



**THE EFFECT OF TRANSCRANIAL DIRECT CURRENT STIMULATION
(TDCS) ON BALANCE CONTROL IN RESPONSE TO PERTURBATION-BASED
TRAINING-RANDOMIZED CONTROLLED TRIAL**

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**DOCTOR OF PHILOSOPHY
DEPARTMENT OF PHYSIOTHERAPY AND REHABILITATION**

**GAZİ UNIVERSITY
GRADUATE SCHOOL OF HEALTH SCIENCES**

DECEMBER 2024

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10/12/2024

THE EFFECT OF TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) ON
BALANCE CONTROL IN RESPONSE TO PERTURBATION-BASED TRAINING-
RANDOMIZED CONTROLLED TRIAL

(Ph. D. Thesis)

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December 2024

ABSTRACT

The specific role of the primary motor cortex (M1) in balance control remains unclear, and a causal contribution to improvements in balance ability after balance training has not yet been proven. The current study aims to explore the role of M1 in acquiring balance skills following short-term perturbation-based balance training. Thirty-four participants were randomly assigned to one of three groups: anodal transcranial direct current stimulation (tDCS), sham tDCS, or control group without stimulation. All participants were involved in a structured, three-session perturbation-based balance training program, with one-week interval between sessions. We analyzed electroencephalography, electromyography, and balance ability during balance perturbations and changes in cortico-spinal excitability at rest. The results indicate that balance ability, measured by the center of mass displacement and joint excursions, was improved in forward perturbation across all groups, with the anodal stimulation group showing the largest improvement following the training. Similarly, the anodal stimulation group showed a significant decrease in alpha band power in forward perturbations compared to before training. While the training did not induce any significant change in short-interval intracortical inhibition (SICI) measured, it increased intracortical facilitation (ICF) in the right tibialis anterior (TA) muscle across all groups, independent of the stimulation condition. This study provides evidence that tDCS over the M1 facilitates balance skill acquisition and retention, possibly by facilitating motor preparation and improving the efficiency of sensorimotor integration processes, as shown by decreased alpha power and N1 latency. These findings may have implications for the potential use of tDCS in balance training.

Science Code : 10105.06

Key Words: : Primary Motor Cortex, tDCS, Balance Training, Motor Skill Learning

Page Number : 106

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Co-Supervisor : Prof. Dr. Charles LAYNE

TRANSKRANYAL DOĞRU AKIM UYARIMI (TDCS)'NİN PERTÜRBASYON
TEMELLİ EĞİTİME CEVAP OLARAK ORTAYA ÇIKAN DENGİ KONTROLÜNE
ETKİSİ – RANDOMİZE KONTROLLÜ ÇALIŞMA

(Doktora Tezi)

Ömer Burak TOR

GAZİ ÜNİVERSİTESİ
SAĞLIK BİLİMLERİ ENSTİTÜSÜ

Aralık 2024

ÖZET

Amaç

Denge kontrolü, vücut bölümlerinin ya da tüm vücudun hareketini gerektiren günlük yaşam ve spor aktivitelerini gerçekleştirmek için gerekli olan temel bir motor beceridir. "Denge kontrolü" genel terimi altında, ayakta dururken denge, insanların günlük işlerini tamamlarken genellikle ayakta durdukları için tüm hareketlerin temelini oluşturur.

Denge kontrol mekanizmaları iki ana stratejiye ayrılabilir: ileri beslemeli (proaktif) ve geri beslemeli (reaktif) denge. İleri beslemeli denge kontrolüne iyi bir örnek, dik pozisyonda durmaktır. Dik duruş sırasında vücut, nefes alma, kalp atışları ve vücuttan gelen daha az güvenilir/gürültülü sinyaller gibi faktörler nedeniyle doğal olarak küçük bir genlikte salınım yapar. Bu durumda merkezi sinir sistemi, yaklaşan hareketleri öngörür ve motor çıktılarının önceden kolayca hazırlanmasını sağlar. Öte yandan, reaktif denge dışsal pertürbasyonlarla ilgilidir. Bu, duyuşal girdilerin hızlı bir şekilde işlenmesini ve buna uygun motor çıktıların üretilmesini gerektirir. Bu strateji, öngörülemez doğası ve düşmeyi önlemek için daha kısa bir işlem süresi gerektirdiğinden daha zorlu denge bozulmalarına yol açar.

İyi bir postural kontrol, iyi duyuşal girdiler ve bu girdilere merkezi sinir sistemi (MSS) ile kas-iskelet sistemi tarafından uygun tepkiler verilmesini gerektirir. Bu giriş-çıkış döngüsü, görsel, vestibüler ve proprioseptif bilgileri bütünleştirerek uygun dengeyi sağlamak için devamlı bir süreçtir. Bu girdiler, üç girdinin göreceli güvenilirliğini belirlemek için duyuşal girdilerin yeniden ağırlıklandırılmasıyla entegre edilir ve ardından ağırlıklandırılmış duyuşal bilgiye göre dik duruş kontrol edilir [1]. Denge bozulmaları sırasında, proprioseptif bilgi diğer duyuşal girdilerden daha hızlı iletilir. Buna ek olarak, bozulma etkisi ayaktan başa doğru ilerledikçe azalır. Sonuç olarak, ayakta durulan yüzeyin yer değiştirmesinden sonra kafa, vücudun en az ve en son etkilenen kısmı olduğundan, görsel ve vestibüler girdiler daha az güvenilir hale gelir [2]. Bu nedenle, MSSpertürbasyonlar sırasında ağırlıklı olarak proprioseptif girdilere güvenir ve bu da hızlı postural tepkilere yol açar [3-5].

Pertürbasyonlara yanıt olarak, MSS, vücudu istenen pozisyona geri döndürecek uygun reaksiyonlar üretir. Bu vücut reaksiyonu, otomatik postural tepkilere (OPT) dayanır. Pertürbasyonlara yanıt olarak denge kontrolünde üç olası OPT devreye girer: kısa, orta ve uzun gecikmeli tepkiler. Bu döngüler, pertürbasyonun başlangıcından sonraki farklı zaman

dilimlerinde aktiftir. Monosinaptik spinal refleks yoluyla üretilen kısa gecikmeli tepki (SLR), pertürbasyon başlangıcından yaklaşık 30–50 ms sonra EMG kaydında görülür. Beyin sapı döngüsü tarafından üretilen orta gecikmeli tepki (MLR), pertürbasyon başlangıcından yaklaşık 65–85 ms sonra ortaya çıkar. Uzun gecikmeli tepki (LLR) ise pertürbasyon başlangıcından yaklaşık 85 ms sonra başlar ve birincil duyuşal ve motor korteksleri içeren transkortikal bir yola dayanır [6].

Otomatik postural tepkiler (OPT), MSS'nin üst merkezleri tarafından önceki deneyimler, bilişsel durum ve başlangıçtaki duyu-motor koşulları tarafından sağlanan öngörücü duyuşal bilgilere göre düzenlenir; bu süreç "merkezi set" olarak bilinir [7, 8]. İstemli tepkiler, pertürbasyon başlangıcından yaklaşık 180 ms sonra başlar [7]. Rahatsızlığa dayalı denge eğitiminin adaptasyonları, MSS'nin üst seviyelerinden başlayıp alt seviyelere doğru sıralanan, iyi ölçeklendirilmiş ve uygun postural tepkilerden oluşur [6, 8]. Kas ateşleme süresinde ortaya çıkan nöromüsküler adaptasyonlar, potansiyel olarak subkortikal merkezlerle iletişim yoluyla korteks tarafından yönetilir. Bu adaptasyonlar, eğitim sonrası "merkezi set" in modüle edilmesiyle sağlanır.

Denge bozulduğu anda vücut, destek tabanı içinde kalabilmek için vücut kütle merkezini (VKM) basınç merkezinin ötesine taşıyarak destek merkezinin içinde tutmaya çalışır. Pertürbasyonlara verilen OPT'lerin postural sonucu, ayakların sabit kaldığı stratejiler ("ayak bileği stratejisi" ve "kalça stratejisi") ile gerçekleşir [7]. MSS, herhangi bir denge bozulmasına yanıt olarak kullanılacak postural kontrol stratejisini, önceki deneyimlere dayanarak seçer. Pertürbasyon küçük ve kolayca başa çıkılabilir olduğunda, vücut ayak bileği stratejisini kullanır. Bu strateji, bacak kasları tarafından kontrol edilen ayak bileği eklemi etrafında ters bir sarkaç gibi tüm vücudun hareket ettirilmesini içerir. Pertürbasyon etkisi, ayak bileği stratejisinin dengeyi geri kazanma eşiğini aştığında, vücut kalça stratejisini kullanır [7, 8]. Kalça stratejisi, kalça eklemi hareketlerini içerir ve VKM'yi ayak bileği stratejisinden daha hızlı hareket ettirme kapasitesine sahiptir [7, 8]. Bu durumda, vücut, dengeyi sağlamak için ayak bileği ve kalça eklemlerinin hareket ettiği ters çift sarkaç modeli gibi davranır. Bu vücut çabası, kütle merkezinin hareketini destek tabanının ötesine taşımayı da içeren bir adımlama yanıtı veya destek değişikliği stratejisi olarak bilinen bir hareketi takip edebilir [1]. Artmış kalça eklemi katılımı, pertürbasyonun daha büyük bir etkisini ifade eder ve VKM'nin daha fazla yer değiştirmesi ile daha yüksek postural instabiliteye yol açar [9]. Bu nedenle, daha küçük kalça eklemi hareketi, daha iyi denge kontrolü anlamına gelir ve rahatsızlık sonrası zirve kalça açısı, postural kontrol stratejisinin bir göstergesi olarak kullanılabilir [10]. Bu anlayışa dayanarak, denge eğitiminin destek yüzeyinin kayma hareketi sırasında daha az VKM yer değiştirmesi sağlaması beklenir.

Önceki çalışmalar, insanların farklı yönlerden gelen pertürbasyonlara farklı şekillerde yanıt verdiğini gösterdi. Biyomekanik perspektiften bakıldığında, vücut, destek yüzeyinin geriye doğru hareket etmesinden kaynaklanan öne doğru denge bozulmaları, ayak bileği plantar fleksiyon torkunun dorsifleksiyon torqundan daha büyük olması ve kalçanın hareket açıklığının fleksiyon yönünde ekstansiyon yönünden daha büyük olması nedeniyle daha kolay toparlayabilir. Oude Nijhuis ve ark., rotasyonel pertürbasyonun ilk deneme etkisini araştırdıkları çalışmalarında, iyileşme oranını belirlemek için ilk ve ikinci pertürbasyonların arasındaki fark ile ikinci ve sonraki denemeler arasındaki farkları farklı pertürbasyon yönlerinde karşılaştırdılar. Araştırma sonunda geriye doğru denge bozulmasına neden olan pertürbasyon yönünde, ilk pertürbasyonda daha büyük postural instabilite olduğunu gösterdiler [65]. İrkilme uyaranları, beklenmedik duyuşal sinyallere karşı hızlı, istemsiz bir

tepki olan irkilme refleksini uyarır. Nonnekes ve ark., öne veya geriye doğru rahatsızlıklar sırasında irkilme işitsel uyarının postural tepkiler üzerindeki etkisini araştırdılar. Öne doğru pertürbasyon (yüzeyin öne doğru kayması) ile ilgili yanıtların, irkilme refleksi yolu ile ortak bir mekanizmaya sahip olabileceğini ve irkilme işitsel sinyalin öne doğru rahatsızlıklarda denge geri kazanım tepkilerini iyileştirdiğini, ancak geriye doğru pertürbasyonlarda etkili olmadığını gösterdiler. Bulguları, farklı pertürbasyon yönlerine yönelik postural yanıtların muhtemelen farklı sinir devreleri tarafından işlendiği şeklinde yorumladılar [11]. Benzer bir mekanizma, Parkinson hastalığının klinik bulgularında da görülebilir. Parkinson hastalığı, postural kontrolde önemli bir rolü olan bazal gangliadaki dopaminerjik nöronları etkileyen nörodejeneratif bir hastalıktır [12]. Parkinson hastalığının ileri aşamalarında, postural instabilite artar ve özellikle geri doğru düşme riski yükselir [13]. Bu bulgular, bazal ganglionların, farklı yönlerdeki pertürbasyonlara karşı hızlı geri dönüş sağlayan merkezi motor ve bilişsel seti modüle ettiğini ima etmektedir [13].

EEG kaydında N1 olarak bilinen büyük bir negatif potansiyel, pertürbasyon başlangıcından 90-200 ms sonra suplemer motor alanda (SMA) ortaya çıkar [14, 15]. N1'in genliği ve altında yatan frekans bantları, özellikle teta frekans bandı (3-7 Hz), denge pertürbasyonları ile güçlü bir ilişkiye sahiptir [16, 17]. N1'in genliği aynı zamanda alt ekstremitelerdeki proprioseptörlerden kaynaklanan afferent girdilerle ilgili bilişsel süreçlerin katılımını yansıtır [18] ve tehdit algısından, pertürbasyonların tahmin edilebilirliğinden ve dikkatten etkilenir [19, 20]. Stokkermans ve arkadaşları, midfrontal kortikal dinamikler ile vücut üzerinde öngörülen pertürbasyon etkisi arasındaki ilişkiyi araştırdı. Eğilme yönünü ve açısını değiştirerek başlangıçtaki vücut duruşunu değiştirdiler. Elde ettikleri bulgular, teta gücünün başlangıç postürü ile modüle edildiğini gösterdi [21]. Aynı laboratuvar da yapılan bir başka çalışmada da benzer bulgular elde edildi. Solis-Escalante ve arkadaşları, N1 genliği ve latansı ile teta, alfa ve beta bantlarının gücünün pertürbasyon yoğunluğuyla modüle edildiğini bulmuştur [14]. Başka bir çalışma, artan pertürbasyon yoğunluğunun Cz elektrotunda N1 genliğinin artmasına ve gecikmenin azalmasına neden olduğunu gösterdi [22]. Pertürbasyon özellikleri ile N1 genlikleri ve frekans bandı gücü arasındaki ilişki çeşitli çalışmalarda araştırılmış olsa da, bildiğimiz kadarıyla, önceki çalışmalar denge eğitiminin (beyin modülasyon teknikleri kullanılarak ya da kullanılmayarak) N1 özellikleri ve frekans bantlarının gücü üzerindeki etkisini özel olarak araştırmadı. Denge eğitimi ile kazanılan gelişmiş duyuusal entegrasyon ve deneyimle, N1 genliği ve gecikmesinin yanı sıra teta ve alfa bantlarının gücünün azalması beklenir, bu da fronto-merkezi kortekste aktivasyonun azaldığını gösterir [19].

Önceleri, dengenin spinal ve subkortikal düzey tarafından kontrol edildiği varsayılmaktaydı [23]. Son yıllarda, primer motor korteksin (M1) denge kontrolündeki rolü daha iyi anlaşılma başlandı. Transkranyal Manyetik Stimülasyon (TMS) çalışmaları, birkaç haftalık denge eğitiminden sonra görevin yürütülmesi sırasında M1'deki uyarılabilirliğin azaldığını gösterdi [24]. Benzer şekilde, iki seans denge eğitiminden sonra bile sensorimotor alanlarda geçici gri madde değişiklikleri gösterildi [63]. Yakın zamanda yapılan bir çalışma, düşük frekanslı tekrarlayan TMS (rTMS) ile M1 aktivitesini bozmanın, altı set denge eğitiminden oluşan tek bir seanstan sonra denge becerisi edinimini etkilemediğini gösterdi. Bununla birlikte, M1 aktivitesindeki bu bozulma, 24 saat sonra denge becerisinin korunmasında bozulmaya neden olmaktadır [25]. Mevcut literatür, M1'in özellikle denge eğitiminin başlangıcında merkezi bir rol oynamasının muhtemel olduğunu, diğer motor kontrol merkezlerinin uzun süreli motor öğrenmede motor kontrolde M1'in yerini aldığını göstermektedir. Benzer bir mekanizma, Hwang ve arkadaşları tarafından yürütülen motor öğrenmede M1'in rolünü gösteren yakın tarihli bir hayvan deneyinde de gösterildi [26].

Eğitimin ilk dört haftasında M1 üzerindeki inaktivasyonun farelerde motor performansda bozulmaya neden olduğunu bulmuşlardır. Bununla birlikte, sekiz haftalık eğitimden sonra inhibisyon uygulandığında önemli bir fark gösterilmedi. Bu sonuçlar, motor öğrenme sürecinin ilk aşamasında primer motor korteksin önemli bir rolü olduğu fikrini destekledi. M1'in denge kontrolündeki rolünü araştıran çalışmalar artmasına rağmen, denge becerisinin kazanılmasındaki kesin mekanizması belirsizliğini korumaktadır. Bu nedenle, bu çalışma M1'in denge becerilerinin kazanılmasındaki rolüne odaklanmaktadır.

M1'in rolünü araştırmak için güvenli, invazif olmayan bir teknik olarak transkraniyal doğru akım stimülasyonu (tDCS) kullanılmaktadır. Anodal tDCS, küçük doğru elektrik akımlarının uygulanması yoluyla nöronların dinlenim membran potansiyelini değiştirerek nöronal uyarılabilirliği artırır [27]. Geliştirilmiş uyarılabilirlik, beceri edinimi ve kalıcılığı için gerekli olan nöroplastisiteyi ve uzun dönemli güçlenmeyi kolaylaştırır. Anodal tDCS, N-metil-D-aspartat reseptörü ve GABAerjik aktiviteyi modüle ederek plastisiteyi indükler [28, 29]. Böylece, elektrotların yerine, akım yoğunluğuna, görev türüne [25] ve görev karmaşıklığına [30] bağlı olarak motor öğrenmeyi geliştirebilir [31-34]. Yakın zamanda yapılan sistematik bir inceleme, M1 üzerindeki anodal stimülasyonun genç yetişkinlerde dinamik dengeyi geliştirdiği sonucuna vardı [35]. Craig ve Doumas, M1 üzerinde anodal stimülasyon uygulamış ve ayakta durma yüzeyinin rotasyonel hareketleri sırasında dinamik dengeyi ölçmüştür. Stimülasyondan hemen sonra ve stimülasyondan 30 dakika sonra kapalı göz koşullarında tepe-tepe basınç merkezi salınımı ile ölçülen dengede iyileşme bulmuşlardır [36]. Kaminski ve arkadaşları da hareketli platform üzerinde denge eğitimi sırasında anodal stimülasyon ile birlikte sham stimülasyon alan gruba kıyasla dengede iyileşme olduğunu gösterdi. Bu iyileşme eğitimden 24 saat sonra da korunmuştur [32].

Dinamik denge kontrolünde tDCS veya rTMS'nin M1 üzerindeki etkisini araştıran çalışmaların çoğunun, Craig ve Doumas tarafından yürütülen çalışma dışında, öncelikle dengenin ileri besleme mekanizmasını test ettiğini belirtmek önemlidir [36]. Bu yaklaşımın temeli, MSS'nin farklı bölümlerinin iyi bilinen rolleri olabilir. M1'in rolü istemli hareketleri ve motor planlamayı içerir. Bu nedenle, M1'in, örneğin denge tahtasını yere paralel bir pozisyonda tutmak gibi, ileri besleme denge mekanizmasını kullanarak daha belirgin bir role sahip olması beklenebilir. Bununla birlikte, takılma ve kayma gibi olası günlük zorlukları simüle eden pertürbasyonlara karşı reaktif denge tepkilerinde yer alan altta yatan kortikal mekanizmaların aydınlatılması çok önemlidir. Reaktif denge mekanizması, vücut pozisyonunun hızlı bir şekilde değerlendirilmesini, duruş bilgisinin SMA ve premotor kortekse aktarılacak motor planın üretilmesini ve son olarak M1 dahil olmak üzere motor kortikal alanların serebellum ve bazal ganglia ile iletişim kurarak uygun motor yanıtları üretmesini gerektirdiğinden muhtemelen ileri besleme mekanizmasından daha karmaşıktır [37]. tDCS'nin kortikal yapılar üzerindeki etkisine ek olarak, subkortikal yapıları da kolaylaştırabilir [38]. Baskın olmayan motor korteks üzerinde on beş dakikalık anodal tDCS, sham tDCS'ye kıyasla ayak bileği kaslarının pertürbasyonlara karşı aktivasyon gecikme tepkisinin azalmasıyla sonuçlanmıştır. Elde edilen bu bulgular, tDCS'nin “merkezi set” rolüne sahip subkortikal yapıların uyarılabilirliğini değiştirdiği ve pertürbasyonlara yanıt olarak daha hızlı kas başlangıç gecikmesine yol açtığı şeklinde yorumlandı [38].

Transkraniyal manyetik stimülasyon, beyin içinde elektromanyetik alan kullanarak elektrik akımı indükleyen ve böylece altındaki kortikospinal ve intrakortikal nöronları aktive eden invazif olmayan bir beyin stimülasyon tekniğidir [39]. Bu nedenle, TMS, denge eğitimi sonucunda M1'in intrakortikal inhibitör ve eksitator devrelerinde kortikal adaptasyon

derecesini değerlendirmek için kullanılabilir. Intrakortikal inhibitör devreler genellikle kısa aralıklı intrakortikal inhibisyon (SICI) ölçülerek değerlendirilirken, eksitator mekanizma intrakortikal fasilitasyon (ICF) ölçülerek değerlendirilir. Her iki ölçüm de bir koşullandırma alt eşiği uyarısı ve ardından bir test uyarısı içerir. Bu çift darbe prosedürleri, gama aminobutirik asit (GABA)_A aracılı inhibitör (SICI) ve glutamaterjik fasilitatör (ICF) bağlantıları araştırabilir. Ayrıca, ICF'nin kısmen GABAerjik devre tarafından düzenlendiği [72] ve temel mekanizmasının tam olarak anlaşılamadığı da belirtilmelidir.

Motor eğitim genellikle kısa süreli motor öğreniminden sonra azalmış inhibisyon (SICI) ve artmış fasilitasyon (ICF) ile ilişkilidir [40, 41]. Azalmış SICI'nin, plastisite yoluyla motor öğrenme sürecini kolaylaştırdığı düşünülmektedir [42]. Bununla birlikte çelişkili sonuçlar da bildirildi. Örneğin, 4 hafta süren squat eğitimi, rectus femoris temsil alanında SICI seviyesini %32 oranında azaltır [43]. Ansdell ve ark. tarafından yapılan benzer bir çalışmada ise 4 hafta süren squat eğitimi sonrasında test koşullarının görev spesifik olmasından bağımsız olarak vastus lateralis kasında SICI ve ICF'de herhangi bir değişiklik gözlemlenmedi [44]. Motor öğrenme sürecinde SICI'nin azaldığı çalışmaların aksine, daha koordinatif becerilerle yapılan eğitimler inhibisyon seviyesini artırır. Bir kesitsel çalışma, elit badminton oyuncularının dinlenme durumunda, acemi oyunculara kıyasla daha yüksek inhibisyon ve eksitasyon gösterdiğini ortaya koymuştur [45]. Mouthon ve Taube, 2 hafta süren denge eğitiminden sonra SICI seviyesinin arttığını bulmuştur [24]. Taube ve ark. ise, 4 hafta süren denge eğitiminden sonra SICI'nin arttığını, ardından 4 hafta süren patlayıcı antrenmana devam edildiğinde ise azaldığını bulmuştur [46]. Bu bulgular, SICI'nin karmaşık motor görevlerden sonra arttığını, daha az karmaşık motor öğrenme görevlerinden sonra ise azaldığını öne süren önceki hipotezleri desteklemektedir.

Motor öğrenme çalışmalarının çoğu ağırlıklı olarak üst ekstremité kaslarındaki SICI ve ICF'yi araştırdı. Önceki çalışmalar üst ekstremité kaslarının alt ekstremitéye kıyasla M1'den daha güçlü kortikospinal projeksiyonlara sahip olduğunu gösterdi [47]. Ancak, tüm alt ekstremité kasları benzer kortikospinal bağlantılara sahip değildir. Örneğin TA, SOL'dan çok daha güçlü, [47, 48] el kaslarıyla karşılaştırılabilir ölçüde güçlü [49] kortikomotor bağlantılara sahip olduğu görülmektedir. Bunu destekleyen yeni bir çalışma, tibialis anterior temsiliinin eldeki abduktör digiti minimi kası ile benzer GABAerjik ve glutamaterjik internöronal devreler gösterdiğini ortaya koymuştur [50].

Literatürde, uyarılabilirlik ölçümlerinin sonuçları muhtemelen motor becerinin türü ve metodolojik farklılıklar nedeniyle değişiklik göstermektedir. Denge çalışmalarında SICI ve ICF ölçümlerindeki varyasyonlar, gerçekleştirilen görev [51] ve test koşulları gibi çeşitli faktörlere bağlıdır. Bu koşullar arasında kasların aktif veya pasif durumda olup olmadığı ve test koşulunun öğrenilen görevle eşleşip eşleşmediği yer alır [24, 46, 52]. Intrakortikal uyarılabilirliğin göreve bağlı doğasına rağmen, daha kontrollü ve standartlaştırılmış koşullar altında daha güvenilir sonuçlar elde etmek ve denge görevi sırasında ölçüm yapmanın getirdiği teknik kısıtlamalar nedeniyle planladığımız bu araştırmada TMS ölçümlerini istirahat halinde gerçekleştirdik. Bu yaklaşım aynı zamanda kas aktivitesinin olası karıştırıcı etkilerini dışlamaya da yardımcı olmaktadır.

MSS, dışardan gelen pertürbasyonlar vücudun dengesini bozduğunda düşmeyi önlemek için uygun tepkiler üretmekten sorumludur. MSS, dengeyi kontrol etmek için iki ana strateji kullanır; Algısal (APA) ve tepkisel (CPA) postüral ayarlamalar [53]. APA'lar, yaklaşan pertürbasyonlardan önce kasların hazırlanmasını içerirken, CPA'lar pertürbasyonlara verilen

reaktif postüral tepkileri ifade eder. MSS APA'ları düzgün bir şekilde ürettiğinde, pertürbasyonlardan sonra VKM yer değiştirmelerinin azalması ve pertürbasyonlardan sonra dengeyi yeniden kazanmanın daha kolay olması beklenebilir. Bu sayede CPA'lara daha az ihtiyaç duyulacaktır. Bununla birlikte, işitsel uyarının, bireyin uyarılma durumu üzerindeki değişiklikler aracılığı ile katılımcıların pertürbasyona karşı postural yanıtlarını ayarlamak için kortikospinal uyarılabilirliği düzenleyebilir [54]. Bu araştırmada ses uyarımının postural dengeye etkisinin denge eğitimiyle ve tDCS ile değişimi test edildi. Bir başka ifadeyle eğer sesli uyarılar primer motor korteksin uyarılabilirliğini değiştiriyorsa denge eğitimine karşı geliştirilen adaptasyon sesli uyarının postural cevaplar üzerindeki etkisini değiştirebilir.

Literatürdeki bulgular pertürbasyon yönünün vücudun biyomekanik özelliklerinden ziyade MSS'nin pertürbasyonu algılayış, işleyiş ve tepki oluşturma sürecine etki eden önemli bir faktör olduğunu göstermektedir. TA kası öne doğru pertürbasyonlarda baskın reflex cevaplar üretirken, aksine SOL kası geriye doğru olan pertürbasyonlarda primer rol oynamaktadır. Bununla birlikte bu iki kasın postüral kontroldeki rolü yalnızca anatomik farklılıklarla ilgili olmayabilir. TA kası daha düşük yoğunluklu TMS darbeleri ile uyarılabilmektedir. Bu da SOL kasına göre TA kasının daha fazla kortikomotor bağlantıya sahip olduğunu göstermektedir. Buna paralel olarak, Fujio ve ark., öne pertürbasyondan önce verilen ses uyarımının TA kası uyarılabilirliğini artırdığını ama SOL kasında bir değişiklik olmadığını ortaya koymuştur [55].

Bu çalışmanın amacı M1'in denge kontrolündeki rolünü araştırmaktır. Hipotezimizi test etmek için, anodal stimülasyon, sham stimülasyon ve kontrol grubu olmak üzere üç grup oluşturuldu. M1'in pertürbasyonlara yanıt olarak denge kontrolündeki iyileşmeyi modüle ettiğini varsaydık. Hipotezimizi test etmek için kas ve kortikal yanıtların (N1 genliği ve latansı ve zaman-frekans analizi) yanı sıra kortikospinal uyarılabilirlik ölçümleri (kısa aralıklı intrakortikal inhibisyon (SICI) ve intrakortikal fasilitasyon (ICF)) ve davranışsal veriler (VKM, VKM'un varyansı ve eklem salınımları) ölçülmüştür. Hipotezimiz, denge eğitiminin N1 genliğini ve latansını azalttığını ve özellikle anodal stimülasyon grubunda teta-alfa bantlarının gücünü düşürdüğü yönündedir. Ayrıca, denge yanıtlarında iyileşme (VKM yer değiştirmesinde ve VKM varyanslarında azalma) ve denge iyileşmelerine bağlı plastisitenin göstergesi olan kortikal uyarılabilirlik değişikliklerini (SICI'de artış ve ICF'de azalma) öngördük. Bunların dışında, ses uyararı ve pertürbasyon yönünün kortikal ve nöromusküler cevapları değiştirmesi bu araştırmanın bir başka hipotezidir.

Gereç ve Yöntem

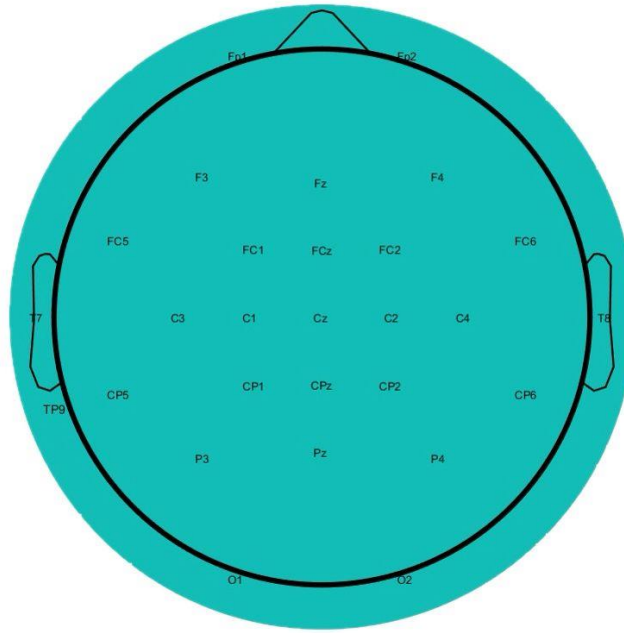
Araştırmaya 34 sağlıklı, sağ el ve ayağını kullanan katılımcılar online ilanlar ve posterler yoluyla dahil edildi. Yalnızca dışlama kriterlerinin hiçbirine uymayan katılımcılar ile ölçüm ve eğitimler planlanmıştır. Dahil edilme kriterleri 18-55 yaş arasında sağ el ve ayağı baskın kullanmak, sigara içmemek, nörolojik ya da psikiyatrik bir hastalığa sahip olmamak olarak belirlendi.

Dışlama kriterleri ise;

1. Kronik veya kalıcı nörolojik hastalıkların geçmişi.
2. Kalp pili varlığı veya derin beyin stimülasyonu uygulanmış kişiler.
3. Baş veya boyun bölgesinde metal implant olanlar (örn. intraserebral anevrizma sonrası ameliyat klipsleri; yapay işitme cihazı implantasyonu).
4. İntraserebral iskemi /kanama geçmişi.
5. Önceden epileptik nöbetler veya epilepsi öyküsü.
6. Kafatası kırığı veya beyin dokusu lezyonu ile birlikte kafa travması geçmişi.
7. Şizofreni, mani veya depresyon dahil olmak üzere herhangi bir ciddi tıbbi durum (iç organlar veya metabolik hastalıklar) veya psikiyatrik hastalık.
8. Gebelik veya emzirme.
9. Alkol veya uyuşturucu bağımlılığı.
10. Sigara içmek.
11. Lokal veya genel afazi.
12. Adayın katılmasına engel herhangi bir yasal durum.
13. Son 4 hafta içinde başka bir bilimsel veya klinik çalışmaya katılma.
14. Merkezi sinir sistemine (CNS) etki eden herhangi bir ilaç alımı.
15. Alt ekstremiteleri içeren ortopedik bir rahatsızlık.
16. Alt ekstremitelerde eklem pozisyonu duyusunun bozulması.
17. Baş dönmesi geçmişi.
18. Omurilik seviyesinde bir cerrahi işlem.
19. Herhangi bir denge eğitimi programına katılma.

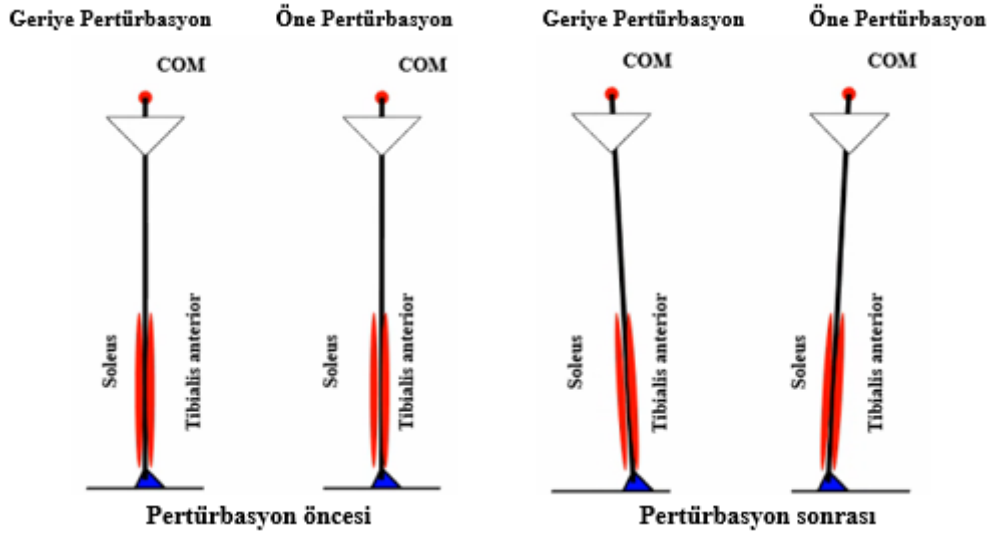
Araştırmayla ilgilenen katılımcılar araştırmaya dair bütün bilgileri içeren bir elektronik posta aldılar ve araştırmanın ilk seansına davet edildiler. Bu seansta araştırmacı katılımcılara araştırmaya dair bütün bilgileri aktardı ve katılımcının sorularını yanıtladı. Katılımcılar bilgilendirilmiş gönüllü onam formunu imzaladı ve sonrasında izleme anketlerini tamamladı. Bu anketler katılımcının dahil edilme ve dışlama kriterlerine uyup uymadığını belirlemek amacıyla yapıldı. Sonrasında araştırmacı katılımcı adaylarının TMS ölçümleri için araştırma başlamadan önce pilot araştırma ile belirlenen Motor uyarılmış potansiyel eşik değerine (0.15-0.5 mV) her bir hedef kas (sağ ve sol tibialis anterior ve soleus) için ulaşım ulaşıldığını test edildi. Araştırmaya katılım için uygun olan adayların ölçüm ve seansları planlandı. Araştırma süreci akış diyagramı şekil.0.1’de gösterildi. Ölçüm seansları birinci ve sekizinci günlerde, eğitim günleri ise ölçüm günlerinin arasında ardışık olmayan günlerde toplam 3 seans olacak şekilde planlandı (Şekil.0.2). Her bir ölçüm seansı prosedürü şekil.0.3’te.

etmek için kullanıldı (Motek Forcelink, Amsterdam, Netherlands). Bu ölçümler sırasında pertürbasyonların başlangıcı ve diğer kayıtları senkronize etmek için bir trigger sinyali üretildi. EMG elektrotları SENIAM standartlarına uygun olarak TA ve SOL kaslarına yapıştırıldı. Bu elektrotlar hem TMS hem de EMG ölçümlerinde kullanıldı. Pertürbasyon ilişkili EEG ölçümlerini yapmak için 28 elektrotlu EEG başlığı kullanıldı. Elektrot lokasyonları şu şekildedir; Fp1, Fp2, F3, Fz, F4, F8, FC5, FC1, FCz, FC2, T7, C3, Cz, C2, C4, T8, TP9, CP5, CP1, CPz, CP2, CP6, P3, Pz, P4, O1, O2. TP10. TP10 online referans elektrodu olarak, AFz ise toprak elektrot olarak kullanıldı. EMG ve EEG için örneklem frekansı 1000 Hz olarak ayarlandı.



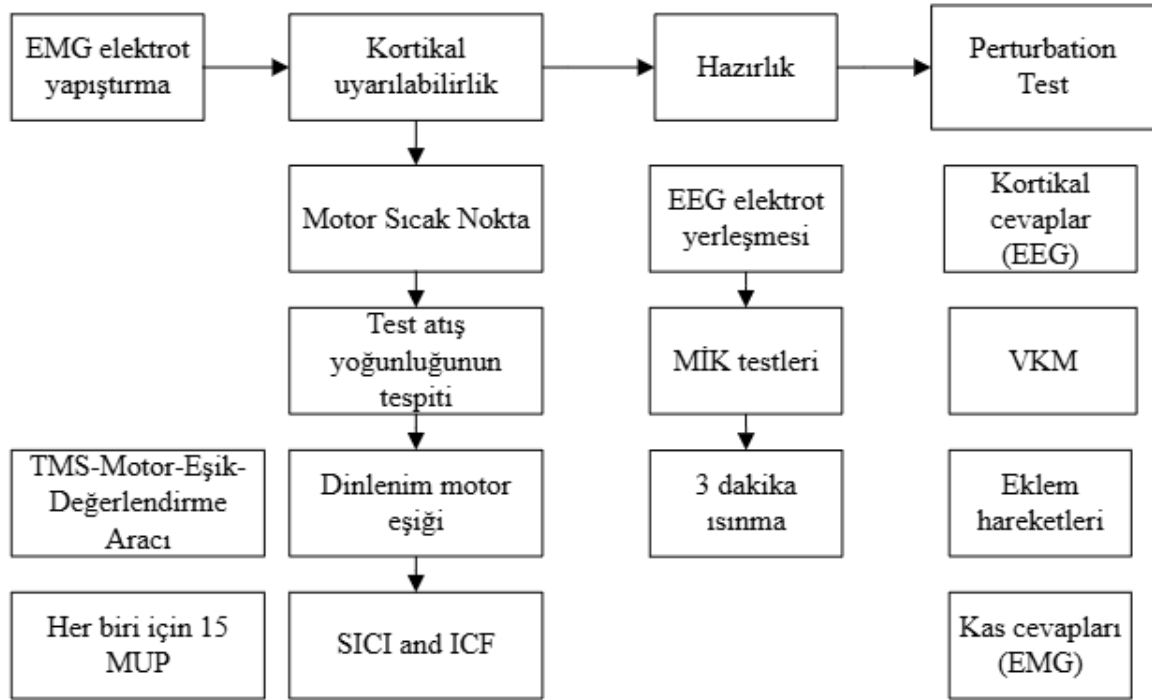
Şekil 0.3 EEG Elektrodlarının yerleşimi.

Bu çalışmada denge testi sırasında öne doğru-ses yok (FNS), geriye doğru-ses yok (BNS), öne doğru-ses var (FS) ve geriye-doğru ses var (BS) olmak üzere 4 farklı koşul uygulandı. Her bir koşulda 15 tane pertürbasyon uygulanmıştır. “Öne doğru pertürbasyon” yüzeyin anterior hareketiyle posterior yönde denge bozukluğuna yol açmasını, ‘Geriye doğru pertürbasyon’ ise yüzeyin posterior yönde hareketiyle anterior yönde denge bozukluğuna yol açmasını ifade etmektedir (Şekil 0.4). Her bir ölçüm seansında katılımcılara 8 farklı durumda toplamda 120 pertürbasyon uygulandı. Bunların yarısında ses uyarını pertürbasyondan 2 sn önce rastgele olarak verildi. Eğitim seanslarında ise katılımcılar 3 farklı amplitüde (2,4 ve 6 cm) ve iki farklı yönde toplam 120 pertürbasyona maruz kaldı. Her bir denge eğitimi 20 dakika sürdü. Katılımcılar katıldıkları gruba göre tDCS uygulandı. Sham stimülasyonda tDCS elektrotları bağlandı ama akım yalnızca 30sn uygulandı. Anodal stimülasyon grubuna 20 dakika boyunca tDCS uygulaması yapıldı. Kontrol grubu ise denge eğitimlerine katıldı fakat tDCS uygulanmadı (Detay için bkz Bölüm 3.4 ve 3.5).

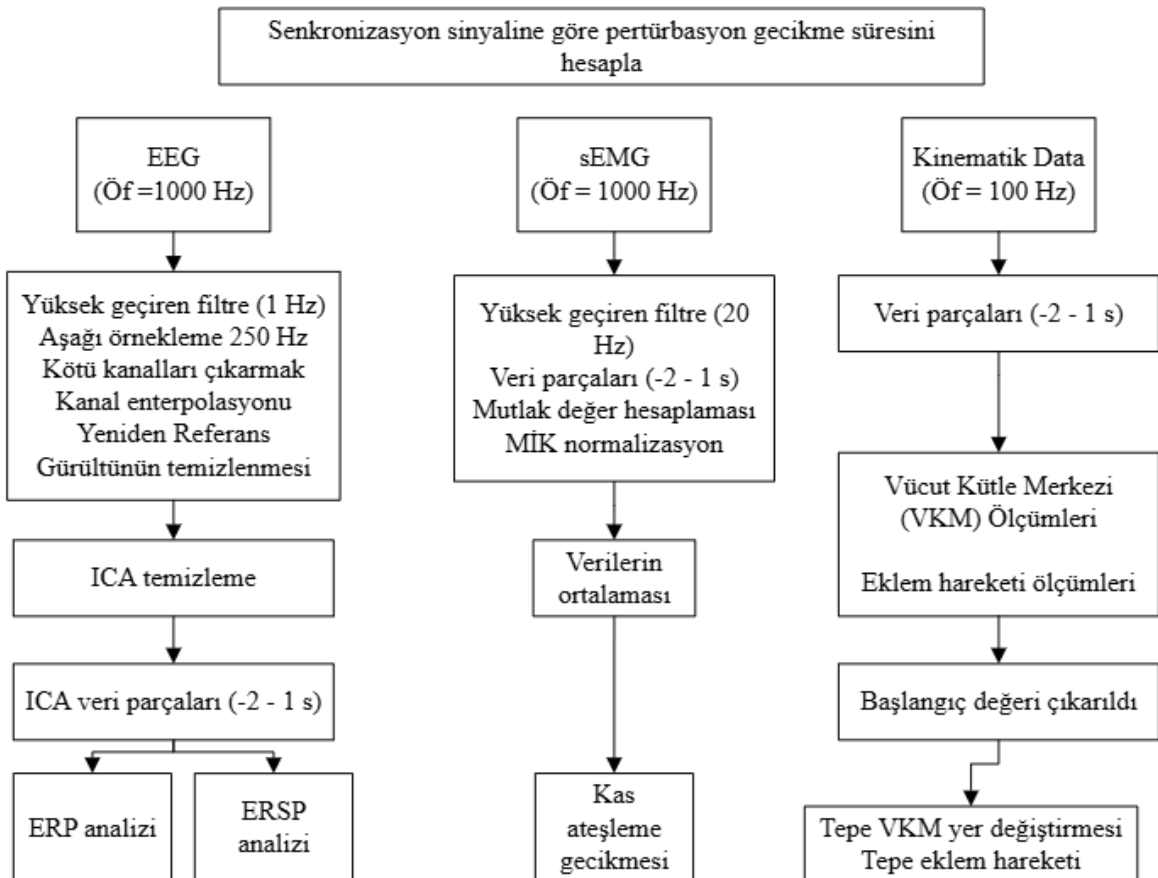


Şekil 0.4 Denge testi ve eğitimleri sırasında kullanılan pertürbasyonlar

Ölçüm seansı prosedürü Şekil 0.5’ te gösterildi. Veri analizinin özeti Şekil.0.6’te gösterildi. EEG analizinde yüksek geçiren filtre uygulamasından sonra sırasıyla 250 Hz frekansında aşağı örnekleme ve EEGLAB kullanılarak gürültülü kanalların çıkarılması ve enterpolasyonları yapıldı. Bütün kanalların ortalaması referans kanal olarak kullanıldı ve kanallar güç hattı gürültüsünden zapline plus kullanılarak temizlendikten sonra veri parçalarına ayrıldı (pertürbasyonun başlangıcına göre -2000 +1000 ms). Beyin kaynaklı olmayan verilerin temizlenmesi için Bağımsız Bileşenler Analizi (ICA) çalıştırıldı. Son olarak, M1 ve SMA üzerindeki Cz kanalında -500 -200 ms referans değerine göre theta ve alpha gücü ile 90-200 ms arasındaki en küçük voltaj değeri (N1) değerleri hesaplanarak istatistiksel analiz için kullanıldı [15, 21, 56].



Şekil 0.5 Ölçüm seansı prosedürü



Şekil 0.6 Veri Analizi

İstatistiksel analiz için R version 4.3.3 (R Foundation for Statistical Computing) kullanıldı. Linear mixed effect modelinin hesaplanması için “lme4” paketi içerisindeki “lmer” fonksiyonu kullanıldı. Sabit etkiler zaman, grup ve ses (var-yok) değişkenleri kullanıldı, katılımcılar ise rastgele etkiler olarak kullanıldı. Post-hoc analizleri için “emmeans” paketi ile tahmini marjinal ortalamalar, her bir çıktı için hesaplanarak karşılaştırmalı istatistik için kullanıldı. Hem gruplar arası, hem de zamanlar arası karşılaştırmalar için “contrasts” fonksiyonu kullanıldı ve tablolara t değeri ile p değerleri her bir grup/zaman için yazıldı. Anlamlılık değeri $p < 0,05$ olarak belirlendi ve tablolardaki anlamlı sonuçlar koyu renk ile belirtildi.

Bulgular

Kinematik Analiz

Tepe VKM yer değiştirmelerinin mixed ANOVA sonuçları Tablo 4.1’de gösterildi. Post hoc karşılaştırmalar ise APPENDIX-6’da sunulmuştur. Öne doğru pertürbasyonlar sırasında anodal stimülasyon grubu eğitim sonunda daha düşük VKM yer değiştirmesi gösterirken diğer gruplarda anlamlı bir değişiklik görülmedi ($t:2,33$, $p:0,02$, APPENDIX-6 Tablo 3).

Her bir alt ekstremit eklemini için tepe eklem açısının ana ve etkileşim etkileri Tablo 4.4’te listelendi. Sağ kalça eklem hareket varyansı eğitim sonunda bütün gruplarda azalma gösterdi ($t:2,46$, $p:0,02$, APPENDIX-6 Tablo 5). Buna ek olarak yalnızca anodal stimülasyon grubu eğitim sonunda anlamlı bir düşüş gösterdi ($t:4,04$, $p:0,0001$).

EEG Analizi

Cz elektrotundaki N1 genliği ve gecikmesinin ana ve etkileşim etkileri Tablo 4.5’te ayrıntılı olarak verildi. Öne doğru pertürbasyon sırasındaki N1 genliğinde ana veya etkileşim etkisi gözlenmedi fakat geriye doğru pertürbasyonlarda N1 genliği denge eğitiminden sonra bütün gruplarda anlamlı bir düşüş gösterdi ($t:2,98$, $p:0,004$, APPENDIX-6, Tablo 16).

Bunun yanında N1 gecikmesinde her iki pertürbasyon yönünde de eğitim sonunda bütün gruplarda anlamlı olarak azaldı (öne doğru pertürbasyon $t:6,14$, $p < 0,0001$, geriye doğru pertürbasyon $t:4,13$, $p:0,0001$). Geriye doğru pertürbasyonlarda zaman ve grup faktörleri arasında anlamlı bir etkileşim gözlemlendi. Post-hoc karşılaştırmaları anodal stimülasyon grubunda N1 gecikmesinin anlamlı olarak düştüğünü ama diğer gruplarda anlamlı bir değişim olmadığını göstermektedir ($t:4,67$, $p < 0,0001$). Theta gücü öne doğru pertürbasyonlar sırasında eğitimden sonra bütün gruplarda anlamlı olarak düştü ($t:4,46$, $p < 0,0001$ APPENDIX-6 Tablo 23). Öne doğru pertürbasyonlar sırasındaki alpha gücü yalnızca anodal stimülasyon grubunda denge eğitimi sonunda anlamlı bir düşüş gösterdi ($t:2,75$, $p:0,01$ APPENDIX-6 Tablo 28).

EMG Analizi

Sağ TA kası pertürbasyon sonrası ateşleme süresinde anodal stimülasyon grubunda eğitim sonunda anlamlı bir düşüş gözlemlendi (t:2,93, p:0,004, APPENDIX-6 Tablo 31).

TMS Analizi

Her bir kas için SICI ve ICF'nin ana ve etkileşim etkileri Tablo 4.15'te gösterildi. Tüm kaslarda SICI'da istatistiksel olarak anlamlı bir ana etki veya etkileşim etkisi bulunmadı. Sol TA kasında ICF'de zamanın ana etkisi bulunmuştur. Post-hoc analizi anodal stimülasyon grubunda ICF'nin gruplardan bağımsız olarak azaldığını gösterdi.

Tartışma

Bu çalışma, erken dönem denge öğreniminde primer motor korteks katılımını ortaya çıkarmak için aldığı tDCS tipine göre üç gruba (kontrol, sham, anodal) ayrılan katılımcılara verilen kısa süreli denge eğitiminden sonra denge pertürbasyonuna kinematik, nöromüsküler ve kortikal yanıtlardaki değişikliklerin yanı sıra kortikospinal uyarılabilirlikteki değişikliklerle birlikte, merkezi sinir sisteminin supraspinal yapısını içerdiği varsayılan uzun gecikmeli yanıtlara odaklanarak nöromüsküler adaptasyonları değerlendirdik. Anodal tDCS ile denge eğitiminin, kas başlangıç gecikmesini düşürdüğünü bulduk. Anodal stimülasyon grubu ayrıca ileri pertürbasyonda kalça eklemi ekstansiyonu ile alpha band gücünde azalma gösterdi ve bu sonuçlar tDCS'in postüral kontrol üzerindeki iyileştirici etkisini göstermektedir.

MSS, VKM hareketlerini yakından izler ve istenen sınırların ötesine geçtiğinde tespit eder ve özellikle beklenmedik pertürbasyonlar sırasında dengeyi yeniden kazanmak için uygun tepkileri başlatır. VKM yer değiştirmesinin azalması, anodal stimülasyon grubunda gelişmiş postüral stabilite ve denge kontrol mekanizmalarını yansıtarak, pertürbasyonlara yanıt olarak dengeyi geri kazanma becerisinin arttığını göstermektedir. Önceki çalışmalar da bu araştırmadaki sonuçları destekleyici bulgular elde etmişlerdir [57, 58].

Biyomekanik açıdan bakıldığında, destek tabanı (BOS), ayaklar, anatomik olarak öne doğru uzamaktadır ve VKM'nin izdüşümü ayakta durma pozisyonunda lateral malleolün biraz önündedir. Bu anatomik düzenleme, vücudun plantar fleksiyon sırasında dorsifleksiyona kıyasla daha fazla tork üretmesini sağlar. Ayrıca, kalça eklemi fleksiyon yönünde ekstansiyona göre daha fazla hareket aralığına sahiptir. Dolayısıyla, posterior vücut salınımına neden olan öne doğru pertürbasyon, geriye doğru pertürbasyondan daha zordur. Bu biyomekanik avantajlar nedeniyle insanların ayakta dik dururken öne doğru arkaya göre daha fazla eğilebildiği fikri anlaşılabilmektedir. Bu bulgu, eğilmeyi ve VKM'i daha sabit tutmayı içeren bir postüral kontrol stratejisinin geriye doğru pertürbasyonlar için iyi bir strateji olabileceğini, yönler arasındaki biyomekanik farklılıklar nedeniyle daha hızlı bir reflex cevapla birlikte ve yüzeyle birlikte hareket etmenin ileri yönlü pertürbasyonlar için daha etkili olabileceğini ima etmektedir.

Bu biyomekanik farklılıklara ek olarak, Nonnekes ve arkadaşları, farklı yönlerdeki pertürbasyonların sensorimotor işlenmesinde muhtemelen farklı nöral devrelerin rol aldığını öne sürmüşlerdir [11]. Pertürbasyonlara verilen EEG yanıtları (N1 genliği ve latansları ile

hem teta hem de alfa gücü) bu bulgulara paralel olarak yönün ana etkisini gösterdi. Önceki çalışmalar N1'in anterior singulat korteks ve posterior parietal korteksin katkısıyla ek motor alandan kaynaklandığını ve genliğinin dikkat, algılanan tehdit ve postüral pertürbasyonların öngörülebilirliği gibi bilişsel komponentlere sahip olduğunu öne sürmüştür [19, 146].

N1 genliği eğitimden sonra anodal uyarım grubunda geriye doğru pertürbasyonlarda önemli ölçüde azaldı (Şekil.4-4), bu sonuç geriye doğru pertürbasyonun dengeye etkisinin veya algılanan postüral tehditin düşmesi sonucu ortaya çıkabilir. N1 gecikme süresi geriye doğru pertürbasyonlarda denge eğitiminden sonra bütün gruplarda azaldı ama anodal stimülasyon grubu daha fazla düşüş gösterdi. Bu sonuçlar duyuşal işleme hızının arttığına işaret etmektedir ve tDCS modülasyonunun duyuşal işlemeyi geliştirdiğini göstermektedir. Buna ek olarak, theta band gücü, geriye doğru pertürbasyonlar sırasında, eğitim sonrası bütün gruplarda düşmüştür. Bu sonuç pertürbasyon temelli denge eğitiminin duyuşal integrasyon ve motor yanıtlar gibi kortikal süreçlerde tDCS modülasyonundan bağımsız olarak etkili olduğunu göstermektedir. Bunun yanında, alpha band gücü öne doğru pertürbasyonlar sırasında sadece anodal stimülasyon grubunda azalmıştır. Bu sonuç, muhtemel olarak tDCS ile birlikte iyileşmiş duyuşal işleme sürecini göstermektedir ve bununla ilişkili olarak öne pertürbasyonlardaki artmış denge kontrolü bulgusunu desteklemektedir.

Önceki çalışmalar da benzer şekilde denge eğitiminin ardından kas başlangıç gecikmesinde azalma olduğunu bildirdi [59-61]. Bu azalma tDCS'in daha önceki çalışmalarda bulunan subkortikal yapılarıdaki uyarılabilirliği artırdığına dair bulguları desteklemektedir [38].

Kısa süreli motor eğitimi, hem üst hem de alt ekstremitelerde artmış ICF ile birlikte azalmış SICI'ye neden olur [40, 41, 62, 63]. Bununla birlikte, önceki çalışmalarda, diğer motor öğrenme çalışmalarıyla çelişkili olarak denge eğitiminden sonra SICI'de artış gözlemlendi. Özetle, Mouthon ve Taube, iki haftalık denge eğitiminin, hareketli bir platformda denge testi sırasında ve sabit ayakta durma sırasında TA kasında gelişmiş SICI seviyesine neden olduğunu, ancak dinlenme sırasında olmadığını bulmuştur [24]. Taube ve arkadaşları, geleneksel denge eğitiminin, posterior pertürbasyonlar (SOL aktivitesi submaksimal aktivitenin %50'sine ulaştığında TMS uyarıları tetiklenir) sırasında test edildiğinde SICI'yi artırdığını, ancak istirahat ve sabit ayakta durma sırasında artırmadığını bulmuşlardır [46]. Bulguları, benzer bir denge eğitiminin uygulandığı ve pertürbasyonlar sırasında SOL kasında kortikal uyarılabilirliğin azalmasına yol açan önceki bir çalışma ile desteklenmektedir [64]. Önceki çalışmalarla uyumlu olarak, bu çalışmada da eğitimden sonra sol TA kasında ICF'de anlamlı bir azalma rapor edildi, bu da kortikal uyarılabilirliğin azaldığını göstermektedir. İntrakortikal inhibisyonadaki artış ve kortikal uyarılabilirlikteki azalma, denge eğitiminden sonra birincil kontrol merkezlerinin M1'den kortikal veya subkortikal yapılara kaymasına bağlanabilir.

Sonuç ve Öneriler

Denge kontrolü, günlük aktivitelerimizi sürdürmek ve sağlıklı yaşlanma sürecini desteklemenin yanı sıra dengeyi etkileyen hastalıkları olan kişiler için de hayati önem taşımaktadır. Denge kontrolünün altında yatan nöral katkının anlaşılması, rehabilitasyon süreçlerini iyileştirmek için bakış açımızı genişletmenin anahtarıdır.

Bu tezde, M1 üzerine tDCS uygulayarak M1'in denge becerisi edinimindeki rolünü araştırdım. Bu çalışma, M1 bacak bölgesi işlevinde tDCS kaynaklı gelişmelerin, genç yetişkinlerde arka yönde denge bozukluklarına neden olan ileri yönlü pertürbasyonlara yanıt olarak denge becerisini ve nöromüsküler işlevi kolaylaştırdığına dair kanıtlar sunmaktadır. Bu çalışma, tDCS'nin pertürbasyon temelli denge eğitimi takiben denge, nöromüsküler ve kortikal gelişmeler üzerindeki etkilerini inceleyen ilk çalışmadır. Anodal stimülasyon ile denge eğitimi yoluyla gelişmiş kas koordinasyonu ile birlikte gelişmiş kas yanıtı gecikmesinin ortaya çıktığını gösterdim. Bu değişiklikler, yaralanma ortaya çıkmadan dengenin yeniden kazanılması için hayati önem taşımaktadır. Bu bulgular davranışsal analizle, özellikle anodal stimülasyon grubu lehine azalmış VKM yer değiştirmesi ve eklem hareketleri değişiklikleri ile desteklenmektedir. Azalan kortikal fasilasyon, üç seans eğitimden sonra denge kazanımında M1'in rolünün azaldığına işaret edebilir. Anodal stimülasyon grubunda öne doğru pertürbasyonlar sırasında gözlemlenen alpha gücündeki azalma da pertürbasyonlardan sonra denge bozulmalarının daha etkin izlenmesi anlamına gelebilir.

Denge becerilerinin geliştirilmesi ve korunması, bazal ganglionlar, serebellum veya SMA gibi M1 ile iletişim halinde olan diğer kortikal veya subkortikal bölgelere de bağlı olabilir. Bu bağlamda, beyin modülasyon teknikleri bu yapıların denge öğrenimine katkılarını ortaya çıkarmak için elzem olmaya devam etmektedir. Gelecekteki çalışmalar, denge kontrolündeki rollerini daha iyi açıklığa kavuşturmak için M1'i denge kontrolüyle ilgili diğer beyin bölgeleriyle birlikte uyarmanın birleşik etkilerini araştırabilir. Ayrıca, diğer gruplarda, örneğin yaşlılar ya da Parkinson hastalarında, M1 üzerinden tDCS ile denge öğrenimi, M1'in denge öğrenimindeki rolü hakkında daha fazla bilgi verecektir.

Bilim Kodu : 10105.06

Anahtar Kelimeler : Primer Motor Korteks, tDCS, Denge Eğitimi, Motor Beceri Edinimi

Sayfa Adedi : 106

Danışman : Prof. Dr. Nevin Aysel GÜZEL

İkinci Danışman : Prof. Dr. Charles LAYNE

ACKNOWLEDGEMENTS

I could not have achieved this promotion alone. I am thankful for the people who greatly supported me and helped me succeed and those who posed significant challenges that motivated me to grow.

First and foremost, I would like to express my sincere gratitude to Prof. Dr. Michael Nitsche for his invaluable support and guidance. Although he was not my official supervisor for this thesis, his contributions and insights greatly enhanced my work. His expertise played a vital role in the success of my doctorate. I feel truly fortunate to have benefited from his guidance.

I am also deeply grateful to Prof. Edmund Wascher for his expert guidance and unwavering support. His valuable contributions to methodology and data analysis have been essential to my work.

Additionally, I would like to sincerely thank Prof. Charles Layne for his encouragement and guidance from the beginning of this thesis research. His kindness and supervision were invaluable throughout this project and greatly enriched my growth.

I want to extend my thanks to my supervisor, Prof. Dr. Nevin Aysel Güzel, and thesis committee members, Prof. Dr. Arzu Güçlü Gündüz and Prof. Dr. Sevil Bilgin, for their incredible support during this process.

I cannot express enough gratitude to my wife, Canan, for her unwavering support and patience, even as she pursues her doctorate. Thank you for being by my side throughout this journey and for your countless sacrifices. I also want to acknowledge the warm companionship of our cat, Izo.

I would like to acknowledge my family — my mother, father, and sister — whose endless belief in me has always been a source of strength. They have provided encouragement during challenging times, and their love has fueled my determination to succeed.

I am also grateful to my friends and colleagues, Julian, Lorena, Tobias, Tin, Barbara, Emad, and James, for their heartfelt support throughout my research.

I would like to express my profound gratitude to the Scientific and Technological Research Council of Türkiye (TÜBİTAK) for their generous support of my thesis through the 2214-A International Research Fellowship Programme for PhD students.

I am also immensely grateful to the Leibniz Research Centre for Working Environment and Human Factors at Dortmund University for providing an excellent environment for conducting my experiments and the essential resources that significantly contributed to this research.

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SYMBOLS AND ABBREVIATIONS

The symbols and abbreviations used in this study are presented below, along with their explanations.

Symbols

Ca⁺²

Calcium

cm

Centimeters

db

Decibel

Hz

Hertz

m

Meters

ms

Milliseconds

Abbreviations

Explanations

APA

Anticipatory Postural Responses

APR

Automatic Postural Responses

BNS

Backward No Sound.

BS

Backward Sound

BoS

Base of Support

CNS

Central Nervous System

COM

Center of Mass

COP

Center of Pressure

CPA

Compensatory Postural Adjustments

EEG

Electroencephalography

EMG

Electromyography

GABA

Gamma Aminobutyric Acid

Abbreviations	Explanations
FNS	Forward No Sound
FS	Forward Sound
ICF	Intracortical Facilitation
LTD	Long-Term Depression
LTP	Long-Term Potentiation
LLR	Long-Latency Response
MEP	Motor Evoked Potential
MLR	Medium-Latency Response
M1	Primary Motor Cortex
NMDA	N-methyl-D-aspartate receptor
SICI	Short-Interval Intracortical Inhibition
SMA	Supplementary Motor Area
PER	Perturbation-evoked Responses
PEP	Perturbation-evoked Potentials
SLR	Short-Latency Response
TMS	Transcranial Magnetic Stimulation
tDCS	Transcranial Direct Current Stimulation
UDP	Use-Dependent Plasticity

1. INTRODUCTION

Balance control is a fundamental motor skill essential for performing a wide variety of activities in daily life and sports, which require the movement of body parts or the whole body. Under the umbrella term "balance control," standing balance forms the foundation for all movements, as people usually stand while completing their daily tasks.

Balance control mechanisms can be divided into two main strategies: feedforward (proactive) and feedback (reactive) balance. A good example for feedforward balance control is standing in an upright position. During an upright stance, the body inherently oscillates in a small amplitude due to factors such as breathing, heartbeats, and the less reliable/noisy signals arising from the body. Thus, the CNS anticipates the upcoming movements, allowing motor outputs to easily be prepared in advance. On the other hand, reactive balance involves external perturbations. This requires rapid processing of sensory inputs and the production of appropriate motor outputs accordingly. This provides more challenging balance disturbances because of its unpredictable nature and the shorter processing time needed to prevent falling.

Good postural control requires good sensorial inputs and appropriate reactions to these inputs by the central nervous system (CNS) and musculoskeletal systems. This input-output loop is a continuous process that integrates visual, vestibular, and proprioceptive information to maintain proper balance. These inputs are integrated by re-weighting sensory inputs to identify the relative reliability of the three inputs and then controlling upright posture according to the weighted sensory information [1]. During balance perturbations, proprioceptive information arises faster than other sensory inputs. In addition to that, the perturbation effect is dampened as it travels from the feet to the head. Consequently, visual and vestibular inputs become less reliable as the head is the least and latest affected part of the body after translation of the standing surface [2]. Thus, CNS relies primarily on proprioceptive inputs during postural perturbations that result in rapid postural responses [3-5].

As soon as the balance is disturbed, the body attempts to hold the COM within the base of support by moving it out beyond the center of pressure. The postural outcome of APRs' to the perturbation is feet-in-place strategies ("ankle strategy" and "hip strategy") [7]. The postural control strategy used to respond to any balance disturbance is selected by the CNS based on previous experience. When a perturbation impact is small and can be easily handled, the body uses the ankle strategy. This strategy involves moving the entire body as an inverted pendulum around the ankle joint controlled by shank muscles. The body uses the hip strategy when perturbations exceed the threshold that the ankle strategy can restore balance [7, 8]. The hip strategy involves hip joint movements, and it is capable of moving COM faster than the ankle strategy [7, 8]. In this situation, the body behaves like an inverted double pendulum model as the ankle and the hip joints are moving to maintain balance. This attempt of the body may be followed by moving the BoS beyond the COM's movement (Stepping response), also known as the change-in-support strategy [1]. An increased hip joint involvement indicates a greater perceived impact of the perturbations and leads to greater COM displacement along with higher postural instability [9]. Therefore, the smaller hip joint excursion would mean better balance control and the peak hip angle after the perturbation can be used as an index of postural control strategy [10]. Based on this understanding, it is expected that balance training causes less COM displacement during perturbations.

Previous studies demonstrated that humans respond to perturbations from different directions in a distinct way. From a biomechanical perspective, the body can recover the balance disturbances in forward direction (results from the backward translation of the supporting surface) easier due to greater ankle plantarflexion torque than dorsiflexion torque and a larger hip flexion movement range compared to extension movement range. Oude Nijhuis et. al. investigated the first trial effect of rotational perturbations. They compared the difference between the first and second perturbation trials to the second and following trials in different directions in order to determine the improvement rate. They found greater postural instability in the very first perturbation especially if perturbation trigger the backward balance disturbance [65]. Startling stimuli elicits startle reflex which is a rapid, involuntary reaction to an unexpected sensory signals. Nonnekes et. al. investigated the startling auditory stimulus on postural responses during forward or backward perturbations. They demonstrated that responses to the forward perturbations (forward translation of the surface) may share a common mechanism with startle reflex pathway as startling auditory signal improved the balance recovery responses in forward perturbations but not in backward

perturbations. Their findings suggested that postural responses to different perturbation directions are possibly processed by different neural circuits [11]. The similar mechanism can be seen in the clinical outcomes in Parkinson's disease. It is a neurodegenerative disease that affects the dopaminergic neurons in the basal ganglia which has significant role in postural control [12]. In the later stages in Parkinson's disease, postural instability is increased resulting the falling risk especially in the backward body sway compared to the forward body sway [13]. These findings imply that basal ganglia modulate central motor and cognitive set that leading to rapid recovery to the perturbations in different directions [13].

Cognitive set shifting defines the ability to switch responses to changes depending on the tasks and/or contexts. Good balance requires precise intermuscular coordination that involves preferential activation of muscles depending on the direction of the perturbation. This selective control of muscle contractions reflects improved coordination. Although tibialis anterior primarily counteracts the forward perturbations and the soleus primarily counteracts the backward perturbations [66], reflex responses are triggered by the perturbation onset in both muscles in both directions [67]. Faster muscle onset might indicate better balance recovery to prevent them from falling.

Beyond muscle responses, a large negative potential, known as the N1, is elicited in the supplementary motor area at 90-200 ms after the perturbation onset [14, 15, 21]. The amplitude of N1 and underlying frequency bands, especially the theta frequency band (3-7 Hz), strongly correlate with the balance perturbations [16, 17]. The amplitude of the N1 also reflects the involvement of cognitive processes related to afferent inputs arising from the proprioceptors in the lower extremities [18]. It is influenced by a perceived threat, predictability of the perturbations and attention [19, 20]. Stokkermans et al. investigated the relationship between mid-frontal cortical dynamics and predicted perturbation impact on the body. They changed the initial body posture by altering the leaning angle and direction. Their findings showed that theta power is modulated by the initial posture [68]. Similar findings were found by another study conducted in the same laboratory, Solis-Escalante et al., found that N1 amplitude and latency along with theta, alpha and beta bands power are modulated by the perturbation intensity [14]. Another study indicated increased perturbation intensity causes increased N1 amplitude on the Cz electrode and decreased latency [22]. Although the relationship between perturbation characteristics and N1 amplitudes and frequency band power has been explored in several studies, to the best of our knowledge, no study has

specifically investigated the effect of balance training with or without brain modulation techniques on N1 characteristics and the power of the frequency bands. With improved sensory integration and experience gained through balance training, the N1 amplitude and latency as well as theta and alpha bands power are expected to decrease, indicating a reduced activation in fronto-central cortex [19].

Previously, it was assumed that balance is controlled by spinal and subcortical level [23]. In recent years, a better understanding of the role of primary motor cortex (M1) in balance control has emerged. TMS studies showed that excitability in M1 is reduced during the execution of task after several weeks of balance training [24]. Similarly, transient gray matter changes in the sensorimotor areas were shown even after two sessions of balance training [69]. A recent study demonstrated that disrupting M1 activity with low-frequency repetitive TMS (rTMS) doesn't impact balance skill acquisition after a single session of six sets of balance training. However, this disruption of M1 activity results in impaired retention of balance skill after 24 hours [25]. Current literature suggests that M1 is likely to play a central role, especially at the beginning of balance training, other motor control centers seem to replace the M1 in motor control in long-term motor learning. A similar mechanism has been shown in a recent animal experiment that demonstrated the role of M1 in motor learning conducted by Hwang et. al. [26]. They found that inactivation on M1 in the first four weeks of training resulted in impaired motor performance in mice. However, no significant difference was demonstrated when inhibition is applied after eight weeks of training. Their study supported the idea that the M1 plays a significant role in the initial stage of motor learning process. Despite an increase in studies investigating the role of M1 in balance control, its exact mechanism in acquiring balance skill remains unclear. Thus, this study focuses on the role of the M1 in acquiring balance skills.

A safe, non-invasive technique to explore the role of M1 is transcranial direct current stimulation (tDCS). Anodal tDCS enhances neuronal excitability by modifying the resting membrane potential of neurons through the application of small direct electrical currents [27]. Enhanced excitability facilitates neuroplasticity and long-term potentiation, which is essential for skill acquisition and retention. Anodal tDCS induces plasticity through modulating N-methyl-D-aspartate receptor (NMDA) and gamma-aminobutyric acid (GABA)ergic activity [29, 70]. Thus, it can improve motor learning [31-34] depending on the montage, intensity, [71] type of task [25] and task complexity [30]. A recent systematic

review concluded that anodal stimulation on M1 improves the dynamic balance in young adults [35]. Craig and Doumas conducted anodal stimulation on M1 and measured the dynamic balance during rotational movements of the standing surface. They found improved balance by measuring the peak-to-peak center of pressure sway in closed eyes conditions immediately after the stimulation and 30 min after the stimulation [36]. Kaminski et al. also demonstrated improved balance during balance training on the movable platform combined with anodal stimulation compared to the group that received sham stimulation. This improvement was preserved 24 hours after the training [32]. Anodal stimulation was selected in this study to enhance motor learning and increase the excitability of the M1.

It is important to note that the most studies investigating the effect of tDCS or rTMS on M1 in dynamic balance control primarily tested the feedforward mechanism of balance except for the study conducted by Craig and Doumas [36]. The basis of this approach could be the well-known roles of the different parts of the CNS. The role of M1 involves voluntary movements and motor planning. Thus, it might be expected that M1 has more pronounced role using feedforward mechanism of balance, for example maintaining the balance board in a position parallel to the ground. However, it is crucial to elucidate the underlying cortical mechanisms involved in reactive balance responses to the perturbations that simulate the possible daily challenges such as trips and slips. The mechanism of reactive balance is possibly more complex than the feedforward mechanism as it requires rapid assessment of body position, transferring the posture information to the SMA and premotor cortex to produce motor plan and finally motor cortical areas including M1 produce appropriate motor responses communicating with cerebellum and basal ganglia [37]. In addition to the effect of tDCS on cortical structures, it can also facilitate subcortical structures [38]. Fifteen minutes of anodal tDCS over the non-dominant motor cortex resulted in a reduced onset latency response of ankle muscles to perturbations compared to the sham tDCS. Their findings implied that tDCS altered the excitability of subcortical structures which has a role “central set” lead to faster muscle onset latency in response to the perturbations [38].

Transcranial magnetic stimulation is a non-invasive brain stimulation technique that uses an electromagnetic field to induce electric current in the brain, which activates underlying corticospinal and intracortical neurons [39]. Therefore, TMS can be employed to evaluate the degree of cortical adaptation in intracortical inhibitory and excitatory circuits of the M1 resulting from balance training. Intracortical inhibitory circuits are typically assessed by

measuring short-interval intracortical inhibition (SICI), whereas excitatory mechanisms can be evaluated by measuring intracortical facilitation (ICF). Both measurements involve a conditioning subthreshold stimulus followed by a test stimulus. These double pulse procedures can probe GABA_A-mediated inhibitory (SICI) and glutamatergic facilitatory (ICF) networks. It should also be noted that ICF is partially regulated by GABAergic circuit [72] and its underlying mechanism is poorly understood.

Motor training typically leads to decreased inhibition (SICI) accompanied by increased facilitation (ICF) after short-term motor learning [40, 41]. Decreased SICI is assumed to facilitate motor learning process through plasticity [42]. In spite of this, conflicting results have been reported. For instance, 4 weeks of squat training, reduces the level of SICI by 32% in rectus femoris representation area [43]. Similar study conducted by Ansdell et. al. demonstrated no changes in SICI and ICF in the vastus lateralis muscle after 4 weeks of squat training, regardless of whether the conditions were task-specific [44]. On the contrary of the studies that showed decreased SICI throughout motor learning, training in more coordinative skills increases the level of inhibition. A cross-sectional study showed that elite badminton players demonstrate a higher inhibition and excitation compared to novice players at rest [45]. Mouthon and Taube found that enhanced level of SICI after 2 weeks of balance training [24]. Taube et. al. found that increased SICI following 4 weeks of balance training and was then decreased when the participants continue with a 4 weeks of explosive training [46]. Their findings support the previous hypotheses that SICI is enhanced after complex motor tasks while it is reduced following less complex motor learning tasks.

Most motor learning studies have predominantly investigated SICI and ICF in upper extremity muscles. The previous studies indicated that upper extremity muscles have stronger corticospinal projections from M1 compared to the lower extremity [47]. However, not all lower extremity muscles have similar corticospinal connections. TA, for example, has much stronger corticomotor connections than SOL [47, 48] and is even comparable to the hand muscles [49]. Supporting this, a recent study showed that tibialis anterior representation shows similar GABAergic and glutamatergic interneuronal circuits as the abductor digiti minimi muscle in the hand [50].

Notably, in the literature, results of excitability measures vary, possibly because of the type of motor skill and methodological differences. Variations in SICI and ICF measurements in

balance studies depend on several factors, such as the task demand [63, 64] and the testing conditions. These conditions include whether the muscles are in an active or passive state and whether the testing conditions match the learning task [24, 46, 52]. Despite the task-dependent nature of intracortical excitability, we conducted these measures at rest to obtain more reliable results under more controlled and standardized conditions and due to the technical restrictions associated with performing measurements during balance tasks. This approach also helps to exclude the possible confounding effects of muscle activity.

In this study, there were 4 different conditions during the balance test consisting of forward-no sound (FNS), backward-no sound (BNS), forward-sound (FS) and backward-sound (BS). “Forward perturbation” refers to the forward translation of the surface that results in posterior balance disturbance and “Backward perturbation” refers to the backward translation of the surface that causes balance disturbance in the anterior direction. As a timing cue, the "beep" sound is provided two seconds before the perturbation onset but does not convey any information regarding the direction of the perturbation.

This study aimed to explore the role of M1 in balance control. To test our hypothesis, we recruited three groups for this study: One receiving anodal stimulation, another receiving sham stimulation, and a control group. We hypothesized that M1 modulates the improvements in balance control in response to perturbations. Muscular and cortical responses (N1 amplitude and latency and time-frequency analysis), as well as corticospinal excitability measures (short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF)) and behavioral data (COM, variance of COM and joint excursions), were measured to test our hypothesis. We hypothesized that balance training decreases N1 amplitude and latency and reduces theta-alpha bands power particularly in the anodal stimulation group. Additionally, we hypothesized improved balance responses (decreased COM displacement and COM variances) as well as cortical excitability changes indicative of plasticity related to the balance improvements (increased SICI and decreased ICF).

2. GENERAL INFORMATION

2.1 What is Balance and Postural Control

Balance or postural equilibrium involves maintaining the body orientation against internal or external perturbations on the body segments that attempt to change the position of body segments. Internal perturbations are created by self-initiating movements such as when flexing hips or raising the arm, while external perturbations result from daily tasks or sport activity such as standing on a moving bus or interacting with opponents during sports competitions. The term “Balance Control” refers to the ability to maintain the center of mass over the base of support while executing other tasks such as walking, carrying something or sports activities. Balance control is essential to reducing falls and subsequent injuries as well as enhancing sports performance [73, 74].

The body continuously oscillates around its base of support even in the quiet standing position because of the relatively small base of support (BoS), due to the bipedal standing and relatively high Center of Mass (COM). Noisy signals from the body receptors, heart pulses and ventilation are other factors causing oscillations during quiet standing. These oscillations are called postural sway. COM is thought as the point where the average body mass is located and it is approximately 2 cm in front of the 2nd lumbar vertebra [7]. Central Nervous System (CNS) minimizes COM movements, also known as body sway, caused by internal or external forces that may cause a danger of falling or losing balance. The COM movements that go beyond the desired borders are detected by sensory systems (somatosensory/proprioceptive, visual, and vestibular systems). In order to prevent bodily harm, CNS must rapidly process these inputs to detect deviations from upright or desired posture and correct them immediately. After processing these sensory inputs, the CNS generates an appropriate motor reaction to keep the COM inside the BOS. The consequences of each motor command are monitored and tuned by CNS to establish fine motor outputs. This is a continuous loop of processing involving sensations and reactions and is defined as a closed-loop feedback control organization [1].

External perturbation can be applied by translation or rotation of the base of support (BoS) or COM under a controlled, laboratory environment to imitate daily life postural challenges. As soon as the balance is disturbed, the body attempts to hold the COM within the BoS by

moving it out beyond the center of pressure. The body's first response to perturbation is stretch reflex, also known as short-latency response that starts ~30 ms after the perturbation [59]. The second response to the perturbation is feet-in-place strategies ("ankle strategy" and "hip strategy") [7]. A control strategy is selected based on the impact of the perturbation and previous experience by the CNS. When a perturbation is small and can be easily handled, the body uses the ankle strategy. This strategy involves moving the entire body as an inverted pendulum around the ankle joint controlled by shank muscles. When the BOS moves forward, the tibialis anterior mainly counteracts the impact of perturbation, while the soleus muscle is maximally active during backward translations [75]. The body uses the hip strategy when the perturbation exceeds the ankle strategy's threshold to restore balance [7, 8].

The hip strategy involves hip joint movements, and it is capable of moving COM faster than the ankle strategy [7, 8]. In this situation, the body behaves like an inverted double pendulum model as the ankle and the hip joints move to maintain balance. After this attempt the body may be followed by moving the BoS beyond the COM's movement (Stepping response) also known as the change-in-support strategy when feet-in-place strategies couldn't recover the balance [1].

2.2. The Role of the Central Nervous System in Balance Control

2.2.1. Sensory systems

All movements and oscillations in the body such as breathing, heart beats, muscle movements must be encoded by sensory systems to enable the CNS to control the body in response to internal or external perturbations. Balance control is an adaptive process that includes a continuous feedback system of processing visual, vestibular and proprioceptive inputs by the spinal cord, brainstem, cerebellum and cerebral cortex [76, 77]. Visual input provides information about potentially destabilizing situations, especially when performing a novel balancing task. Vestibular input is important for maintaining balance on an unstable surface and during head movements. The proprioceptive signals originated from mechanoreceptors in the soles of feet and muscles and tendons around ankle joints provide information about the motion of the body relative to the surface. These sensory inputs are re-weighted to identify the relative reliability of each of them and then this weighted sensory information is used for generating motor outputs to control upright posture [1]. When we move in a dark environment, for example, visual information is less reliable than vestibular

and proprioceptive inputs, meaning that vestibular and proprioceptive inputs are weighted more. When an ankle joint is injured, for another instance, proprioceptive signals become noisier, resulting in less reliable proprioceptive information. Thus, other sensory inputs are upweighted after the ankle sprains.

After the balance perturbation begins, proprioceptive information arises faster than other sensory inputs. In addition to that, the perturbation effect is dampened as it travels from the feet to the head. Consequently, visual and vestibular inputs become less reliable as the head is the least and latest affected part of the body after translation of the standing surface [2]. Thus, CNS relies primarily on proprioceptive inputs during postural perturbations since proprioceptive system triggers faster responses than input from other sensory systems. [3-5].

Proprioception generally implies the sense of ability of the position and movement of our body in space and muscle force and tone, sense of effort, and balance [78, 79]. Proprioceptive information arises from proprioceptors which are specialized mechanosensory organs within muscles, joints and skin. The most prominent proprioceptors in the musculoskeletal system are the muscle spindle and Golgi Tendon Organ. Neuronal signals are initiated by both receptors in response to biomechanical circumstances in the respective body parts [80].

Muscle spindles are embedded in the skeletal muscle that provide information about the muscle's length and the rate of the muscle length changes. As a common occurrence, muscle fibers stretch when load is added to them in the form of weight or resistance. Because of its anatomy, a stretch/contraction of the extrafusal muscle fibers causes a simultaneous response of the much smaller intrafusal muscles. Each intrafusal fiber has its own motor innervation and sensory innervation coming from axons of the largest diameter in a sensory nerve. The muscle spindle is never disabled and continuously sends information about the muscle length and the rate of speed and amplitude of the muscle to the CNS.

Muscle spindles are innervated by 1a afferent fibers, conducted with alpha motor neurons via interneurons. Through this loop, a change in muscle spindle length results in an immediate contraction of the muscle called the 'stretch reflex' [81]. Thus, proprioceptive information from the muscle spindles is essential in reactive postural control even if the

‘stretch reflex’ is generally not strong enough to control the COM after unexpected perturbations.

When perturbation occurs under a controlled condition or slips and trips happen during daily life. The feet are the most affected part of the body, so proprioceptors in the ankle sense the positional and angular changes before other sensory systems. It leads to an immediate recovery response through spinal and subcortical structures after balance perturbations [6].

2.2.2 Control systems

Anticipatory Postural Adjustments (APAs) and Compensatory Postural Responses (CPRs)

The central nervous system (CNS) is responsible for generating appropriate responses to prevent falling when external perturbations disrupt the balance of the body. CNS employs two main strategies for controlling balance; Anticipatory (APAs) and Compensatory (CPAs) postural adjustments [53]. APAs involve preparations of the muscles prior to the upcoming perturbations, while CPAs refer to the reactive postural responses to the perturbations. When CNS generates APAs properly, COM displacements after the perturbations will be decreased, and recovering the balance after the perturbations will be easier and require smaller CPAs. The central nervous system learns how to generate APAs correctly and in a timely manner through experiences [82]. These responses are well organized and include highly adaptive patterns of muscle synergies.

The SMA and pedunculopontine nuclei (PPN) are involved in the planning of APAs [7]. The Supplementary Motor Area (SMA) is located on the dorsomedial frontal cortex and anterior to the M1 leg representation area. Many studies have supported the role of SMA in modulating APAs. A previous study showed that inhibition of SMA by using repetitive TMS (rTMS) led to impaired APAs [83]. Nomura and Kirimoto investigated the effect of anodal tDCS on SMA during rapid arm flexion tasks by measuring the EMG activity of deltoid and biceps femoris muscles and COP sway. APAs in older adults were improved with anodal tDCS by reducing COP sway and improving the muscle onset time of the biceps femoris (postural muscle) [84]. Besides its role in APAs, studies also demonstrated that SMA is involved in cognitive processing, movement preparation, voluntary control and coordination [85-89]. SMA integrates sensory, motor, and cognitive information due to its location

between the primary motor cortex and the frontal lobe and through its connections with M1, dorsolateral prefrontal cortex and subcortical structures involved in movement control such as basal ganglia, cerebellum and brainstem [90, 91] The SMA's role in the sensory integration process is supported by its role in the initiation and coordination of complex movements, postural stabilization, and the planning of internally generated actions.

Although it was believed that spinal reflexes are responsible for the postural control, recent studies showed that this process is more complex. It involves cortical, subcortical and brainstem structures including cerebellum, thalamus, temporo-parietal cortex, sensorimotor and prefrontal areas, brainstem and basal ganglia [6, 81]. Three potential neural loops are involved to control unpredictable perturbations. These loops are active during different times after the perturbation onset. A monosynaptic spinal reflex pathway produces the short-latency response (SLR) and appears in the EMG recording ~30–60 ms after perturbation onset. This short period of time implies that group I afferent fibers are responsible for generating SLR, also known as stretch reflex, as this is the only route that is short enough. The torque generated around the joints by SLR is insufficient to control the COM [7]. Immediately following SLR, the medium-latency response is observed in muscle activity in the interval of ~60–85 ms after perturbation onset. This response is also generated by a subcortical level and is likely considered group II afferents involvement arising from muscle spindles [92, 93]. The third, long-latency response occurs between ~85–120 ms after perturbation onset. It relies on a transcortical pathway involving the primary sensory and motor cortices that include stepping and reaching responses to perturbation [59]. The medium-latency response and the long latency responses may converge into each other depending on the type of perturbation and the initial posture. These responses depend on too many factors such as characteristics of the perturbations (the amplitude, acceleration, direction) and body (height or initial position) or expectation and experience of the perturbation condition [6]. However, the latencies after the perturbations can be calculated with different time frames after the perturbations to separate the neural loops from each other and guarantee waiting enough time to involve the responsible part of the central nervous system for each neural loop. As the fastest voluntary reactions to sensory signals occur around 180 ms, as reported by [7], responses within the 120–180 ms range were also analyzed in this research to capture further automatic postural responses. The compensatory stepping response, a critical reaction to maintain balance, typically occurs approximately 250 ms after the onset of a perturbation [7]. Therefore, the time period between 180–250 ms was also

calculated to encompass the transition from initial voluntary reactions to the execution of the stepping response.

The Role of Motor Cortices in Balance Control

Historically, it was thought that the primary motor cortex (M1) has a relatively limited role in postural control and the locomotion is conducted mainly by spinal/brainstem reflexes [23]. However, more recent investigations have revealed that the motor cortex and other cortical areas play an important role in postural control [93-95]. It is known that M1 is responsible for performing voluntary movements and recovering the balance after the perturbation involves postural responses generated before voluntary movements. Although many studies investigated the role of M1, its role in motor skill acquisition remains elusive [6, 46, 96].

Mierau et al. reported that the posterior parietal cortex and the supplementary motor area have an important role in balance control based on EEG responses to perturbations [19]. Cortical activities related to movement have two main components: early and late components. The late component includes a rapidly increasing negative potential starting approximately 400 ms before the movement, while the early component is a gradually increasing negative potential; this occurs between about 1500 to 400 ms before the movement onset [97]. The late component is known as readiness potential and is generated by the primary motor cortex whereas the supplementary motor area and premotor cortex generate the early component. These potentials are cortical correlates of planning, preparation, and initiation of voluntary movements [97, 98]. Goel et al. identified the critical role of a cortical neural network in calibrating the postural response in a study in which they investigated the effect of transcranial magnetic stimulation (TMS) over supplementary motor areas during perturbation tasks performance [94]. Their results suggest the role of fronto-parietal regions in monitoring postural changes and contributing to motor outputs.

By exciting or inhibiting areas of the cortex and evaluating the response to perturbation, scientists can gain additional insight into the role of a specific cortical area in postural control. Therefore, the use of tDCS for neuromodulation has increased in recent years. Several studies have investigated the effect of tDCS on balance in specific groups (e.g., Parkinson's disease, cerebral palsy, stroke, young adults) [31]. However, no reports of the effects of tDCS on balance recovery strategies during reactive balance training are available.

This thesis will, therefore, provide important additional information related to postural control mechanisms.

Peterson et al. examined corticospinal excitability in lower extremity muscles before EMG onset during three distinct tasks: voluntary activation, postural reactions, and unanticipated postural perturbations [99]. They found that the M1 is involved in APA initiation before voluntary movements but not before unanticipated perturbations. A recent study investigated the role of M1 by using low-frequency repetitive TMS on M1 during balance learning sessions. There was no difference in balance learning between the sham-rTMS and rTMS groups after six sets of balance training in one day, but there was a difference in retention. The results suggest that M1 is involved in the early period of balance learning and consolidation [25].

The literature suggests that the primary motor cortex (M1) is likely to be the central part of the system at the beginning of balance training, like any type of motor skill acquisition [95]. Rapid and transient gray matter changes in the sensorimotor areas were shown even after two sessions of balance training [69]. Besides, an animal model showed that the inhibition of the M1 caused impaired motor learning in the first stage of motor learning in mice. Hwang et al. trained mice to move a joystick after an acoustic signal to reach an award, and they performed optogenetic inactivation on M1 [26]. The results showed that activation of inhibitory neurons impaired motor performance in the first 4 weeks, but there was no significant change after 8 weeks of training. According to the findings, other motor control centers may replace the primary motor cortex in motor control in long-term motor learning. Specifically, this study examines the primary motor cortex's role in balance training's effectiveness. Therefore, the number of training sessions in the current study was set at three sessions to see the effect of tDCS during short-term training when the motor cortex might show relatively more adaptation as compared to other areas.

2.3 Motor Learning

Learning motor skills involves practicing movements to acquire new motor behaviors or execute already known ones more effectively. Motor tasks can be very basic, e.g., calisthenics, or much more complex tasks, such as visuomotor tasks. The motor learning process highly depends on the motor task that is being studied. Balance control is already

developed to varying degrees in healthy adults. Thus, the motor learning process during balance training is more about adaptation than a skill acquisition process. This adaptation involves fine-tuning existing motor skills through improving motor coordination to improve balance and stability.

Motor learning encompasses several learning processes that are likely to differ depending on which task is being performed and which part of CNS is being used. These processes include instructive (strategy-based, explicit), reinforcement (reward-based), sensorimotor adaptation-based (recalibration, implicit), and use-dependent plasticity (repetition-based) [100].

Instructive learning is a method of solving motor problems through cognitive or explicit knowledge. This motor learning strategy is elicited by specific external feedback provided by the physiotherapist about the movement errors and/or performance [100, 101]. Multidimensional cognitive processes are involved in instructive motor learning, including comprehension of instructions and the prefrontal cortex primarily mediates it and the cognitive load is high [100]. Although perturbation-based balance training mainly involves sensorimotor adaptation-based motor learning [102] (see below), This motor learning strategy is used in balance learning processes by physiotherapists to reduce movement errors in patients during rehabilitation. Reinforcement or reward-based motor learning requires exploring the optimal motor command for achieving a successful outcome without paying attention to how the movement was done. Like sensorimotor adaptation-based motor learning, reinforcement motor learning uses error prediction. As part of reinforcement learning, the prediction error encodes the probability of success in the movement [101]. The individual updates the motor command based on the outcome (reward or punishment) of the particular action. According to the feedback (positive or negative) the previous action may either be repeated or updated. Both reinforcement motor learning and instructive motor learning have a feedback system after a movement or task is performed. Unlike reinforcement signals, instructive signals include details on how to improve movement and task quality, while reinforcement signals do not [101].

Sensorimotor adaptation-based motor learning is a short-term motor learning that is driven by sensory prediction errors. Sensory prediction errors are the difference between the expected sensory output of intended movement and the sensory consequences of actual movement. This form of learning is the ability to perform accurate movements considering changing environmental conditions or unexpected task demands. When CNS senses sensory prediction errors, the motor commands are quickly updated to decrease the amplitude of the sensory prediction errors. Since standing balance is a well-learned ability for healthy adults, perturbation-based balance training can be considered motor adaptation instead of skill learning [103]. It aims to improve the body's responses to perturbations in specific speeds and directions. The discrepancies between predicted movement and the actual balance disturbance after the perturbations drive the adaptation in the CNS through the perturbation-based balance training. This adaptation occurred implicitly and is believed to rely primarily on the cerebellum [100].

Motor learning that is driven by repeated practice is defined as use-dependent motor plasticity (UDN) [100]. Repetition of a balance task leads to more similar and improved responses to perturbations. Through repetition, movement planning and execution are facilitated which reduces variability and increases speed [101]. Structural and functional changes throughout the CNS mediate this mechanism of learning. To conduct a movement pattern automatically, a use-dependent learning strategy is probably required [100] as it also enables sensorimotor adaptation and can be used with other motor learning strategies mentioned above [104]. Balance training promotes use-dependent plasticity by repetitions of similar motor actions. The underlying mechanism of use-dependent plasticity is GABAergic inhibition [105].

The terms “Proprioceptive training” and “neuromuscular training” as well as “sensorimotor training” have been extensively used interchangeably with “balance training”. However, there are some concerns about using these terms synonymously [93]. The term “proprioceptive training” implies improving proprioception, while neuromuscular and sensorimotor training encompasses a broader range of motor training tasks that target neuromuscular and sensorimotor improvements. Balance training, on the other hand, induces adaptation across all systems involved in balance control, including vestibular, visual, and proprioceptive systems, as well as integration of these sensory inputs and motor systems such as sensory-motor cortices, prefrontal cortex, basal ganglia, and cerebellum. CNS

adaptations to produce rapid and proper postural responses to the perturbations require “central set” changes. The term “Central set” refers to the regulation of automatic postural responses, allowing for the modification of these responses to perturbations based on prior experience and predictive sensory information [106]. In this way, the response quality can be tuned in advance to make more appropriate and rapid muscle responses possible. Although the central set is often considered as a supraspinal modification of responses, it defines adjustments to automatic postural responses, which refers to the adaptation of subcortical and spinal structures as well. Wälchli et al. defined a concurrent change in Ia-afferent transmission accompanying cortical activity changes, which may imply these cortical changes lead to modifying central set [107].

The adaptation to the balance training occurs in two main mechanisms: anticipatory (feedforward, proactive) and compensatory (feedback, reactive) [108]. In the anticipatory mechanism, the brain predicts the consequences of a balance disturbance through experience or practice and prepares for the perturbations beforehand by adjusting corticospinal excitability [55, 109]. In the compensatory mechanism, however, the brain adapts to the perturbations and their consequences on postural balance and adjusts motor commands through training.

2.3.1 Plasticity

The capacity of the brain to change its structure and neuronal activity in response to short- or long-term environmental changes is called plasticity. The cellular mechanism of plasticity includes both modifying the preexisting neurons/synapses and restructuring the cortical circuits [110]. Synaptic plasticity subserves a type of neuroplasticity and refers to changes in the strength and efficacy of synaptic transmission in response to external stimuli [111].

Long-term Potentiation (LTP) and Long-term Depression (LTD) are two extensively studied forms of synaptic plasticity. LTP is a rapid and long-lasting increase in synaptic strength induced by a neuronal activity pattern that is usually brief and strongly correlated with pre- and postsynaptic activity. Conversely, LTD involves a fast and enduring decrease in synaptic strength usually caused by a neuronal activity pattern that is typically sustained and weakly correlated with pre- and postsynaptic activity [110].

Both LTP and LTD are largely dependent on N-methyl-D-aspartate (NMDA) receptors which are calcium (Ca^{2+}) channels activated by glutamate. Under resting conditions, NMDA receptors are blocked by magnesium (Mg^{2+}) ions. These Mg^{2+} ions are separated from the receptor upon depolarization of postsynaptic neuron leading the Ca^{2+} ions enter the postsynaptic neuron through the NMDA receptors. The influx rate of Ca^{2+} determines whether LTP or LTD is induced. LTP is triggered by a high rate of Ca^{2+} influx into the postsynaptic neuron whereas LTD is triggered with low rate of Ca^{2+} influx. Intracellular stores and voltage gated Ca^{2+} channels are other sources of the calcium influx into the postsynaptic neuron [112].

Motor skill learning also causes gray matter alterations that are detectable with Magnetic Resonance Imaging (MRI). It was thought that these changes slowly occurred through the training, but the studies show that short period of time (90 min within two weeks) of balance training increased motor cortical thickness [69]. Taubert et. al. showed that after only one hour of complex motor task increases the motor cortical thickness in the representation areas involved during the balance training (leg and trunk) [113]. Landi et. al. demonstrated that one-week of intensive non-balance motor training may cause long-lasting adaptations by modifying the structural changes in the CNS. Thus, the adaptation resulting from one-week of training may be “stored” in the M1 for one year [114].

Neuromodulation involves an enhancement or reduction of the excitability of a particular area of the cortex and is one of the methods of investigating the role of the cortex in the response to a perturbation. Transcranial direct current stimulation is one of these neuromodulation techniques which induces reversible changes in functional properties of neurons and synapses. tDCS alters the neuronal excitability modulating resting potentials which increase or decrease the probability of generating action potential during the stimulation [115]. These changes in excitability last beyond the stimulation duration and it is fundamental to produce behavioral changes [116]. It is hypothesized that after-effects of tDCS depend on glutamatergic system and is likely to be regulated by LTP-, LTD-like mechanisms [28, 117]. Similarly, LTP-like mechanisms are thought to play a role in motor learning in humans [95]. A decrease in GABAergic inhibition preceding motor learning facilitates plasticity [95], while an increase in GABAergic inhibition reduces LTP-like mechanisms. LTP induction in M1 requires a transient reduction in GABA-mediated inhibition [118, 119]. Supporting this, another study showed that GABA concentration is

reduced by 20% in the sensorimotor region after a motor learning task with [120] or without tDCS [121]. Glutamatergic synapse appears to be one of the contributor to direct current stimulation-induced plasticity [115]. This plasticity is likely to be facilitated by a decrease in GABA activity.

2.4. Transcranial Direct Current Stimulation

2.4.1 Underlying mechanism of tDCS

Transcranial direct current stimulation is a form of non-invasive brain stimulation (NIBS) techniques used for neuromodulation that refers to reversible changes in functional properties of neurons and synapses. This technique is proposed to work by providing low levels of electrical stimulation over the scalp and bringing the stimulated neurons either depolarized or hyperpolarized depending upon the direction of the stimulation. These alterations mean that less afferent activity is required to fire an action potential after the membrane depolarization by tDCS which means increased excitability, and when tDCS induced hyperpolarization, excitability is reduced resulting in more afferent activity is required to induce an action potential. Anodal tDCS enhances excitability of the stimulated brain area while cathodal tDCS reduces excitability of the target area [122]. Nitsche and Paulus were first to show an increased MEP amplitude after the anodal stimulation while decreasing after cathodal stimulation. These immediate changes last few seconds and are driven only by alterations in membrane potential, not by alterations in synaptic efficacy [115]. In addition to acute effects, these MEP changes tDCS are prolonged for 2 hours when stimulation is applied for 15 min [123]. This aftereffect duration is within the range of early phase LTP- and LTD-like plasticity lasting 60 min [124]. This long-lasting effect of tDCS, LTP- and LTD-like plasticity depends on the glutamatergic system. Supporting this, blocking NMDA receptors prevents the after-effects of tDCS [117], while NMDA receptor agonists prolong them [28].

GABA activity also plays a role in tDCS-induced plasticity. A Magnetic Resonance Spectroscopy study showed that GABA is reduced under the stimulated area after anodal tDCS application, while cathodal stimulation caused a reduction of glutamatergic activity correlated with reduced GABA [125]. The literature suggests that tDCS induces plasticity

by contributing two possible mechanisms: modulation of glutamatergic and GABAergic activity.

The montage of tDCS electrodes is one of the factors that may affect the outcome measures [126]. In the current study, the montage was chosen based on previous studies and to cover all the hotspots of the target muscles [32]. The effect of tDCS is also task specific [127, 128]. In the literature, most of the studies that investigated the dose-response relationship focused on upper extremities motor learning. The intensity is likely to have no significant effect on cortical excitability in M1 for low intensities [123] but performance outcomes might be affected by the intensity. Cuypers et al found that increased retention in performance in the group who received 1,5 mA tDCS compared to sham stimulation [123]. On the other hand, longer or more intense stimulation does not necessarily improve the performance [129]. Despite the increasing number of studies investigating effect of dosage of tDCS, the dose response relationship between tDCS and the outcome measures such as corticospinal excitability or motor performance remains unclear.

The possible concurrent effects in non-stimulated cortical or subcortical areas are still unknown. On the other hand, previous findings imply the remote effects of tDCS. During M1 stimulation, Nonnekes et al. found decreased muscle onset latency after the perturbation, indicating enhanced excitability in subcortical structures. Polania et al. demonstrates that M1 stimulation modulates cortico-striatal and thalamo-cortical connectivity assessed by fMRI after 10 min stimulation [38, 130]. Providing support to the idea that tDCS can impact non-stimulated areas, anodal tDCS applied to the left sensorimotor area of healthy young adults may improve sensory integration [131]. Besides, 2mA anodal tDCS decreased the muscle onset latency, which is likely to involve subcortical structures, and decreased the prefrontal cortex activity during balance recovery after the perturbations (posterior translation of the supporting surface) in people with Parkinson's disease [132]. These findings imply that both cortical and subcortical enhancements could be achieved via M1 stimulation.

2.4.2 tDCS combined with balance training

Balance training is commonly recommended to provide proper control of balance for injury prevention [133-135], to improve sports performance [136], and to decrease rehabilitation time after injuries [137] Improving its effectiveness is important to decrease rehabilitation

costs and time and improve quality of life. Understanding the underlying mechanisms of balance learning is essential to developing new training methods. tDCS provides an opportunity to investigate the role of different brain parts in the balance learning process.

Postural control is a complex ability involving multiple degrees of freedom and dynamic sensorimotor processes in the CNS. Postural control skills can rapidly enhance in healthy adults with around 20 min of training in the initial phase of training (up to 3 sessions) [74]. Although a vast number of studies have been conducted about balance training in different contexts, there are gaps in our understanding of the neural mechanisms underlying balance skill acquisition. By understanding the balance learning mechanism, researchers may be able to develop more effective training programs and assistive tools for both healthy people and those with balance-affecting disorders such as Parkinson's disease.

There are two subtypes of balance training: feedforward and feedback. Feedforward balance involves assistive materials such as wobble boards or soft surfaces. COM (punctum mobile) oscillates around the feet (punctum fixum) during feedforward balance training. The oscillations happening during the standing position can be exaggerated during the balance exercise using the stance and sensory manipulations. This causes increased displacements of COM movement and a threat of disturbing balance. Thus, progression is met by decreasing the support surface (i.e. standing with single leg or tandem stance), manipulating the sensorial inputs (i.e. standing on a soft surface or closing eyes) throughout the training. On the other hand, feedback, also known as reactive or perturbation-based balance training, involves external perturbations during balance exercises. Perturbation-based balance training involves sudden, unexpected translations of the stepping surface in different directions and provides clinicians and researchers with more challenging intervention methods that simulate similar fall mechanisms in everyday life. COM (punctum mobile) oscillates around the feet (punctum fixum) during feedforward balance training.

When feedforward balance training is conducted, the center of mass is the moving point (punctum mobile) and the base of support is the fixed point (punctum fixum). Punctum fixum and punctum mobile are exchanged in perturbation-based training since perturbations are applied to the feet. After a perturbation, the body is forced to move COM into the translated base of support as a feet-in-place response. This may result in the more challenging balance disturbance compared to the conventional balance training [59].

The combination of both types of training is commonly used in sports centers or rehabilitation clinics. For instance, a person stands on a soft surface in hands akimbo and eyes closed position and a therapist applies perturbations on their shoulders or pelvis with or without information about the perturbation (i.e. I am going to push you forward). These perturbations are similar to the feedforward biomechanical model in terms of the moving and stable parts of the body as COM is oscillating around the fixed BoS. The perturbation can also be applied by translating or rotating the standing surface. Punctum fixum and punctum mobile are exchanged in perturbation-based training since perturbations are applied to the feet. After a perturbation, the body is forced to move COM into the translated base of support as a feet-in-place response. This may result in the more challenging balance disturbance compared to the conventional balance training [59]. This approach is also similar to slip and trip falling mechanisms which may cause severe injuries especially in people with balance affecting disorders or older adults. Balance disturbances are triggered by using perturbations that produce unpredictable, multi-directional movement of the standing support surface has recently been introduced and gained popularity over the last decade [58, 93, 138]. In addition, this approach facilitates the objective assessment of balance responses by repeatedly applying the same perturbations.

It is known that use-dependent adaptation to perturbations can be gained rapidly, even after one training session [25, 139]. Through more training sessions, the practiced task becomes automatic and can be completed using subcortical structures. Optimizing training for different sports and clinical settings is crucial to improving performance. To explore the optimal frequency for balance training, we examined previous studies. It has been found that three sessions per week is the optimal frequency for balance training [73]. Building on this finding three training sessions per week were commonly used in the literature [59, 73, 140]. Besides, three sessions of training can be considered as the initial phase of balance training [74]. Thus, the frequency of training in the current study was determined as three sessions per week to meet the aim of the study as we investigate the role of the M1 in the initial phase of balance learning.

Through the CNS as well as the musculoskeletal system, balance training causes structural and physiological changes. These adaptations can be measured by EEG, TMS, EMG or behavioral (kinematic or kinetic) analysis (see Chapter 2.5). In the literature, it has been demonstrated that anodal tDCS may improve lower extremity functions such as jump height

[141, 142], flexibility and running endurance [142]. Studies also demonstrated that anodal tDCS increased balance ability measured by CoP displacements and area compared to the sham tDCS in different groups such as older people or people with cerebral palsy [31]. Studies investigating the effect of tDCS on balance ability have used a variety of methods in terms of electrode montage, intensity, and target population. Thus, the standardized application of tDCS to specific populations or diseases remains uncertain.

2.5 Assessing Plasticity After Balance Training

2.5.1 Electroencephalography (EEG)

Assessing cortical activity in reactive balance provides a model to examine relationships between perception, movement, and brain states in a functional whole-body context. Balance perturbations are associated with characteristic changes in electroencephalographic (EEG) activity, called perturbation-evoked response (PER) or perturbation evoked potential (PEP). Since EEG measures provides an opportunity to assess activations of cortical pyramidal neurons related to responses to the balance perturbations with an excellent temporal resolution [15]. Mainly, a positive potential (P1) is typically generated over the centro-parietal region within the first 50–70 ms after the onset of perturbation. This is followed by a large negative potential (N1) over the fronto-central region specifically on supplementary motor area (SMA), peaking at 90–200 ms after the onset of perturbation. The latency of the cortical N1 response to balance perturbation is faster than the rise of conscious perception of body movement following the perturbation onset. Balance perturbation elicits the N1 even before the conscious perception. The N1 response, occurs even before the conscious perception of whole-body motion elicited by reactive balance [14, 19, 143]. The N1 response originates from supplementary motor area (SMA) with contributions of anterior cingulate cortex and posterior parietal cortex [19, 143].

The functional role of the N1 remains unclear. There are two major hypotheses about the role of N1 are: 1) It represents the sensory integration to coordinate responses to perturbations. 2) It represents an error signal for detecting postural disturbances [77]. The evaluation of an error involves comparison of expected and detected position of the body. In the literature, it has been shown that N1 response is modulated by various factors. N1 peak amplitude is higher for unpredictable perturbations [144-146], and increases with the

amplitude of perturbation intensity [146-148]. These factors support their role in error detection. It is heightened under postural threat, such as when standing on an elevated support surface [149]. Conversely, the N1 amplitude decreases with longer perturbation durations and increased attention to concurrent cognitive tasks [150]. Additionally, proprioceptive ambiguity, such as vibration of the patellar tendon preceding perturbations, can modulate the N1 response [151]. These results suggest that N1 amplitude doesn't only reflect the processing of sensory signals, as suggested earlier [145] but also higher-order cognitive involvement in response to anticipated balance disturbances.

Time-frequency analysis of EEG data during balance tasks indicates that mid-frontal theta dynamics play a crucial role in postural control and action monitoring scaling with task difficulty and signaling balance disturbances. Increased theta power has been observed during higher demands of balance control or balance lost [152]. For instance, the unipedal stance showed higher theta power than the bipedal stance in Brodmann area 5 [153]. This area lies centrally between the primary motor, somatosensory, cingulate, and posterior parietal association cortex [154]. These findings highlight the importance of midfrontal theta dynamics in monitoring and adjusting behavior in response to balance challenges.

The supplementary motor area (SMA) is a hub for information flow related to sensorimotor and cognitive processes, particularly during external perturbations. Supporting this, a previous study showed strong theta connectivity between SMA and other motor cortices and the anterior cingulate cortex after the perturbation [91]. The power increase in alpha and beta rhythms associated with the perturbation-evoked N1 response also occurs after perturbation [16]. Solis-Escalante et al. suggested that these frequency bands may reflect communication between the SMA and other sensorimotor cortices [14]. In the context of balance control, modulations in alpha and beta power have been reported on midfrontal SMA during balance recovery responses [17]. Enhancements in sensory integration process and SMA activity responses to the perturbation could possibly be affected by tDCS on M1 [131] (see Chapter 2.4).

Recent studies have highlighted the role of cortical beta oscillatory activity during reactive balance recovery, which is scaled with perturbation difficulty and individual balance ability. Greater cortical engagement during balance reactions has been observed in individuals with lower balance performance, suggesting a compensatory role of cortical mechanisms in

balance control. This engagement is particularly evident in older adults, where interactions between prefrontal and motor cortical regions are associated with distinct aspects of balance behavior.

2.5.2 Surface electromyography (sEMG)

When perturbation occurs, the ankle muscles contract in response. These contractions depend on the direction and intensity of the perturbation [155]. Rapid perturbations trigger strong reflex responses known as automatic postural responses (APRs). These unconscious responses involve the spinal and subcortical levels to counteract the perturbation and restore balance. As previously mentioned, there are three latency responses: short-, medium-, and long-latency responses. The short latency response, also known as the stretch reflex, is produced at the spinal level. Then, medium-latency response is generated by the brainstem, while long latency response, which starts approximately 85 ms after the perturbation, relies on the transcortical pathway [6]. APRs are functional and goal-directed responses rather than a collection of stretch reflexes produced by multiple CNS levels [156]. The late phase of APRs and voluntary responses to perturbations involve cortical adaptation through training.

The magnitude of APRs is greatly influenced by “central set”, which refers to preparatory neural modulations, affected by prior experience and the expectations. For example, if someone expects a sudden brake while standing on a bus, the “central set” adjusts the responses to potential balance disturbances. Perturbation-based balance training possibly enhances the central set by improving the efficiency of postural responses to the perturbations and enabling faster balance recovery after disturbances.

These adaptations likely involve higher magnitude contractions during long latency responses and voluntary contractions, as well as improved intermuscular coordination. Enhanced coordination enables individuals to counteract perturbations more effectively. For example, forward surface translations primarily trigger tibialis anterior responses, soleus and gastrocnemius contractions, and vice versa. Thus, how these muscles contract according to the direction of the perturbation is one example of muscle coordination. Specifically, it is expected that the tibialis anterior will contract more strongly during the anterior translation

of the surface than the posterior translation, while the soleus muscle contracts stronger during backward translations than the anterior translations. Improved selective contractions of each muscle can be considered adaptations resulting from reactive balance training.

As an indirect method of calculating comparable results between muscles, the “modulation index” was introduced by Kelly and Bastian [157]. This formula was modified by different studies and used as an alternative method of measuring the coactivation index [31], called “muscle specificity.” The formula of this measurement is the absolute value of the difference between the activity of one muscle during forward and backward perturbations divided by the maximum value across different directions of the same muscle. This measurement gives insight into how each muscle reacts to the different directions of the perturbations. Because of the natural variability in electrode locations and thickness of subcutaneous tissue, the direct comparisons of the amplitude of muscle activity can lead to an error. Instead, using this formula results in comparable results between muscles and serves as an indicator of muscle co-activation.

2.5.3 Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation is a vital tool for revealing the underlying mechanism of neural adaptation to reactive balance training. Motor skill learning is a complex process that defines improving the efficiency of motor outcomes. Motor skill acquisition is the initial process of motor skill learning and it has been shown that short interval intracortical inhibition (SICI) is decreased accompanied by increased intracortical facilitation (ICF) in both upper and lower body after short-term motor training [40, 41, 62, 63]. SICI is mediated by GABA_A receptors [158] while ICF is produced by a separate population of interneurons by NMDA receptors. Several studies showed that GABA_A receptors play an essential role in the induction of plasticity [42, 45]. These two mechanisms are likely to be controlled differently during balance control. Thus, the adaptation to balance training may rely on a complex interplay between these inhibitory and excitatory mechanisms [41].

In the time-excitability graph, corticospinal excitability initially increases during the early phase of training but gradually decreases as the training progresses [105]. Supporting this, Weier et al. demonstrated that 4 weeks of squat training reduces the SICI by 32%, in line with the short-term studies [55], and a cross-sectional study showed that elite badminton

players demonstrate a higher level of inhibition than novice players [45]. Conversely, previous studies have shown a reduction in cortical contributions during balance training indicated by decreased corticospinal and cortical excitability and increased (SICI) [74]. Mouthon and Taube found an enhanced level of SICI during the balance test after 2 weeks of balance training but no measurement during rest [24]. Taube et al. tested whether cortical adaptation is influenced by the type of training by comparing the effects of four weeks of explosive with balance training on inhibitory mechanisms [46]. They found that increased SICI after balance training and reduced SICI after explosive training. However, they found no differences in SICI after balance training when it is tested at rest, suggesting that these changes depend on the testing conditions [46]. Similarly, Bakker et al. found that one balance training session doesn't induce SICI and ICF changes when tested in sitting and standing positions [159]. This result contradicts a study that showed one session balance training increased both cortical thickness in M1 and balance performance [113] and another study that demonstrated the disruption of M1 activity prior to single balance training session interferes with the retention of acquired balance skills [25].

While decreased inhibition and enhanced cortical excitability are observed after motor training, balance training induced the opposite changes. It is important to note that these findings mentioned above suggested that cortical adaptations observed when it is tested during task execution or while standing [24, 46, 159] not at rest or during non-practiced tasks. Thus, these findings are task-specific in studies investigating the effect of balance training. Furthermore, these studies applied feedforward balance training, and to the best of our knowledge, cortical adaptation has yet to be tested after perturbation-based balance training.

Another study demonstrated that the level of inhibition is influenced by the postural demands and not by muscle activity level [51]. They found lower levels of inhibition in a leaning posture while standing compared to leaning with support or sitting, despite matched EMG contraction levels. These findings are reasonable as an increased challenge leads to decreased intracortical inhibition when the risk of falling rises, allowing the muscles to be more easily activated.

3. MATERIAL AND METHODOLOGY

3.1 Participants

This study took place at the Department of Neuroscience and Psychology and the Department of Ergonomics, Leibniz Research Centre for Working Environment and Human Factors, Dortmund, Germany. Thirty-four healthy right-handed and right-footed participants were recruited via online advertising and through flyers. Only candidates who met none of the exclusion criteria were eligible to participate.

Before starting the study, potential participants were invited for a screening interview. The “TMS/tDCS screening questionnaire” (Appendix A), adapted from Keel et al. and Rossi et al. [39], and the Modified Physical Activity Readiness Questionnaire (PAR-Q) (Appendix B) were used to screen potential participants to determine whether they are suitable to participate. Edinburg Handedness Inventory (Appendix C) was used to determine the handedness of potential participants. The participants were asked the following question to determine their foot preference, “If you would kick a ball at a target, which leg would you use to kick the ball?”[160]. Potential participants read the participant information sheet, detailing information regarding the study, including the health and safety considerations of all protocols used, and be asked to sign an informed consent form.

Inclusion criteria

Healthy adults aged 18 – 55, right-handed and -footed, non-smoker, with no history of neurological or psychiatric disorders, were included in this study. As a result of the typical aging process, individuals over the age of 55 have modified responses to postural perturbations relative to younger individuals and were not included. The exclusion criteria are listed below.

Exclusion criteria

1. History or evidence of chronic or residual neurological diseases.
2. Pacemaker or deep brain stimulation.

3. Metal implants in the head or neck area (e.g., postoperative clips after intracerebral aneurysm; implantation of an artificial hearing aid).
4. The age is not between 18 to 55 years.
5. History of intracerebral ischemia/ bleeding.
6. Prior evidence of epileptic seizures, history of epilepsy.
7. History of head injury with skull fracture or brain tissue lesion.
8. Any serious medical conditions (internal organs or metabolic diseases) or psychiatric illness, including schizophrenia, mania, or depression.
9. Pregnancy or breast-feeding.
10. Alcohol or drug addiction.
11. Cigarette smoker
12. Local or global aphasia.
13. Any legal reason why the candidate cannot participate.
14. Participation in another scientific or clinical study within the last 4 weeks.
15. Intake of any central nervous system (CNS)-acting medication
16. Have an orthopedic disorder involving lower limbs,
17. Lack of joint position sense in the lower limbs
18. A history of vertigo,
19. Surgical procedure at the level of the spinal cord
20. Participated in any kind of balance training.

3.2 Experimental Procedure

Two data collection sessions before and after one week of balance training were conducted. Each assessment session took approximately 6 hours, and each training session lasted about one hour long. Participants were permitted to eat or drink as needed during this time. Participants underwent three training sessions within one week separated by one day. Participants were assigned to one of three experimental groups; anodal, sham or no stimulation (control). Participants received one of these stimulations during the training sessions. The design of the study is shown in Figure 3.1.

All data used for this thesis were collected in the GRAIL laboratory at the Leibniz Research Centre for Working Environment and Human Factors (Dortmund, Germany). The interested

participants received an email that contains information and related documents about the study and an invitation to the first screening session. In this pre-measurement session, the researcher provided the potential participants with all the information and explained to them the procedures and answered all questions they had about the experiment. Potential participants completed informed consent forms before they filled out the screening questionnaires. The researchers conducted a TMS measurement with eligible participants to determine whether hotspots could be identified with high enough MEPs to have more reliable and consistent results across the measurement sessions. The range of MEP amplitude was determined as 150-500 μV . Next, participants who were eligible for the study were scheduled for the assessment and training sessions. The research process flow diagram is shown in Figure 3.2. The procedure of each measurement session is shown in Figure 3.3.

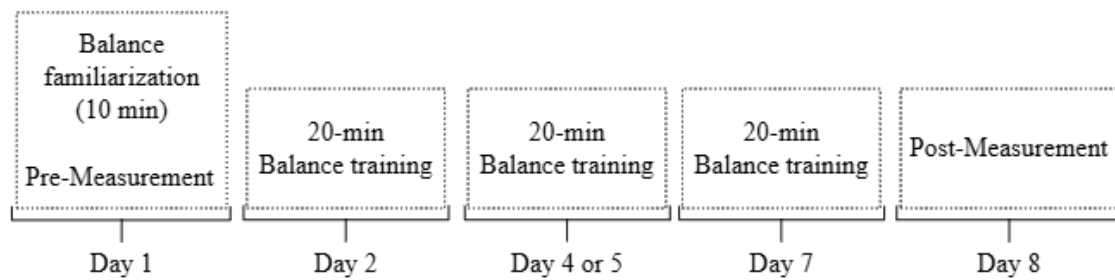


Figure 3.1. Experimental design.

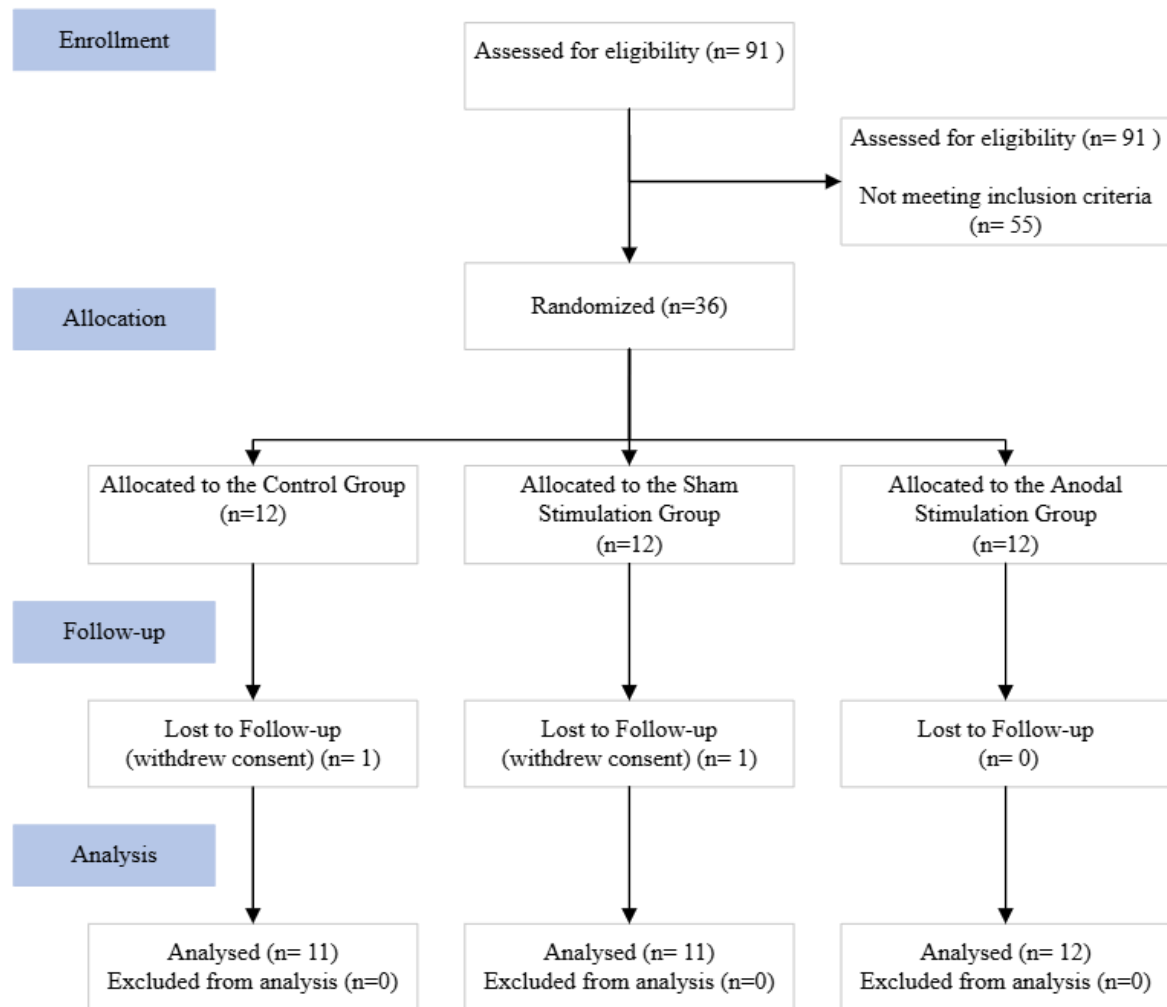


Figure 3.2. CONSORT flow diagram illustrating the participants in the study.

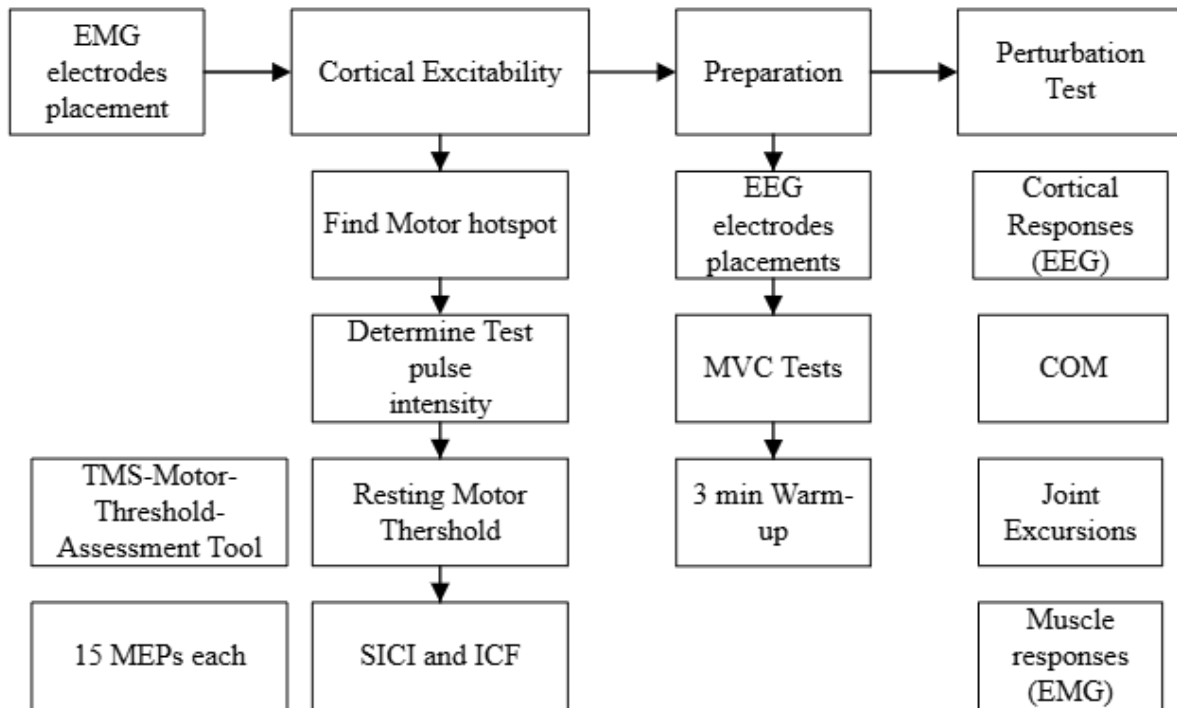


Figure 3.3 The procedure of a measurement session of the experiment.

EMG: Electromyography, SICI: Short-interval intracortical inhibition, ICF: Intracortical Facilitation, EEG: Electroencephalography, MVC: Maximal Voluntary Contraction, COM: Centre of Measurement.

A butterfly coil (D-B80, MagVenture A/S, Farum, Denmark; Ø 95 mm, 120° angle) connected to a transcranial magnetic stimulator (MagPro X100, MagVenture A/S, Farum, Denmark) was used for cortico-spinal excitability measurements (Short-interval intracortical inhibition (SICI) and intra-cortical facilitation (ICF)). SICI and ICF were measured during rest before the perturbation test. The other outcome measures (EEG, EMG and kinematic analysis) were measured during the balance test. These recordings were done in the GRAIL laboratory. The GRAIL laboratory is equipped with a dual-belt treadmill equipped with two embedded force plates, a VICON motion capture system (VICON, Oxford, United Kingdom) using ten infrared cameras, a 180° projection screen placed in front of the treadmill, and three projectors to display the visual scene. The treadmill platform was also able to produce perturbations at the sagittal and frontal planes. D-flow software was used to operate the treadmills (Motek Forcelink, Amsterdam, Netherlands). To prevent falls and injuries, participants wore safety harnesses attached to the ceiling. The participants stood on the platform with their arms akimbo, feet shoulder-width apart and eyes on a cross at eye

level on the screen. The distance between their first toes and cross height was measured to ensure they could be positioned the same during the post-training session.

A trigger signal was generated using an external trigger interface (Phidget Interface Kit, Phidgets Inc., Canada) when the perturbation starts to synchronize the perturbation onsets and ongoing EEG/EMG recordings. The trigger signals and EEG/EMG data were recorded simultaneously using the wireless trigger set by Brain Products (Gilching, Germany).

The location of EMG electrodes and hotspots for each muscle were marked with a water-proof marker in the pre-training session and checked during the training session. This ensured that the electrode and hotspot locations remained consistent for the post-training session.

3.3. Data Collection

3.3.1 Cortico-spinal excitability measures

During the assessment sessions, cortico-spinal excitability was determined by single and paired-pulse TMS. Single-pulse and paired-pulse TMS have been widely used to measure the excitability of the corticospinal tract [39]. The TMS coil, which delivers magnetic pulses, was situated over the skull in the leg area of the motor cortex and is used to identify the motor hot spots for TA, SOL muscles of both hemispheres. TMS was applied using a cone-shaped coil (MagVenture, Denmark).

As part of this study, the motor hot spot in the cortex that elicited the largest amplitude motor evoked potentials (MEP) were identified in the resting TA and SOL muscles on both sides.

The optimal location for eliciting MEPs from the leg muscles was identified by moving the coil to various locations to find the grid location where a stimulus of medium intensity elicits the largest MEP of the target muscle during rest.

The resting motor threshold (rMT) was then determined by the TMS-Motor-Threshold-Assessment Tool (MTAT 2.0) (Awiszus and Borckardt, 2012) using “without a priori information” method. In order to determine rMT, the researcher provides input depending on whether the MEP amplitude exceeds 50 volts. The program displays the next TMS

intensity to be given depending on the input provided by the researcher. After a sufficient number of attempts, the rMT was identified. The software program displays 95% confidence intervals of intensity estimates during testing, and the target intensity is determined when the 95% confidence intervals fall within safety guidelines.

Moreover, the test stimulus intensity which elicits MEP within the range between 150 – 500 μ V was determined. This range was determined after a pilot study to find the most proper MEP amplitude for the target muscles. The stimulus intensities for each muscle and for each session are demonstrated in Table 3.1.

Table 3.1. Test stimulus intensities (%rMT)

	Right TA	Right SOL	Left TA	Left SOL
Session 1	122,62 $\pm$ 10,24	132,92 $\pm$ 14,71	126,82 $\pm$ 14,48	135,36 $\pm$ 16,14
Session 2	122,21 $\pm$ 10,46	136,60 $\pm$ 16,03	130,03 $\pm$ 13,56	137,45 $\pm$ 15,57

After the optimal stimulus area has been identified to probe the intracortical inhibition (SICI) and intracortical facilitation (ICF), paired-pulse TMS (two single pulses separated by 2 ms for SICI and 10 ms for ICF) were used. This is accomplished by providing a subthreshold TMS conditioning stimulus pulse delivered prior to a test stimulus. We utilized a conditioning stimulus intensity of 80% rMT. Providing the conditioning stimulus before the test stimulus (2 ms or 10 ms depending on the outcome measure) changes the amplitude of the MEP in response to the test stimulus. The researcher delivered 15 stimuli for each condition (double pulse (2 ms and 10 ms interval), and single pulse). The individual means of fifteen MEPs were calculated for each, SICI, ICF, and the single TMS pulse condition. SICI and ICF were quantified by dividing the MEP amplitude in response to the test stimulus in the double pulse condition by the MEP amplitude in the single pulse condition. This process was repeated for each muscle. For each muscle, a water-proof marker was used to mark the electrode attachment area and the motor hot spots on the representation area in order to conduct measurements at the same location. These markers were checked during the training sessions in between the assessment sessions and remarked if necessary.

3.3.2 Electroencephalography (EEG)

Participants wore an EEG cap (actiCap Snap, Brain Products GmbH, Germany) equipped with slim, active Ag/Cl electrodes (actiCap slim, Brain Products GmbH, Germany). EEG data were collected during the perturbation test using the LiveAmp (Brain Products GmbH, Germany). Electroencephalography (EEG) data were collected through 28 Ag/AgCl electrodes placed in a cap (LiveAmp: Brain Products, Gilching, Germany). EEG electrodes were placed at the following locations: Fp1, Fp2, F3, Fz, F4, F8, FC5, FC1, FCz, FC2, T7, C3, Cz, C2, C4, T8, TP9, CP5, CP1, CPz, CP2, CP6, P3, Pz, P4, O1, O2. TP10 was used as the online reference electrode and AFz served as the ground electrode. A cap size of 54 to 60 cm was selected based on the participant's head circumference. After fitting the cap, the electrodes were filled with electrolyte gel to reach an impedance below 10 k Ω . Next, Participants wore a belt carrying the LiveAmp amplifiers (LiveAmp 64, Brain Products GmbH, Germany), battery, sensor&Trigger Extension (LiveAmp 64, Brain Products GmbH, Germany) and BIP2Aux channels for EMG data collection (Brain Products GmbH, Germany). To avoid motion artifacts, electrode cables were arranged to prevent crossing and sway was minimized.

EEG and EMG data were recorded with a sampling rate of 1000 Hz and a bit depth of 24 bits directly onto a micro-SD card inserted into both connected amplifiers. At the same time, the online data stream received from the amplifiers' Bluetooth connection was monitored from the lab's D-Flow controller computer using the Brainvision Recorder software (Brain Products GmbH). After completion of the recordings, the EEG/EMG data were transferred from the SD card to the PC using the LiveAmp File Converter software (Brain Products GmbH). The files containing kinematic variables as well as belt movements were also transferred for analysis.

3.3.3 Surface electromyography

The EMG data was recorded in both TMS and balance measurements using Ag/AgCl electrodes (Ambu BlueSensor N) with a 2 cm inter-electrode distance and an electrode diameter of ~11 mm. Prior to electrode application, the skin where the electrodes are to be placed was shaved, gently abraded with abrasive skin prepping gel (Nuprep), and cleaned with 70% alcohol in order to decrease skin resistance below 2,5 kOhm. After electrode

application, the participants performed three maximal voluntary isometric contractions (MVCs) for three seconds for each muscle (TA and SOL) [161] after 3 min of walking and a few submaximal contractions. During the MVC test, participants were instructed and verbally encouraged to contract each muscle maximally against a strap. The strap was placed dorsally over the foot for the tibialis anterior and over the knee for the soleus muscle during sitting. Participants were asked to dorsiflex the ankle and invert the foot against the strap/hand for maximal isometric TA contraction. Participants were instructed to plantarflex the ankle against the strap/hand over the knee for maximal isometric soleus contraction. Three repetitions of 3-5 seconds were performed for each muscle, with a rest period of one minute between each repetition. EMG measurements were completed according to the SENIAM recommendations (Hermens et. Al., 2000).

For each muscle, the sEMG amplitude data of the contraction with the greatest amplitude obtained during the MVCs was used to normalize the sEMG data obtained during postural perturbations. The sEMG data is affected by many factors including electrode positions, and the time of measurement physiological and anatomical characteristics of muscles and surrounding tissues that may differ between muscles, inter-electrode distance, orientation relative to muscle fibers, time of measurement and the muscle fiber orientation. To obtain comparable data between time points, muscles and participants, the normalization process was performed as part of each balance assessment session [162]. The sampling rate was set at 1000 Hz during the recordings.

3.3.4 Kinematic measurements

The GRAIL system was used to collect data on the movement of the center of mass of the body using a 10-camera Vicon Nexus 3D motion analysis system. Reflective markers with 0,14 cm diameter were placed on the body according to the Human Body Model (HBM) with the trunk model. The markers are located at base of second toe, base of fifth toe, medial and lateral malleolus, heel, medial and lateral epicondyles, midline of the shank and thigh of both sides and RASIS, LASIS, RPSIS, LPSIS, T10, C7, jugular notch and xiphoid process of sternum. Online low-pass filter with a cut-off frequency of 6 Hz was applied using D-flow software (Motek Forcelink, Amsterdam, Netherlands). The COM displacements and variances as well as joint excursions for each lower extremity joints (Hip, knee and ankle on both sides) were obtained using kinematic analysis.

3.4. Perturbation Training Protocol

Perturbation training included 10 blocks of 12 perturbations each, applied every three to six seconds. There was a one-minute break after each block. The training period lasted one week in total and comprised three sessions, with each session being separated by at least one day [93, 138]. Participants were exposed to six different conditions involving two directions (forward and backward) and three amplitudes (2, 4, 6 cm), each with a specific velocity. The first 2 sessions were conducted during the feet shoulder-width apart position and the last session was done in feet together position to increase the level of difficulty. Standing balance becomes more challenging with the feet together because the base of support is narrower which reduces stability and demands greater control to maintain balance. Table 3.2 shows the perturbation characteristics. During the training, transcranial direct current stimulation (tDCS) was delivered according to the group to which the participants were assigned. The duration of both the stimulation and the balance training was 20 minutes.

Table 3.2 Perturbation Characteristics in Balance Training Sessions

Perturbation direction	Anterior-Posterior
Amplitude of Perturbation	2-4-6 cm displacement

During Perturbation Training, transcranial direct current stimulation (tDCS) was applied over the motor cortex throughout all 20-minute perturbation sessions. tDCS was set to 3mA and was delivered through two sponge electrodes (Target and reference electrode area: 35cm²) resulting in an applied current density of 0.085 mA/cm². The current was initially increased in 0,1 mA increments for 30 seconds until the target current intensity was reached. During tDCS cortex stimulation, the stimulating electrode was placed 1 cm behind the vertex (Cz) on the mid-sagittal line to cover both leg motor cortices [32]. The stimulating electrode always covered the motor hotspots of all target muscles. The reference electrode was placed with the center over Fpz. Regardless of the participant's experimental group (sham or anodal stimulation), the electrodes were placed in the same position. Before placing the saline-soaked sponge electrodes, a topical anesthetic cream (EMLA, 2,5% lidocaine & 2,5% prilocaine) was applied over the stimulation site to improve the level of blinding by reducing somatosensory perception of the stimulation. The electrodes were fixed using rubber straps.

In the sham group, the current was turned off at the 30th second of the perturbation training [163, 164]. The control group didn't receive tDCS stimulation.

3.5 Balance Test Protocol

The Gait Real-time Analysis Interactive Lab (GRAIL) by the Motekforce Link was used to produce perturbations and collect center of Mass (COM) data. Perturbations were applied by translation of the support surface (fig 3.4). During the assessment sessions, EEG, EMG, and COM data were collected during forward and backward perturbations with specific velocities and amplitudes (15 stimuli for each). In the first assessment session, participants participated in a 10-minute familiarization session once they wore the EEG cap, the belt and the harness [67].

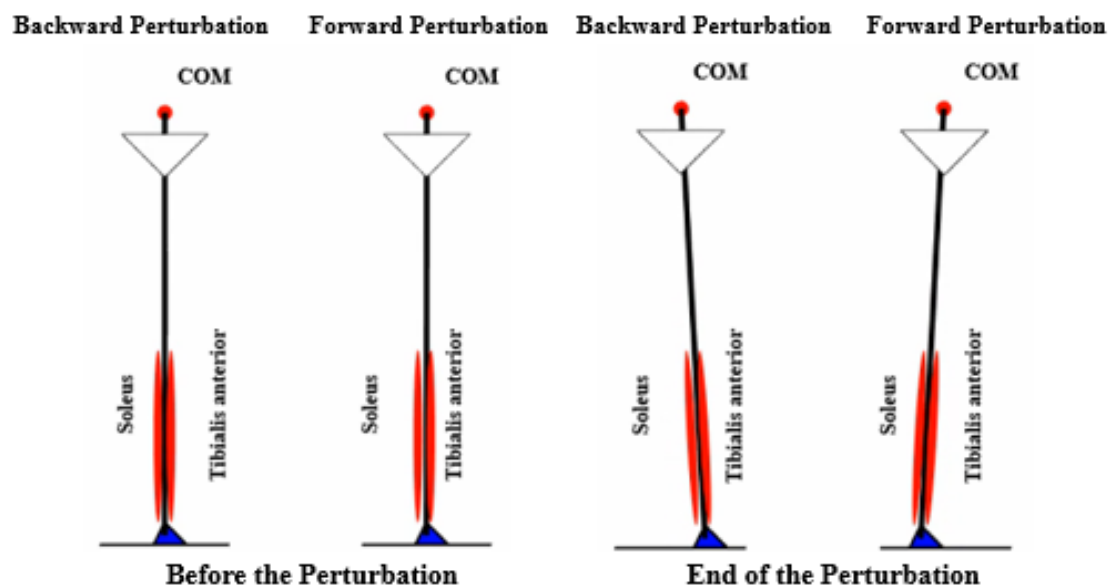


Figure 3.4 Visualization of mechanical perturbations in both balance tests and trainings.

Two different velocities ($0,467 \pm 0,01$ m/s and $0,518 \pm 0,01$ m/s) and two different amplitudes (5 cm and 6 cm) were chosen for each direction (forward and backward) for the assessment sessions. A random acoustic signal was presented two seconds prior to the perturbation stimulus in order to determine the effect of acoustic stimulus on neuromuscular and cortical responses. There were eight conditions during the assessment session, and they were defined as forward/backward for direction and sound/no sound for the acoustic signal. The perturbation conditions are shown in Table 3.3.

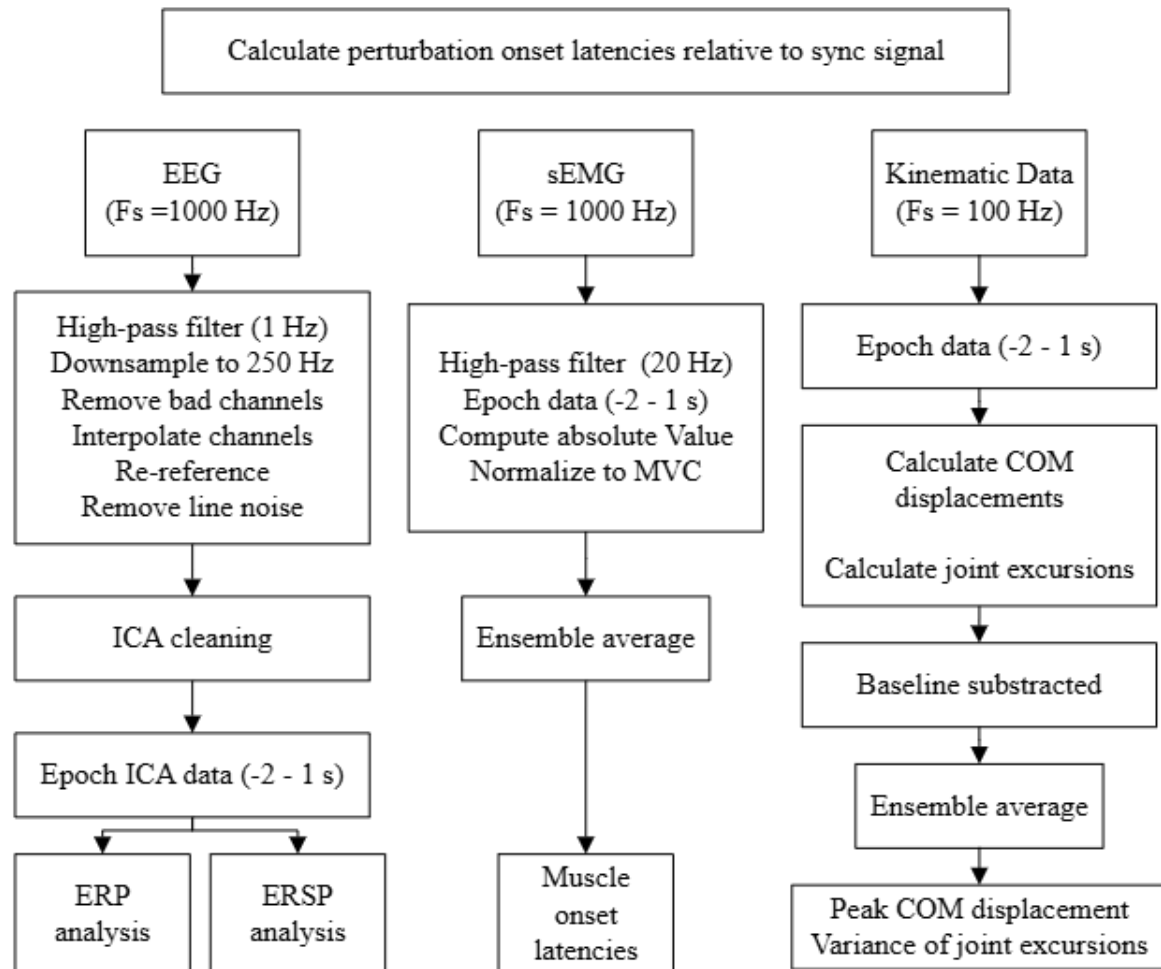
Table 3.3 Perturbation conditions.

Direction	Acoustic Signal	Distance
Forward	No Sound	6 cm
Forward	Sound	6 cm
Backward	No Sound	6 cm
Backward	Sound	6 cm

Perturbation stimuli was separated by three to six seconds randomly. During an assessment session, participants were exposed to one hundred twenty perturbation stimuli, fifteen perturbations for each condition. Thus, 4 different conditions are expressed in this research: Forward/No sound (FNS), Backward/No sound (BNS), Forward/Sound (FS), and Backward/Sound (BS).

3.6 Data Processing

Figure 3.5 shows a summary of data processing for each outcome measure.

**Figure 3.5.** Data analysis protocols for each outcome measure

3.6.1 EEG analysis

An online anti-aliasing filter of 499 Hz was used during EEG data collection. The data was first high-pass filtered using a 4th order, zero-phase Butterworth filter with a 1 Hz cutoff, followed by down sampling to 250 Hz to improve line noise removal and to facilitate ICA decomposition. To identify the problematic channels, `bemobil_detect_bad_channel` function was used before re-referencing using `bemobil_avref` function to employ the full rank average reference. The data was processed with `zapline plus` to remove the noisy frequency components. Then the data were epoched between -2000 and +1000 ms relative to perturbation onset before independent component analysis (ICA) was run to reject the non-brain origin components. Further analysis was focused on Cz electrode over the M1 and SMA. Finally, event-related spectral perturbations (ERSP) analysis was conducted to calculate change in power relative to the baseline (-1000 -200 ms) in different frequency bands (theta (3-7 Hz) and alpha (8-12 Hz) in the relevant time bin (90-250 ms). N1 potential was also calculated as the minimum value between 90-200 ms relative to the baseline.

3.6.2 Surface electromyography

An online anti-aliasing filter of 499 Hz was used during EMG data collection. The Maximal Voluntary Contractions (MVC) data was first high-pass filtered using a 4th order, zero-phase Butterworth filter with a 20 Hz cutoff, followed by calculation of absolute values. The onset and offset points of muscle activity during MVC were then detected using a custom-made algorithm. To ensure accuracy, the first and last 500 ms of each repetition were excluded. The MVC data was then smoothed using a zero-phase moving average filter with a 200 ms time window. The MVC value was calculated as the peak value across all repetitions.

The collected data during perturbation tests were filtered using 4th order, zero-phase Butterworth high pass filter with a 20 Hz cut-off frequency. The EMG data were mean-subtracted and rectified. The EMG data were then normalized to the MVC before it was epoched between -2000 ms to +1000 ms relative to perturbation onset. The EMG signal was then averaged for each perturbation condition and for each participant.

Onset latency was defined as the first frame where activity exceeded 2 standard deviations above the baseline (-200 ms to -20 ms) and remained above this threshold for at least 20 ms. These onset latencies were calculated for each individual trial and then averaged for each condition and participant [165].

3.6.1 Kinematic analysis

The movement of the center of mass (COM) relative to the ankle joint was calculated for a 1.2-second epoch, spanning from -200 ms to +1000 ms. The peak COM displacement after a perturbation was measured relative to a baseline period that ranged from -700 to -200 ms prior to the perturbation onset. The average of these calculations was then calculated for each participant and condition.

Joint excursions were averaged for each condition and each participant then normalized to the baseline (-1000 ms to -200 ms). Peak hip, knee and ankle joint excursions and velocities in 0-300 ms were calculated. As an index of postural control strategy, hip joint excursion was used [10].

3.7 Statistical Analysis

A linear mixed-effects model was fitted using the “lmer” function from the “lme4” package in R version 4.3.3 (R Foundation for Statistical Computing). We treated time (pre, post), group (control, sham, anodal) and sound (No sound, sound) as fixed effects and participants as random effects in the model for EEG, EMG and kinematic analysis. Time, group and muscle (Right TA and SOL, left TA and SOL) factors were considered as fixed effects and participants as random effect in intracortical excitability measures. The “emmeans” package was used for post-hoc analysis. This analysis used the “emmeans” function to obtain “estimated marginal means” by averaging over time, sound, and group within the linear mixed-effects ANOVA model. Following this, the “contrasts” function was employed to perform pairwise comparisons between these estimated means. The model p-values were determined using Satterthwaite's method. The level of significance was <0,05. Tukey adjustments were applied in the post-hoc analysis.

Partial eta square (η_p^2) was calculated by using “eta_square” function in “effectsize” package in R to estimate effect sizes. Effect sizes were interpreted as small ($\geq 0,01$ and $< 0,06$),

medium ($\geq 0,06$ and $< 0,14$) and large ($\geq 0,14$) effects.

4. FINDINGS

The demographics of each group are demonstrated in Table 4.1.

Table 4.1. Demographic characteristics of participants

	Control (n=11)	Sham (n=11)	Anodal (n=12)
Age (years)	25,77 $\pm$ 1,6	27,33 $\pm$ 3,23	25,2 $\pm$ 1,2
Weight(kg)	71,1 $\pm$ 5,3	66,77 $\pm$ 4,64	71,5 $\pm$ 4,89
Height(cm)	173 $\pm$ 2,3	169,8 $\pm$ 3,16	173,1 $\pm$ 3,56

4.1 General Outline of the Outcome Measures

Average data of all participants for each outcome measure at each time point is demonstrated in Figure 4.1. Each subplot displays a 1200 ms epoch, 200 ms before and 1000 ms after the perturbations. The shaded gray areas indicate the time bins of interest.

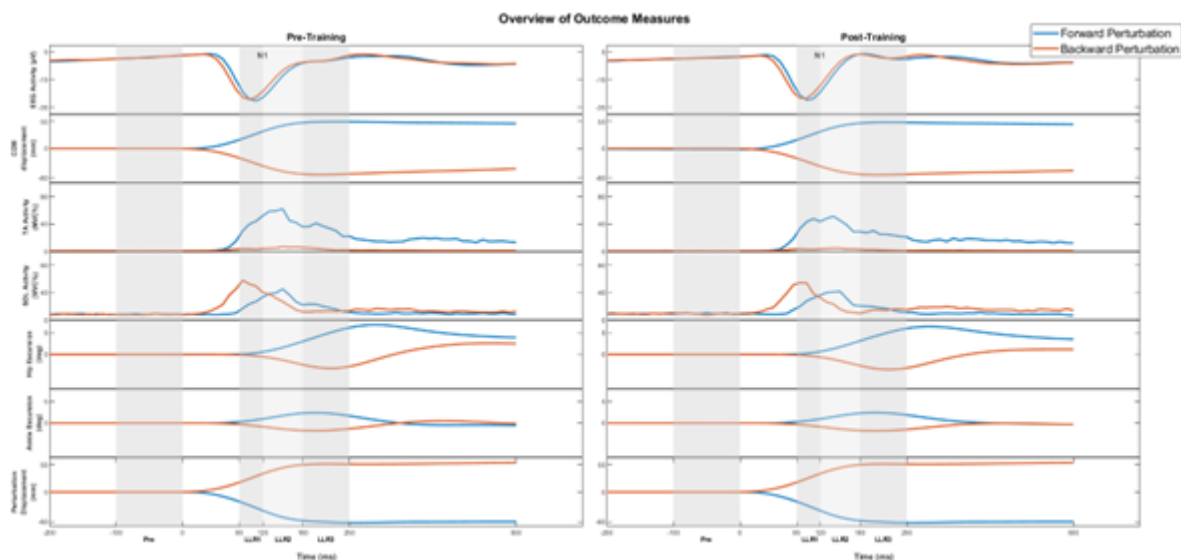


Figure 4.1 General outline of perturbations and outcome measures

Grand averaged Perturbation-Related Potentials (PRP), COM displacements, activity of right tibialis anterior and soleus muscles, right hip and ankle joint excursions, and perturbation displacements are shown. The two different colors for the outcome measures indicate the direction of the perturbation (blue for forward and orange for backward).

4.2 Kinematic Analysis

Mixed ANOVA results of peak COM displacements are shown in Table 4.2. The sound factor had a main effect on COM displacement in both forward and backward perturbation, the effect sizes were high. An interaction between time and group factors was observed in forward perturbations with high effect size. No other main or interaction effects were significant.

According to the post-hoc comparisons, the sound factor had a main effect on COM displacement in both forward and backward perturbation in an opposite way. In forward perturbation, an acoustic signal caused a smaller COM displacement than the no sound condition ($t:2,93$, $p:0,004$, Figure 4.2 APPENDIX-6 Table 1). It, however, a greater COM displacement than the no sound conditions in the backward perturbations ($t:-3,6$, $p:0,0005$, Figure 4.2, APPENDIX-6 Table 4). Post-hoc comparisons also revealed that only anodal stimulation group showed significantly decreased peak COM displacements following the training ($t:2,33$, $p:0,02$, APPENDIX-6, Table 3, Figure 4.2).

4.2.1. Peak COM displacement

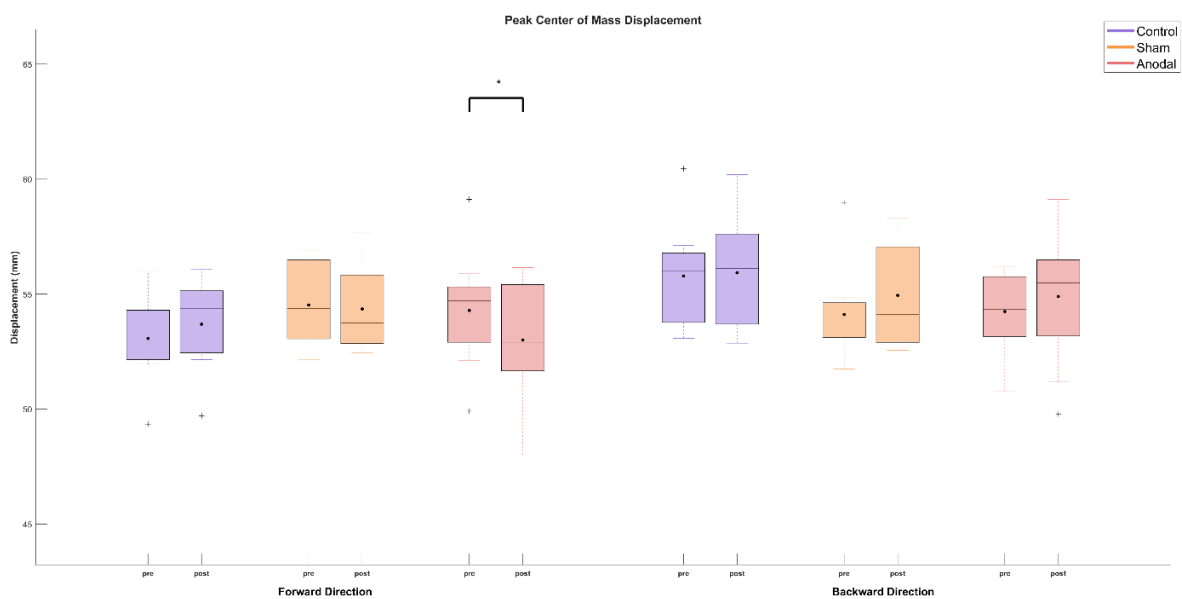


Figure 4.2 Peak COM displacements from the baseline

The results were illustrated for each group and each perturbation direction (averaged for sound and no sound conditions) in the period of perturbation duration. Each box shows the interquartile range (25th-75th percentiles) and the horizontal line in each box indicates the median while the black dot indicates the mean. Outliers are indicated with a "+" and whiskers represent the range of data. Asterisks indicate significant differences before and after training.

Table 4.2. Mixed-ANOVA Results for the effect of tDCS on COM displacements

	Main/Interaction	df	F	p	η_p^2
Forward Perturbation	Time	1	0,68	0,41	0,01
	Sound	1	8,61	0,004*	0,09
	Group	2	1,11	0,34	0,07
	Time:Sound	1	1,21	0,27	0,01
	Time:Group	2	3,10	0,049*	0,06
	Sound:Group	2	0,15	0,86	0,00
	Time:Sound:Group	2	0,85	0,43	0,02

Backward Perturbation	Time	1	3,67	0,06	0,01
	Sound	1	12,90	0,001*	0,09
	Group	2	1,60	0,22	0,07
	Time:Sound	1	0,07	0,79	0,01
	Time:Group	2	0,51	0,60	0,06
	Sound:Group	2	3,06	0,052	0,00
	Time:Sound:Group	2	0,41	0,66	0,02

4.2.2 Variance of joint angle excursions

The main and interaction effects of peak joint angle for each lower extremity joint are listed in Table 4.3. A time main effect was observed in the right hip, right knee and right ankle joints in forward perturbations, and in right and left knee joints in backward perturbations. The effect sizes ranged from medium to high. An interaction between time and group factors was observed in right and left hip joints, with medium effect size and left ankle joint, with high effect size, in the forward perturbations. Other main or interaction effects were not significant.

Post-hoc comparisons showed that the perturbation-based balance training caused a reduction of joint excursion in right hip ($t:2,46$, $p:0,02$, APPENDIX-6 Table 5), right knee ($t:3,6$, $p:0,0006$, APPENDIX-6 Table 10) and right ankle ($t:2,32$, $p:0,02$, APPENDIX-6 Table 11) joints in forward perturbations across all participants. On the other hand, right and left knee joint excursions were increased following the training in backward perturbations ($t:-3,66$, $p:0,01$ and $t:-4,14$, $p:0,0001$, respectively, APPENDIX-6 Tables 14 and 15).

The post hoc analysis revealed that only anodal stimulation group showed a significant decrease in the hip joint excursion on both sides in the forward perturbations following the training compared to the pre-training session ($t:4,04$, $p:0,0001$ and $t:2,82$, $p:0,01$, right and left side, respectively, APPENDIX-6 Tables 6 and 8) despite the lack of a significant difference between groups.

Left ankle joint excursion was increased only in the control group in the forward perturbations following the training ($t:-3,3$, $p:0,002$, APPENDIX-6 Table 12). Left ankle joint excursion of anodal stimulation group was significantly smaller than control group in backward perturbations in the post-training session ($t:2,81$, $p:0,02$, Appendix 1 Table 13).

The joint excursions before and after the training for each group for each joint were illustrated in Figure 4.3.

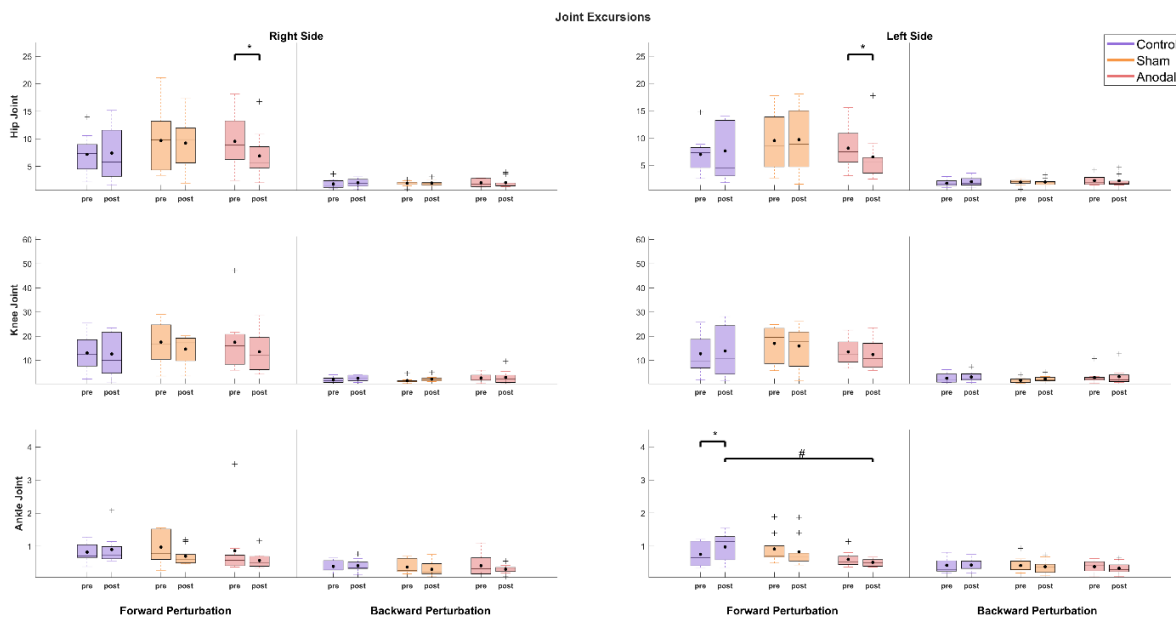


Figure 4.3. Peak joint excursions in the period of interest after perturbation onset

The figure illustrates the variance of joint excursions in each group and each perturbation condition. The time of interest is 100-300 ms after the perturbation onset. Each box shows the interquartile range (25th-75th percentiles) and the horizontal line in each box indicates the median while the black dot indicates the mean. Outliers are indicated with a "+" and whiskers represent the range of data. Asterisks indicate significant differences before and after training

Table 4.3. Mixed-ANOVA results for the effect of tDCS on joint excursions

		Right Hip			Left Hip			Right Knee			Left Knee			Right Ankle			Left Ankle		
Forward Perturbation	df	F	p	η^2	F	p	η^2	F	p	η^2	F	p	η^2	F	p	η^2	F	p	η^2
Time	1	6,06	0,02*	0,07	0,49	0,49	0,01	12,95	0,0006*	0,14	0,40	0,53	0,005	5,40	0,02*	0,06	0,29	0,59	0,004
Sound	1	0,04	0,84	0,00	0,02	0,89	0,01	0,02	0,89	0,005	0,00	0,96	0,01	0,13	0,72	0,001	0,08	0,78	0,001
Group	2	1,81	0,17	0,04	1,03	0,37	0,07	1,54	0,22	0,03	1,49	0,24	0,05	1,38	0,26	0,03	2,88	0,06	0,16
Time:Sound	1	0,00	0,99	0,00	0,00	0,95	0,0001	0,00	0,96	0,00	0,06	0,81	0,001	0,09	0,77	0,001	0,17	0,68	0,002
Time:Group	2	4,98	0,01*	0,11	4,30	0,02*	0,10	2,25	0,11	0,05	2,55	0,08	0,06	2,83	0,07	0,07	7,04	0,002*	0,15
Sound:Group	2	0,33	0,72	0,00	0,28	0,76	0,01	0,29	0,75	0,005	0,24	0,78	0,01	0,09	0,92	0,00	0,02	0,98	0,0001
Time:Sound:Group	2	0,21	0,81	0,01	0,17	0,84	0,004	0,19	0,83	0,005	0,16	0,85	0,004	0,04	0,96	0,00	0,02	0,98	0,0004
Backward Perturbation																			
Time	1	2,07	0,15	0,03	3,25	0,08	0,04	13,41	<0,0001*	0,14	17,15	<0,0001*	0,18	3,19	0,08	0,04	1,14	0,29	0,01
Sound	1	1,00	0,32	0,01	0,61	0,44	0,01	0,08	0,78	0,001	0,30	0,58	0,004	0,05	0,83	0,001	0,01	0,93	0,0001
Group	2	0,05	0,95	0,004	0,42	0,66	0,03	1,29	0,29	0,09	0,87	0,43	0,06	0,35	0,71	0,02	0,42	0,66	0,03
Time:Sound	1	0,03	0,86	0,0004	0,85	0,36	0,01	0,03	0,87	0,0003	0,05	0,83	0,001	0,61	0,44	0,01	0,44	0,51	0,01
Time:Group	2	0,52	0,60	0,01	2,41	0,10	0,06	0,60	0,55	0,01	0,55	0,58	0,01	1,80	0,17	0,04	0,45	0,64	0,01
Sound:Group	2	0,05	0,95	0,001	0,07	0,93	0,002	0,02	0,98	0,001	0,02	0,98	0,0004	0,16	0,86	0,004	0,04	0,96	0,001
Time:Sound:Group	2	0,19	0,83	0,005	0,17	0,84	0,004	0,11	0,90	0,003	0,66	0,52	0,02	0,06	0,94	0,002	0,99	0,38	0,02

4.3 N1 Responses

Main and interaction effects of N1 amplitude and latency at the Cz electrode are presented in Table 4.4. N1 amplitude showed main effects of time, sound, and group in backward perturbation. A significant main effect of time was observed in N1 latency in both forward and backward perturbations, with high effect sizes. There was also an interaction between time and group factors in N1 latency in backward perturbations, with the medium effect size. No additional main or interaction effects were observed.

Post-hoc comparisons showed that the perturbation-based balance training reduced the N1 amplitude in backward perturbation across all groups ($t:2,98$, $p:0,004$ APPENDIX-6 Table 16). N1 amplitude was smaller in the sound conditions compared to the no sound conditions in backward perturbation condition ($t: 3,4$, $p:0,001$, APPENDIX-6, Table 17). Lastly, N1 amplitude in sham stimulation group was greater in sham stimulation group compared to the control group in backward stimulation ($t:-2,55$, $p:0,04$ APPENDIX-6 Table 18).

The perturbation-based balance training caused a reduction in N1 latency across all groups in both forward and backward perturbation, respectively ($t:6,14$, $p:<0,0001$ and $t:4,13$, $p:0,0001$, respectively, APPENDIX-6 Tables 19 and 20). This improvement also depended on the group factor in backward perturbations. Only anodal stimulation group demonstrated a reduction in N1 latency following a training ($t:4,67$, $p:0,0001$, APPENDIX-6 Table 21). The changes in each group for both N1 amplitude and latency were illustrated in Figure 4.4.

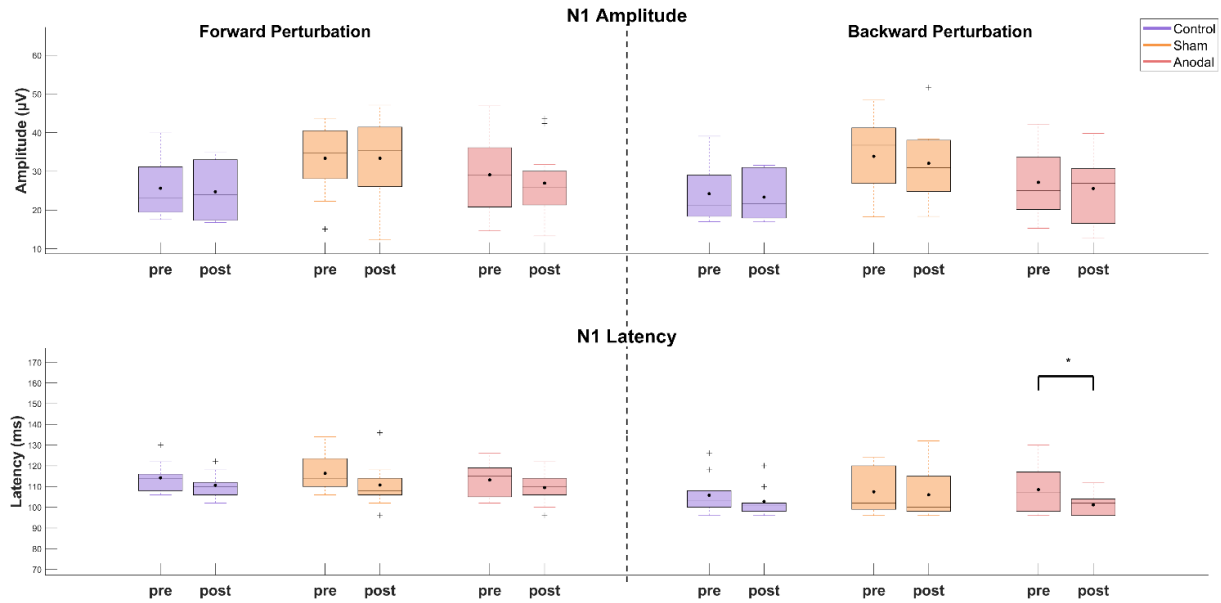


Figure 4.4. N1 amplitudes for each group and each perturbation direction.

The amplitude data were standardized via baseline correction. The period of -1000 ms to -200 ms was used to calculate the baseline value. Each box shows the interquartile range (25th-75th percentiles), and the horizontal line in each box indicates the median while the black dot indicates the mean. Outliers are indicated with a "+" and whiskers represent the range of data. Asterisks indicate significant differences before and after training, and hash signs indicate significant differences between groups.

Table 4.4. Mixed-ANOVA results for the effect of tDCS on N1 responses.

			Cz Amplitude		Cz Latency	
	Main/Interaction	df	F	p	F	p
Forward Perturbation	Time	1	3,56	0,06	37,60	<0,0001*
	Sound	1	1,05	0,31	0,00	0,98
	Group	1	2,47	0,10	0,24	0,79
	Time:Sound	2	0,51	0,48	0,66	0,42
	Time:Group	1	1,42	0,25	0,91	0,41
	Sound:Group	1	0,07	0,93	0,77	0,47
	Time:Sound:Group	1	0,02	0,98	0,18	0,84
Backward Perturbation	Time	2	8,85	0,004*	17,09	<0,0001*
	Sound	2	11,53	0,001*	0,52	0,47
	Group	2	3,54	0,04*	0,22	0,81
	Time:Sound	1	0,01	0,91	1,08	0,30
	Time:Group	2	0,33	0,72	3,62	0,03*
	Sound:Group	2	0,91	0,41	1,19	0,31
	Time:Sound:Group	2	0,60	0,55	0,20	0,82

4.4 Average Theta and Alpha Band Power (Cz)

Main and interaction effects of average Theta and Alpha bands power at Cz electrode are detailed in Table 4.5. A significant main effect of time with a high effect size was found in theta power in forward perturbations. We also found a significant sound main effect in the theta power in both forward and backward perturbations. The ANOVA results revealed a significant effect for the sound factor in alpha power only in backward perturbation. A statistically significant interaction between time and group factors was observed for theta band power in the backward perturbation condition. In contrast, alpha band power showed a significant interaction between time and group in the forward perturbation direction. No other main or interaction effects were significant.

Post-hoc comparisons revealed that theta power was reduced following the perturbation-based balance training across all groups in forward perturbations ($t:4,46$, $p:<0,0001$, APPENDIX-6 Table 23). Post-hoc comparisons also showed that the acoustic signal reduced the theta power compared to the no sound conditions in both forward and backward perturbations, respectively ($t:1,99$, $p:0,049$ and $t:3,0$, $p:0,004$, respectively, APPENDIX-6 Tables 24 and 25). Alpha power also showed a reduction in the presence of the acoustic signal in backward perturbations but not in forward perturbations ($t:3,03$, $p:0,003$, APPENDIX-6, Table 30).

Training reduced the theta power in both sham and anodal stimulation groups with medium effect size ($t:2,53$, $p:0,01$ and $t:2,0$, $p:0,049$, respectively, Figure 4,5, APPENDIX-6 Table 26). Alpha power significantly decreased only in the anodal stimulation group after training ($t:2,75$, $p:0,01$, Figure 4,5, APPENDIX-6 Table 28). Figures 4.6 and 4.7 illustrate the EEG ERSPs and the N1 mean amplitude across both sessions and directions, for the no-sound and sound conditions, respectively.

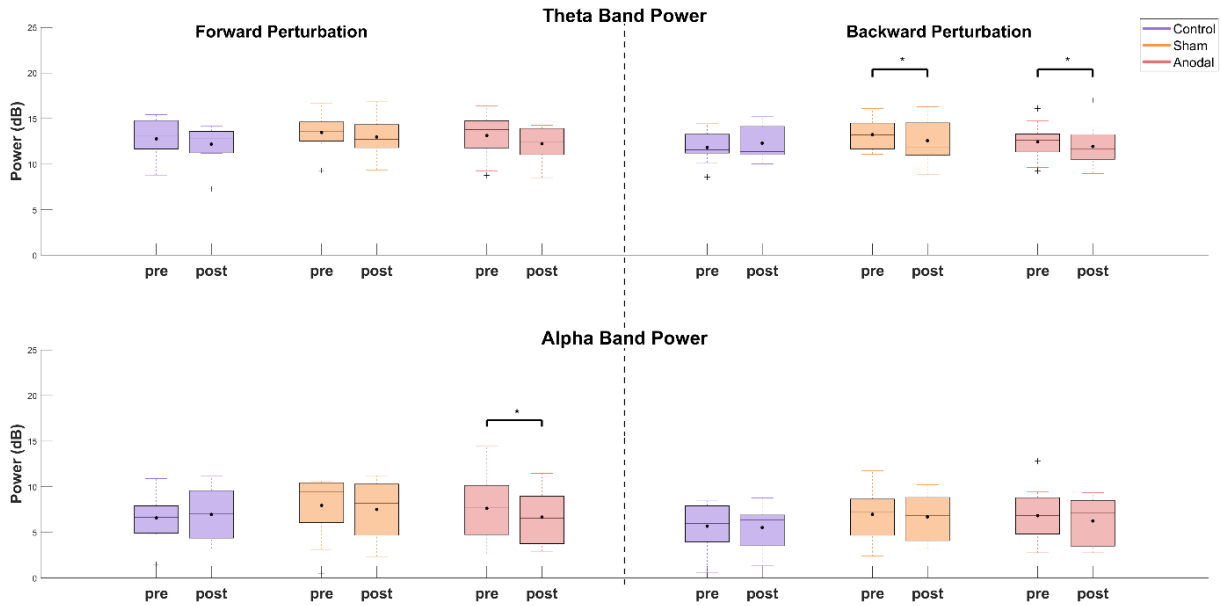


Figure 4.5. Average Theta and Alpha band power

The average band powers were calculated over 90-250 ms after perturbation onset relative to baseline (from 1000 to 200 ms before perturbation onset). This time range of interest was determined according to previous studies showing that cortical involvement starts at ~90 ms and stepping responses starts at around 250 ms [7, 166, 167].

Table 4.5. Mixed-ANOVA results for the effect of tDCS on EEG Band Power

			Averaged Theta Power (3-7 Hz)			Averaged Alpha Power (8-13 Hz)		
	Main/Interaction	df	F	p	η_p^2	F	p	η_p^2
Forward Perturbation	Time	1	19,92	<0,0001*	0,18	2,65	0,11	0,03
	Sound	1	3,96	0,049*	0,04	2,25	0,14	0,02
	Group	1	0,40	0,67	0,03	0,27	0,77	0,02
	Time:Sound	2	1,09	0,30	0,01	0,57	0,45	0,01
	Time:Group	1	0,74	0,48	0,02	3,35	0,04*	0,07
	Sound:Group	1	0,28	0,76	0,01	0,42	0,66	0,01
	Time:Sound:Group	1	0,40	0,67	0,01	0,29	0,75	0,01
Backward Perturbation	Time	2	2,31	0,13	0,03	2,97	0,09	0,03
	Sound	2	8,98	0,004*	0,09	9,18	0,003*	0,09
	Group	2	0,63	0,54	0,04	0,71	0,50	0,04
	Time:Sound	1	0,88	0,35	0,01	0,31	0,58	0,003
	Time:Group	2	5,20	0,01*	0,10	0,44	0,65	0,01
	Sound:Group	2	0,66	0,52	0,01	0,17	0,84	0,004
	Time:Sound:Group	2	0,19	0,82	0,004	0,91	0,41	0,02

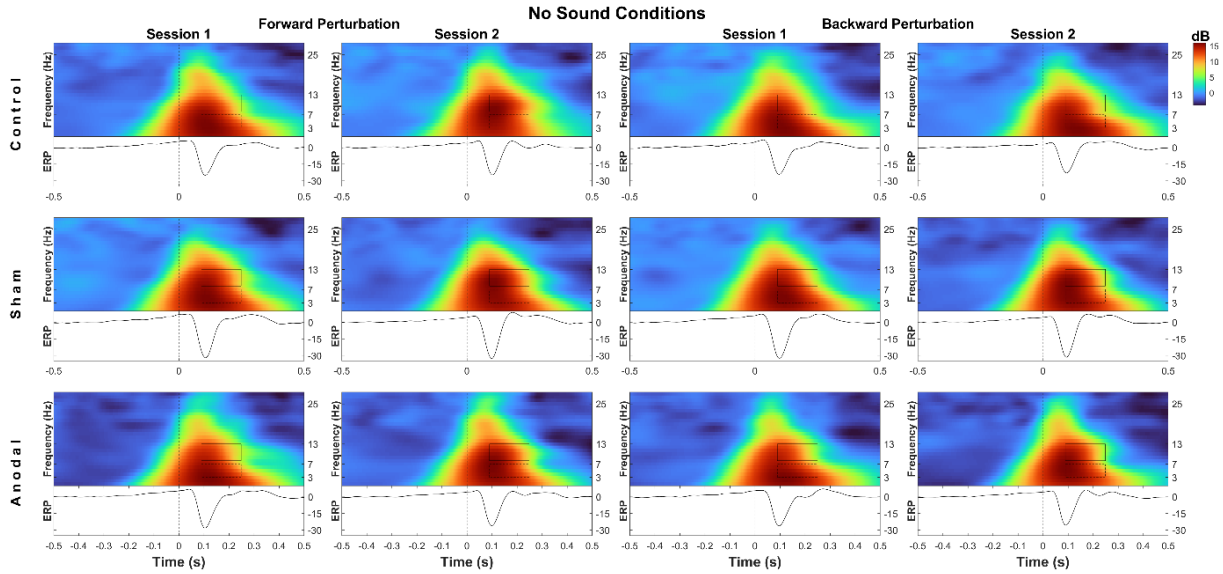


Figure 4.6. Characteristic cortical responses to perturbations without sound

The figure illustrates both time-frequency and ERP components for no sound conditions. The vertical dashed line marks the onset of the perturbation. The time-frequency domain maps illustrate the average power modulations for each group and session, highlighting typical broadband power increases (represented by warm colors). The dashed boxes delineate the theta frequency range (3-7 Hz), and the solid boxes represent the alpha frequency range (8-13 Hz) in the temporal window of interest (90-250 ms after perturbation onset).

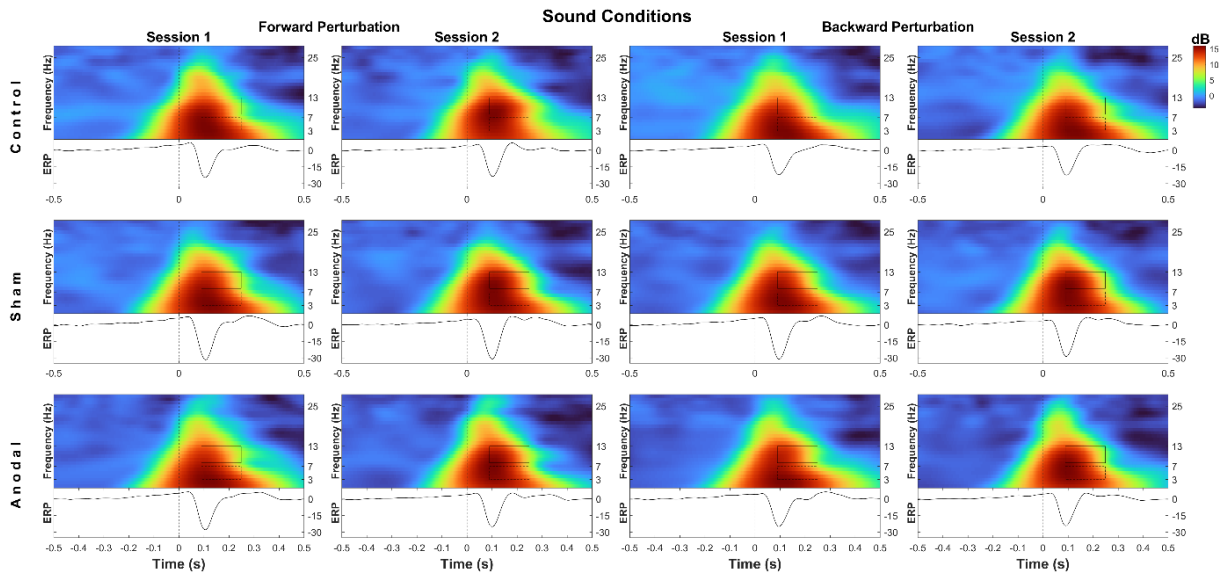


Figure 4.7. Characteristic cortical responses to perturbations with sound

The figure illustrates both time-frequency and ERP components for sound conditions. The vertical dashed line marks the onset of the perturbation. The time-frequency domain maps illustrate the average power modulations for each group and session, highlighting typical broadband power increases (represented by warm colors). The dashed boxes delineate the theta frequency range (3-7 Hz), and the solid boxes represent the alpha frequency range (8-13 Hz) in the temporal window of interest (90-250 ms after perturbation onset).

4.5 Muscle Onset Latencies

Main and interaction effects of onset latencies for each muscle are shown in Table 4.6. There was a time main effect in both right and left TA muscles. Besides, interaction between time and group factors was found in the left TA muscle. No additional main or interaction effect was observed. Post-hoc analysis revealed that a significant decrease in both right and left TA muscles across all groups ($t:2,07$, $p:0,04$ and $t:2,05$, $p:0,04$, respectively, APPENDIX-6 Tables 31 and 32). There was a significant decrease in onset latency only in anodal stimulation group following the training in the left TA muscle ($t:3,08$, $p:0,003$, APPENDIX-6 Table 34). Post-hoc comparisons are illustrated in Figure 4.8.

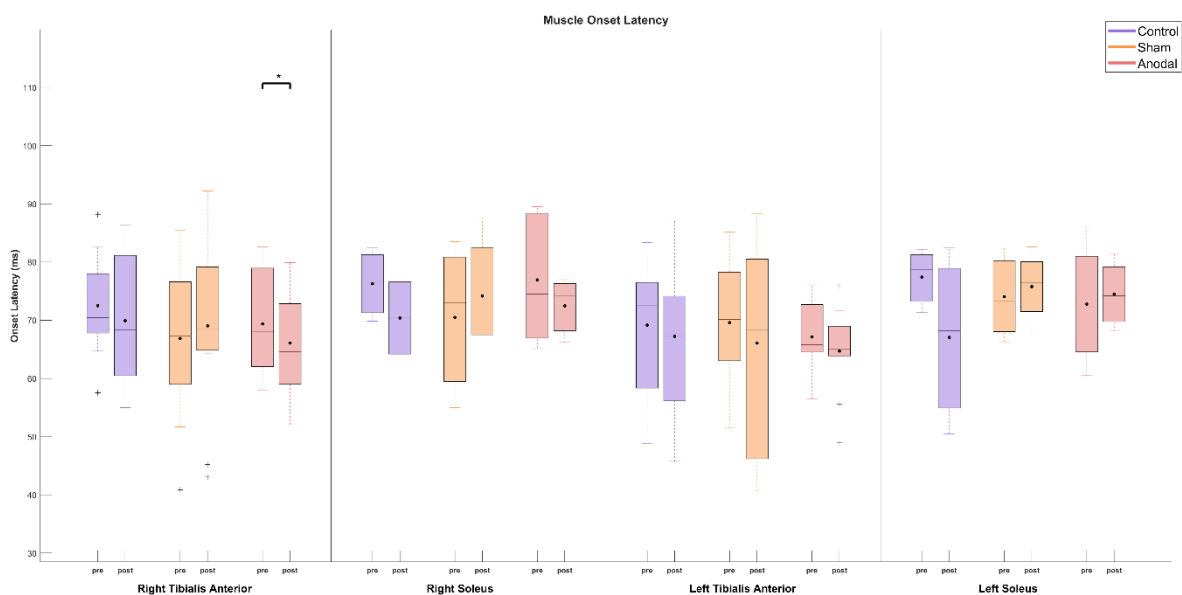


Figure 4.8. Onset latencies of each muscle

Two time points are shown for each group (pre and post). Each box shows the interquartile range (25th-75th percentiles) and the horizontal line in each box indicates the median while the black dot indicates the mean. Outliers are indicated with a "+" and whiskers represent the range of data. Asterisks indicate significant differences before and after training, and hash signs indicate significant differences between groups.

Table 4.6. Mixed-ANOVA results for the effect of tDCS on onset latency

		Right TA			Right SOL			Left TA			Left SOL		
Main/Interaction	df	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2
Time	1	4,28	0,04*	0,05	0,58	0,45	0,01	4,21	0,04*	0,05	1,71	0,19	0,02
Sound	1	0,37	0,54	0,00	0,19	0,67	0,00	0,02	0,90	0,00	0,01	0,91	0,00
Group	2	0,21	0,82	0,01	0,83	0,45	0,05	0,13	0,88	0,01	1,24	0,30	0,08
Time: Sound	1	0,23	0,63	0,00	0,05	0,82	0,00	0,85	0,36	0,01	0,15	0,70	0,00
Time: Group	2	2,69	0,07	0,06	0,88	0,42	0,02	3,13	0,048*	0,07	1,16	0,32	0,03
Sound: Group	2	0,79	0,46	0,02	0,45	0,64	0,01	0,32	0,73	0,01	0,98	0,38	0,02
Time: Sound: Group	2	0,10	0,91	0,00	1,34	0,27	0,03	0,13	0,88	0,00	1,10	0,34	0,02

4.6 Intracortical Excitability

Main and interaction effects of SICI and ICF for each muscle are shown in Table 4.7. There was a significant muscle main effect in both SICI and ICF. ICF also shows a significant interaction between time and muscle factors. These main and interaction effects were observed with small effect sizes. No additional main or interaction effect was observed.

Post-hoc analysis indicated that left TA showed higher inhibition than right and left SOL ($t:3,29$, $p:0,01$ and $t:-2,62$, $p:0,046$, respectively, APPENDIX-6, Table 35). Right TA showed higher facilitation compared to the right soleus ($t:3,09$, $t:0,01$, APPENDIX-6 Table 36). Although there was no statistically significant difference between muscles in the pre training session, right TA showed higher ICF than right SOL following the training ($t:3,65$, $p:0,002$, APPENDIX-6, Table 37). Besides, ICF in the right TA muscle significantly increased after the perturbation-based balance training across all groups ($t:-2,35$, $p:0,02$, APPENDIX-6 Table 38). Post-hoc comparison results between groups and time points are presented in Figure 4.9.

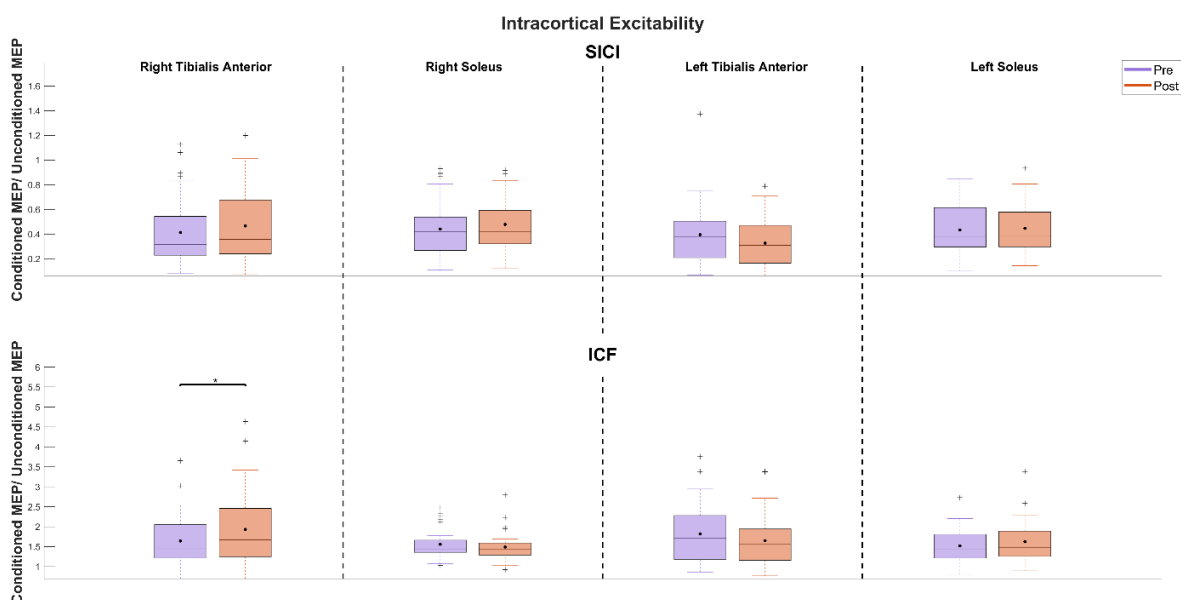


Figure 4.9. SICI and ICF for each muscle

Each box shows the interquartile range (25th-75th percentiles) and the horizontal line in each box indicates the median while the black dot indicates the mean. Outliers are indicated with a "+" and whiskers represent the range of data. Asterisk indicates significant differences before and after training.

Table 4.7. Mixed-ANOVA results for the effect of tDCS on TMS Measures

		df	F	p	η_p^2
SICI	Time	1	0,15	0,70	0,001
	Group	2	1,00	0,38	0,06
	Muscle	3	4,20	0,01*	0,05
	Time:Group	2	0,15	0,86	0,001
	Time:Muscle	3	1,48	0,22	0,02
	Group:Muscle	6	1,25	0,28	0,03
	Time:Group:Muscle	6	0,56	0,76	0,02
ICF	Time	1	0,42	0,52	0,002
	Group	2	0,72	0,50	0,04
	Muscle	3	4,41	0,005*	0,06
	Time:Group	2	0,20	0,82	0,002
	Time:Muscle	3	2,67	0,049*	0,04
	Group:Muscle	6	1,28	0,27	0,03
	Time:Group:Muscle	6	0,81	0,56	0,02

5. DISCUSSION

This study examined changes in kinematic and cortical responses to balance perturbation and changes in corticospinal excitability after short-term balance training to reveal the primary motor cortex's involvement in early balance learning. Our findings indicate that combining balance training with anodal tDCS significantly improved balance performance in forward perturbations. Specifically, COM displacement and hip joint excursions on both sides were significantly reduced in the anodal stimulation group post-training, suggesting enhanced postural control mechanisms facilitated by the neuromodulatory effects of tDCS.

CNS closely monitors the COM movement, detects when it goes beyond the desired boundaries, and initiates appropriate responses to regain the balance, particularly during unexpected perturbations. When the balance is disturbed, proprioceptive signals arising from the ankle trigger reflex responses originating from the spinal and supraspinal structures. Rapid and robust responses and intermuscular coordination prevent the body from falling. Thus, decreased COM displacement in the forward perturbation indicates an enhanced ability to recover balance in response to perturbations, reflecting improved postural stability and balance control mechanisms in the anodal stimulation group. Supporting this, previous studies reported a reduction in peak COM displacement following perturbation-based balance training of varying durations, similar to the current study [57, 58].

We also calculated the variance of each lower extremity joint to consider both peak joint excursion and the variability of joint excursions. The immediate reaction of the ankle joint compensates for the balance disturbance and promotes faster balance recovery [59, 168, 169]. When a perturbation strongly disturbs the balance, hip strategy, involving hip joint excursion to move the COM rapidly, is used to recover the balance [7, 10]. The decrease in the right hip, knee, and ankle joint excursions observed after the training, regardless of the group, suggests that perturbation-based balance training improved balance control in response to forward perturbations across all participants. Furthermore, the reduced right and left hip excursions only in the anodal stimulation group in forward perturbations and significant interaction effect imply that anodal tDCS combined with perturbation-based balance training further facilitated balance control.

It can be anticipated that the variance of joint excursions differs depending on the direction of the perturbation. For example, hip joints have a greater flexion range of motion than extension. Thus, forward perturbations may elicit larger joint excursions than backward perturbations. Similarly, the knee joint has a very small joint extension while standing but knee flexion can be used to recover balance rapidly by means of lowering the COM height [170]. In the current study, right knee joint excursions were significantly decreased across all participants in forward perturbations, while both knee joint excursions increased in backward perturbations following the training across all participants. This finding supports the idea that different balance control strategies are used for different perturbation directions. While balance training increased the stability in forward perturbations, it led to a more dynamic and flexible balance control strategy in backward perturbations.

From the biomechanical point of view, the base of support (BoS) and the feet are anatomically extended in the forward direction. The COM projection is slightly anterior to the lateral malleolus in the standing position. This anatomical arrangement allows the body to generate greater torque while leaning forward rather than backward. Thus, due to its anatomical advantages, the body can easily maintain the COM away from the BoS during backward perturbations than forward perturbations. Therefore, maintaining the COM more stable might be a good strategy for backward perturbations, whereas a stiffer response and moving with the surface might be more effective for forward perturbations because of biomechanical properties.

A previous study showed that forward perturbation and startle reflex may share a common mechanism to generate more rapid responses to perturbation [11]. Their findings suggested that different neural circuits are possibly involved in the sensorimotor processing of perturbations in different directions. In the current study, no main or interaction effect was found in N1 amplitude in forward perturbation. However, the training significantly reduced the N1 amplitude in backward perturbation across all participants. Supporting this finding, previous studies showed that individuals with impaired balance ability exhibit a larger N1 response [22] which decreases even through ten perturbation trials [19]. Although the improved balance control ability, as evidenced by decreased joint excursions in forward perturbations, N1 amplitude didn't change through training in forward perturbations, possibly showing a decreased impact of backward perturbations to the balance or perceived threat.

N1 amplitude has cognitive components including attention [171], perceived threat [146, 149] and predictability of the postural perturbations [144, 146, 149, 172, 173]. Previous studies defined its role in sensory integration, error detection, and movement initiation [15, 77], even though the exact mechanisms remain unclear. Cognitive components of the N1 response suggest that the balance recovery process becomes more automatic through training, and perturbations are no longer perceived as significant postural threats, diminishing the need for heightened attention. Our findings regarding N1 amplitude indicate that forward perturbations generate a more significant postural threat even after training, possibly because forward perturbations are more challenging than backward perturbations. Therefore, the participants may commit more cognitive resources for sensory integration or attention

In line with the current findings, a previous study demonstrated decreased N1 latency when perturbation intensity and probability of stepping response increased regardless of the direction of perturbation. The authors suggested that increasing computational load before determining the need for a stepping response is associated with decreased N1 latency since reduced latency enables a longer time to generate longer latency responses such as stepping [14]. If more challenging perturbations lead to decreased N1 latency, it would be expected that the balance training wouldn't reduce the latency since the perturbations are likely to be more easily handled after the training. However, in the current study, latency was decreased in both directions after the training across all participants, suggesting increased sensory processing speed. Furthermore, only the anodal stimulation group showed further reduction in N1 latency in backward perturbations, which suggests a modulation of tDCS on N1 latency. Although the behavioral improvements in the anodal stimulation group were most prominent during forward perturbations, a significant reduction in N1 latency was observed only in the anodal stimulation group in the backward direction. The observed dissociation between behavioral and neural outcomes may be attributed to the complicated effect of M1 stimulation on sensorimotor pathways involved in balance control.

Furthermore, we observed significant modulations in the theta and alpha band powers in the respective time bin between 90 and 250 ms. Specifically, theta band power decreased in both the sham and anodal stimulation groups during backward perturbations and across all groups in forward perturbations, implying that the balance training, regardless of the type of stimulation, influenced cortical processes, possibly related to enhanced sensory integration

and motor output. However, alpha band power was reduced in forward perturbations, only in the anodal stimulation group after the training, potentially reflecting enhanced sensory processing in the forward direction facilitated by tDCS. These findings prove that anodal tDCS over M1 may modulate sensorimotor processing, facilitating balance ability.

Sensorimotor processing is associated with N1 amplitude and underlying modulations of theta and alpha rhythms [16, 143, 174]. Supporting this, a previous study suggested that theta band power scale with the perturbation intensity [68] and its impact on the balance. When the body leans forward before a backward perturbation, amplifying the impact of perturbation, theta power is increased more quickly [68]. This increase in theta power may represent an error between the current and desired posture and may precede the level of long latency response behaviors after the perturbation [14, 68]. It was demonstrated that theta power increases in the instance of balance loss supporting its role in balance monitoring. In addition, Peterson and Ferris found increased theta power connectivity between SMA and several other brain regions involving right and left sensorimotor and anterior cingulate cortices, which refers to the interaction between various brain regions during a standing balance task. Their finding indicates a possible contribution of various brain regions to N1 response and increased sensorimotor processing during balance recovery [91]. SMA serves as a hub for theta band connectivity with motor areas [91] and for sensory integration with connections to the prefrontal cortex [143], and brainstem [90].

The results of the present study support the previous findings suggested theta rhythms may be involved in the error detection process and cognitive control during balance disturbances [14], as decreased theta power was observed in both directions following the training without any causal effect of tDCS over M1. Alpha power, on the other hand, is known for its involvement in sensorimotor processing [14, 17] and is also associated with balance control, possibly associated with motor preparation and execution of reactive responses to the balance disturbances [14, 17, 77]. Therefore, the observed decrease in alpha power after training only in the anodal stimulation group implies an improved motor adaptation possibly through strengthening of communication between the SMA and motor cortices resulting in better balance during forward perturbations.

Previous findings showed that tDCS can also facilitate subcortical structures along with altering the cortical excitability [175]. The muscle onset latency after a perturbation stimulus

is one indicator that shows the facilitated or inhibited subcortical structures. Fifteen minutes of anodal tDCS over the non-dominant motor cortex resulted in a reduced onset latency response of ankle muscles to perturbations compared to the sham tDCS. Their findings implied that tDCS altered the excitability of subcortical structures which has a role “central set” lead to faster muscle onset latency in response to the perturbations [38]. The adaptation of central set likely influences the automatic postural responses [176]. Current study showed that right TA muscle onset latency was significantly reduced after the training only in anodal stimulation, indicating facilitation of subcortical adaptation with anodal tDCS. On the other hand, onset latency was reduced across all participants in left TA muscle, suggesting perturbation-based balance training improved the onset latency. These results may imply that dominant and non-dominant sides can be affected by tDCS in a different way.

While decreased inhibition and enhanced cortical excitability are observed after motor training, balance training induced the opposite changes. Previous studies have shown a reduction in cortical contributions during balance training indicated by decreased corticospinal and cortical excitability and increased SICI [74]. A few studies reported intracortical excitability changes after balance training [24, 46, 52, 128, 159]. Mouthon and Taube found an enhanced level of SICI during the balance test after two weeks of balance training [24]. This opposite effect was also confirmed by a study that compared the effect of 4 weeks of different types of training on cortical adaptation. They found that increased SICI after balance training and reduced SICI after explosive training [46]. It is important to note that these findings mentioned above suggested that cortical adaptations observed when it is tested during task execution or while standing [24, 46, 159] not at rest or during non-practiced tasks suggesting that these changes depend on the testing conditions.

Although ICF is used to assess facilitatory mechanisms in the brain, its role in balance skill acquisition is not fully clear. Only two studies reported ICF changes after balance training and found no significant change at rest or during standing [128, 159]. In the current study, however, training induced increased ICF in the right TA muscle across all participants. Besides the studies investigating balance skill acquisition, a previous study found decreased ICF in musicians compared to the control group in a hand muscle at both rest and active conditions, implying that improving complex motor ability may decrease the ICF level [177]. By improving balance ability and facilitating long-term potentiation (LTP) through

training, heightened neural facilitation might have been induced. This finding might contribute the role of glutamatergic facilitation in possible balance skill learning mechanism.

It should also be noted that the patterns in ICF differ between right and left TA muscles. Specifically, after the training, ICF was significantly increased in right TA muscle, left TA showed a decreased ICF despite the lack of statistical significance. This observation may imply that bilateral balance training may stimulate adaptation differently in both hemispheres. Furthermore, these above-mentioned studies, investigating intracortical excitability in balance skill acquisition, conducted conventional but not perturbation-based balance training, which is more challenging and requires faster sensory processing and motor output. To the best of our knowledge, this is the first study that tested cortical excitability changes after perturbation-based balance training. Therefore, the findings may differ from the previous studies because of the difference in the type of balance training.

This study provides evidence that tDCS-induced improvements in M1 leg area function facilitate balance ability and neuromuscular function, especially in response to forward perturbations that cause posterior balance disturbances in young adults. tDCS did not significantly modulate N1 amplitude, theta power and intracortical facilitation beyond the effects of training alone. This finding suggests that the observed changes in these parameters are primarily attributable to the balance training protocol rather than the neuromodulation via tDCS. However, the current results suggested alpha power was modulated by tDCS intervention combined with balance training.

Furthermore, the acoustic signal, given two seconds before the perturbation, had varying effects on COM displacement depending on the direction of the perturbation. Specifically, acoustic signals decreased COM displacement in forward perturbations while increasing it in backward perturbations. This directional difference in response to the acoustic signal may be attributed to the postural control strategy. When individuals receive a warning signal before the perturbation, they may intentionally lean forward, anticipating the forward perturbation. These anticipatory adjustments are likely since backward perturbations can be easily handled due to the biomechanical factors mentioned earlier. Although the acoustic signal provided a timing cue for the onset of the perturbation, it did not convey any directional information to the participants. This may have influenced the effect of the acoustic signal based on the perturbation direction, possibly due to distinct neural processing

of different perturbation directions. Nonnekes et al. suggested that forward perturbations may have a common mechanism with startle reflex, which generates rapid postural responses and possibly accompanying cortical differences [11]. In the current study, preparing for the perturbation after the acoustic signal, caused more flexible reactions with increased COM displacements and accompanying decreased N1 amplitude and underlying frequency bands power in backward perturbations. In the forward perturbations, on the other hand, acoustic signal caused a decrease in only theta band power, possibly because of decreased error between expected and current body posture with preparation to the perturbation.

Our findings suggest that balance training induces significant changes in both cortical and behavioral parameters regardless of the groups. Specifically, we found decreased hip, knee and ankle joint excursions in forward perturbations as well as increased knee joint excursions, demonstrating improved balance control across all participants. These improvements were supported by cortical adaptations measured by decreased N1 amplitude and latency as well as average theta power. We also found a decreased ICF in the left TA muscle. Only anodal tDCS showed significant improvement in COM displacement and hip joint excursions in the forward direction. Supporting these behavioral findings, we also observed a reduction in alpha band power during the forward perturbations following the training with anodal stimulation. These results suggest that anodal tDCS enhances the effects of perturbation-based balance training by modulating sensorimotor processing and facilitating neuroplasticity in M1. Lastly, it should be noted that the results of the current study showed the retention of balance skill acquisition, as the last measurement sessions were conducted the day after the last training session.

5.1 Limitations

Potential limitations of the study must be considered. First, we used the same perturbation displacement in both directions to elicit similar proprioceptive signals although this may cause backward perturbations are not sufficiently challenging, possibly causing a ceiling effect in the behavioral analysis. Second, these findings may not be translatable to older adults or people with balance-affecting disorders. Third, we did not measure SICI and ICF during the task, which limits our ability to observe the full range of inhibition and facilitation between active and passive conditions. Assessing cortical excitability only at rest may lead to misinterpretations regarding the cortical adaptations that occur during balance tasks.

Fourth, the limited timeline and excluded participants (e.g. those not meeting MEP amplitude criteria) led to a smaller sample size than expected.

6. CONCLUSION AND SUGGESTIONS

Balance control is vital to continue our daily activities and to support the healthy aging process, besides for people who have balanced diseases. The understanding of the underlying neural contribution of balance control is the key to widening our sights to improve the rehabilitation processes. In this thesis, I investigated the role of M1 on balance acquisition by applying tDCS over M1. This study provides evidence that tDCS-induced improvements in M1 leg area function facilitate balance ability and neuromuscular function in response to forward perturbations that cause posterior balance disturbances in young adults. Notably, this is the first study to examine the effects of tDCS on balance, neuromuscular and cortical enhancements following perturbation-based balance training. I demonstrated enhanced muscle response latency along with improved muscular coordination through balance training with anodal stimulation. These changes are vital to recovering balance without bodily harm. These findings are supported by behavioral analysis, specifically, COM displacement and variance changes in favor of anodal stimulation group. Decreased cortical facilitation may signal a decreased role of M1 in balance acquisition after three sessions of training. Decreased theta power also supported the idea of decreased cortical involvement in monitoring role of balance disruptions after perturbations.

It is my hope that the findings of this thesis will contribute to the understanding of the role of cortical centers and lead to further research to reveal the mechanisms underlying balance control.

6.1. Future Directions

Reactive balance is important for various groups including athletes, older adults and individuals with balance affecting disorders. Understanding the underlying mechanisms of how humans respond to balance disturbances can lead us to develop therapeutic training programs and devices such as neuromodulation techniques to enhance balance abilities more rapidly. Improving balance can help in injury recovery and maintaining balance ability in a good level during aging process, ultimately enhancing quality of life. There is growing evidence supporting the critical role of M1 in balance skill acquisition particularly in the first phase of training. This thesis supports this hypothesis as well. However, the improvement and retention of balance skills may also depend on other cortical or subcortical

regions which communicate with M1 such as basal ganglia, cerebellum or SMA. In this context, brain modulation techniques remain essential to reveal the contributions of these structures to balance learning. Future studies could explore the combined effects of stimulating M1 along with other brain regions related to balance control to better clarify or exclude their role in balance control. Besides, balance learning with tDCS over M1 in other groups, such as older people or people with Parkinson's disease, would give more insights into role of M1 in balance learning. Anodal stimulation may also help athletes enhance their balance abilities.

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APPENDICES

APPENDIX-1. TMS/tDCS Safety Screening Questionnaire

It is important that you answer all of the following questions truthfully.

If any of the questions/terms on this form are unclear, or if you are unsure how to answer them, please do not hesitate to ask the researcher of the study.

Participant Reference Number:

Dominant leg:

Previous injury of your legs:

How old are you?:

Weight:

Height:

Questions

Answer “Yes” or “No” to the following questions by ticking the appropriate box.

	YES	NO
1. Do you have epilepsy, or have you ever had a convulsion or a seizure?		
2. Have you ever had a severe (i.e., followed by loss of consciousness) head trauma or a neurological illness (including neurosurgery)?		
3. Do you have any metal in your head (outside of the mouth,) such as shrapnel, surgical clips, or fragments from welding or metalwork?		
4. Do you have cochlear implants?		
5. Do you have an implanted neurostimulator (e.g., DBS, epidural/subdural, VNS)?		
6. Do you have a cardiac pacemaker or intracardiac lines or metal in your body?		
7. Do you have an implanted medical pump?		
8. Are you taking any central nervous system acting medications?		
9. Did you ever have surgical procedures to your spinal cord?		
10. Do you have spinal or ventricular derivations?		
11. Have you ever had a stroke?		
12. Do you suffer from frequent or severe headaches?		
13. Have you ever had an adverse reaction to TMS/ tDCS in the past?		
14. Do you smoke?		

APPENDIX-1. (Continued) TMS/tDCS Safety Screening Questionnaire

	YES	NO
15. Have you ever had any other brain-related symptoms or diseases?		
16. Have you ever had any condition that caused brain injury or skull fracture?		
17. Are you been addicted to alcohol or drugs?		
18. Are you pregnant or is there any chance that you might be?		
19. Do you have vertigo?		
20. Have you ever had any surgery and/or injury in your lower extremities?		
21. Do you have a lack of joint position sense?		
22. Have you participated in any other clinical study within the last 4 weeks?		
23. Do you have any serious medical conditions? (internal organs or metabolic diseases or psychiatric illness, including schizophrenia, mania, or depression)		
24. Have you participated in any kind of balance training before?		
25. Do you have any problem with the scalp skin (e.g. eczema)?		
26. Do you have a plaster tape allergy?		
27. Do you have hearing deficiencies?		

Signature: _____

Date: _____

Witnessed by (signature): _____

Witnessed by (print name): _____

APPENDIX-2. Physical Activity Readiness Questionnaire (PAR-Q)

Participant Reference Number:

Please read each question carefully and answer every question honestly:

	Yes	No
1) Has a physician ever said you have a heart condition, and you should only do physical activity recommended by a physician?		
2) When you were doing or not doing physical activity, have you had chest pain in the past month?		
3) Do you have breathing problems at rest or during physical activity?		
4) Do you ever lose consciousness, or do you lose your balance because of dizziness?		
5) Do you have a joint or bone problem that may be made worse by a change in your physical activity?		
6) Is a physician currently prescribing medications for your blood pressure or heart condition?		
7) Do you know of any other reason you should not exercise or increase your physical activity?		

Participant signature	Date
-----------------------	------

APPENDIX-3. Edinburgh Handedness Inventory

For the following activities or objects, please indicate which hand you use for this by choosing "left +" or "right +". If your preference is so strong that you have never tried to use the other hand, then choose "left ++" or "right ++". Please use the "neutral" category only if you are really undecided. Some of the following activities require both hands. In this case, the part of the task for which hand preference is sought is in parentheses. Please try to answer all items. Please leave an item unanswered only if you have no experience with the object or task at all.

	left ++	left +	Neutral	right +	right ++
Writing	☐	☐	☐	☐	☐
Drawing	☐	☐	☐	☐	☐
Throwing	☐	☐	☐	☐	☐
Using Scissors	☐	☐	☐	☐	☐
Using a Toothbrush	☐	☐	☐	☐	☐
Knife (without fork)	☐	☐	☐	☐	☐
Using Spoon	☐	☐	☐	☐	☐
Broom (upper hand)	☐	☐	☐	☐	☐
Opening box (holding the lid)	☐	☐	☐	☐	☐
Striking a match	☐	☐	☐	☐	☐
Which foot do you prefer to kick with?	☐	☐	☐	☐	☐

APPENDIX-4. Information sheet

The Effect of Transcranial Direct Current Stimulation (tDCS) on Balance Control in Response to Perturbation-Based Training

We hereby invite you to voluntarily participate in the study mentioned above, thank you for your interest in this study! We would like to explain the study to you by this information sheet.

In case you agree to participate, there will be three questionnaires to fill in in order to determine your eligibility for this study. These include two questionnaires about your previous and current health state and a questionnaire to determine your handedness. We will also examine your neurological health state, including a walking, and an eye movement test by a short physical examination.

Aims of the study

Standing and walking are important for daily life activities, and need good balance control. Older people or patients with neurological diseases may have decreased balance control. Athletes also face situations that challenge their balance control because of specifically demanding conditions. Several brain areas play a role in balance recovery after balance is disturbed. Temporarily modifying the activity of these brain areas in balance control will contribute to our understanding of the role of these areas in response to the loss of balance. This study aims to investigate the effect of transcranial direct current stimulation (tDCS), which stimulates the brain via weak currents delivered via the skull with electrodes mounted on the head with weak electrical currents. TDCS will temporarily modify brain functions during postural control. We will determine how modification of respective brain function affects how you learn to respond to the loss of balance. The potential outcome of this research is to use the knowledge gained to develop new technologies and therapy methods that will help to improve the balance of patient populations or athletes.

Study Course

If one or more of the exclusion criteria listed below apply to you, you cannot participate in the study:

1. History or evidence of chronic or residual neurological diseases.
2. Pacemaker or deep brain stimulation.
3. Metal implants in the head or neck area (e.g., postoperative clips after intracerebral aneurysm; implantation of an artificial hearing aid).
4. Age is not between 18 to 55 years.
5. History of intracerebral ischemia/ bleeding.
6. Prior evidence of epileptic seizures, history of epilepsy.
7. History of head injury with skull fracture or brain tissue lesion.
8. Any serious medical conditions (internal organs or metabolic diseases) or psychiatric illness, including schizophrenia, mania, or depression.
9. Pregnancy or breast-feeding.
10. Alcohol or drug addiction.
11. Cigarette smoker
12. Local or global aphasia.
13. Any legal reason why the candidate cannot participate.
14. Participation in another scientific or clinical study within the last 4 weeks.
15. Intake of any central nervous system (CNS)-acting medication
16. have an orthopedic disorder involving lower limbs,
17. lack of joint position sense in the lower limbs
18. a history of vertigo,
19. surgical procedure at the level of the spinal cord
20. Participation in any kind of balance training
21. Any problem with the scalp skin
22. Plaster tape allergies
23. Hearing deficiencies

In addition to above, contact lenses, dreadlocks and hair-styling products are not allowed during the assessment sessions.

In general, your participation in the research involves testing your balance and balance training periods. Balance testing will be conducted via a device that produces brief movements (perturbations) of the ‘floor’ that you will be standing on and we will measure your response to these movements. You will also participate in a balance training program that lasts four weeks. During this training, you will stand on the balance platform and the platform will move 12 times within approximately a minute. You will then be given a one-minute rest time and then the platform motions will be repeated. This process will continue until you have completed 10 blocks of 12 platform motions each. This training will be conducted three times a week during the training weeks. During balance training, tDCS might be applied to your scalp, depending on which group you have been assigned to. Before the posture training program, you will be assigned to one of four experimental groups which differ with the kind of tDCS applied. The basic plan of the study involves having your balance tested, and then complete one week of balance training combined with tDCS. Your balance will again be tested, and you will complete one more week of balance training. After that, your balance will be tested one more time. One week after balance training, your balance will be tested one final time.

Each time before your balance is tested, your brain functions will be measured by a non-invasive brain stimulation technique called Transcranial Magnetic Stimulation (TMS) in a sitting position. This technique produces magnetic pulses that are transmitted through your skull to a very specific area of your brain, and activates nerve cells in this brain area. This measurement will determine the strength of the link between your brain and the leg muscles during the balance test. During this procedure, magnetic pulses will be delivered through a coil. You will hear a clicking sound and feel a “tapping” sensation on your scalp. Your leg muscle will contract and we will monitor those contractions with small sensors attached to the skin over the leg muscles. This measurement technique is called electromyography (EMG). We will attach two electrodes to your legs for each muscle we will examine, resulting in 16 electrodes placed over 8 leg muscles. The EMG sensors measure the electrical activity of your muscles during both the TMS measurement and balance test. Prior to applying the electrodes, your skin will be shaved and cleaned with 70% alcohol. The sensors are attached to your skin with tape.

We will then attach 24 small electrodes to the scalp to record brain activity with EEG. Before this protocol, we clean your skin to reduce resistance of the skin. During the balance test, you will hear an acoustic signal before some perturbations.

For the center of mass (COM) analysis 26 reflective markers will be taped to your body to record full body motion after perturbation stimuli. During the assessment sessions COM data will be calculated.

The balance platform that you will stand on measures the forces you apply to it and by using specialized software, calculates the motion of your body. This measure is called center of pressure (COP).

During balance testing and balance training, you will stand on a balance platform and the platform will suddenly move a bit backwards or forwards with different amplitude. You will try to maintain your balance after the platform movement. You will be in no danger of falling since you will be wearing a harness attached to the metal frame of the posture platform.

If you revoke your willingness to participate in the study, already collected data will be removed from the study record, and the compensation will be based on the hours you already participated.

Risk and Side Effects

EEG and EMG are examination methods that are used for many decades in diagnostics and also in basic research, and have few side effects. In rare cases, the preparation of the skin (cleaning to reduce skin resistance) can lead to skin irritations.

Transcranial magnetic stimulation, which is used to determine the link between leg muscles and the part of the cerebral cortex which is relevant for the conduction of movements, is a non-invasive (i.e. carried out without violating the integrity of the body) and painless examination method. The extensive experience available has shown that this procedure has few risks and side effects if exclusion criteria are observed. In rare cases, mild headaches and slight discomfort can be expected.

When transcranial direct current stimulation (tDCS) is used during balance training, you may experience a light itching sensation under the electrode, mild headache, and slight burning sensations of your scalp. The most common side effects of tDCS application are redness of the skin under the area on your scalp where the electrodes are placed but these disappear rapidly after tDCS is stopped.

Any time you are standing on the balance platform you will be in a safety harness that will prevent you from falling. Thus you are not exposed to relevant risks by this method.

Before the start of the main study, you will be informed about the exclusion criteria for participation. You will receive free medical assistance if the study results in adverse health effects.

Personal benefit of participation

There are no known benefits to you from your taking part in this research. However, as this study aims to gain knowledge about how the brain is involved in balance control, possible benefits include the development of new rehabilitation techniques and/or rehabilitation technologies that may occur as a result of the new knowledge gained from this study.

Data protection

The personal data are collected and stored in paper form and the measurement data electronically on a laboratory computer at IfADo. Only the investigator has access to the data, with the exception of anonymized measurement data, which will be available for interested scientists in an open data repository. The data will be stored for 10 years after collection. In the event of an oral or written revocation of participation, the data collected up to that point will be deleted. The data is used pseudonymized. This means that the data is recorded encoded with numbers, but not with clear names of the participants. The assignment of the data to a person is only possible if the key is used with which the data was pseudonymized. The personal data are stored separately from the pseudonymized data under special protective measures. Decryption is only possible by the responsible investigator.

Third parties do not have access to the original documents. It is intended to publish the results of this study. The data is used anonymously for this purpose.

Expense allowance

For your participation in this study, you will receive an expense allowance of €12 per hour, which will be paid out on a pro-rata basis if your participation in the study is terminated prematurely.

APPENDIX 6. Post-Hoc Comparisons

PEAK COM

Forward Perturbation

Table 1 Post-hoc comparisons between directions for all participants (*Results are averaged over the levels of: Time, Group*)

	Estimate	SE	t	p
No Sound - Sound	0,88	0,30	2,93	0,004*

Table 2 Post-hoc comparisons between groups in both pre- and post-training sessions (*Results are averaged over the levels of: Sound*)

	Pre				Post			
	Estimate	SE	t	p	Estimate	SE	t	p
Control - Sham	-1,45	0,85	-1,72	0,21	-0,67	0,85	-0,79	0,71
Control - Anodal	-1,09	0,83	-1,30	0,40	0,72	0,83	0,86	0,67
Sham - Anodal	0,37	0,83	0,44	0,90	1,38	0,83	1,66	0,23

Table 3 Post-hoc comparisons between time points for each group (*Results are averaged over the levels of: Sound*)

		Estimate	SE	t	p
Pre-Post	Control	-0,62	0,52	-1,19	0,24
	Sham	0,17	0,52	0,33	0,74
	Anodal	1,18	0,51	2,33	0,02*

Backward Perturbation

Table 4 Post-hoc comparisons between directions for all participants (*Results are averaged over the levels of: Time, Group*)

	Estimate	SE	t	p
No Sound - Sound	-1,04	0,29	-3,6	0,0005*

APPENDIX 6. (Continued) Post-Hoc Comparisons

JOINT EXCURSIONS

Forward Perturbation*Right hip joint***Table 5** Post-hoc comparisons between directions for all participants (*Results are averaged over the levels of: Sound, Group*)

	Estimate	SE	t	p
Pre-Post	0,91	0,37	2,46	0,02*

Table 6 Post-hoc comparisons between time points for each group (*Results are averaged over the levels of: Sound*)

		Estimate	SE	t	p
Pre-Post	Control	-0,23	0,66	-0,35	0,73
	Sham	0,46	0,63	0,73	0,47
	Anodal	2,49	0,62	4,04	0,0001*

Table 7 Post-hoc comparisons between groups in both time points (*Results are averaged over the levels of: Sound*)

	Pre				Post			
	Estimate	SE	t	p	Estimate	SE	t	p
Control - Sham	-2,51	2,12	-1,18	0,47	-1,82	2,12	-0,86	0,67
Control - Anodal	-1,86	2,08	-0,89	0,65	0,86	2,08	0,41	0,91
Sham-Anodal	0,66	2,02	0,32	0,94	2,68	2,02	1,33	0,39

*Left hip joint***Table 8** Post-hoc comparisons between time points for each group (*Results are averaged over the levels of: Sound*)

		Estimate	SE	t	p
Pre-Post	Control	-0,65	0,57	-1,14	0,26
	Sham	-0,18	0,54	-0,33	0,75
	Anodal	1,49	0,53	2,82	0,01*

APPENDIX 6. (Continued) Post-Hoc Comparisons

Table 9 Post-hoc comparisons between groups in both time points (*Results are averaged over the levels of: Sound*)

	Pre				Post			
	Estimate	SE	t	p	Estimate	SE	t	p
Control - Sham	-2,55	2,09	-1,22	0,45	-2,07	2,09	-0,99	0,59
Control - Anodal	-0,72	2,05	-0,35	0,93	1,43	2,05	0,70	0,77
Sham-Anodal	1,83	1,99	0,92	0,63	3,50	1,99	1,76	0,20

Right knee joint**Table 10** Post-hoc comparisons between directions for all participants (*Results are averaged over the levels of: Sound, Group*)

	Estimate	SE	t	p
Pre-Post	2,32	0,65	3,60	0,0006*

Right Ankle Joint**Table 11** Post-hoc comparisons between directions for all participants (*Results are averaged over the levels of: Sound, Group*)

	Estimate	SE	t	p
Pre-Post	0,16	0,07	2,32	0,02*

Left ankle joint**Table 12** Post-hoc comparisons between time points for each group (*Results are averaged over the levels of: Sound*)

		Estimate	SE	t	p
Pre-Post	Control	-0,22	0,07	-3,30	0,002*
	Sham	0,09	0,06	1,38	0,17
	Anodal	0,07	0,06	1,18	0,24

Table 13 Post-hoc comparisons between groups in both time points (*Results are averaged over the levels of: Sound*)

	Pre				Post			
	Estimate	SE	t	p	Estimate	SE	t	p
Control - Sham	-0,16	0,15	-1,07	0,54	0,15	0,15	0,96	0,61
Control - Anodal	0,12	0,15	0,83	0,69	0,42	0,15	2,81	0,02*
Sham-Anodal	0,29	0,15	1,98	0,13	0,27	0,15	1,88	0,16

APPENDIX 6. (Continued) Post-Hoc Comparisons

Backward Perturbation***Right knee joint*****Table 14** Post-hoc comparisons between directions for all participants (*Results are averaged over the levels of: Sound, Group*)

	Estimate	SE	t	p
Pre-Post	-0,53	0,15	-3,66	0,001*

Left knee joint**Table 15** Post-hoc comparisons between directions for all participants (*Results are averaged over the levels of: Sound, Group*)

	Estimate	SE	t	p
Pre-Post	-0,48	0,12	-4,14	0,0001*

N1 AMPLITUDE**Backward Perturbation****Table 16** Post-hoc comparisons between time points for all participants (*Results are averaged over the levels of: Sound, Group*)

	All Participants			
	Estimate	SE	t	p
Pre-Post	1,42	0,48	2,98	0,004*

Table 17 Post-hoc comparisons between sound conditions for all participants (*Results are averaged over the levels of: Time, Group*)

	All Participants			
	Estimate	SE	t	p
No Sound - Sound	1,63	0,48	3,4	0,001*

Table 18 Post-hoc comparisons between groups in both time points (*Results are averaged over the levels of: Sound*)

	Estimate	SE	t	p
Control - Sham	-9,21	3,61	-2,55	0,04*
Control - Anodal	-2,59	3,54	-0,73	0,75
Sham-Anodal	6,62	3,45	1,92	0,15

APPENDIX 6. (Continued) Post-Hoc Comparisons

N1 LATENCY

Forward Perturbation**Table 19** Post-hoc comparisons between time points for all participants (*Results are averaged over the levels of: Sound, Group*)

	All Participants			
	Estimate	SE	t	p
Pre-Post	4,30	0,70	6,14	<0,0001*

Backward Perturbation**Table 20** Post-hoc comparisons between time points for all participants (*Results are averaged over the levels of: Sound, Group*)

	All Participants			
	Estimate	SE	t	p
Pre-Post	3,93	0,95	4,13	0,0001*

Table 21 Post-hoc comparisons between time points for each group (*Results are averaged over the levels of: Sound*)

		Estimate	SE	t	p
Pre-Post	Control	3,00	1,72	1,74	0,08
	Sham	1,45	1,64	0,89	0,38
	Anodal	7,33	1,57	4,67	<0,0001*

Table 22 Post-hoc comparisons between groups in both points (*Results are averaged over the levels of: Sound*)

	Pre				Post			
	Estimate	SE	t	p	Estimate	SE	t	p
Control - Sham	-1,65	4,12	-0,40	0,92	-3,20	4,12	-0,78	0,72
Control - Anodal	-2,70	4,04	-0,67	0,78	1,63	4,04	0,40	0,91
Sham-Anodal	-1,05	3,94	-0,27	0,96	4,83	3,94	1,23	0,44

APPENDIX 6. (Continued) Post-Hoc Comparisons

AVERAGED THETA POWER**Forward Perturbation****Table 23** Post-hoc comparisons between time points for all participants (*Results are averaged over the levels of: Sound, Group*)

	All Participants			
	Estimate	SE	t	p
Pre-Post	0,66	0,15	4,46	<0,0001*

Table 24 Post-hoc comparisons between sound conditions for all participants (*Results are averaged over the levels of: Time, Group*)

	All Participants			
	Estimate	SE	t	p
No Sound - Sound	0,30	0,15	1,99	0,049*

Backward Perturbation**Table 25** Post-hoc comparisons between time points for all participants (*Results are averaged over the levels of: Time, Group*)

	All Participants			
	Estimate	SE	t	p
No Sound-Sound	0,46	0,15	3,0	0,004*

Table 26 Post-hoc comparisons between time points for each group (*Results are averaged over the levels of: Sound*)

		Estimate	SE	t	p
Pre-Post	Control	-0,48	0,28	-1,72	0,09
	Sham	0,67	0,27	2,53	0,01*
	Anodal	0,51	0,25	2,00	0,049*

Table 27 Post-hoc comparisons between groups in both time points (*Results are averaged over the levels of: Sound*)

	Pre				Post			
	Estimate	SE	t	p	Estimate	SE	t	p
Control - Sham	-1,42	0,85	-1,67	0,23	-0,27	0,85	-0,32	0,95
Control - Anodal	-0,63	0,84	-0,75	0,74	0,36	0,84	0,43	0,90
Sham-Anodal	0,80	0,81	0,98	0,59	0,64	0,81	0,78	0,72

APPENDIX 6. (Continued) Post-Hoc Comparisons

AVERAGED ALPHA POWER**Forward Perturbation****Table 28** Post-hoc comparisons between time points for each group (*Results are averaged over the levels of: Sound*)

		Estimate	SE	t	p
Pre-Post	Control	-0,37	0,38	-0,98	0,33
	Sham	0,44	0,36	1,22	0,23
	Anodal	0,95	0,35	2,75	0,01*

Table 29 Post-hoc comparisons between groups in both time points (*Results are averaged over the levels of: Sound*)

	Pre				Post			
	Estimate	SE	t	p	Estimate	SE	t	p
Control - Sham	-1,36	1,34	-1,01	0,57	-0,54	1,34	-0,41	0,91
Control - Anodal	-1,04	1,31	-0,79	0,71	0,28	1,31	0,22	0,97
Sham-Anodal	0,31	1,28	0,25	0,97	0,83	1,28	0,65	0,80

Backward Perturbation**Table 30** Post-hoc comparisons between sound conditions for all participants (*Results are averaged over the levels of: Group*)

	All Participants			
	Estimate	SE	t	p
No Sound - Sound	0,59	0,19	3,03	0,003*

ONSET TIME**Right Tibialis Anterior****Table 31** Post-hoc comparisons between time points for all participants (*Results are averaged over the levels of: Sound, Group*)

	All Participants			
	Estimate	SE	T	p
Pre-Post	2,48	1,2	2,07	0,04*

APPENDIX 6. (Continued) Post-Hoc Comparisons

Left Tibialis Anterior**Table 32** Post-hoc comparisons between time points for all participants (*Results are averaged over the levels of: Sound, Group*)

	All Participants			
	Estimate	SE	T	p
Pre-Post	3,25	1,58	2,05	0,04*

Table 33 Post-hoc comparisons between groups in both time points (*Results are averaged over the levels of: Sound*)

	Pre				Post			
	Estimate	SE	t	p	Estimate	SE	t	p
Control - Sham	1,02	7,19	0,14	0,99	-3,12	7,19	-0,43	0,90
Control - Anodal	-0,48	7,07	-0,07	1,00	4,86	7,07	0,69	0,77
Sham-Anodal	-1,50	6,89	-0,22	0,97	7,98	6,89	1,16	0,49

Table 34 Post-hoc comparisons between time points for each group (*Results are averaged over the levels of: Sound*)

		Estimate	SE	t	p
Pre-Post	Control	2,85	2,85	1,00	0,32
	Sham	-1,29	2,72	-0,47	0,64
	Anodal	8,19	2,66	3,08	0,003*

INTRACORTICAL EXCITABILITY**Short-Interval Intracortical Inhibition (SICI)****Table 35** Post-hoc comparisons between time points for all participants (*Results are averaged over the levels of: Sound, Group*)

Muscle Comparisons	Estimate	SE	t	p
Right Tibialis Anterior – Right Soleus	-0,02	0,03	-0,73	0,88
Right Tibialis Anterior – Left Tibialis Anterior	0,08	0,03	2,56	0,055
Right Tibialis Anterior – Left Soleus	0,00	0,03	-0,06	1,00
Right Soleus – Left Tibialis Anterior	0,10	0,03	3,29	0,01*
Right Soleus – Left Soleus	0,02	0,03	0,67	0,91
Left Tibialis Anterior – Left Soleus	-0,08	0,03	-2,62	0,046*

APPENDIX 6. (Continued) Post-Hoc Comparisons

Intracortical Facilitation (ICF)**Table 36** Post-hoc comparisons between muscles for all participants (Results are averaged over the levels of Time and Group)

Muscle Comparisons	Estimate	SE	t	p
Right Tibialis Anterior – Right Soleus	0,27	0,09	3,09	0,01*
Right Tibialis Anterior – Left Tibialis Anterior	0,05	0,09	0,64	0,92
Right Tibialis Anterior – Left Soleus	0,22	0,09	2,55	0,06
Right Soleus – Left Tibialis Anterior	-0,21	0,09	-2,46	0,07
Right Soleus – Left Soleus	-0,05	0,09	-0,54	0,95
Left Tibialis Anterior – Left Soleus	0,17	0,09	1,91	0,23

Table 37 Post-hoc comparisons between muscles for all participants in both time points (Results are averaged over the level of Group) (TA: Tibialis Anterior, SOL: Soleus)

Muscle Comparisons	Estimate	SE	t	p	Cohen's d	Estimate	SE	t	p
Right TA – Right SOL	0,09	0,12	0,73	0,89	0,18	0,45	0,12	3,65	0,002*
Right TA – Left TA	-0,17	0,12	-1,40	0,50	-0,34	0,28	0,12	2,30	0,10
Right TA – Left SOL	0,13	0,12	1,06	0,72	0,26	0,31	0,12	2,55	0,06
Right SOL – Left TA	-0,26	0,12	-2,13	0,15	-0,52	-0,16	0,12	-1,34	0,54
Right SOL – Left SOL	0,04	0,12	0,33	0,99	0,08	-0,13	0,12	-1,10	0,69
Left TA – Left SOL	0,30	0,12	2,46	0,07	0,60	0,03	0,12	0,25	0,99

Table 38 Post-hoc comparisons between time points for each muscle (Results are averaged over the level of Group)

		Estimate	SE	t	p
Pre-Post	Right Tibialis Anterior	-0,29	0,12	-2,35	0,02*
	Right Soleus	0,07	0,12	0,56	0,57
	Left Tibialis Anterior	0,17	0,12	1,35	0,18
	Left Soleus	-0,10	0,12	-0,86	0,39

CURRICULUM VITAE

PERSONAL INFORMATION

Name, Surname : Ömer Burak, Tor
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EDUCATION

Degree	School/Program	Graduation Year
Ph.D.	Gazi University/ Physiotherapy and Rehabilitation	2024
M.Sc.	Yeditepe University/ Sports Physiotherapy	2017
B.Sc.	Suleyman Demirel University/ Physiotherapy and Rehabilitation	2014

Work experience, Year	Place	Position
2022-2024	IfADo	Research Assistant
2018-2024	Gazi University	Research Assistant
2017-2018	Balıkesir University	Research Assistant
2015-2017	Bolu Izzet Baysal State Hospital	Physiotherapist

Foreign Languages

English, German

Publications

1. Tor, O. B., Ecemis, Z. B., ÇOBANOĞLU, G., SUNER KEKLİK, S., KAFA, N., Soylu, R., GÜZEL, N. A.(2019). What is the Optimal Frequency for Ankle Muscles During Whole-Body Vibration Exercises?. *International Journal Of Applied Exercise Physiology* , vol.8, no.3.

Hobbies

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GAZİLİ OLMAK AYRICALIKTIR..