankle sprain. 2) occurring the initial ankle sprain 1 year prior to the study. 3) self-reported functional deficit detected by AII. 4) at least 2 episodes of a feeling of giving way. *Exclusion Criteria* 1) history of previous surgeries or fractures. 2) acute lower extremity injuries within 3 months. 3) balance deficits caused by vestibular, visual, neuropathies, diabetes, and bilateral ankle instability. 4) positive sign of Anterior Drawer or Talar tilt tests.	*Biodex balance system* 1) assessing fluctuation in A/P and M/L directions. 2) single-limb stance on a balance platform. 3) Performing 3, 20s balance. 4) outcome measures: OASI, APSI, and MLSI.

Table 4- 1 Continued

Kim et al.[157]	*BAL* n = 25 age = 29.76±1.01 years; height = 167.48±22.95 cm; mass = 73.22 ± 21.12 kg. *BAL w/ SV* n = 24 age = 27.38±7.38 years; height = 170.63±8.79 cm; mass = 71.94 ± 9.89kg. *Control* n = 24 age = 29.67±9.41 years; height = 170.50±9.76 cm; mass = 69.38 ± 9.19kg.	*Inclusion Criteria* 1) at least one ankle sprain within 6 months before the study. 2) self-reported functional deficit detected by CAIT. 3) no history of lower extremity injuries or neuromuscular deficits. 4) mental and physical autonomy to participate in the intervention. *Exclusion Criteria* 1) self-reported balance or vestibular dysfunction affecting balance deficits. 2) an acute ankle sprain within the last 6 weeks. 3) history of surgeries. 4) history of epilepsy or seizures. 5) missing more than 3 sessions of the intervention.	*SEBT* 1) measuring maximum reaching distance while single-leg standing. 2) assessing three directions: A, PM, PL. 3) performing three trials for each direction.
Linens et al.[158]	*BAL* n = 17 age = 22.94±2.77 years; height = 170.22±8.71 cm; mass = 75.57 ± 13.55 kg. *Control* n = 17 age = 23.18±3.64 years; height = 168.57±9.81 cm; mass = 77.19 ± 18.93kg.	*Inclusion Criteria* 1) performing cardiovascular or resistance exercises for at least 1.5 hours per week. 2) at least one ankle sprain. 3) at least 2 episodes of giving way. 4) self-reported functional deficit detected by CAIT. *Exclusion Criteria* 1) any visual or vestibular dysfunction affecting balance deficits. 2) any acute hip and knee injury limiting function. 3) any signs and symptoms of acute injury.	*Time in balance* 1) single-limb stance with EO. 2) maintaining balance as long as they can but 60s was the maximum length for each trial. 3) performing three trials. *SEBT* 1) measuring maximum reaching distance while single-leg standing. 2) assessing three directions: AM, M, and PM. 3) performing three trials for each direction. *Figure-of-Eight Hop Test* 1) hopping in the figure-of-eight pattern as fast as they could. 2) Performing twice to assess the fastest time.

Table 4- 1 Continued

McKeon et al.[29]	*BAL* n = 16 age = 22.20±4.50 years height = 168.90±7.70 cm; mass = 63.00 ± 8.80 kg. *Control* n = 15 age = 19.50±1.20 years; height = 173.10 cm; mass = 67.30.	*Inclusion Criteria* 1) At least one ankle sprain. 2) Subsequent episodes of giving way quantified by AII. 3) Self-reported functional deficit detected by FADI and FADI-S. *Exclusion Criteria* 1) a history of lower extremity injuries within 6 weeks. 2) a history of lower extremity surgery. 3) any deficits such as neuropathies, diabetes, or others, of which can affect balance function.	*SEBT* 1) measuring maximum reaching distance while single-leg standing. 2) assessing three directions: A, PM, PL. 3) performing three trials for each direction. *Postural sway measured by COP and TTB* 1) single-limb stance on a stable force plate for 10 s. 2) performing 3 trials. 3) EO and EC. 4) Outcome measures: - SD of COP excursion, range of COP excursions, and mean velocity of COP excursions in AP and ML directions. - TTB minima in AP and ML directions.
Mettler et al.[159]	*BAL* n = 16 age = 22.20±4.50 years height = 168.90±7.70 cm; mass = 63.00 ± 8.80 kg. *Control* n = 15 age = 19.50±1.20 years; height = 173.10 cm; mass = 67.30.	*Inclusion Criteria* 1) at least one history of an ankle sprain. 2) subsequent episodes of giving way quantified by AII. 3) self-reported functional deficit detected by FADI and FADI-S. *Exclusion Criteria* 1) history of lower extremity injuries within 6 weeks. 2) history of lower extremity surgery. 3) any deficits such as neuropathies, diabetes, or others, of which can affect balance function.	*Postural sway measured by COP* 1) single-limb stance on a stable force plate for 10 s. 2) performing 3 trials. 3) EO and EC. 4) Outcome measures: - COP data points in the four innermost sections including AM, AL, PM, and PL.

Table 4- 1 Continued

Sierra-Guzmán et al.[160]	*BAL with Vib* n = 17 age = 22.40±2.60 years; height = 172.00±8.30 cm; mass = 70.20 ± 8.20 kg. *BAL* n = 16 age = 21.80±2.10 years; height = 171.30±9.00 cm; mass = 66.20 ± 10.10kg. *Control* n = 17 age = 23.60±3.40 years; height = 172.80±10.80 cm; mass = 70.60 ± 11.70 kg.	*Inclusion Criteria* 1) at least one ankle sprain within 3 months before study enrollment. 2) at least two episodes of giving way in 6 months before the study. 3) self-reported functional deficit detected by CAIT. *Exclusion Criteria* 1) acute lower extremity injuries within 3 months, resulting in at least 1 day off from activities. 2) history of lower extremity surgery. 3) fracture in the lower extremity.	*Biodex balance system* 1) assessing fluctuation in AP and ML directions. 2) single-limb stance on a balance platform. 3) performing 3, 20s balance. 4) outcome measures: OASI, APSI, and MLSI. *SEBT* 1) measuring maximum reaching distance while single-leg standing. 2) assessing three directions: A, AM, M, PM, PL, and composition of 5 directions. 3) performing three trials for each direction.
Sulewski et al.[161]	*BAL with IAF* n = 8 age = 21.10±2.40 years; height = 173.70±8.30 cm; mass = 87.10 ± 15.90 kg. *BAL with EAF* n = 8 age = 22.30±3.80 years; height = 166.10±7.50 cm; mass = 74.80 ± 20.90kg. *Control* n = 16 age = 26.60±5.20 years; height = 171.90±11.70 cm; mass = 71.40 ± 14.30 kg.	*Inclusion Criteria* 1) at least one ankle sprain that required crutches and immobilization. 2) at least one repetitive ankle sprain. 3) at least one episode of rolling or giving way. 4) having pain, instability, or weakness in the involved ankle. *Exclusion Criteria* not provided.	*Biodex balance system* 1) assessing fluctuation in AP and ML directions. 2) single-limb stance on a balance platform. 3) performing 3, 20s balance. 4) outcome measures: OASI, APSI, and MLSI. *SEBT* 1) measuring maximum reaching distance while single-leg standing. 2) assessing three directions: A, PM, and PL. 3) performing two trials for each direction.

Table 4- 1 Continued

Uzlaşır et al.[162]	*BAL with SV* n = 13 age = 19.08±0.40 years; height = 1.70±0.02 m; mass = 63.19 ±3.39 kg. *BAL with Non SV* n = 13 age = 20.46±0.51 years; height = 1.68±0.02 m; mass = 61.69 ± 2.69kg. *Control* n = 13 age = 20.23±0.39 years; height = 1.72±0.02 m; mass = 66.06 ± 2.40 kg.	*Inclusion Criteria* 1) at least one ankle sprain causing ≥ 8 days of sports time loss, pain, and swelling within 1 year prior to study enrollment. 2) at least two episodes of giving way in 6 months before the study. 3) self-reported functional deficit detected by IdFAI and FAAM-ADL&S. *Exclusion Criteria* 1) history of ankle fracture. 2) history of surgery in the lower extremity. 3) history of head injuries within 3 months before study enrollment. 4) chronic musculoskeletal injuries influencing balance function. 5) neurological deficits affecting vision.	*Postural sway measured by COP velocity* 1) measuring COP velocity while participants switched from bipedal stance to single-limb stance via a HUBER® 360 device offering rotation and oscillation of the platform. 2) performing for 30 s while EEG results were recorded.
Youssef et al.[163]	*WEBB* n = 13 age = 21.76±1.96 years; height = 162.00±8.78 cm; mass = 62.15 ± 8.97 kg. *UBAL* n = 12 age = 20.83±1.85 years; height = 161.16±7.44 cm; mass = 66.16 ± 11.63kg. *Control* n = 10 age = 22.40±3.16 years; height = 162.50±2.14 cm; mass = 66.70 ± 6.54 kg.	*Inclusion Criteria* 1) at least one ankle sprain within 1 year prior to study enrollment. 2) history of repetitive ankle sprains, the most recent of which occurred more than 3 months before study enrollment. 3) at least one episode of giving way. 4) having more dysfunction in the involved limb as compared to the uninvolved limb. *Exclusion Criteria* 1) history of fractures or surgeries in the lower extremity. 2) acute musculoskeletal injuries in 3 months before study enrollment.	*Biodex balance system* 1) assessing fluctuation in AP and ML directions. 2) single-limb stance on a balance platform. 3) performing 3, 20s balance. 4) outcome measures: OASI, APSI, and MLSI.

Table 4- 2 Methodological assessment

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	Total
Anguish et al. (2018)	X	X	X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X		X			X	X	22
Bernier et al.(1998)	X	X	X	X		X	X			X			X			X	X	X	X	X	X		X				X	16
Burcal et al.(2017)	X	X	X	X	X	X	X		X	X			X			X	X	X	X	X	X		X		X	X	X	19
Conceição et al.(2016)	X	X	X	X	X	X	X	X	X	X			X			X		X	X	X	X	X	X		X	X	X	21
Cruz-Diaz et al.(2014)	X	X	X	X	X	X	X		X	X			X		X	X		X	X	X			X		X	X	X	19
Elsotohy et al.(2020)	X	X	X	X	X	X	X		X	X			X		X	X		X	X	X			X			X	X	18
Kim et al.(2021) et al	X	X	X	X	X	X	X	X	X	X			X		X	X		X	X	X	X		X			X	X	20
Linens et al.(2016)	X	X	X	X	X	X	X			X			X			X	X	X	X	X			X				X	16
McKeon et al.(2008)	X	X	X	X	X	X	X			X			X			X		X	X	X			X		X		X	16
Mettler et al.(2015)	X	X	X	X	X	X	X			X			X			X		X	X	X			X		X	X	X	17
Sierra-Guzmán et al.(2018)	X	X	X	X	X	X	X		X	X			X		X	X	X	X	X	X	X		X			X	X	20
Sulewski et al.(2012)	X	X	X	X	X	X	X			X			X			X	X	X	X	X	X		X					16
Uzlaşır et al.(2021)	X	X	X	X	X	X	X		X	X			X		X	X		X	X	X	X		X		X	X	X	20
Youssef et al.(2018)	X	X	X	X	X	X	X		X	X			X			X	X	X	X	X	X		X			X	X	19

4.3.2 Assessment of methodological quality

The results of quality assessments via the Downs & Black quality assessment tool for each of the studies are presented in Table 4-2. Eight studies were of good quality [30,31,154,155,157,160,162,163] and six studies were of moderate quality.[29,149,156,158,159,161]

4.3.3 Data Synthesis

Training period

From the 14 included studies, the training periods of the studies were categorized as 6-weeks, 4-weeks, and 1-week respectively for within-subject comparisons. Six studies provided the within-subject comparisons for 6-weeks of balance training (Figure 4-2) and demonstrated a significant effect with a large effect size (SMD = 0.89[0.77, 1.00], $P < 0.01$). Six studies provided the within-subject comparisons for 4-weeks of balance training (Figure 4-3) and though a significant effect was found, the size of the effect was weak (SMD = 0.34[0.26, 0.42], $P < 0.01$). Two studies were classified as 1-week of balance training (Figure 4-4), which revealed a significant but weak effect (SMD = [0.26[0.12, 0.40], $P < 0.01$].

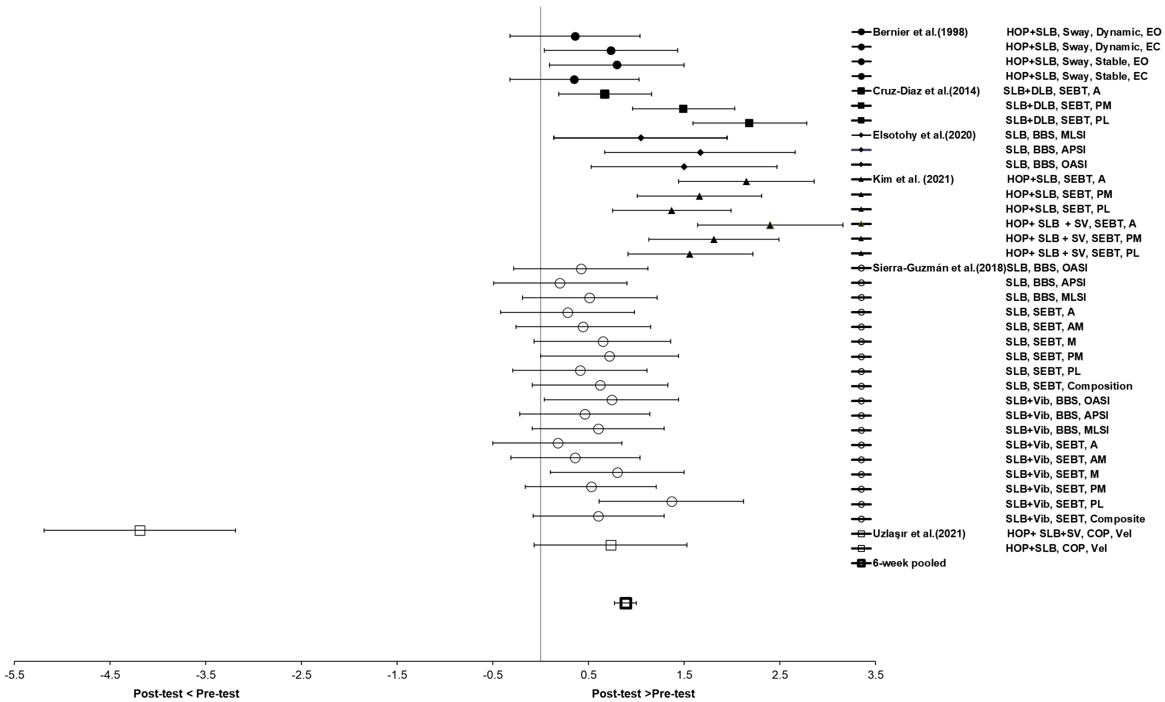

Figure 4- 2 The effects of 6-week balance training.

A anterior, AM anteromedial, APSI anteroposterior stability index, BBS biodex balance system, COP center-of-pressure measurement, EC eyes closed, EO eyes open, HOP+SLB hopping and single-limb balance exercises, HOP+SLB+SV, hopping+single-limb balance+stroboscopic vision, M medial, MLSI mediolateral stability index, OASI overall stability index, PL posterolateral, PM Posteromedial, SEBT star excursion balance test, SLB single-limb balance, SLB+DLB single-limb balance + double-limb balance, SLB+Vib single-limb balance + vibration, Vel velocity.

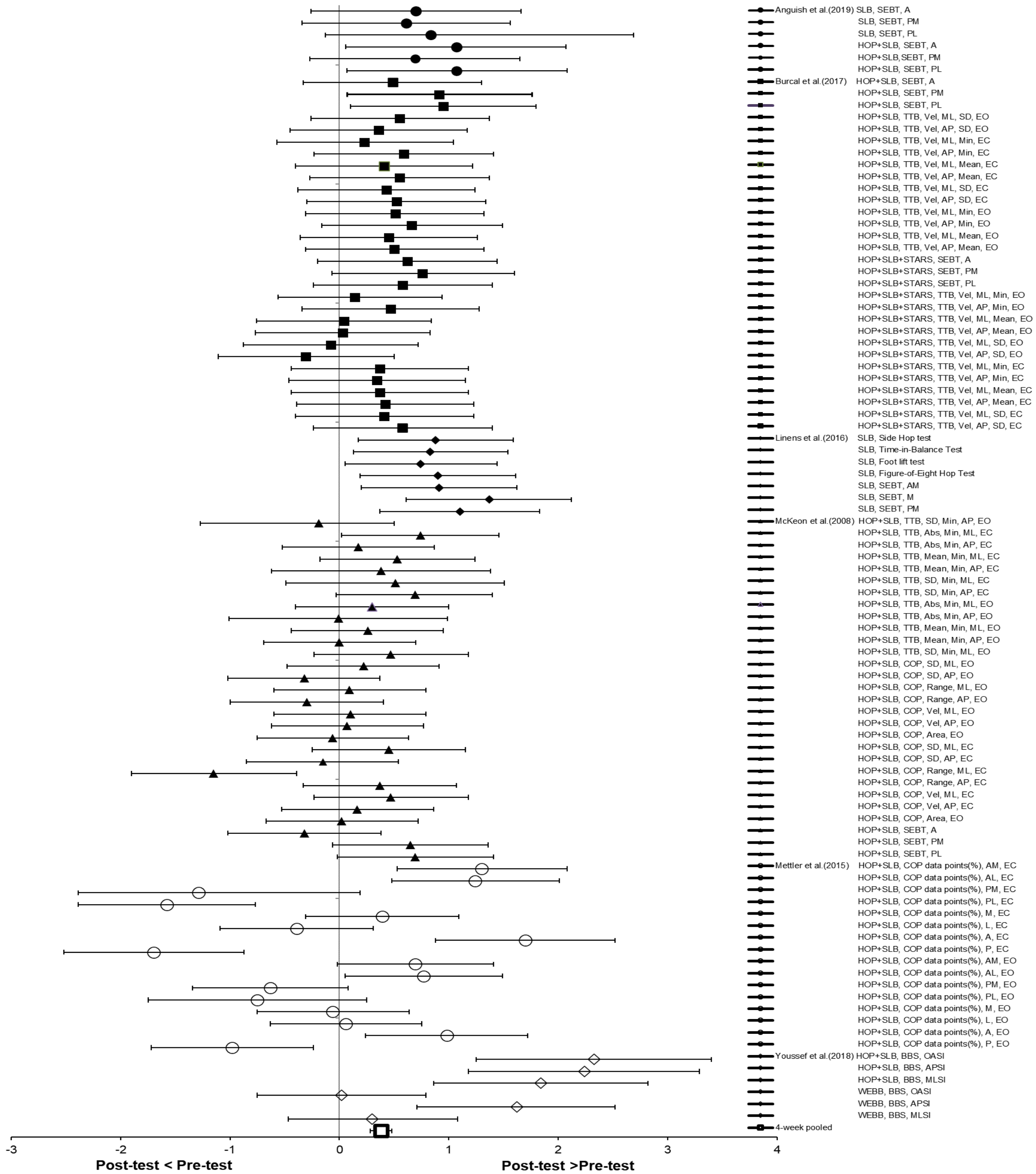

Figure 4- 3 The effects of 4-week balance training.

A anterior, Abs absolute, AL anterolateral, AM anteromedial, AP anterior/posterior, APSI anteroposterior stability index, BBS biodex balance system, COP center-of-pressure measurement, EC eyes closed, EO eyes open, HOP+SLB hopping and single-limb balance exercises, HOP+SLB+STARS, hopping+single-limb balance+sensory targeted ankle rehabilitation strategies, L lateral, M medial, Min minima, ML medial/lateral, MLSI mediolateral stability index, OASI overall stability index, P posterior, PL posterolateral, PM Posteromedial, SD standard deviation, SEBT star excursion balance test, SLB single-limb balance, TTB time-to-boundary, Vel velocity, WEBB weight-bearing exercise for better balance program.

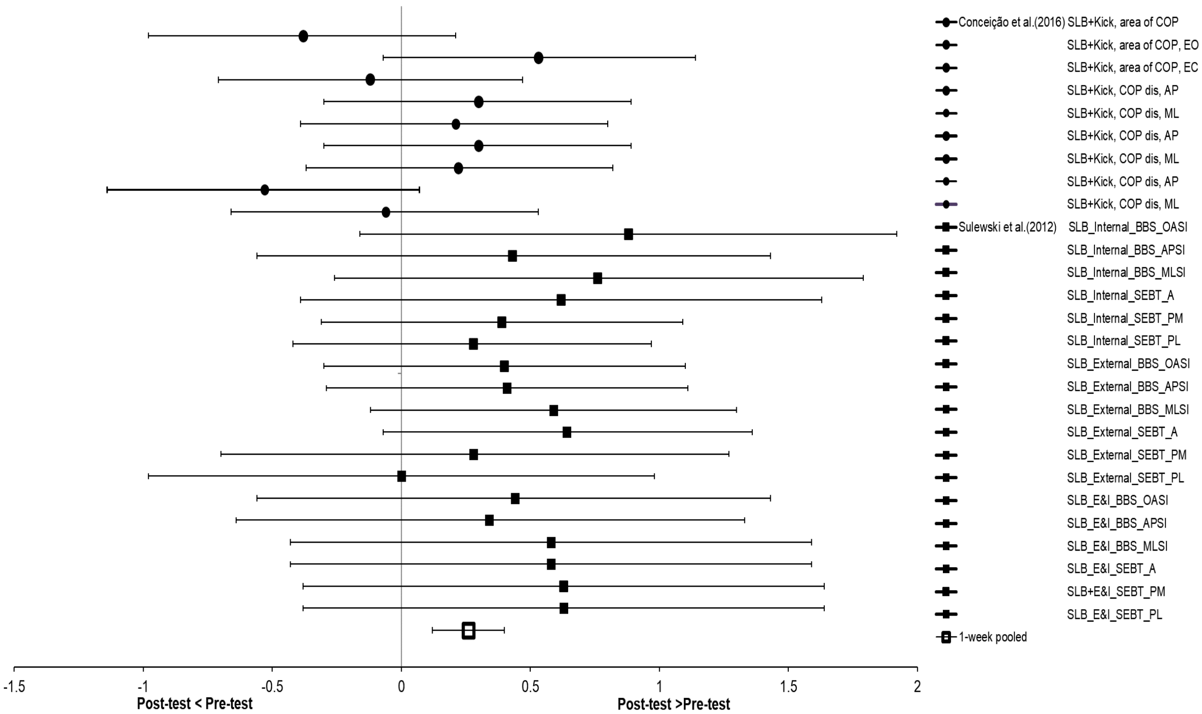

Figure 4- 4 The effects of 1 week balance training.

A anterior, AP anterior/posterior, APSI anteroposterior stability index, BBS biodex balance system, COP center-of-pressure measurement, COP dis center-of-pressure measurement distance, EC eyes closed, EO eyes open, ML medial/lateral, MLSI mediolateral stability index, OASI overall stability index, PL posterolateral, PM Posteromedial, SLB single-limb balance.

Training frequency

A training frequency of 3 sessions per week was identified in 13 of the included studies and 1 session per week in one study for within-subject comparisons. Due to this, the study with 1 session per week was not eligible for meta-analysis. Therefore, the forest plot for the result of 3 sessions/week is presented in Figure 4-5 and demonstrated a significant moderate effect (SMD = 0.51[0.45, 0.57], P < 0.01).

Figure 4- 5 The effects of 3 sessions/week balance training.

A anterior, Abs absolute, AL anterolateral, AM anteromedial, AP anterior/posterior, APSI anteroposterior stability index, BBS biodex balance system, COP center-of-pressure measurement, EC eyes closed, EO eyes open, HOP+SLB hopping and single-limb balance exercises, HOP+SLB+STARS hopping+single-limb balance+sensory targeted ankle rehabilitation strategies, HOP+SLB+SV hopping+single-limb balance+stroboscopic vision, L lateral, M medial, Min minima, ML medial/lateral, MLSI mediolateral stability index, OASI overall stability index, P posterior, PL posterolateral, PM Posteromedial, SD standard deviation, SEBT star excursion balance test, SLB single-limb balance, SLB+DLB single-limb balance + double-limb balance, SLB+Vib single-limb balance + vibration, TTB time-to-boundary, Vel velocity, WEBB weight-bearing exercise for better balance program.

Total training sessions

Based on the results of the review, 6 studies were categorized as 18 sessions (6 weeks * 3 sessions/week) and 6 studies used 12 sessions (4 weeks * 3 sessions/week) of balance training volume. The within-subject comparison results showed that 18 sessions (Figure 4-6) presented a large, significant effect (SMD = 0.89[0.77, 1.00], $P < 0.01$). On the other hand, 12 sessions (Figure 4-7) resulted in a weak, significant effect (SMD = 0.34[0.26, 0.42], $P < 0.01$). Two studies conducted 1 session and 3 sessions individually and therefore, were not included in the meta-analysis.

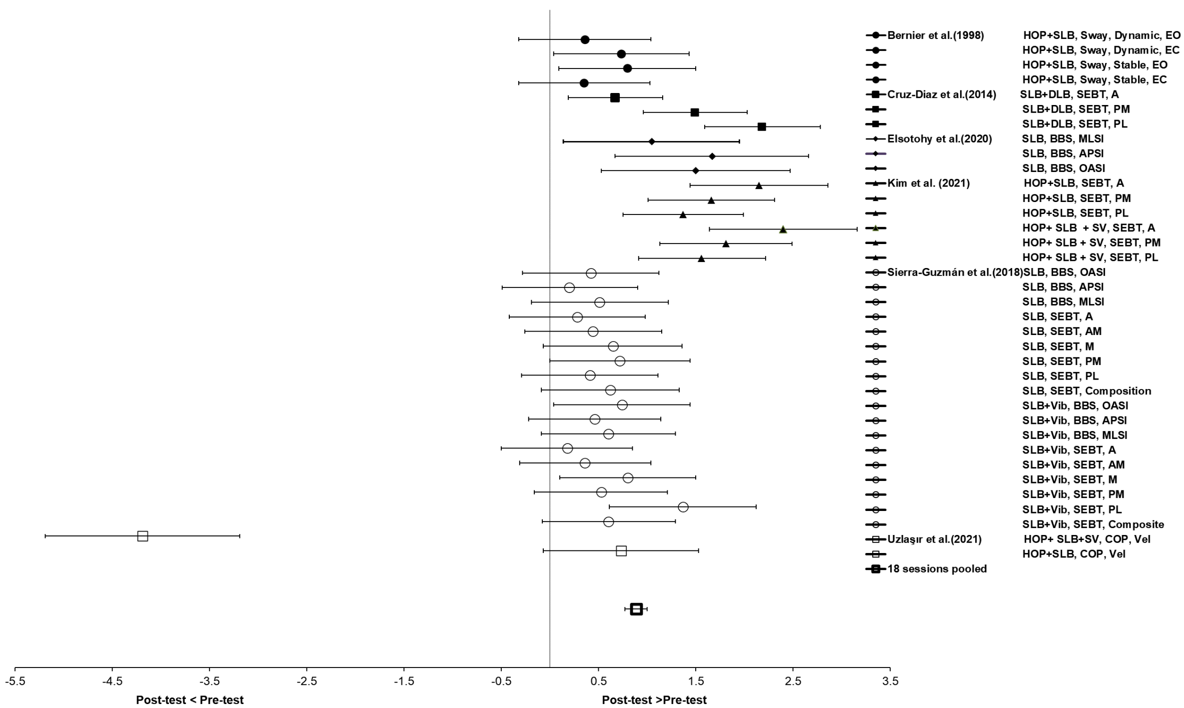

Figure 4- 6 The effects of balance training over a total of 18 sessions.

A anterior, AM anteromedial, APSI anteroposterior stability index, BBS biodex balance system, COP center-of-pressure measurement, EC eyes closed, EO eyes open, HOP+SLB hopping and single-limb balance exercises, HOP+SLB+SV, hopping+single-limb balance+stroboscopic vision, M medial, MLSI mediolateral stability index, OASI overall stability index, PL posterolateral, PM Posteromedial, SEBT star excursion balance test, SLB single-limb balance, SLB+DLB single-limb balance + double-limb balance, SLB+Vib single-limb balance + vibration, Vel velocity.

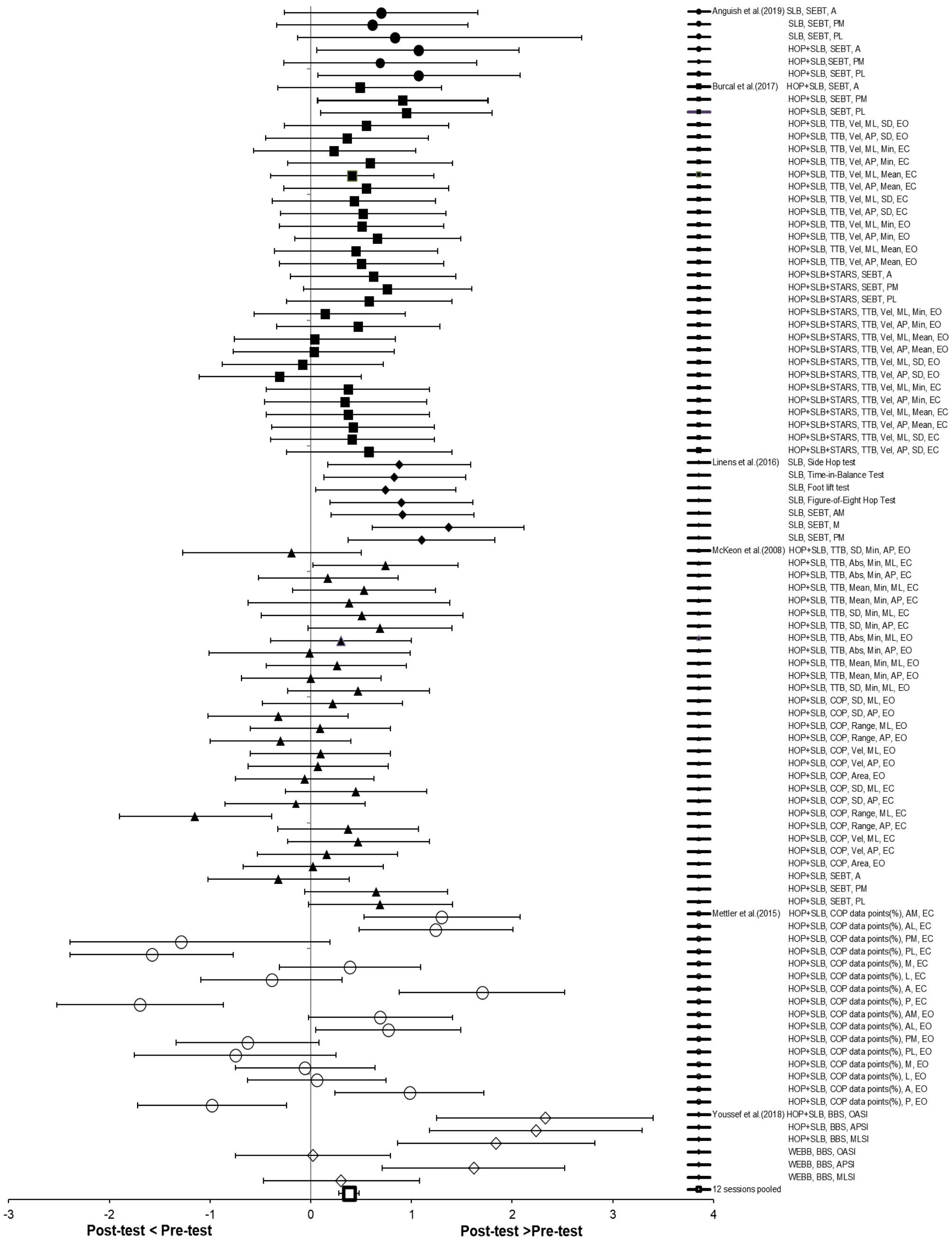

Figure 4- 7 The effects of balance training over a total of 12 sessions.

A anterior, Abs absolute, AL anterolateral, AM anteromedial, AP anterior/posterior, APSI anteroposterior stability index, BBS biodex balance system, COP center-of-pressure measurement, EC eyes closed, EO eyes open, HOP+SLB hopping and single-limb balance exercises, HOP+SLB+STARS, hopping+single-limb balance+sensory targeted ankle rehabilitation strategies, L lateral, M medial, Min minima, ML medial/lateral, MLSI mediolateral stability index, OASI overall stability index, P posterior, PL posterolateral, PM Posteromedial, SD standard deviation, SEBT star excursion balance test, SLB single-limb balance, TTB time-to-boundary, Vel velocity, WEBB weight-bearing exercise for better balance program.

Duration of a single training session

Only 8 studies reported the precise duration of a single session of balance training. Among 8 studies that reported the duration of a single session of balance training, 5 studies conducted 20 mins, 2 studies conducted 30 mins, and 1 study conducted 10 mins of a single session of balance training, respectively. To include the study with 10 mins in the meta-analysis, the studies were categorized for the within-subject comparison as 30 mins and equal to or less than 20 mins. According to the result, 30 mins of balance training (Figure 4-8) revealed no significant effects between pre- and post-test results with a weak effect size (SMD = 0.17[-0.01, 0.35], P = 0.06). The equal to or less than 20 mins exercise (Figure 4-9) also resulted in a weak effect size (SMD = 0.36[0.28, 0.44], P < 0.01), though was found to be significant.

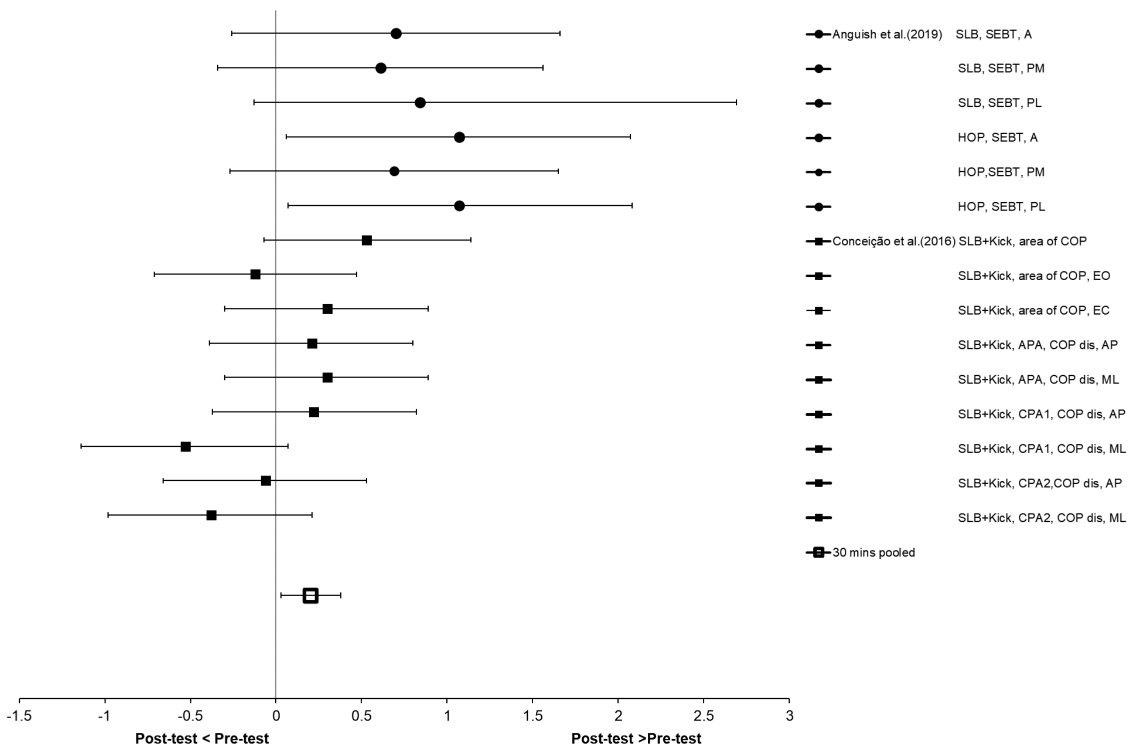

Figure 4- 8 The effects of a single balance training session performed for 30 minutes.

A anterior, AP anterior/posterior, APA anticipated postural adjustment, COP center-of-pressure measurement, COP dis center-of-pressure measurement distance, CPA1 compensatory postural adjustment, CPA2 compensatory postural adjustment 2, EC eyes closed, EO eyes open, HOP hopping exercises, ML medial/lateral, PL posterolateral, PM Posteromedial, SEBT star excursion balance test, SLB single-limb balance.

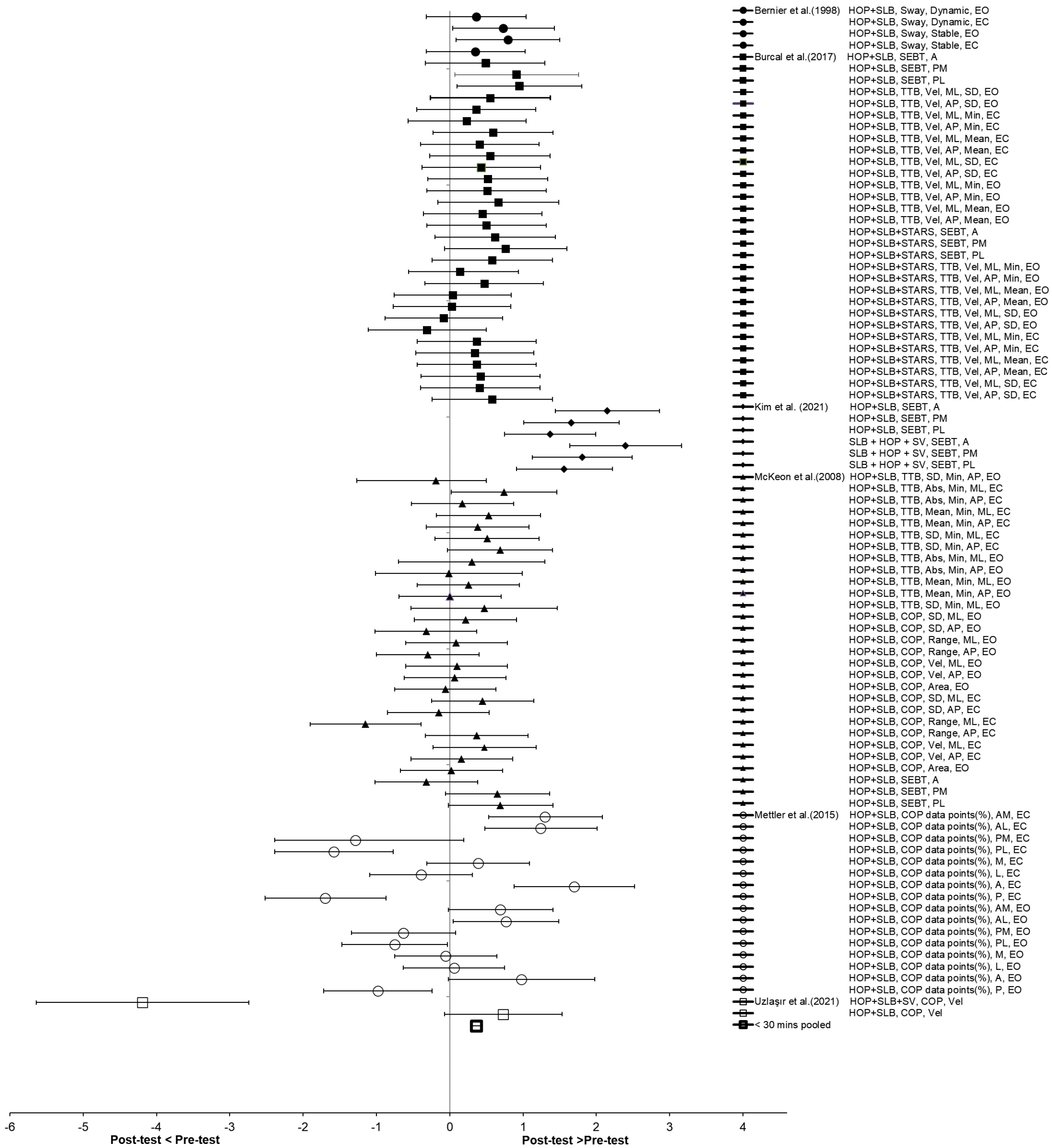

Figure 4- 9 The effects of a single balance training session performed equal to or less than 20 minutes.

A anterior, Abs absolute, AP anterior/posterior, COP center-of-pressure measurement, EC eyes closed, EO eyes open, HOP+SLB hopping and single-limb balance exercises, HOP+SLB+STARS, hopping+single-limb balance+sensory targeted ankle rehabilitation strategies, HOP+SLB+SV, hopping+single-limb balance+stroboscopic vision, Min minima, ML medial/lateral, PL posterolateral, PM Posteromedial, SD standard deviation, SEBT star excursion balance test, TTB time-to-boundary, Vel velocity.

Type of balance training

Sub-analysis for types of balance training was not conducted due to heterogeneity in the intervention protocol across the studies. Our investigation showed that the 13 studies used a combination of static and dynamic balance exercises. There was only one study conducted by Sulewski et al. that implemented only static balance exercises. Common exercises across protocols included single-limb stance, stability exercises with upper or lower body movements, and hopping tasks, often varying in their utilization of unstable surfaces and visual perturbation. The diverse nature of these protocols hindered our ability to categorize them effectively for comparison.

4.4 Discussion

The aim of this systematic review and meta-analysis was to determine the optimal parameters for balance training to enhance balance performance in individuals with CAI. The key findings indicate that the most significant improvements in balance performance for individuals with CAI were achieved with a 6-week training period, involving three sessions per week, totaling 18 training sessions, with each session lasting ≤20 minutes. Notably, a sub-analysis for the type of balance training was not conducted due to the heterogeneity of protocols among the studies. In a previous systematic review, Webster et al. recommended a training period of 4 to 6 weeks and a frequency of 3 to 5 times per week for interventions targeting dynamic postural control in individuals with CAI.[164] Their approach involved calculating effect sizes for each outcome measure in individual studies rather than conducting a meta-analysis. Furthermore, our study provides an updated and comprehensive recommendation for individuals with CAI undergoing balance training, considering eight additional studies were published since Webster et al.'s review.[164]

4.4.1 Training Period

The results of this systematic review and meta-analysis suggest a 6-week balance training period to improve balance performance in individuals with CAI. Previous research has demonstrated a single balance training session elevated spinal reflex excitability modulation and corticospinal excitability in individuals with CAI, indicating immediate improvements in the neurosignature which was not reflected to improved balance performance.[165] However, it was unknown if long-term balance training could optimize these neural effects in the CAI population. There was evidence showing that a brief 2-week balance training program induced neural plasticity in the brain, but the effects were short-lived, indicating the need for a more prolonged training period to induce lasting neuroplastic changes.[166] These outcomes align with recommendations that balance training should be performed for at least 6 weeks to achieve training effects in healthy individuals.[167] In a systematic review, static balance performance on stable platforms improved after 6 weeks of balance training, while there was no discernible improvement after a 4-week intervention.[167] This indicates that sensorimotor adaptation requires a minimum of 6 weeks of balance training.[167] Additionally, Taubert et al. observed an increase in gray matter volume in the prefrontal cortex after 6 weeks of balance training, which was associated with a positive enhancement in balance performance.[166] In summary, these findings collectively indicate that 6-weeks is an optimal balance training period for improving balance performance in individuals with CAI.[165-167] However, it is essential to acknowledge that the studies included in this systematic review and meta-analysis predominantly focused on balance training periods of 1 week, 4 weeks, and 6 weeks. Consequently, future research is necessary to determine the effects of balance training extending beyond 6 weeks to evaluate the potential for further enhancement in balance performance. This investigation would help to identify the possible existence of an inverted U-shaped relationship between training efficacy and training periods for individuals with CAI.

4.4.2 Training Frequency

This systematic review and meta-analysis discovered that the majority of studies employed a frequency of 3 sessions per week, yielding moderate effects. It is crucial to interpret these findings cautiously since the absence of comparable parameters precludes an exploration of the dose-response relationship in this study. Nevertheless, insights from prior systematic reviews indicate that a frequency of 3 sessions per week could be considered optimal for balance training in both young and older adults because it was better than the effects observed with training frequencies of 1, 2, or 4 sessions per week.[34,126] Also, Maughan et al. demonstrated that performing balance training three times a week led to increased balance confidence and static and dynamic balance performance in active older adults when compared to elderly engaging in the training once a week.[168] Given this previous evidence, prescribing a frequency of 3 sessions per week might be reasonable for individuals with CAI in current rehabilitation practices. However, contrasting findings from other studies suggest that training frequency might not be the decisive factor influencing changes in balance performance.[169,170] For instance, one study reported that there were no training effects of balance training when comparing 5 sessions per week for one week to once per week for 5 weeks.[169] Additionally, others have found equivalent improvements in balance performance for soccer players undergoing either 3 sessions per week for 6 weeks or 6 sessions per week for 3 weeks.[170] Thus, it appears that total training volume may be a more crucial parameter than training frequency. Further research is warranted to understand the effects of alternative training frequencies and establish the dose-response relationships for individuals with CAI.

4.4.3 Training Volume (Number of total training sessions)

Our study suggested a total of 18 training sessions was the most effective training volume to elicit improvement in balance performance in individuals with CAI, as compared to a total of 12 training sessions. Like the previous outcome, however, this needs to be very cautiously interpreted due to the lack of variety in training volume. Despite the limitation, a total of 18 sessions seems to be meaningful balance training parameters based on the previous studies' outcomes.[34,170] For example, Lesinski et al. indicated that a total of 16 to 19 training sessions was the optimal training volume to improve static balance performance in healthy young adults when compared to the effects of performing less than 16 and more than 19 total training sessions.[34] On the other hand, a systematic review and meta-analysis revealed that a total of 36 to 40 training sessions was the optimal balance training parameter for older adults, expecting that there would be a need for a greater number of total training sessions in the older population due to age-related deficits in neuromuscular function.[126] Given that sensorimotor deficits in individuals with CAI can be persistent and worsen with age,[171,172] and studies in our systematic review studies investigated mostly young people with CAI (Pooled averaged age, 23.72 year-old), performing more than 18 total training sessions might be particularly beneficial for older adults with CAI, which means aging should likely be considered when determining the optimal balance training volume.

4.4.4 Training Volume (Duration of a single training session)

Our analysis indicated that a duration of less than or equal to 20 minutes for a single balance training session was optimal for individuals with CAI. While further investigation is required to determine the true optimal duration of a single balance training session, conducting less than or equal to 20 minutes of a single balance training session appears to be advantageous.[126] A previous study found that balance training was most effective for healthy young adults when performed for 11 to 15 minutes.[34] The same author suggested that older adults might require a comparable duration per training session as healthy young adults, but the optimal range was reported that 30 to 45 minutes per balance training session including 10 to 15 minutes of warming-up was the most effective.[126] Although the reasons why a shorter training duration was more effective in both CAI populations and healthy individuals remain unclear, it is plausible that a longer session could potentially impact patients' compliance with rehabilitation negatively. Rehabilitation guidelines for individuals with ankle sprains or CAI typically recommend three or four types of exercises, including balance training, range of motion, ankle strengthening, and functional rehabilitation.[173] Consequently, prolonging the duration of balance training may extend the overall rehabilitation protocol, creating a potential obstacle for patients in adopting a consistent therapeutic exercise routine.[174] Given the significance of adherence to rehabilitation, implementing a manageable duration of ≤20 minutes is likely to be beneficial for those with CAI.[175]

4.4.5 Type of balance training for individuals with CAI

The present study suggested a limited understanding of the effects of various types of balance training on balance performance. Our investigation observed that the majority of balance training protocols involved a combination of static and dynamic exercises, with considerable variation in the specific exercises employed across studies. Although a meta-analysis was not feasible in our study, a prior review indicated that static balance function was most frequently assessed in individuals with CAI, followed by dynamic balance assessment.[176] This suggests that the primary focus of rehabilitation for individuals with CAI targets to improve both static and dynamic balance functions.[175] Also, a recent clinical practice guideline provided a suggestion that clinicians are required to not only assess static and dynamic postural deficits but also address both impairments in the rehabilitation of individuals with CAI.[177] Given the lack of evidence comparing the effects of different types of balance training and the evidence supporting successful outcomes with combined static and dynamic balance exercises, a balance training protocol incorporating both types of balance training can be recommended as the optimal type of balance training protocol for individuals with CAI. In addition, assessing the effects of balance training including diverse types of exercises requires proper balance measurement that is responsive to the interventions.[126] However, some studies in our review included balance measurements that were not trained during balance training. For example, Conceição et al. evaluated balance performance with eyes closed which was not introduced to their participants during the training.[155] Also, Elsotohy et al. only assessed static balance performance following the intervention incorporating static and dynamic balance exercises.[156] This may not allow the investigators to determine if balance tests can detect the changes in balance performance, suggesting that selection of proper balance assessment tools is imperative in designing studies investigating the effects of balance training on balance performance.[178]

4.5 Clinical implications

Balance deficits are one of the most common sensorimotor deficits in individuals with CAI, causing balance training to be the crucial rehabilitation protocol. However, the large heterogeneity of balance training parameters can lead clinicians to find it difficult to seek the best therapeutic exercises for their patients with CAI. Providing evidence-based guidelines through systematic review and meta-analysis regarding the optimal balance training parameters could empower clinicians to prescribe a rehabilitation protocol that yields the best outcomes which is improved balance function in those with CAI. This, in turn, may facilitate individuals with CAI in returning to their daily activities without persistent symptoms, potentially transforming them into copers who fully recover from the residual symptoms and avoid the risk of recurrent ankle sprains.

4.6 Limitation

The primary limitation of this systematic review and meta-analysis is the lack of diversity in balance training parameters across the included studies. Performing meta-analysis for only one or two variables in each balance training parameter elicited challenges in determining the optimal dose of balance training for individuals with CAI. This led us to shift our focus to providing recommendations for each training parameter that yielded the most favorable effects. It is imperative for future studies to explore the effects of balance training with additional dosages to determine the true optimal balance training parameters for people with CAI. Another limitation included the large heterogeneity of inclusion and exclusion criteria, balance measurements, and detailed balance training protocol across the studies, creating challenges to performing meta-analysis. Lastly, only 8 out of 14 studies reported the duration of a single training session, resulting in the categorization into two groups (30 minutes vs ≤20 minutes). Future research should provide detailed information about training interventions to conduct more comprehensive meta-analysis.

4.7 Conclusion

The aim of this systematic review and meta-analysis was to determine the most effective balance training parameters for individuals with CAI. The current evidence suggested that the optimal balance training for those with CAI needs to be performed at least 6 weeks, with sessions conducted 3 days per week, totaling 18 sessions, and each session lasting ≤20 minutes. The limited diversity in balance training parameters across the included studies did not lead authors to identify the true optimal dose of balance training for CAI populations. Although there was about a 10-year difference between the previous review and the current study, the recommended balance training dose for individuals with CAI has not been changed dramatically. However, this does not imply that the suggested dose of balance training was appropriately defined due to the lack of evidence, meaning that further research should explore different training periods, frequencies, and volumes beyond previous recommendations to establish the true dose-response relationship for various balance training parameters in individuals with CAI.

CHAPTER 5

THE EFFECTS OF 6-WEEKS OF BALANCE TRAINING ON CORTICOSPINAL EXCITABILITY, SPINAL REFLEXIVE EXCITABILITY MODULATION, AND BALANCE PERFORMANCE IN INDIVIDUALS WITH CHRONIC ANKLE INSTABILITY

5.1 Introduction

Acute ankle sprains are a significant risk for people participating in sports activities, with lateral ankle sprains (LAS) being the most prevalent type of this injury.[43] Despite the higher incidence rate, LAS was thought of as a minor injury that required minimal treatment and resolved quickly.[45] However, this misconception of this injury may lead to the impairments becoming persistent within the ankle joints, which can cause repeated injury in individuals with chronic ankle instability (CAI).[4] Balance deficits are one of the most common, but severe deficits since they can be closely associated with negative consequences such as recurrent ankle sprains and increased risk of falling. It is imperative that these deficits are targeted in patients with ankle sprain injury to prevent long-term health impacts. [71,179]

Traditional perspectives on balance deficits in individuals with CAI began with the idea that peripheral sensory deficits after the initial ankle sprain cause balance impairments.[26] Specifically, joint receptors sending sensory input to the CNS can be damaged after the injury resulting in somatosensory deficits within the ankle joint, and leading to diminishing postural control ability of CAI patients.[85] However, this sensory perspective has been challenged by newer evidence suggesting that there may be impairments in motor mechanisms causing balance deficits in those with CAI.[4] For example, McCann et al. demonstrated hip strength deficits in people with CAI as compared to people without a history of ankle sprains and copers who have had full recovery following ankle sprains, which was associated with impaired balance performance in those with CAI.[70] Also, Sousal et al. presented that there were bilateral deficits in proprioceptive function exhibited in individuals with unilateral CAI.[100] Along with the evidence that cannot be explained solely by the feedback perspectives, the CNS may also rely on cutaneous sensory receptors after damage to joint receptors to maintain balance.[81] Thus, feedforward mechanisms, motor commands from the CNS, also need to be considered to describe balance deficits in individuals with CAI.

Hoffmann-reflex (H-reflex) has been suggested as a technique to measure spinal reflexive excitability by delivering electrical stimulation to the target nerve.[112] Using this method, the ability of the CNS to recruit alpha motor neurons from the spinal cord has been assessed for individuals with CAI, representing the reduced spinal reflexive excitability of the ankle stabilizers such as soleus and fibularis longus muscles.[10] Furthermore, Kim et al. demonstrated reduced modulation of spinal reflexive excitability in the soleus as people with CAI changed testing positions from prone to double-limb standing and double-limb standing to single-limb standing.[18] This suggests that the CNS may have diminished ability to inhibit the spinal reflex to transfer balance control to the supraspinal level as there were increased postural demands in those with CAI.[18] The supraspinal balance control can be achieved by the active involvement of the motor cortex providing co-contraction of the soleus and tibialis anterior to counteract postural sway to maintain upright posture.[21] However, it was observed that there was reduced corticospinal excitability measured by transcranial magnetic stimulation (TMS) while performing single-limb standing, meaning that individuals with CAI may rely less on supraspinal control to maintain balance as compared to healthy individuals.[55] Collectively, CNS alterations represent a modified neurosignature that causes balance deficits in individuals with CAI. Thus, addressing the neurosignature is a crucial rehabilitation target for this population.[4]

Studies 1 and 2 provided evidence that balance training is a valuable intervention for individuals with CAI. Specifically, the result of study 1 suggested that a single session of balance training resulted in improved modulation of spinal reflexive excitability as participants changed testing posture from prone to single-leg standing. Furthermore, there was a significant improvement in CSP in the balance training group when compared to the control group after balance training. These results suggest that a single session of balance training could begin to shift motor control from spinal to supraspinal centers. Study 2 indicated that balance training is most effective for improving balance function of individuals with CAI when conducted for 6 weeks, 3 sessions per week, and 20 mins per session. Previously, Sefton et al. demonstrated the effect of 6-weeks of balance training on spinal reflex excitability as well as improved balance function in individuals with CAI.[20] However, no previous study has investigated the effects of balance training on the modulation of spinal reflex excitability and corticospinal excitability in people with CAI. Therefore, the purpose of study 3 was to investigate if balance training conducted with optimal parameters can improve corticospinal excitability, spinal reflexive excitability modulation, and balance function in individuals with CAI.

5.2 Method

5.2.1 Study design

We used a randomized controlled trial design. The two independent variables were group (BAL and CON) and time (baseline and post-training). Dependent variables involved balance function, spinal-reflexive excitability modulation, and corticospinal excitability. This study was approved by the institutional review board of the Old Dominion University.

5.2.2 Participants

A total of 30 adults (15 BAL, 15 CON) were recruited to participate in this study. The sample size was estimated using the mean differences and standard deviations from spinal reflexive excitability (H:M ratio) modulation data reported by Mynark et al.[23] We conducted an a priori sample size estimate using G*Power 3.1.9.7 software. The predetermined alpha level of 0.05 and estimated power of 0.80 allowed us to estimate 12 participants in each group (24 total) were needed to detect group differences with an effect size of at least 0.80. However, in order to ensure sufficient sampling, we increased the recruiting rate by 25%, which resulted in 15 participants in each group. Participants were recruited from Old Dominion University as well as within the surrounding Norfolk community. Participants from Old Dominion University were verbally contacted during classes and by the investigators. Also, volunteers were recruited via campus flyers. The randomization sequence was created by an independent investigator who prepared a sealed envelope to determine to which group the subject would be allocated. All participants were between 18 to 40 years old with CAI as defined by the International Ankle Consortium.[44] The selection criteria for CAI included the following conditions: 1) previous history of a significant ankle sprain that caused pain and swelling (initial ankle sprain is required to occur at least 12 months prior to study enrollment; the most recent ankle sprain must occur at least 3 months prior to study enrollment); 2) at least one recurrent episodes of "giving way," "feeling of instability," or repeated ankle sprains in the six months before the study enrollment; 3) scored ≥5 on the Ankle Instability Instrument (AII), ≥11 on the Identification of Functional Ankle Instability (IdFAI), and ≤24 on the Cumberland Ankle Instability Tool (CAIT). If participants had bilateral CAI, an independent investigator who conducted the screening procedure selected a limb revealing worse grade assessed via the patients-reported outcomes.

Participants were excluded if they had a history of acute head or lower extremity injuries within 3 months before testing and any history of lower extremity fracture or surgery. Also, participants were not eligible for this study if they had any limitations for the corticospinal excitability test. A guideline represented by the National Institutes of Neurological Disorders and Stroke was utilized to screen the participants.[139] The guideline consists of 1) history of heart disease, stroke, cardiac pacemaker or implanted cardiac defibrillator, epilepsy or seizures, migraines or severe headaches, cancer in brain or leg muscles, diagnosed psychiatric disorder, and intracranial metallic clips; 2) currently pregnant or breastfeeding; 3) currently taking pain-relieving medication or neuroinhibiting or stimulating medication; 4) metal implants anywhere in the head, neck, or shoulders (excluding dental work); 5) personal or familial history of seizures or epilepsy; 6) ocular foreign objects or cochlear implants; 7) implanted brain stimulators, aneurysm clips, implanted medication pumps, intracardiac lines, or cardiac pacemakers; 8) history of or is currently abusing illicit drugs or alcohol or is currently withdrawing from any substance; 9) use of any medication that may lower seizure threshold (including, but not limited to, tricyclic antidepressants, neuroleptic agents, Baclofen, and Tramadol); and 10) history of serious intracranial pressure.[139]

5.2.3 Procedure

Researchers conducted baseline measurements of patient's corticospinal, spinal reflexive excitability, and balance function on the first day. Then, BAL participated in 6-weeks of balance training starting on the first visit, while CON did not perform any intervention and was asked to maintain their physical activity levels. BAL were asked to visit the lab 3 times a week to perform balance training. The post-test was conducted after the last balance training session to identify the effect of balance training. Briefly, the testing procedures were completed in the following order: 1) corticospinal excitability (1st day); 2) spinal-reflexive excitability modulation (1st day); 3) static balance testing (1st day); 4) dynamic balance testing (1st day); 5) 6-week of balance training (starts 1st day); 6) post-testing (within a week after the last training). For baseline and post-testing, participants were asked to avoid caffeine and alcohol 24 hours prior to the tests.

Corticospinal excitability

Corticospinal excitability of the soleus was measured while participants maintained single-leg stance. The investigator cleaned the skin over the soleus belly using fine sandpaper and isopropyl alcohol. Then, two pregelled Ag/AgCl electrodes were attached 1.75cm apart over the soleus of the testing limb. A ground electrode was placed on the ankle bone of the testing limb. The EMG signal was converted from analogue to digital with a 16-bit converter (MP160WSW, Biopac Systems, Inc., Goleta, CA), and then sampled at 2000 Hz and amplified at a gain of 1000 (EMG100C, Biopac Systems, Inc.).[16]

Transcranial magnetic stimulation (TMS) was delivered to the primary motor cortex of each participant using a Magstim Super RAPID^2 PLUS^1 System (Magstim C, LTD., Wales, UK). Dependent variables from the TMS included active motor threshold (AMT), motor-evoked potential (MEP), and cortical silent period (CSP). Before stimulation, a swim cap was worn by participants to determine an approximate location on the motor cortex that can activate the soleus of the testing limb. A line was drawn to bisect the hemispheres sagittally and another line was drawn to connect the external auditory meatuses. The intersection of these lines with a 1 cm by 1 cm grid played a role in coordination on the head, which allowed us to identify the appropriate location of the primary motor cortex. A Double Cone Coil (Magstim Company, Wales, UK) was placed over the head for stimulation. Then, 40% of the maximum stimulator output was provided three times to multiple points on the primary motor cortex by moving the coil systematically by 1 cm intervals. From the output of the MEP, the spot that generates the highest EMG amplitudes with consistency was identified as the "hotspot". Then, the coil was fixed over the point.

To acquire the AMT, three peak amplitudes of the background EMG signal were averaged while participants conducted the single-leg balance without magnetic stimulus.[16] From the result, 2 standard deviations plus the averaged amplitude was a cut-off threshold. AMT was the lowest stimulator intensity to result in 4 out of 8 stimulations whose peak-to-peak amplitudes exceeded the cut-off threshold. A higher AMT suggests reduced corticospinal excitability. Once the AMT was acquired, 100% and 120% of AMT were delivered to the hotspot to achieve MEP. A higher MEP indicated greater corticospinal excitability. CSP was measured from the time starting from the end of MEP to a return of baseline EMG signal. This was assessed in both 100% and 120% of AMT. A longer CSP suggests greater corticospinal inhibition of the calf muscle. Like MEP, 5 CSPs were recorded during the test.

Spinal reflexive excitability modulation

Spinal reflexive excitability modulation was measured while the participants were in the prone position and a single-leg stance. For the prone position, participants were instructed to relax their ankle joints so that the soleus muscle was not stretched, preventing the influence of the stretch reflex of the soleus on the results. As a first step, the spinal reflexive excitability during prone and single-leg balance was determined using a ratio of the Hoffmann-reflex (H-reflex) to the muscle response (M-wave) (H:M).[18] This ratio indirectly measured the number of motor neurons that can be excited through the spinal reflex loop compared to the total available alpha motor neuron pool.

The two recording electrodes and one ground electrode used for corticospinal excitability measurements remained in the same place for spinal reflexive measurements. The

EMG signal was converted from analogue to digital with a 16-bit converter (MP160WSW, Biopac Systems, Inc., Goleta, CA), and then sampled at 2000 Hz and amplified at a gain of 1000 (EMG100C, Biopac Systems, Inc.). H-reflex and M-wave were elicited by BIOPAC stimulator module (STIM100A, BIOPAC Systems, Inc., Goleta CA, USA) with a 2mm shield disk stimulating electrode. The electrode was attached to the superior portion of the popliteal fossa to stimulate and deliver a series of 1-ms square-wave pulses to the tibial nerve. The stimulation was progressively increased with 0.2V until the maximal H-reflex and M-wave were obtained. Five the maximal H-reflex and M-wave were recorded to calculate the H:M ratio.

The modulation of H-reflex was measured by using percentage changes in H:M ratio from the prone position to single-leg balance. Five modulation trials were recorded and averaged for the final analysis. The following formula was employed to calculate the modulation of H-reflex.[18,165]

$$\frac{Prone - Single\ leg\ standing\ H{:}M\ Ratio}{Prone\ H{:}M\ ratio} \times 100$$

Static balance function (TTB)

Balance performance was measured via a force platform (AccuSway Plus, AMTI, Watertown, MA, USA) and single-leg standing. The force platform was connected to the Balance Clinic software (AMTI, Watertown, MA, USA) to acquire the center of pressure (COP) data. Balance function testing included two visual conditions (Eyes open vs Eyes closed) while participants maintained single-leg balance on the involved limb with barefoot. Each condition was conducted in three 20-second trials. Averaged COP maximum velocity in anterior-posterior and medial-lateral directions was utilized for the final data analysis. MATLAB (The MathWorks, Inc., Natick, MA, USA) code was used to calculate the time-to-boundary (TTB) minimum in anterior-posterior and medial-lateral.[73]

Dynamic balance function (SEBT)

An independent investigator who was a certified athletic trainer and supervised balance training measured dynamic balance performance. To measure the dynamic balance function, we utilized the simplified Star Excursion Balance Test (SEBT).[88] Participants were instructed to maintain single-leg balance barefoot while they reached with their non-standing limb for maximum distance in three directions: anterior (ANT), posteromedial (PM), and posterolateral (PL). While reaching, they were required to maintain their stance heel on the ground and their hands on their hips. Four practice trials were conducted followed by three actual test trials in each direction. The order of direction was decided randomly. Reach distances were normalized to leg length which was measured from the anterior superior iliac spine to the most distal aspect of the medial malleolus (cm). Thereby, the averaged three reaching distances were divided by the leg length.

Balance training

Table 5-1 and Figure 5-1 describe the protocol of balance training. Participants underwent a 6-week balance training protocol modified from that described by McKeon et al.[29] Participants underwent clinician-supervised balance exercise 3 times a week for approximately 20 minutes per session. Participants were instructed to wear stroboscopic glasses (Nike SPARQ Vapor Strobes, Nike Inc, Beaverton, OR, USA) while they performed balance training. The stroboscopic glasses can provide intermittent visual perturbation with rapid cycles between opaque and transparent for 100 ms periods.

Table 5- 1 Balance training protocol

	Exercises in rehabilitation	Progression

Single-leg balance with EO	Single-leg balance with involved limb (3 sets, 60s)	1. Increasing standing time to 90s 2. Changing base of support to a foam pad for 30s 3. 60s 4. 90s
Single-leg balance with EC	Single-leg balance with involved limb (3 sets, 30s)	1. Increasing standing time to 60s 2. Increasing standing time to 60s 3. Changing base of support to a foam pad for 30s 4. 60 s 5. 90 s
Hop and stabilization	Single-leg hop to target distance (5 reps, 18 in)	1. Increasing target distance to 27 in 2. Increasing target distance to 36 in
Hop and stabilization with reach	Single-leg hop to target distance and reach floating leg to where participants hop from (5 reps, 18 in)	Time (30s, 60s, and 90s) Base of supports (secured floor and a foam pad)

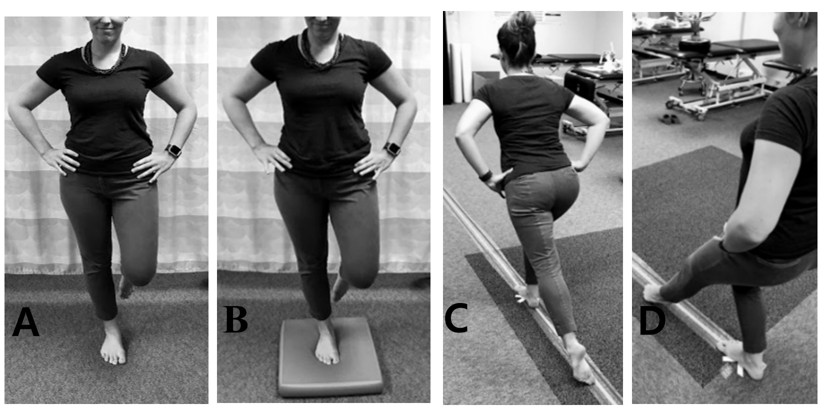

Figure 5- 1 Single-leg balance & Single-leg hops (A, stable; B, unstable; C, anterior hop & posterior reach; D, posterior hop & anterior reach)

For single-leg balance training, participants were instructed to maintain the quiet standing position with eyes open and eyes closed conditions. The eyes open condition started with 60-second of single-limb balance on the hard floor. As participants completed the exercise without errors, the level of difficulty progressed to 30-second balance on a foam pad, which was also progressed by increasing time (60s and 90s). Single-limb balance training with eyes closed condition was started with 30-second quiet standing on a hard floor, and the progression was the same as the protocol of eyes open condition. Each exercise was conducted in three trials and a 60-second rest between trials. Errors included 1) touching the floor with an untrained limb; 2) excessive trunk motion (> 30 degrees of lateral flexion); 3) hands off from the trunk; and 4) bracing the non-standing limb against the standing limb. When the errors were made by participants, they were instructed to repeat the trial.

For hop and stabilizing training, participants were instructed to hop to the target distance and stabilize their body sway. This activity was conducted in four paired directions: anterior/posterior, medial/lateral, anteromedial/posterolateral, and posteromedial/anterolateral. Five repetitions for each direction were performed by participants. If they completed the activities without errors, the activities progressed with increased target distance (18, 27, and 36 inches). The hop and stabilization plus reaching exercises were performed by having participants reach their limb to the target where they hop from. The process and progression of the exercise were the same as the hop and stabilizing exercise. The errors consisted of the following: 1) touching the floor with an untrained limb; 2) excessive trunk motion (> 30 degrees of lateral flexion); 3) hands off from the trunk; 4) bracing the non-standing limb against the standing limb; and 5) missing the target. When the errors were made by participants, they were instructed to repeat the trial.

5.2.4 Statistical analysis

Separate 2x2 mixed-model ANOVAs were used to determine the effect of group (BAL and CON) and time (baseline and post-training) on each dependent variable. When a statistically significant interaction or group main effect was identified, we conducted the Bonferroni post hoc test for pairwise comparisons. Also, Cohen's d effect sizes (small = 0.2-0.49, moderate=0.5-0.79, large >0.8) with 95% confidence intervals were computed to determine the magnitude of significant differences.[144] All statistical significance was set a priori at P<0.05. All statistical analyses were performed through IBM SPSS statistics, version 24 (IBM Corporation, Armonk, NY).

5.3 Result

Table 5-2 presents the demographic characteristics of participants. Two participants assigned to CON withdrew after enrolling. One participant did not want to undergo procedures after visiting the lab, while the other was unable to endure TMS because of undesirable feelings. Table 5-2 presents the means and standard deviation for all outcome measures.

Table 5- 2 Participant demographic

	Mean (SD)		
Dependent Variable	BAL(n=15)	CON(n=13)	P-Value
Age, y	21.00 (3.29)	24.08 (3.95)	0.30
Height, cm	167.29 (10.52)	165.79 (7.64)	0.67
Mass, kg	72.99 (17.70)	65.66 (8.64)	0.18
Previous ankle sprains, No.	3 (2.70)	3 (2.45)	1.00
AII (# of Yes)	5.33 (1.23)	5.87 (3.13)	0.30
IdFAI	15.67 (3.13)	18.33 (4.62)	0.08
CAIT	16.56 (4.40)	18.54 (5.85)	0.34

Table 5- 3 Mean and standard deviation for outcome measures

Dependent Variable	Group Mean (SD) Pre-test	Post-test
TMS variables		
AMT (%)		
BAL	51.44 (13.86)	54.38 (11.12)
CON	46.54 (8.10)	47.92 (11.13)
MEP_{100} (mv/mv)		
BAL	0.21 (0.10)	0.31 (0.23)
CON	0.18 (0.08)	0.18 (0.06)
MEP_{120} (mv/mv)		
BAL	0.22 (0.10)	0.27 (0.24)
CON	0.21 (0.13)	0.19 (0.08)
CSP_{100} (ms)		
BAL	100.67 (38.78)	72.40 (30.42)
CON	81.15 (47.12)	80.80 (40.48)
CSP_{120} (ms)		
BAL	102.43 (36.03)	73.38 (31.59)
CON	86.60 (36.46)	88.82 (47.97)
H-reflex variables		
H:M ratio in prone		
BAL	0.61 (0.19)	0.62 (0.20)
CON	0.64 (0.16)	0.59 (0.18)
H:M ratio in single-leg standing		
BAL	0.46 (0.20)	0.30 (0.12)
CON	0.47 (0.16)	0.43 (0.14)
H:M ratio modulation (%)		
BAL	29.51 (35.16)	43.90 (21.77)
CON	27.43 (16.22)	26.99 (15.84)
Static Balance function variables		
COP Maximum velocity in anterior to posterior direction with EO (cm/s)		
BAL	6.36 (3.24)	4.61 (1.53)
CON	4.55 (1.42)	4.57 (1.04)
COP Maximum velocity in anterior to posterior direction with EC (cm/s)		
BAL	12.40 (5.17)	9.71 (3.46)
CON	10.31 (2.98)	11.41 (7.33)
COP Maximum velocity in medial to lateral direction with EO (cm/s)		
BAL	7.29 (2.17)	5.54 (1.92)
CON	5.18 (1.37)	5.02 (1.35)
COP Maximum velocity in medial to lateral direction with EC (cm/s)		
BAL	13.27 (3.29)	11.40 (2.85)
CON	10.28 (2.53)	11.04 (2.78)
TTB absolute minimum in anterior to posterior direction with EO (s)		
BAL	2.64 (1.20)	3.15 (1.31)
CON	2.89 (0.91)	2.98 (0.94)
TTB absolute minimum in medial to lateral direction with EO (s)		
BAL	0.94 (0.31)	1.04 (0.34)
CON	1.03 (0.26)	1.10 (0.15)

TTB absolute minimum in anterior to posterior direction with EC(s)		
BAL	1.09 (0.33)	1.35 (0.39)
CON	1.24 (0.39)	1.21 (0.48)
TTB absolute minimum in medial to lateral direction with EC(s)		
BAL	0.40 (0.09)	0.47 (0.11)
CON	0.50 (0.27)	0.47 (0.11)
Dynamic Balance function variables		
Star Excursion Balance Test Anterior direction		
BAL	60.65 (7.32)	62.22 (5.08)
CON	62.37 (6.23)	62.43 (4.85)
Star Excursion Balance Test Posteromedial direction		
BAL	82.35 (9.94)	86.31 (8.78)
CON	82.41 (9.66)	84.16 (9.63)
Star Excursion Balance Test Posterolateral direction		
BAL	77.35 (7.52)	82.68 (7.32)
CON	77.20 (11.89)	78.99 (11.99)

5.3.1 TMS variables

AMT

There was no significant group by time interaction ($F_{(1, 26)}$ = 0.215, P = 0.65), group main effect, ($F_{(1, 26)}$ = 2.106, P = 0.16), or time main effect ($F_{(1, 26)}$ = 1.662, P = 0.21) for AMT.

MEP_{100}

There was no significant group by time interaction effect, ($F_{(1,26)}$ = 2.593, P = 0.12), group main effect, ($F_{(1, 26)}$=2.975, P=0.10), or time main effect ($F_{(1, 26)}$ = 3.672, P = 0.07) for MEP_{100}.

MEP_{120}

There was no significant group by time interaction effect, ($F_{(1,26)}$ = 1.227, P = 0.27), group main effect, ($F_{(1, 26)}$=0.741, P=0.40), or time main ($F_{(1, 26)}$ = 0.358, P =0.56) for MEP_{120}.

CSP_{100}

There was a significant group by time interaction for CSP_{100} ($F_{(1, 26)}$ = 21.717, P = 0.01). A large effect size (*d*=1.12 [0.32, 1.85]) indicates CSP_{100} was significantly reduced in BAL after balance training while there was no significant difference in CSP_{100} of CON between baseline and post-testing (P=0.98).

CSP_{120}

There was a significant group by time interaction for CSP_{120} ($F_{(1,26)} = 19.634$, $P < 0.01$). BAL exhibited a large effect (*d* =0.83 [0.09, 1.58]) for CSP_{120} after balance training while there was no significant difference in CSP_{120} of CON between baseline and post-testing (P = 0.73).

5.3.2 H-reflex variables

H:M in prone

There was no significant group by time interaction effect, ($F_{(1,26)} = 1.931$, P = 0.18), group main effect, ($F_{(1, 26)} = 0.200$, P = 0.96), or time main ($F_{(1, 26)} = 1.032$, P = 0.32) for H:M in prone.

H:M in single-leg standing

The group by time interaction result showed that there was significant effect, ($F_{(1, 26)} =$ 5.059, P = 0.03). There was a large effect size (*d* =0.97, [0.19, 1.70]) indicating that H:M ratio was significantly reduced while performing single-limb standing after balance training. Also, a large effect size (*d* =1.00, [0.19, 1.76]) indicates H:M ratio was significantly reduced in BAL at post-testing when compared to CON.

H:M modulation

There was a significant group by time interaction for H:M modulation ($F_{(1, 26)} = 8.061$, P = 0.01). A moderate effect size (*d* =0.49, [0.25, 1.20]) signifies increased H:M ratio modulation in BAL after balance training. Also, BAL's post-test H:M ratio modulation had a large effect (*d* =0.88, [0.08, 1.63]) relative to CON.

5.3.3 Static Balance function

COP maximum velocity in anterior to posterior direction with eyes open (EO)

There was a significant group by time interaction for AP COP (EO), ($F_{(1, 26)}$ = 5.912, P = 0.02). A moderate effect size (*d* =.69, [0.06, 1.41]) suggested that the maximum velocity of COP was significantly reduced in BAL after balance training.

COP maximum velocity in medial to lateral direction with EO

There was no significant group by time interaction effect, ($F_{(1, 26)}$ = 2.384, P = 0.13), group main effect, ($F_{(1, 26)}$ = 2.583, P = 0.12), or time main ($F_{(1, 26)}$ = 3.480, P = 0.07) for COP maximum velocity in medial to lateral direction with EO.

COP maximum velocity in anterior to posterior direction with eyes closed (EC)

There was no significant group by time interaction effect, ($F_{(1, 26)}$ = 3.172, P = 0.09), group main effect, ($F_{(1, 26)}$ = 0.016, P = 0.90), or time main ($F_{(1, 26)}$ = 0.568, P = 0.46) for COP maximum velocity in anterior to posterior direction with EC.

COP maximum velocity in medial to lateral direction with EC

There was no significant group by time interaction effect, (F(1, 26) = 1.994, P = 0.17), group main effect, ($F_{(1, 26)}$ = 4.109, P = 0.53), or time main ($F_{(1, 26)}$ = 2.033, P = 0.17) for COP maximum velocity in medial to lateral direction with EC.

TTB absolute minimum in medial to lateral direction with EO

There was no significant group by time interaction effect, ($F_{(1, 26)}$ = 0.091, P = 0.77), group main effect, ($F_{(1, 26)}$ = 0.735, P = 0.40), or time main ($F_{(1, 26)}$ = 3.848, P = 0.06) for TTB absolute minimum in medial to lateral direction with EO.

TTB absolute minimum in anterior to posterior direction with EO

There was no significant group by time interaction effect, ($F_{(1, 26)}$ = 4.405, P = 0.05), group main effect, ($F_{(1, 26)}$ = 2.848, P = 0.10), or time main ($F_{(1, 26)}$ = 0.178, P = 0.35) for TTB absolute minimum in anterior to posterior direction with EO.

TTB absolute minimum in medial to lateral direction with EC

There was no significant group by time interaction effect, ($F_{(1, 26)}$ = 2.600, P = 0.12), group main effect, ($F_{(1, 26)}$ = 2.616, P = 0.12), or time main ($F_{(1, 26)}$ = 0.198, P = 0.66) for TTB absolute minimum in medial to lateral direction with EC.

TTB absolute minimum in anterior to posterior direction with EC

There was no significant group by time interaction effect, ($F_{(1, 26)}$ = 3.669, P = 0.07), group main effect, ($F_{(1, 26)}$ = 0.965, P = 0.34), or time main ($F_{(1, 26)}$ = 0.233, P = 0.63) for TTB absolute minimum in anterior to posterior direction with EC.

5.3.4 Dynamic Balance Function (SEBT)

SEBT anterior

There was no significant group by time interaction effect, ($F_{(1, 26)}$ = 0.586, P = 0.45), group main effect, ($F_{(1, 26)}$ = 0.233, P = 0.63), or time main ($F_{(1, 26)}$ = 0.673, P = 0.42) for SEBT anterior.

SEBT posteromedial

There was no significant group by time interaction effect, ($F_{(1, 26)}$ = 0.949, P = 0.34), group main effect, ($F_{(1, 26)}$ = 0.097, P = 0.76), or time main ($F_{(1, 26)}$ = 6.274, P = 0.19) for SEBT posteromedial.

SEBT posterolateral

The group by time interaction result revealed that there was no significant effect, ($F_{(1, 26)}$ = 2.174, P = 0.15). There was no significant main effect of the group, ($F_{(1, 26)}$ = 0.097, P = 0.76). On the other hand, there was a significant time main effect ($F_{(1, 26)}$ = 8.750, P = 0.01). A moderate effect size (*d* =0.72, [-0.04, 1.44]) indicates SEBT PL was significantly improved in BAL after balance training while there were no significant differences in SEBT posterolateral of CON between baseline and post-testing (P = 0.35). However, the confidence interval crossed zero, meaning that the effect size was negligible.

5.4 Discussion

The aim of this study was to identify the effects of 6-week balance training on corticospinal excitability of the soleus, spinal reflexive excitability modulation of the soleus, and balance performance in individuals with CAI. The main findings were that balance training significantly increased corticospinal excitability and modulation of spinal reflexive excitability in those with CAI. Furthermore, people with CAI exhibited improved balance performance following 6-weeks of balance training. Collectively, the results of this study might indicate that balance training can address the neurosignature accompanied by restoration of balance deficits for CAI populations. Given that measurements of neural excitability are task-dependent, however, the results must be interpreted cautiously since our data is specific to sing-limb standing.

According to the results, 6 weeks of balance training diminished the CSP of the soleus while maintaining single-limb standing, meaning that the single-limb balance control might be shifted to supraspinal control in individuals with CAI. This finding was consistent with the results of the first study suggesting the reduction in the CSP after a single-session balance training.[165] Previously, Burle et al. demonstrated that increased CSP was associated with increased reaction time.[180] From this perspective, reduced CSP of the soleus from the two studies indicates that the CNS can activate the soleus muscle more quickly, which would be valuable for maintaining single-limb balance in those with CAI.[16] However, the reduced CSP does not always mean better since the ability to modulate the inhibitory mechanisms within the motor cortex depends on different populations and tasks.[181] For example, Swanson et al. demonstrated that young adults presented better walking coordination with reduced CSP while older adults showed better walking coordination with increased CSP.[182,183] Thus, further investigation is necessary to identify how the CSP is modulated during balance training for individuals with CAI.[184]

Along with the changes in the motor cortex, we also observed spinal reflexive excitability modulation was significantly increased after 6-weeks of balance training. Thus, the CNS of CAI patients had an increased ability to inhibit the spinal reflex pathway to transfer balance control to the supraspinal level, leading to co-contraction of the soleus and tibialis anterior muscles and improved single-limb standing.[21] This result was in accordance with the results of the first study presented increased modulation of spinal reflexive excitability following a single session of balance training.[165] Also, Trimble and Koceja et al. demonstrated that H-reflex was down-regulated in the soleus after 2 hours of balance training.[19] Furthermore, the increased modulation of spinal reflexive excitability was caused by diminished spinal reflexive excitability of single-limb standing while the excitability was not changed much during prone, meaning that the CNS might elicit changes in spinal reflex while performing only trained motor tasks. When considered collectively, it indicates that spinal plasticity plays a vital role in acquiring new motor skills. This implies that spinal motor neurons not only enable quick responses to unexpected disruptions encountered in daily life but also facilitate adjustments in spinal circuitry to adapt to specific training tasks.[185] However, these results must be interpreted with caution due to some limitations in this study. This is because we did not measure neural excitability of the tibialis anterior for people with CAI. That is, it is necessary for future studies to investigate if there would be neural plasticity that happens to the tibialis anterior after the identical training protocol that was utilized in this study.[28]

Six weeks of balance training improved the static balance function measured using a force plate in individuals with CAI. According to the result, COP velocity in the anterior to posterior direction was significantly reduced in BAL following balance training, indicating improvement in static balance function in individuals with CAI. Previously, balance performance was improved in people with CAI following current balance training, which was also observed in this study.[28] From the traditional perspective, the improved balance performance was caused by a restoration of somatosensory function after balance training for CAI patients.[29] However, our study suggests that the neural plasticity in the CNS might also result in improved balance performance in individuals with CAI. In other words, balance training might improve the feed-forward mechanism of the nervous system to control the soleus muscle playing a crucial role in postural control ability in people with CAI. In contrast, dynamic balance performance measured using SEBT was not significantly improved after 6-week of balance training. SEBT has been broadly implemented to detect dynamic balance deficits or improvement in those with CAI.[87,186] There could be reasons why SEBT did not detect improvement in balance performance while COP data did. Participants were asked to put on the stroboscopic glasses while performing balance training, providing visual perturbations leading to postural challenges. Through this process, the investigators expected to elicit the positive effects of balance training, which was observed in a previous study.[157,162] However, it could be the opposite of the authors' expectations, suggesting that the glasses might hinder progress in reaching distance during balance training because of the strong level of visual challenges provided through the glasses. This might cause no significant improvement in SEBT even after 6-week of balance training. In contrast to the result of our study, Kim et al. demonstrated a significantly improved dynamic balance performance assessed using SEBT following 6-week balance training with the stroboscopic glasses in those with CAI.[157] The difference between the two studies was the way to provide the intensity of visual perturbations. Our study selected 3, out of 8 visual difficulties for all participants while Kim's study provided customized levels of challenges based on the execution of balance performance for each participant. Thus, the diversity in response to the same level of visual perturbation might result in the dissimilarity of training effects, leading to non-significant improvements in dynamic balance performance following 6-week of balance training in our study.

Future studies may be required to explore the effects of balance training with other therapeutic interventions on neurosignature in individuals with CAI since ankle sprains can bring diverse deficits leading clinicians and patients to seek comprehensive rehabilitation guidelines.[187] For example, rehabilitation for people with CAI typically includes exercises for balance training, range of motion, ankle strengthening, and functional rehabilitation.[173] Previously, Zarzycki et al. reported increased MEP and reduced resting motor threshold for individuals with anterior cruciate ligament reconstruction following rehabilitation, which were not the changes in the CNS that were observed for people with CAI in our study.[188] Thus, identifying the effects of multimodal rehabilitation on neurosignature in those with CAI would provide us significant insight into determining how patients get full recovery so that they can become Copers who have had a history of ankle sprains but get back to normal physical activity level without residual symptoms.[4]

5.5 Clinical implications

Balance training has resulted in successful outcomes in preventing repetitive ankle sprains and improving balance performance in individuals with CAI. However, it remained unknown if balance training can address the neurosignature in individuals with CAI. Through this study, we learned that balance training addresses the neurosignature in those with CAI since we observed positive changes in neural excitability along with improved static balance performance. Given that the neurosignature is influential in the development of CAI, balance training should be considered a crucial rehabilitation component for people with CAI.

5.6 Limitations

There were several limitations associated with this study. First, the alteration of muscle fiber length caused by postural sway while performing single-limb standing may affect the results of neural excitability results, which cannot be controlled.[147] Thus, different patterns of sway may lead to diversity in the muscle fiber length of each participant, affecting the outcomes of TMS and H-reflex variables. Secondly, as mentioned in the discussion, findings must be interpreted cautiously due to the nature of the assessment conditions. In this study, participants were asked to maintain single-limb standing to measure their neural excitability, indicating that the findings cannot be extrapolated to tasks other than single-limb standing. Thirdly, post hoc power analysis using the results of a study[189] that reported corticospinal excitability data such as active motor threshold revealed a total of 42 participants to detect group differences with an effect size of at least 0.80. Given that 28 subjects participated in this study, the underpower of the sample size could be a reason why there were no significant differences in corticospinal excitability variables other than CSP. Lastly, we were not able to control participants' physical activity outside of the lab which might affect the results of our study.

5.7 Conclusion

Through this study, we observed that 6-weeks of balance training elicited increased corticospinal excitability and modulation of spinal reflexive excitability, which was accompanied by improved balance performance. CAI is a neurophysiologic dysfunction leading to changes in the CNS that contribute to various neuromuscular impairments, the most common of which is reduced balance performance. Due to this reason, improving balance and restoring CNS function are among the most crucial goals for rehabilitation in individuals with CAI. While balance training is an effective method for improving postural control, it was unknown if balance training can address the neurosignature for those with CAI. Specifically, individuals with CAI have reduced ability to modulate spinal reflexive excitability of the soleus muscle when transitioning from simpler to more complex balance conditions. This reliance on spinal reflexes contributes to erratic activation of stabilizing muscles in the lower leg. To effectively maintain balance, spinal reflex excitability needs to be suppressed and motor control must be shifted to supraspinal centers. However, individuals with CAI have reduced supraspinal control of the lower leg, evidenced by increased cortical inhibition of the soleus muscle. This study provides evidence of the effects of balance training on the neurosignature, leading to improved postural control ability in individuals with CAI.

CHAPTER 6

SUMMARY

6.1 Purpose, Aims, and Hypothesis

There were multiple purposes of this dissertation to further understand the effects of balance training on neural excitability in individuals with CAI. The first purpose was to determine the effects of a single session of balance training on spinal reflex modulation, corticospinal excitability, and balance performance in individuals with CAI. The second purpose was to systematically review the literature to identify the optimal dose of balance training for individuals with CAI. The third purpose was to explore the effects of an optimally-dosed balance training intervention on spinal reflex modulation, corticospinal excitability, and balance performance in individuals with CAI.

Aim 1.1: To determine the effects of a single session of balance training on corticospinal excitability of the soleus in individuals with CAI.

Hypothesis 1.1.1: Balance training group (BAL) and control group (CON) will not differ in MEP, AMT, or CSP at baseline.

Hypothesis 1.1.2: BAL will have greater MEP and lower AMT and CSP at post-test compared to baseline.

Hypothesis 1.1.3: BAL will have greater MEP and lower AMT and CSP at post-test compared to CON.

Aim 1.2: To examine the effects of a single session of balance training on spinal reflexive excitability modulation of the soleus in individuals with CAI.

Hypothesis 1.2.1: BAL and CON will not differ in H:M ratio modulation at baseline.

Hypothesis 1.2.2: BAL will have greater H:M ratio modulation at post-test compared to baseline.

Hypothesis 1.2.3: BAL will have greater H:M ratio modulation at post-test compared to CON.

Aim 1.3: To identify the effects of a single session of balance training on balance performance in individuals with CAI.

Hypothesis 1.3.1: BAL and CON will not differ in COP velocity and TTB variables at baseline.

Hypothesis 1.3.2: BAL will have lower COP velocity and TTB variables at post-test compared to baseline.

Hypothesis 1.3.3: BAL will have greater lower COP velocity and TTB variables at post-test compared to CON.

Aim 2: To examine the optimal dose of balance training on balance performance in individuals with CAI.

Hypothesis 2.1: A systematic review of the literature will identify the optimal dose of balance training for individuals with CAI, including the most effective period, frequency, number of total training volume, duration of a single training session, and mode of balance exercise.

Aim 3.1: To determine the effects of optimally-dosed balance training on corticospinal excitability of the soleus in individuals with CAI.

Hypothesis 3.1.1: Balance training group (BAL) and control group (CON) will not differ in MEP, AMT, or CSP at baseline.

Hypothesis 3.1.2: BAL will have greater MEP and lower AMT and CSP at post-test compared to baseline.

Hypothesis 3.1.3: BAL will have greater MEP and lower AMT and CSP at post-test compared to CON.

Aim 3.2: To examine the effects of optimally-dosed balance training on spinal reflexive excitability modulation of the soleus in individuals with CAI.

Hypothesis 3.2.1: BAL and CON will not differ in H:M ratio modulation at baseline.

Hypothesis 3.2.2: BAL will have greater H:M ratio modulation at post-test compared to baseline.

Hypothesis 3.2.3: BAL will have greater H:M ratio modulation at post-test compared to CON.

Aim 3.3: To identify the effects of optimally-dosed balance training on spinal reflexive excitability modulation of the soleus in individuals with CAI.

Hypothesis 3.3.1: BAL and CON will not differ in COP velocity and TTB variables at baseline.

Hypothesis 3.3.2: BAL will have lower COP velocity and TTB variables at post-test compared to baseline.

Hypothesis 3.3.3: BAL will have greater lower COP velocity and TTB variables at post-test compared to CON.

6.2 Summary of Findings

Aim 1.1: To determine the effects of a single session of balance training on corticospinal excitability of the soleus in individuals with CAI.

Findings: Our hypothesis was accepted by showing that CSP was significantly reduced, meaning that corticospinal excitability was increased following a single session of balance training in individuals with CAI. This indicated that balance training might be able to initiate the CNS to transfer balance control to the supraspinal level to maintain single-limb standing.

Aim 1.2: To examine the effects of a single session of balance training on spinal reflexive excitability modulation of the soleus in individuals with CAI.

Findings: Our hypothesis was supported since we observed increased modulation in people with CAI after a single-session balance training. This suggested that balance training increased the ability of the CNS to inhibit the spinal reflex circuit so that it may more rely on the supraspinal centers to maintain single-limb balance.

Aim 1.3: To identify the effects of a single session of balance training on spinal reflexive excitability modulation of the soleus in individuals with CAI.

Findings: Our hypothesis was not supported since no significant improvement in balance function occurred after completion of a lone session of balance training in those with CAI. This could be because a single-session balance training was not of high enough volume to elicit improvement in balance performance in CAI populations. Another possibility could be the limitation of balance assessment using COP variables to detect balance improvement after the intervention in people with CAI.

Aim 2: To examine the optimal dose of balance training on balance performance in individuals with CAI.

Findings: The results of this systematic review and meta-analysis supported the hypothesis which was that a systematic review of the literature would identify the optimal dose of balance training for individuals with CAI, including the most effective period, frequency, number of total training volume, duration of a single training session, and mode of balance exercise. This study suggested that 6 weeks, 3 sessions a week, 18 total training sessions, and ≤20 minutes as the optimal balance training parameters for those with CAI. However, further research investigating the effects of balance training with parameters other than the suggested ones to determine the true inversed U-shape relationship between balance training parameters and the balance performance are needed since most comparisons in this study were 1 vs 1 comparisons.

Aim 3.1: To determine the effects of optimally-dosed balance training on corticospinal excitability of the soleus in individuals with CAI.

Findings: Balance training in study 3 was conducted for 6 weeks, 3 sessions a week, and 18 total training sessions, all of which were suggested by study 2. As observed in Study 1, CSP was significantly reduced after 6-week of balance training in individuals with CAI. This suggested that balance training increased corticospinal excitability, indicating the CNS might rely on the motor cortex controlling the soleus muscle to maintain single-limb standing in CAI people following the intervention.

Aim 3.2: To examine the effects of optimally-dosed balance training on spinal reflexive excitability modulation of the soleus in individuals with CAI.

Findings: Along with the results of corticospinal excitability, the modulation of spinal reflexive excitability was significantly increased in individuals with CAI following 6-

weeks of balance training. This means that the CNS reduced reliance on the spinal cord following the intervention in those with CAI. Given that the ability of the CNS to modulate spinal reflexive excitability is crucial when faced with increased postural demand, the changes in the CNS following the intervention in this study were considered favorable changes for individuals with CAI.

Aim 3.3: To identify the effects of optimally-dosed balance training on balance performance in individuals with CAI.

Findings: Six weeks of balance training improved static balance performance in individuals with CAI. This result was in accordance with previous evidence suggesting that current balance training is effective in improving balance performance in those with CAI. The improvement in balance performance might be associated with the alteration of neurosignature that was observed in this study even though further research is necessary to determine if there would be significant relationships between the improved balance performance and the changes in the CNS after balance training for people with CAI.

6.3 Conclusion

This dissertation provided evidence that balance training was effective in addressing neurosignature in individuals with CAI. Our results demonstrated that a single session of balance training began the changes in the CNS, which were represented in the increased modulation of spinal reflexive excitability and corticospinal excitability after the intervention. Furthermore, the results of Study 3 also supported Study 1's results that balance training could elicit the CNS to transfer balance control from the spinal level to the supraspinal level to maintain single-limb standing, which was considered favorable alterations for individuals with CAI. This suggested why balance training has been successful in preventing recurrent ankle sprains as well as improving balance performance in those with CAI. Also, Study 2 revealed that balance training was the most effective when performed for 6 weeks, 3 sessions a week, 18 total training sessions, and ≤20 minutes for people with CAI. This indicated that balance training needed to be performed with an appropriate training dose rather than conducting just long-duration training. However, further investigation is still necessary to determine the effects of balance training for doses that exceed previously reported parameters in individuals with CAI.

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PUBLICATIONS
Published Refereed Manuscripts

1. Reyes M, Suttmiller AMB, Chung S, Ramirez V, Johnson K, Foreman N, McCann RS. Cross-Education Effects of Balance Training in Individuals with Chronic Ankle Instability. Journal of Bodywork & Movement Therapies. Submitted December 2023. In Review.
2. Foreman NN, Suttmiller AMB, Chung S, Gruskiewicz VM, Johnson KR, Reyes MC, McCann RS. Cross-Education Effects of Hip Strengthening in Individuals with Chronic Ankle Instability. Translational Journal of the American College of Sports Medicine. Submitted September 2023 and accepted January 2024.
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4. Lawry-Popelka, B., Chung, S., & McCann, R. S. (2022). Cross-Education Balance Effects After Unilateral Rehabilitation in Individuals With Chronic Ankle Instability: A Systematic Review. Journal of Athletic Training, 57(11-12), 1055-1061.