BMJ Open Sport & Exercise Medicine

No additive effect of transcranial direct current stimulation on balance exercises for brain activity and clinical outcomes in patients with chronic ankle instability: a randomised controlled trial

Zivar Beyraghi, Roya Khanmohammadi

To cite: Beyraghi Z, Khanmohammadi R. No additive effect of transcranial direct current stimulation on balance exercises for brain activity and clinical outcomes in patients with chronic ankle instability: a randomised controlled trial. *BMJ Open Sport & Exercise Medicine* 2025;**11**:e002401. doi:10.1136/bmjsem-2024-002401

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjsem-2024-002401).

Accepted 2 April 2025

Physical Therapy Department, Tehran University of Medical Sciences, Tehran, Iran (the Islamic Republic of)

Correspondence to
Dr Roya Khanmohammadi; dr.rkhanmohammadi96@gmail.com

ABSTRACT

Objectives This study explored whether adding transcranial direct current stimulation (tDCS) to balance exercises enhances preparatory brain activity and clinical outcomes in individuals with chronic ankle instability.

Methods 30 participants were randomised into two groups: balance exercises with real tDCS and balance exercises with sham tDCS. Neurophysiological measures, including late contingent negative variation (CNV) amplitude, peak amplitude and peak time, served as primary outcomes, while biomechanical (anticipatory postural adjustment duration) and clinical (dynamic balance and perceived ankle instability) outcomes were secondary. Both groups completed 12 sessions, each lasting 60 min.

Results The results revealed no significant group-by-time interaction for late CNV amplitude, CNV peak amplitude, perceived ankle instability scores or dynamic balance, indicating no added benefit of real tDCS over sham. However, both groups demonstrated significant post-treatment improvements in late CNV amplitude (C3, Cz, C4: $p \leq 0.017$, $\eta^2 = 0.177–0.276$) and CNV peak amplitude at the C3 electrode ($p = 0.026$, $\eta^2 = 0.158$), reflecting enhanced preparatory brain activity. Similarly, dynamic balance improved significantly in the anterior, posterior-medial and posterior-lateral directions ($p \leq 0.010$, $\eta^2 = 0.204–0.350$) and perceived ankle instability scores increased notably, indicating reduced instability ($p < 0.001$, $\eta^2 = 0.391$), regardless of the tDCS condition. Furthermore, significant correlations ($r = 0.381–0.553$) were observed between treatment-induced changes in neurophysiological variables and biomechanical and clinical outcomes.

Conclusions Although tDCS did not show a distinct advantage, the improvements in neurophysiological and clinical outcomes suggest that balance exercises effectively target central mechanisms. Additionally, relationships were found between enhancements in neurophysiological outcomes and other measures, emphasising the pivotal role of central mechanisms in driving these positive effects.

Trial registration number IRCT20210604051488N1.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Chronic ankle instability (CAI) is associated with deficits in both central and peripheral neural mechanisms. Balance exercises are effective in improving motor control and stability, while transcranial direct current stimulation (tDCS) has been explored as a potential adjunct for enhancing neuroplasticity.

WHAT THIS STUDY ADDS

⇒ Building on our previous work (Beyraghi *et al*), this study shifts the focus from biomechanical measures to central neurophysiological mechanisms. By analysing the relationships between neurophysiological outcomes and clinical and biomechanical measures, this study offers deeper insights into the neural mechanisms underlying rehabilitation in individuals with CAI. Our findings indicate that while balance training improves neurophysiological markers, dynamic balance and perceived ankle stability in individuals with CAI, adding tDCS does not confer any additional benefits. Strong correlations between neurophysiological, biomechanical and clinical improvements highlight the central mechanisms' role in recovery.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings highlight that balance exercises can effectively target central mechanisms and improve outcomes in individuals with CAI, questioning the added value of combining tDCS with such interventions. This emphasises the importance of optimising exercise-based rehabilitation protocols as a primary treatment strategy. Clinically, the study reinforces the value of balance exercises as an evidence-based, stand-alone intervention, guiding practitioners towards effective, non-invasive treatments. From a policy perspective, these findings advocate for prioritising affordable, accessible and scalable exercise-based programmes in rehabilitation services for CAI.

INTRODUCTION

Chronic ankle instability (CAI) is a prevalent and debilitating condition characterised by persistent symptoms, including recurrent episodes of the ankle 'giving way,' weakness, pain, swelling and significant functional limitations.[1] These issues are commonly linked to

insufficient rehabilitation rather than the grade of the initial ligamentous tear caused by a sprain. CAI not only impairs functional performance but also increases the risk of joint degeneration, leading to long-term mobility issues and a substantial decline in quality of life.[2 3] Despite extensive rehabilitation efforts, the effectiveness of current treatment options for CAI remains inadequate, highlighting the need for more comprehensive and innovative rehabilitation approaches.

The pathophysiology of CAI involves both peripheral and central impairments.[4] Traditional rehabilitation approaches primarily target peripheral deficits, such as ligament laxity, muscle weakness and impaired joint position sense, but emerging evidence suggests that CAI is also a neurophysiological disorder.[4] CAI is associated with significant alterations in central nervous system (CNS) function, which contribute to persistent instability and motor deficits.[5–7] Brain regions crucial for motor control, such as the supplementary motor area (SMA) and primary motor cortex (M1), show altered activation patterns in individuals with CAI.[8 9] These neurophysiological changes suggest that CAI involves not just ankle joint dysfunction, but also disruptions in the central mechanisms that govern motor coordination and postural control, increasing the risk of reinjury.

Preparatory brain activity, indicated by the contingent negative variation (CNV), is a critical component of motor control for maintaining dynamic stability during functional tasks, such as transitioning from a double-limb stance to a single-limb stance.[7 10 11] In healthy individuals, well-coordinated CNV patterns are linked to efficient motor planning and anticipatory postural adjustments (APAs), enabling smooth transitions between movements, such as during gait initiation (GI).[7 10] However, individuals with CAI exhibit altered CNV patterns, such as reduced late CNV amplitude, a lower CNV peak, an earlier signal peak and impaired postural adjustments, contributing to impaired balance and gait instability.[7]

Given the central and peripheral impairments associated with CAI, there is increasing interest in rehabilitation approaches that target both aspects. Balance exercises are a cornerstone of CAI rehabilitation, primarily addressing peripheral deficits.[12 13] Traditional balance training does not directly target the central dysfunctions observed in CAI. For example, Burcal *et al*'s research found that despite improvements in functional tests and balance scores, conventional balance training did not lead to significant changes in brain activity, indicating that traditional rehabilitation approaches may be insufficient in promoting the necessary cortical adaptations.[14] Thus, there is growing recognition that addressing CNS dysfunctions through supplementary interventions may be essential for achieving more comprehensive rehabilitation outcomes.

One promising approach to complement traditional balance exercises is transcranial direct current stimulation (tDCS), a non-invasive neuromodulation technique that modulates cortical excitability through low-intensity electrical currents. Anodal stimulation enhances cortical excitability by inducing a depolarising effect on the neuronal membrane, promoting neuroplasticity.[15]

Recent studies suggest that combining tDCS with exercises may improve rehabilitation outcomes in individuals with musculoskeletal disorders, including chronic low back pain[16 17] and CAI.[18 19] However, our previous study offers a nuanced perspective, demonstrating that while balance exercises significantly improved APAs, anodal tDCS over the SMA did not offer additional benefits beyond sham stimulation.[20] This is despite the SMA's crucial role in APAs, motor preparation and GI,[21] as well as evidence linking altered SMA activity to increased perceived ankle instability in individuals with CAI.[9] A 2018 systematic review of 27 studies underscored the potential of non-invasive brain stimulation techniques, including those targeting the SMA, in enhancing motor preparation by improving reaction times in healthy individuals.[22] However, despite promising findings, research on the efficacy of tDCS in musculoskeletal rehabilitation remains limited and inconsistent, with studies yielding mixed results.[16–20 23] While some studies[16–19] have reported notable functional improvements, others[20 23] have found no significant benefits compared with sham conditions. This variability in outcomes emphasises the need for further rigorous research. Specifically, the impact of tDCS on preparatory brain activity in individuals with CAI remains unexplored. Apart from Bruce *et al*'s study, most research has not focused on brain-related parameters to examine the link between treatment-induced neurophysiological changes and clinical outcomes.

This study aims to address these gaps by examining the combined effects of tDCS and balance training on preparatory brain activity, dynamic stability and perceived ankle instability in CAI patients. By integrating neurophysiological and functional perspectives, the research seeks to advance our understanding of how neuromodulation can enhance rehabilitation outcomes for CAI, offering a more evidence-based and holistic approach to treatment. Additionally, by addressing both central and peripheral mechanisms of CAI, the study may contribute to the development of more effective and integrative rehabilitation strategies that target the complex nature of the condition. We hypothesised that both groups engaging in balance exercises would exhibit improvements, including increased late CNV amplitude, greater CNV peak amplitude, a closer alignment of CNV peak timing to the response stimulus, reduced APA duration, enhanced ankle stability and better dynamic balance. Furthermore, we anticipated that combining balance exercises with SMA-targeted tDCS would further enhance these effects.

METHODS

Trial design

This study used a parallel, randomised, single-blind, sham-controlled design. Participants were evenly assigned to either the real or sham tDCS group, receiving the intervention alongside balance exercises in a 1:1

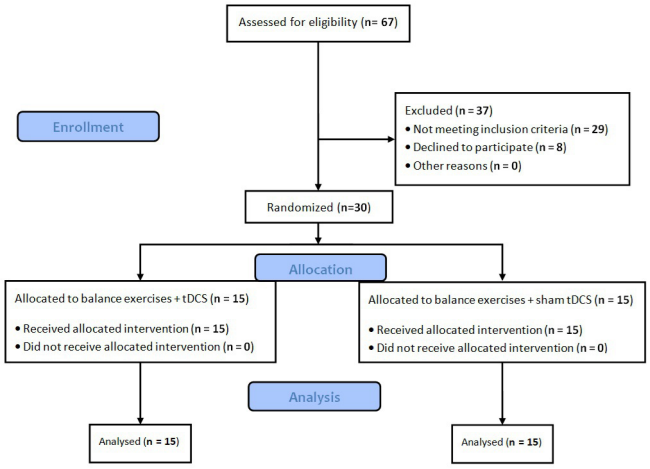

Figure 1 The CONSORT flow chart. CONSORT, Consolidated Standards of Reporting Trials; tDCS, transcranial direct current stimulation.

allocation ratio. Outcome measures were assessed both before and after the intervention. This study was registered as a clinical trial on the Iranian Registry of Clinical Trials (IRCT20210604051488N1) on 28 June 2021.

Participants

30 individuals with CAI participated in the study. Participants were recruited through posters and social media advertisements targeting the university community, sports clubs and federations. A Consolidated Standards of Reporting Trials (CONSORT) flow diagram illustrates participant progression from enrolment to analysis (figure 1).

Participants were included if they met the following criteria: (1) age between 18 and 40 years[24]; (2) self-reported history of the first acute ankle sprain occurring more than 1 year ago[1]; (3) at least two episodes of 'giving way' or sensations of ankle joint instability within the past 6 months[1]; (4) most recent ankle sprain occurring more than 3 months prior to enrolment[1]; (5) Cumberland Ankle Instability Tool (CAIT) score ≤24 (scores) range from 0 to 30, with lower scores indicating greater instability)[1]; (6) Foot and Ankle Ability Measure scores below 90% for daily activities and below 80% for sports activities[25]; (7) no self-reported history of fractures or surgery in the lower extremities; (8) no psychological or neurological disorders; (9) no history of migraines, epilepsy, seizures or head injuries resulting in loss of consciousness; (10) no metallic implants (eg, surgical clips, intracranial electrodes, pacemakers) and (11) no current use of prescription or self-medication.[26] Participants were excluded if they missed three or more non-consecutive sessions or two consecutive sessions.

Interventions

The participants were randomly assigned to two groups: (1) the intervention group (balance exercises combined with real tDCS) and (2) the control group (balance exercises combined with sham tDCS). In both groups, tDCS was administered prior to the balance exercises. Each group completed 12 sessions over 4 weeks, with three sessions per week. Each session lasted 60 min, comprising 20 min of tDCS followed by 40 min of balance exercises. All treatments were conducted in a controlled laboratory environment. Participants were allowed to continue their usual daily activities and routine care; however, they were advised to avoid any new rehabilitation programmes or treatments for CAI during the study to ensure that the observed effects were solely attributable to the assigned intervention. Based on self-reports, no participants indicated engaging in additional interventions during the study period.

Balance exercises

The balance exercise programme included a variety of tasks aimed at improving dynamic stability. Activities involved single-leg stance with modifications to visual and proprioceptive inputs, single-leg stance while throwing and kicking a ball, single-leg hopping to stabilisation and hopping to stabilisation with reaching. Details of the specific exercises and progression criteria are provided in table 1.[12 13 20 27] Participants progressed to more challenging levels only after demonstrating error-free performance at their current level. The required number of error-free repetitions for progression is outlined in table 1. Throughout the exercises, the therapist provided verbal instructions to correct errors and reinforce proper technique. Over time, instructions were gradually reduced to encourage participants to perform the exercises independently. All exercise sessions were conducted individually (in person) under the supervision of a licensed physiotherapist with 5 years of experience in managing patients with ankle instability.

transcranial direct current stimulation

tDCS was administered using a NEUROSTIM2 device (MEDINA TEB GOSTAR, Iran) with two 25 cm² electrodes soaked in sterile saline (0.9% NaCl) to ensure optimal conductivity. The 'anode' electrode was positioned 1.8 cm anterior to Cz, corresponding to the SMA according to the international 10–20 EEG electrode placement system. The 'cathode' electrode served as the reference and was placed centrally on the forehead, just above the eyebrows.[28] For the intervention condition, a current of 1.5 mA was delivered for 20 min, with a 30 s ramp-up (fade-in) at the beginning and a 30 s ramp-down (fade-out) at the end to minimise discomfort. For the sham condition, the same 30 s ramp-up was applied, but the current was discontinued after this initial period, mimicking the sensation of active stimulation without delivering therapeutic effects.[20]

Both real and sham tDCS sessions were conducted individually in a quiet, temperature-controlled room to ensure participant comfort and consistency. tDCS was administered by a licensed physiotherapist with 2 years of experience. Participants were seated comfortably in an upright position and instructed to remain relaxed

Table 1 The description of balance exercises

	Difficulty levels	Instructions	Criteria for progression	Errors
Single-limb stance	1. Eyes open, hard surface, 30 s, 3 Reps 2. Eyes open, hard surface, 60 s, 3 Reps 3. Eyes open, foam surface, 30 s, 3 Reps 4. Eyes open, foam surface, 60 s, 3 Reps 5. Eyes open, foam surface, 90 s, 3 Reps 6. Eyes open, foam surface, 30 s, ball throwing, 3 Reps 7. Eyes open, foam surface, 60 s, ball throwing, 3 Reps 8. Eyes open, foam surface, 90 s, ball throwing, 3 Reps 9. Eyes closed, hard surface, 30 s, arms out, 3 Reps 10. Eyes closed, hard surface, 30 s, arms across, 3 Reps 11. Eyes closed, foam surface, 30 s, arms out, 3 Reps 12. Eyes closed, foam surface, 30 s, arms across, 3 Reps	The participant attempted to maintain balance on the affected limb while facing challenges such as altering the base of support, closing eyes, extending the duration and throwing a ball.[12 48]	If the participant could complete 3 repetitions without errors at each level of difficulty.	Errors were defined as: 1. Touching the ground with the opposite foot. 2. Excessive trunk motion (more than 30° of lateral flexion). 3. Resting the opposite limb against the stance limb. 4. Lifting the hands from the chest while standing.
Limb stance with ball kicking	1. Double-limb stance, hard surface, ball Kicking, 3 Reps 2. Single-limb stance, hard surface, ball Kicking, 3 Reps 3. Double-limb stance, mini-trampoline, ball Kicking, 3 Reps 4. Single-limb stance, mini-trampoline, ball kicking, 3 Reps	The participant was instructed to return the ball to the therapist and maintain balance as much as possible after kicking. During this training, the uninjured limb was used for kicking, while the affected limb served as the supporting limb.[27]	If the participant successfully completed 3 repetitions without any errors at each difficulty level.	Errors included A, B, C and D mentioned earlier.

Continued

Table 1 Continued

	Difficulty levels	Instructions	Criteria for progression	Errors
Single-limb hop to stabilisation	1. Target at 18 inch, using arms to aid in stabilising, 10 Reps 2. Target at 18 inch, hands on hips while stabilising, 10 Reps 3. Target at 27 inch, using arms to aid in stabilising, 10 Reps 4. Target at 27 inch, hands on hips while stabilising, 10 Reps 5. Target at 36 inch, using arms to aid in stabilising, 10 Reps 6. Target at 36 inch, hands on hips while stabilising, 10 Reps	The participant was instructed to perform 10 hops in four directions: 1. Anterior–posterior 2. Medial–lateral 3. Anteromedial–posterolateral 4. Anterolateral–posteromedial Three target distances (18, 27 or 36 inches) from the starting point were set. The participant hopped to these targets, stabilised their balance on one limb, then hopped back in the opposite direction to the starting position and stabilised again on one limb.[48]	If the participant successfully completed 10 repetitions without any errors at each level of difficulty.	Errors included A, B, C and D mentioned earlier.
Hop to stabilisation and reach	1. Target at 18 inch, using arms to aid in stabilising, 5 Reps 2. Target at 18 inch, hands on hips while stabilising, 5 Reps 3. Target at 27 inch, using arms to aid in stabilising, 5 Reps 4. Target at 27 inch, hands on hips while stabilising, 5 Reps 5. Target at 36 inch, using arms to aid in stabilising, 5 Reps 6. Target at 36 inch, hands on hips while stabilising, 5 Reps	The participant hopped, stabilised and reached back to the starting position. Then, they returned to the starting position and reached to the target position.[48]	If the participant successfully completed 5 repetitions without errors at each difficulty level.	Errors included A, B, C and D mentioned earlier.

.Reps, repetitions.

throughout the stimulation to optimise the intervention's effectiveness.

The SMA is a key brain region involved in APAs, motor preparation and GI.[21] It also plays a significant role in generating the CNV.[10] Supporting these roles, numerous studies have shown that anodal stimulation of the SMA can notably improve reaction times and enhance APAs in healthy individuals.[28–31] Additionally, evidence indicates that individuals with CAI exhibit altered SMA activity, with a strong correlation between SMA activation and perceived ankle instability. This altered activity sheds light on the disrupted postural control mechanisms seen in CAI.[9] Based on these findings, tDCS was used to stimulate this brain region in the present study.

Outcome measures

The independent variables in the study were the group (real vs sham tDCS) and time (pretreatment and posttreatment). The primary dependent variable was late CNV amplitude, as it most accurately represents the key neurophysiological changes associated with the intervention. The secondary dependent outcomes included other neurophysiological measures, such as CNV peak amplitude and CNV peak time, as well as biomechanical

outcomes like APA duration and clinical outcomes, including dynamic balance and the severity of perceived ankle instability.

Neurophysiological outcomes

Brain activity was recorded using a 64-channel EEG system with Ag-AgCl ring electrodes (Brain Quick System 98, Micromed, Mogliano Veneto, Italy). The system included a 32-bit A/D converter, a gain of 10 µV/Div, and a band-pass filter ranging from 0.02 Hz to 70 Hz. Electrodes were positioned on the scalp at Fz, Cz, Pz, F3, F4, C3, C4, P3 and P4 locations based on the international 10–20 system. A common reference electrode was placed on the mastoid process in a monopolar montage, with the ground electrode attached at Fpz.

Additionally, four bipolar electrodes were used for electrooculogram recordings: two positioned on the outer canthi to monitor horizontal eye movements and two placed above and below the right eye to detect blinks. Electrode impedances were maintained below 5 kΩ. The signals were sampled at 1024 Hz, and a 50 Hz notch filter was applied to eliminate line noise.

Participants stood comfortably with their arms relaxed at their sides and their eyes open. They were instructed to avoid muscle contractions, head or neck movements, teeth clenching, swallowing or pulling wires to minimise artefacts. Auditory stimuli were delivered through a loudspeaker positioned 1 m behind them, consisting of two sounds with a 2 s interstimulus interval. The first sound (S1) served as a warning stimulus, while the second (S2) acted as a response cue. Both auditory stimuli had a duration of 100 ms, an intensity of 60 dB and a frequency of 2 kHz.

Participants were asked to concentrate on the stimuli and step as quickly as possible using the affected limb in response to S2. To maintain natural behaviour, no specific instructions were given regarding the speed or length of the steps. A total of 50 trials were performed per participant, with a 30 s interval between trials. Data acquisition began 2 s before the warning stimulus.[7 10 32] Participants completed at least three practice trials prior to the main tests to familiarise themselves with the procedure.

Data analysis was conducted using EEGLAB V.7.1.4, a signal processing platform that separates artefacts from electrocortical signals using independent component analysis.[33] Initially, all epochs were visually inspected, and noisy epochs were excluded. ICA was then applied to eliminate residual artefacts, such as muscle activity, eye blinks and eye movements, while preserving the EEG data.

For analysis, EEG signal epochs were time-locked to the response stimulus, spanning from −2500 to 0 ms, with a 500 ms baseline window before the warning stimulus (−2500 to −2000 ms) (figure 2). Artefact-free signals were baseline corrected and ensemble-averaged for each electrode and subject to improve the signal-to-noise ratio. Next, for each ensemble-averaged signal, the mean amplitude during the 200 ms before the response stimulus was calculated and used as the late CNV amplitude.[19] The maximum amplitude within the warning-response interval was identified as the CNV peak amplitude, and its latency relative to S2 was considered the CNV peak time.[10]

Since CNV is most prominent at the Fz, Cz, Pz, C3 and C4 electrodes, data from these sites were analysed statistically. Across all participants, the number of artefact-free epochs per subject ranged from 46 to 50.

Biomechanical outcomes

Participants stood barefoot on a force plate (Bertec, Columbus, Ohio, USA) with their feet angled outward at 10° and their heels separated by 6 cm. Body weight was evenly distributed between both feet. To ensure

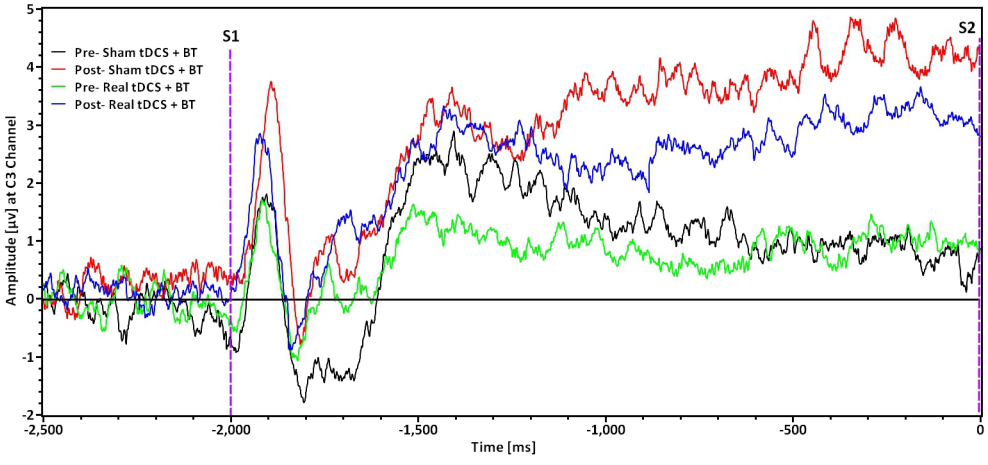

Figure 2 Grand-average potentials recorded in the two groups before and after the intervention. The baseline period spans from −2500 to −2000 ms. The vertical blue line at −2000 ms marks the warning stimulus (S1), while the line at 0 ms indicates the response stimulus (S2). The late CNV was defined as the final 200 ms preceding the response stimulus. Each trace represents the mean amplitude values averaged across all participants in both groups, measured before and after the intervention. BT, balance test; CNV, contingent negative variation; tDCS, transcranial direct current stimulation.

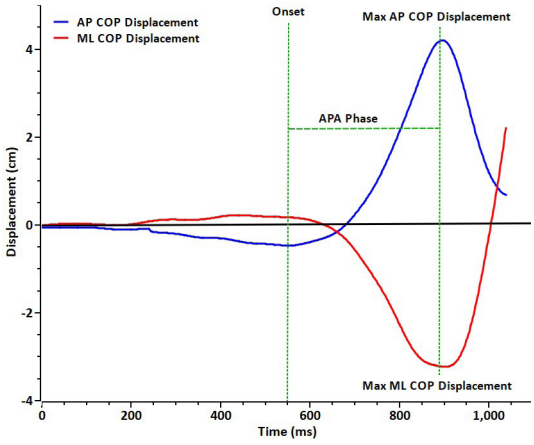

Figure 3 The schematic representation of the centre of pressure (COP) trajectory during gait initiation. 0 ms is the moment when the response stimulus is presented. APA, anticipatory postural adjustment.

consistent foot positioning throughout the trials, the outline of each foot was traced onto a sheet of paper and secured to the force plate for the entirety of the test. For data analysis, the raw data were processed with a zero-phase shift, sixth-order Butterworth low-pass filter, with a cut-off frequency of 10 Hz.[34 35] The duration of the APA phase of GI was defined as the time interval from the onset of centre of pressure (COP) displacement to the most posterior-lateral point of the COP path under the swing limb (figure 3). The onset of COP displacement was identified as the moment when the vertical ground reaction force exceeded the mean plus 2 SDs of the force during the initial 500 ms of quiet stance.[34 35]

Clinical outcomes

Dynamic balance

The Y-balance test was employed to assess dynamic balance. Participants stood on their injured leg while extending the other leg in three designated directions on the ground: anterior, posterior-medial and posterior-lateral. The posterior-medial and posterior-lateral directions were set at 90° angles to each other, with both forming 135° angles with the anterior direction. Participants were instructed to reach as far as possible with their moving foot in each direction while maintaining balance. The distance from the centre to the farthest point reached was recorded. To normalise the results, the distance was divided by the length of the lower limb (measured from the anterior superior iliac spine to the centre of the medial malleolus) and then multiplied by 100 to express it as a percentage of the lower limb length. Each participant performed the test three times in each direction, and the average distance from the three trials was used for data analysis. Trials were considered invalid if the standing leg was lifted off the ground or if the participant was unable to maintain balance on the support leg during the test. In such cases, the trial was repeated.[12 13]

Severity of perceived ankle instability

The CAIT was used to evaluate the severity of perceived ankle instability. It contains nine questions, with a maximum score of 30, where higher scores indicate greater ankle stability. The Persian version of this questionnaire has shown good internal consistency (Cronbach's α of 0.78 for the right ankle and 0.79 for the left ankle) and strong reliability (Intraclass Correlation Coefficient [ICC(2,1)]=0.88; 95% CI 0.86 to 0.90) in athletes.[36]

Sample size

The sample size was determined using G*Power V.3.1.9.2 software based on a pilot study with 10 subjects, focusing on the late CNV amplitude at Cz. The calculation was based on a within-between interaction effect size of 0.071, derived from preliminary data in the pilot study. This effect size reflected the magnitude of the observed effects, forming the basis for the sample size estimation. The parameters included a power of 0.8, α=0.05, a non-sphericity correction (ε) of 1 and a correlation among repeated measures of 0.5. The analysis indicated that at least 28 participants were required to detect a within-between interaction effect in a design with 2 groups and 2 measurements. To account for a potential 10% dropout rate, 30 participants were recruited.

Randomisation and blinding

Participants were randomly allocated to either the intervention group (balance exercises combined with real tDCS) or the control group (balance exercises combined with sham tDCS) in a 1:1 ratio. Randomisation was conducted through a web-based randomisation service (www.randomization.com) by a third party independent of the study. Block randomisation with a block size of four participants was employed; a technique that organises participants into blocks and then randomly assigns them to different groups within each block. By setting a block size of four, a balanced allocation was maintained by assigning two participants to the intervention group and two to the control group within each block, ensuring consistent group sizes throughout the enrollment process. To ensure allocation concealment from the primary researchers, group assignments were recorded on cards and placed in sequentially numbered, opaque, sealed envelopes. Participants were unaware of their group assignments throughout the study, ensuring a single-blind design. In general, unblinding might have been required if a participant had experienced a serious adverse event following brain stimulation, had developed severe unexpected side effects or had faced a potentially life-threatening condition where knowing the treatment assignment was crucial for immediate medical intervention. In such cases, unblinding would have enabled healthcare providers to make informed decisions regarding the participant's care. However, in this study, no such circumstances occurred, and all participants remained unaware of their group assignments

Table 2 Mean and SD of Numeric Sensation Scores reported by participants in both groups

	Control (N=15)		Intervention (N=15)	
Side effects	Mean	SD	Mean	SD
Itching	1.20	0.77	2.07	0.96
Tingling	1.60	0.63	2.20	0.41
Burning	0.80	0.56	0.93	0.80
Headache	0.53	0.52	0.53	0.64
Neck pain	0.00	0.00	0.00	0.00
Skin redness	0.13	0.35	1.27	0.70
Drowsiness	0.07	0.26	0.07	0.26
Difficulty concentrating	0.07	0.26	0.00	0.00
Mood swings	0.00	0.00	0.00	0.00

Note: 0 represents no sensation, while 10 indicates the worst imaginable sensation.

throughout the trial, maintaining the single-blind design and ensuring unbiased results.

Side effects

The occurrence and severity of various side effects, including itching, tingling, burning, headache, neck pain, skin redness, drowsiness, difficulty concentrating and mood swings, were systematically monitored in all participants. To assess potential discomfort at the electrode sites during or after the intervention, participants completed a questionnaire using a Numeric Analogue Scale, where 0 indicated no sensation and 10 represented the worst imaginable sensation. This scale measured the intensity of reported side effects. Table 2 displays the mean Numeric Sensation Scores for participants in both the real and sham tDCS groups.

Statistical analysis

For statistical analysis, IBM SPSS Statistics V.23.0 was used. The Shapiro-Wilk test assessed the normality of the data distribution. Most variables followed a normal distribution, with the exception of time since last sprain and CNV peak time. The Fisher's exact test compared the proportions of gender and affected side between groups. For normally distributed data, an independent t-test was conducted, while the Mann-Whitney U test was applied to non-normally distributed data.

To analyse the main effects of group (balance exercises+tDCS vs balance exercises+sham tDCS), time (pretreatment and post-treatment), and their interactions, a generalised linear mixed effects model (GLMM) was employed. Group, time and their interaction effects were treated as fixed effects, with participants as random effects. For CNV peak time, a gamma distribution and log link function were used, while a normal distribution and identity link function were applied to other normally distributed variables. When significant interactions were found, the groups were analysed independently to gain more detailed insights. Additionally, partial eta squared (η^2) was used to measure effect size, with thresholds indicating small (0.01–0.06), moderate (0.06–0.14) and large (≥0.14) effects.

Additionally, to examine the relationship between treatment-induced changes (post-test minus pretest) in neurophysiological, biomechanical and clinical outcomes, Pearson's correlation coefficient was used, as the change values followed a normal distribution. These correlations were computed for all participants, regardless of group assignment. The strength of correlation was assessed using the correlation coefficient r, with values between 0.80 and 1.0 indicating a very strong correlation; 0.60–0.79 a strong correlation; 0.40–0.59 a moderate correlation; 0.20–0.39 a weak correlation and values less than 0.20 indicating a negligible correlation.[37]

Modifications to the registered study protocol

The protocol originally specified a double-blind design, but the final study implemented a single-blind design. Additionally, the protocol listed an age range of 18–35 years, whereas the final study included participants aged 18–40 years. The sample size was initially reported as 46 but was adjusted to 30 based on final calculations. Details and justifications for these modifications are provided in online supplemental file 1.

RESULTS

Participants

A total of 67 participants were initially screened for this study, of which 37 were excluded, resulting in 30 participants being enrolled. These participants were randomised into intervention and control groups. The trial proceeded as planned, with all 30 participants completing the study. Some participants reported mild sensations typically associated with tDCS; however, none experienced side effects severe or intolerable enough to discontinue treatment (table 2).

Demographic and clinical characteristics were comparable between the two groups (table 3). Descriptive data for all outcome measures at baseline and postintervention are presented in tables 4 and 5, while GLMM results are summarised in table 6. Additionally, figure 4 illustrates the results of the correlation analysis. Preintervention comparisons showed no significant differences between groups in any outcome measures, confirming their equivalence prior to the intervention. No subgroup or adjusted analyses were performed.

Neurophysiological outcomes

The GLMM analysis indicated that the interaction effect of group and time on the late CNV amplitude at the C3, Cz and C4 electrodes was not significant, suggesting that both groups exhibited similar behaviour before and after treatment. Additionally, the group effect was not significant, suggesting no superiority of one group over the other. However, the main effect of time was significant,

Table 3 The demographical and clinical characteristics of subjects at baseline

Characteristics	Control (N=15)		Intervention (N=15)		P value
	Mean/median	SD/Q1–Q3	Mean/median	SD/Q1–Q3	
Female (N (%))*	5 (33.37)		4 (26.67)		1.00
Right affected side (N (%))*	10 (66.67)		9 (60)		1.00
Age (years)†	28.41	5.58	27.47	6.57	1.00
Height (cm)†	175.41	9.96	172.40	10.01	0.27
Weight (kg)†	75.89	13.34	73.87	12.50	0.69
CAIT (0–30)†	14.73	6.02	14.07	4.50	0.66
FAAM- ADL (0–100)†	86.19	11.72	85.65	9.81	0.89
FAAM-Sport (0–100)†	66.93	14.17	65.29	18.15	0.78
Time since first sprain (months)†	21.04	5.09	19.80	8.22	0.62
Time since last sprain (months)‡	3.00	3.00–12.00	3.00	3.00–6.00	0.78
Number of giving way episodes†	7.26	4.06	5.27	2.37	0.11

Q1 and Q3 represent the first and third quartiles of a parameter, respectively, while SD represents the SD.
*Fisher's exact test was used.
†Independent t-test was used.
‡Mann-Whitney U test was applied.
ADL, activities of daily living; CAIT, Cumberland Ankle Instability Tool; FAAM, Foot and Ankle Ability Measure.

indicating a notable difference between pretreatment and post-treatment measurements in both groups. Specifically, the late CNV amplitude increased significantly at all three electrodes following treatment, with a large effect size ($p \leq 0.017$) (tables 4 and 6).

For the CNV peak amplitude at the C3 electrode, similar findings were observed. The interaction effect of group and time was not significant, again showing no difference in group behaviour pretreatment and post-treatment. The group effect remained insignificant,

Table 4 The descriptive data (mean and SD) for normally distributed parameters

Outcomes		Control (N=15)				Intervention (N=15)			
		Pre		Post		Pre		Post	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Neurophysiological Outcomes									
	Channels								
Late CNV Amplitude (µv)	Fz	−0.14	1.57	1.55	2.53	1.26	2.87	1.28	1.98
	C3	0.67	2.47	4.14	5.48	0.99	4.34	3.15	2.80
	CZ	0.45	2.77	2.37	2.01	1.97	1.98	2.96	2.43
	C4	0.27	1.50	2.66	3.00	0.32	2.17	0.96	2.07
	Pz	−0.26	1.68	2.26	4.56	1.53	3.51	1.81	2.30
CNV peak amplitude (µv)	Fz	4.95	3.86	5.86	3.37	4.56	3.18	5.01	1.89
	C3	5.59	3.06	7.69	6.34	4.03	4.20	6.32	2.66
	CZ	5.55	3.04	6.26	3.20	5.48	2.74	6.37	2.82
	C4	4.37	3.04	6.03	4.18	4.20	2.88	4.96	2.28
	Pz	4.59	3.94	6.01	5.01	4.58	3.73	4.38	2.17
Biomechanical outcomes									
APA duration (ms)		264.72	69.56	269.36	85.20	297.47	49.91	270.83	41.52
Clinical outcomes									
Y-balance test (anterior) (%)		86.36	6.76	90.49	8.55	85.73	10.12	89.24	10.24
Y-balance test (posterior–medial) (%)		104.56	11.51	111.05	11.87	102.89	12.14	110.96	14.66
Y-balance test (posterior–lateral) (%)		101.38	11.69	103.12	9.30	99.54	13.12	107.56	15.92
CAIT (0–30)		14.07	4.50	20.93	7.41	14.93	6.02	21.27	6.66

APA, anticipatory postural adjustment; CAIT, Cumberland Ankle Instability Tool; CNV, contingent negative variation.

Table 5 The descriptive data (median and first and third quartiles) for non-normally distributed parameters

Outcomes		Control (N=15)				Intervention (N=15)			
		Pre		Post		Pre		Post	
		Median	Q1–Q3	Median	Q1–Q3	Median	Q1–Q3	Median	Q1–Q3
Neurophysiological outcomes									
	Channels								
CNV peak time (ms)	Fz	1386.53	878.49–1860.37	1855.49	909.75–1899.45	1458.82	601.99–1516.47	1472.50	1014.29–1900.43
	C3	1081.70	92.98–1428.54	1062.16	625.44–1882.84	1337.68	258.09–1692.33	1402.16	190.68–1791.98
	CZ	1386.53	890.21–1860.37	974.23	406.59–1855.49	1393.36	320.62–1603.42	1402.16	302.06–1748.99
	C4	1710.89	877.51–1904.34	1855.49	909.75–1882.84	1675.72	603.95–1904.34	1402.16	278.61–1748.02
	Pz	1083.66	72.46–1830.08	909.75	324.53–1855.49	601.99	258.09–1393.36	1244.86	271.77–1557.5

CNV, contingent negative variation.

confirming no superiority between groups. However, the time effect was significant, with a substantial increase in the CNV peak amplitude after treatment compared with before, demonstrating a large effect size (p=0.026) (tables 4 and 6).

Table 6 Results of the generalised linear mixed effects model

Outcomes		Time effect			Group effect			Interaction effect		
		F	P value	η^2	F	P value	η^2	F	P value	η^2
Neurophysiological outcomes										
	Channels									
Late CNV amplitude	Fz	2.176	0.146	0.072	0.871	0.355	0.030	2.082	0.155	0.069
	C3	10.673	**0.002***	0.276	0.082	0.776	0.003	0.585	0.447	0.021
	Cz	5.999	**0.017***	0.177	3.030	0.087	0.098	0.612	0.437	0.021
	C4	6.821	**0.012***	0.196	1.787	0.187	0.060	2.234	0.141	0.074
	Pz	2.848	0.097	0.092	0.661	0.420	0.023	1.840	0.180	0.062
CNV peak amplitude	Fz	0.859	0.358	0.030	0.487	0.488	0.017	0.097	0.757	0.004
	C3	5.267	**0.026***	0.158	1.385	0.244	0.047	0.010	0.923	0.000
	Cz	1.608	0.210	0.054	0.000	0.985	0.000	0.018	0.894	0.001
	C4	3.177	0.080	0.102	0.440	0.510	0.016	0.431	0.514	0.015
	Pz	0.581	0.449	0.020	0.504	0.481	0.018	1.011	0.319	0.035
CNV peak time	Fz	1.453	0.233	0.050	0.082	0.776	0.003	0.035	0.853	0.001
	C3	0.263	0.610	0.009	0.025	0.874	0.001	0.231	0.632	0.008
	CZ	0.709	0.403	0.025	0.033	0.856	0.001	0.614	0.437	0.021
	C4	0.322	0.573	0.011	1.051	0.310	0.036	1.154	0.287	0.040
	Pz	0.212	0.647	0.008	0.641	0.427	0.022	0.445	0.507	0.016
Biomechanical outcomes										
APA duration		0.780	0.381	0.027	0.753	0.389	0.026	1.577	0.214	0.053
Clinical outcomes										
Y-balance test (anterior)		9.614	**0.003***	0.256	0.095	0.759	0.003	0.064	0.802	0.002
Y-balance test (posterior–medial)		15.054	**<0.001***	0.350	0.044	0.835	0.002	0.175	0.677	0.006
Y-balance test (posterior–lateral)		7.176	**0.010***	0.204	0.092	0.763	0.003	2.967	0.091	0.096
CAIT		17.986	**<0.001**	0.391	0.149	0.701	0.005	0.029	0.865	0.001

*Bold text and * indicate significant differences (P ≤ 0.05)
$\eta\eta^2$ is effect size (small=0.01–0.06, medium=0.06–0.14 and large ≥0.14).
APA, anticipatory postural adjustment; CAIT, Cumberland Ankle Instability Tool; CNV, contingent negative variation.

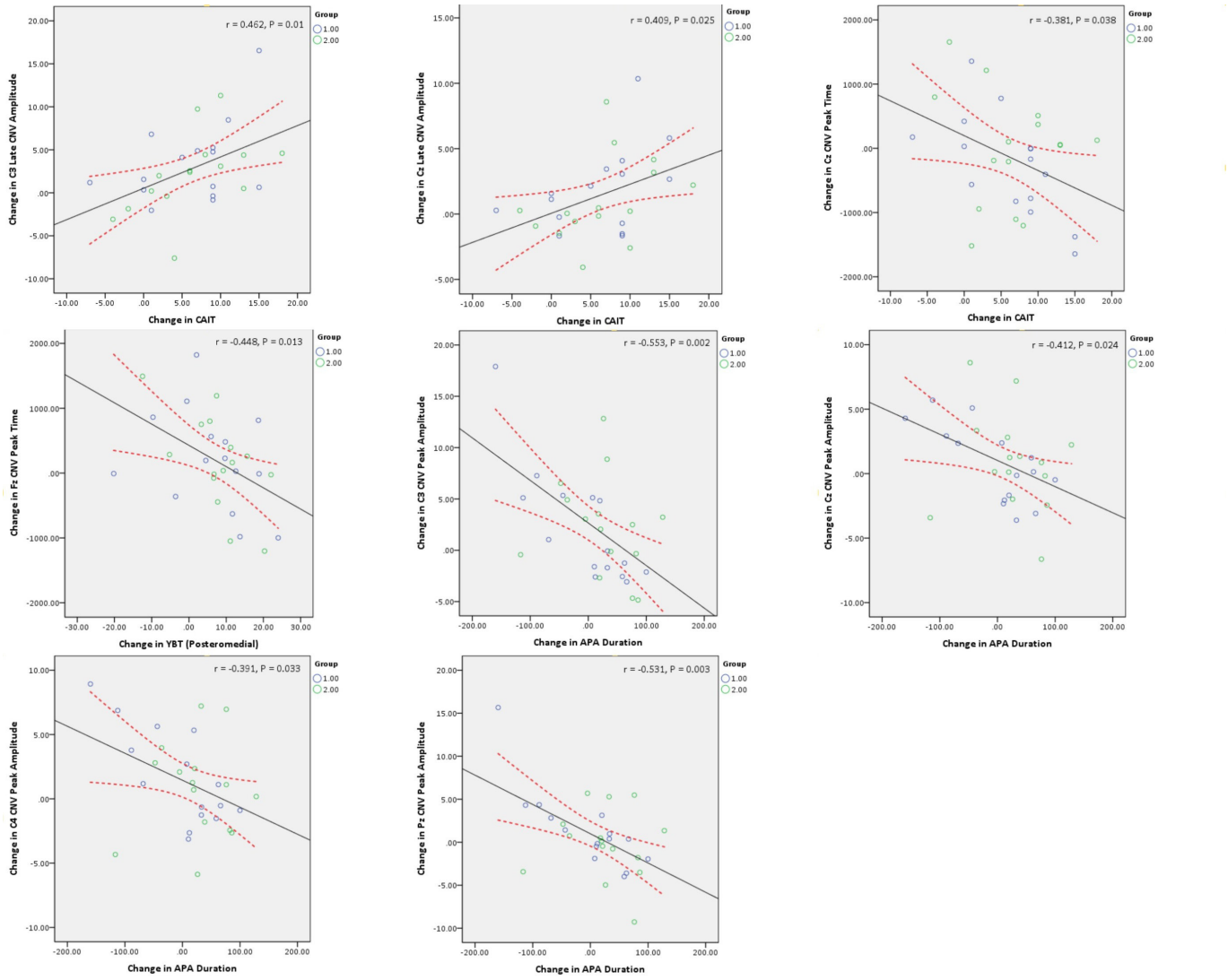

Figure 4 Relationship between treatment-induced changes (post-test minus pretest) in neurophysiological, biomechanical and clinical outcomes. APA, anticipatory postural adjustment; CAIT, Cumberland Ankle Instability Tool; CNV, contingent negative variation; YBT, Y-balance test.

No significant differences were found for the other parameters (table 6).

Biomechanical outcomes

The effects of time, group and their interaction on APA duration were not statistically significant (table 6).

Clinical outcomes

Regarding dynamic balance in anterior, posterior-medial and posterior-lateral directions, the interaction effect between group and time was not significant, indicating consistent group behaviour pretreatment and post-treatment. Similarly, the group effect was not significant, showing no group superiority. However, the time effect was significant, with balance in all directions showing significant improvement after treatment compared with before in both groups, accompanied by a large effect size ($p \leq 0.010$) (tables 4 and 6).

For severity of perceived ankle instability, neither the interaction between group and time nor the group effect was significant. However, the time effect was significant, as CAIT scores increased notably in both groups after treatment, reflecting a reduction in ankle instability. This change was associated with a large effect size ($p<0.001$) (tables 4 and 6).

Relationships

The results revealed a significant positive correlation between treatment-induced changes in CAIT scores and changes in late CNV amplitude at the C3 (r=0.462) and Cz (r=0.409) electrodes (figure 4). Additionally, a significant negative correlation was found between changes in CAIT scores and the CNV peak time at the Cz electrode (r=−0.381). Specifically, shorter intervals between the CNV peak and the response stimulus after treatment

were linked to higher CAIT scores, while longer intervals were associated with lower scores (figure 4).

Furthermore, the results showed a significant negative correlation between treatment-induced changes in dynamic balance in the posterior-medial direction and changes in CNV peak time at the Fz electrode (r=−0.448). In particular, shorter intervals between the CNV peak and the response stimulus post-treatment were associated with greater improvements in posterior-medial balance (figure 4).

Finally, a significant negative correlation was observed between the duration of APA and the CNV peak amplitude at the C3, Pz, C4 and Cz electrodes (r=−0.391 to −0.553). Specifically, as the CNV peak amplitude significantly increased after treatment, the duration of APA decreased and vice versa (figure 4).

DISCUSSION

Both groups demonstrated increased late CNV amplitude, CNV peak amplitude, improved ankle stability and enhanced dynamic balance. The lack of significant differences between the groups suggests that anodal tDCS over the SMA did not provide additional benefits over sham stimulation. This indicates that the observed improvements were primarily driven by balance exercises, highlighting their effectiveness in promoting neurophysiological and clinical enhancements.

Exercise enhances the efficiency of Ia afferents (primary afferent type 1A fibres) in activating low-threshold motor neurons, resulting in spinal adaptations that enhance lower limb muscle control.[38–40] Additionally, it induces supra-spinal adaptations, strengthening corticospinal projections to ankle muscles.[40 41] This study's neurophysiological findings support these adaptations, with correlation analyses linking cortical changes to improvements in both biomechanical and clinical outcomes.

The study found neurophysiological evidence of CNS adaptations, as indicated by significant increases in both late CNV amplitude and CNV peak amplitude, which are markers of brain excitability. A negative correlation was observed between posterior-medial balance and CNV peak time at the Fz electrode, with shorter intervals between the CNV peak and the response stimulus post-treatment linked to better balance improvements. These results suggest a connection between brain changes and enhanced balance following the intervention.

The improvement in dynamic balance following treatment may be attributed to reduced anxiety, fear of recurring ankle sprains and a lower perception of ankle instability. Participants in both groups reported feeling more stable after treatment. This increased stability may result from improved movement patterns, reduced neuromuscular inhibition, increased muscle strength and enhanced proprioception. Studies suggest that balance training can improve muscle activity patterns, reduce muscle activation time,[42 43] strengthen ankle-stabilising muscles[24] and enhance proprioception in individuals with CAI.[44]

Beyraghi *et al* investigated the effects of balance training combined with tDCS over the SMA on APAs during GI in individuals with CAI. Their biomechanical analysis demonstrated that balance training, even without brain stimulation, can enhance both the anticipation and execution phases of GI.[20] The current study expands on this previous work, using a common cohort with approximately 95% participant overlap. Despite identical intervention protocols—including the same balance training exercises and tDCS parameters—the two studies differ significantly in their research focus and outcome measures. The previous study primarily examined the biomechanical aspects of APAs, focusing on COP displacement and velocity across different GI phases (anticipatory, weight transition and locomotor). In contrast, the current study focuses on the central neurophysiological mechanisms underlying these processes, using EEG-derived measures such as late CNV amplitude, CNV peak amplitude and CNV peak time. Additionally, while the previous study emphasised APA amplitude, the current study prioritises APA duration, as research suggests it is a more sensitive marker for detecting SMA-related changes, particularly in conditions like Parkinson's disease.[45] The previous study assessed biomechanical aspects without investigating whether the observed improvements were linked to changes in brain activity. In contrast, this study examines whether balance training combined with tDCS induces cortical activity changes associated with clinical and biomechanical improvements. By analysing neurophysiological findings alongside other outcomes, this study provides deeper insights into the neural mechanisms of rehabilitation, offering a broader understanding of how these interventions influence brain function and physical performance. Together, these studies present complementary findings that contribute to a more comprehensive understanding of rehabilitation strategies for CAI.

Correlation analysis showed that greater increases in late CNV amplitude after treatment were linked to higher CAIT scores, indicating a connection between improved cortical motor preparation and perceived ankle stability. Additionally, a negative relationship was found between APA duration and CNV peak amplitude, with higher CNV peak amplitude post-treatment associated with shorter APA duration, suggesting more efficient postural preparation.

The significant increase in late CNV amplitude and CNV peak amplitude from pretest to post-test in both groups highlights the critical role of balance exercises in enhancing preparatory brain activity, which can be attributed to the characteristics of the balance exercises used, such as those incorporating sensory components, visual elements and proprioception, which provided additional stimulation to the sensory system. Continuous exposure to varied sensory inputs during exercise likely stimulated the brain's sensory processing centres, fostering sensorimotor interaction that promotes motor learning and drives neuroplastic changes, thereby

enhancing motor preparation, as evidenced by the increased CNV amplitudes.

Furthermore, perturbation-based exercises, practised over 12 sessions, effectively enhanced postural control strategies by promoting motor learning. This allowed participants to apply these strategies more effectively to both predictable and unpredictable perturbations, as reflected in improved preparatory brain activity. Studies show that even a single session of perturbation-based exercises like ball-kicking or ball-catching can enhance APAs in both individuals with CAI and healthy adults.[27 46]

This study incorporated hop-to-stabilisation exercises, which were shown in a 2024 study to improve preparatory muscle activity in both healthy individuals and soccer players with CAI, compared with a simple warm-up.[47] These plyometric exercises, involving rapid stretch-shortening cycles, stimulate afferent pathways and enhance balance, joint position sense and neuromuscular control.[47] Consequently, it can be inferred that the rapid muscle length changes likely boost proprioception, stimulate sensory pathways and send crucial sensory information to the brain, potentially promoting exercise-induced neuroplastic changes.

Contrary to the second hypothesis, adding tDCS to balance exercises did not significantly affect cortical activity or clinical parameters. This result contrasts with prior research. A 2018 systematic review of 27 studies concluded that non-invasive brain stimulation techniques enhance motor preparation in the brain, as evidenced by improved reaction times in healthy individuals.[22] Specifically, research indicates that electrical stimulation of the SMA enhances motor preparation and facilitates movement initiation in both healthy younger and older adults.[28–31] However, these studies typically assessed tDCS alone, comparing it to sham or no stimulation conditions. A possible explanation for the current study's findings is the ceiling effect, where balance exercises were effective, leaving little room for additional improvements from tDCS.

The correlation analysis revealed that CNV peak timing closer to the response stimulus was linked to better balance and ankle stability. A previous study suggests that individuals with CAI show earlier CNV peaks as an adaptive strategy, allowing sufficient time for postural preparation to ensure successful GI and reduce the risk of further injury.[7] Moreover, Fujiwara *et al* observed that increased task difficulty leads to higher CNV amplitude and earlier peak timing due to the need for greater attention and earlier postural preparation.[11] Post-treatment, GI may become less demanding, causing the CNV peak to occur closer to the response stimulus, which likely reflects improved postural preparation and enhanced task performance, stability and confidence.

LIMITATIONS

This study has several notable limitations. A major drawback is the absence of control groups, such as those receiving only balance exercises, tDCS alone or sham tDCS. Including these groups would have provided a clearer understanding of the individual and combined effects of the interventions. Without such comparisons, it is challenging to accurately evaluate the clinical impact of each intervention and their potential synergy.

Another limitation is the lack of evaluation of the durability of therapeutic effects. As a result, it remains unclear whether adding tDCS enhances long-term outcomes compared with sham stimulation. Furthermore, the study did not employ a longitudinal design with regular weekly assessments, which could have provided insights into the progression of changes and helped estimate the optimal timeline for achieving the desired therapeutic effects.

Additionally, the study was conducted exclusively on participants with CAI, limiting the generalisability of the findings to other populations. The investigation also included multiple outcome measures and extensive correlation analyses, which increased the risk of type I errors and the possibility of false-positive results due to the large number of statistical tests performed.

Finally, the relatively small sample size limited the statistical power of the study. Future research with larger sample sizes will be crucial to validate these findings and further explore the potential synergistic effects of tDCS when combined with exercise rehabilitation.

CONCLUSIONS

The findings indicate that balance exercises, whether combined with tDCS or sham tDCS, effectively enhance preparatory brain activity, dynamic balance and perceived ankle stability in individuals with CAI. However, the absence of significant differences between the tDCS and sham tDCS groups suggests that tDCS does not provide additional clinical benefits beyond balance exercises. These results highlight the cost-effectiveness and accessibility of balance exercises as a standalone intervention.

Clinical implications

The observed correlations between neurophysiological improvements and clinical outcomes underscore the importance of central mechanisms in functional recovery. This highlights the potential of future interventions targeting neuroplasticity to enhance rehabilitation for individuals with CAI. However, further research is required to explore the possible benefits of combining exercise with neuromodulation strategies to optimise clinical outcomes.

Acknowledgements The authors declare that this study did not receive any financial support.

Contributors RK contributed to conceptualisation, resources, methodology, supervision and writing—review and editing. ZB contributed to data curation, formal analysis and writing—original draft preparation. All authors have read and agreed to the published version of the manuscript. RK is the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Ethics Committee of the Tehran University of Medical Sciences (IR.TUMS.FNM.REC.1400.020). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

ORCID iD

Roya Khanmohammadi http://orcid.org/0000-0003-4679-1445

REFERENCES

1 Gribble PA, Delahunt E, Bleakley C, *et al*. Selection criteria for patients with chronic ankle instability in controlled research: a position statement of the International Ankle Consortium. *J Orthop Sports Phys Ther* 2013;43:585–91.
2 Houston MN, Van Lunen BL, Hoch MC. Health-related quality of life in individuals with chronic ankle instability. *J Athl Train* 2014;49:758–63.
3 Hintermann B, Boss A, Schäfer D. Arthroscopic findings in patients with chronic ankle instability. *Am J Sports Med* 2002;30:402–9.
4 Kandić M, Moliadze V, Andoh J, *et al*. Brain Circuits Involved in the Development of Chronic Musculoskeletal Pain: Evidence From Non-invasive Brain Stimulation. *Front Neurol* 2021;12:732034.
5 Needle AR, Lepley AS, Grooms DR. Central Nervous System Adaptation After Ligamentous Injury: a Summary of Theories, Evidence, and Clinical Interpretation. *Sports Med* 2017;47:1271–88.
6 Hertel J. Sensorimotor deficits with ankle sprains and chronic ankle instability. *Clin Sports Med* 2008;27:353–70.
7 Beyraghi Z, Khanmohammadi R, Hadian MR. Reduction in preparatory brain activity preceding gait initiation in individuals with chronic ankle instability: A movement-related cortical potential study. *Eur J Neurosci* 2024;60:5284–99.
8 Shen Y, Wang W, Wang Y, *et al*. Not Only in Sensorimotor Network: Local and Distant Cerebral Inherent Activity of Chronic Ankle Instability-A Resting-State fMRI Study. *Front Neurosci* 2022;16:835538.
9 Rosen AB, Yentes JM, McGrath ML, *et al*. Alterations in Cortical Activation Among Individuals With Chronic Ankle Instability During Single-Limb Postural Control. *J Athl Train* 2019;54:718–26.
10 Khanmohammadi R, Talebian S, Hadian MR, *et al*. Preparatory postural adjustments during gait initiation in healthy younger and older adults: Neurophysiological and biomechanical aspects. *Brain Res* 2015;1629:240–9.
11 Fujiwara K, Kiyota N, Maeda K. Contingent negative variation and activation of postural preparation before postural perturbation by backward floor translation at different initial standing positions. *Neurosci Lett* 2011;490:135–9.
12 Anguish B, Sandrey MA. Two 4-Week Balance-Training Programs for Chronic Ankle Instability. *J Athl Train* 2018;53:662–71.
13 McKeon PO, Ingersoll CD, Kerrigan DC, *et al*. Balance training improves function and postural control in those with chronic ankle instability. *Med Sci Sports Exerc* 2008;40:1810–9.
14 Burcal CJ, Jeon H, Gonzales JM, *et al*. Cortical Measures of Motor Planning and Balance Training in Patients With Chronic Ankle Instability. *J Athl Train* 2019;54:727–36.
15 Matsunaga K, Nitsche MA, Tsuji S, *et al*. Effect of transcranial DC sensorimotor cortex stimulation on somatosensory evoked potentials in humans. *Clin Neurophysiol* 2004;115:456–60.
16 Hejazi HS, Khanmohammadi R, Olyaei G, *et al*. The effects of combining sensorimotor training with transcranial direct current stimulation on the anticipatory and compensatory postural adjustments in patients with chronic low back pain. *Disabil Rehabil* 2025;47:1512–24.
17 Jafarzadeh A, Ehsani F, Yosephi MH, *et al*. Concurrent postural training and M1 anodal transcranial direct current stimulation improve postural impairment in patients with chronic low back pain. *J Clin Neurosci* 2019;68:224–34.
18 Bruce AS, Howard JS, VAN Werkhoven H, *et al*. The Effects of Transcranial Direct Current Stimulation on Chronic Ankle Instability. *Med Sci Sports Exerc* 2020;52:335–44.
19 Ma Y, Yin K, Zhuang W, *et al*. Effects of Combining High-Definition Transcranial Direct Current Stimulation with Short-Foot Exercise on Chronic Ankle Instability: A Pilot Randomized and Double-Blinded Study. *Brain Sci* 2020;10:749.
20 Beyraghi Z, Khanmohammadi R, Hadian MR. Effects of Combining Transcranial Direct Current Stimulation With Balance Training on Anticipatory Postural Adjustments in Persons With Chronic Ankle Instability. *Sports Health* 2025;17:19417381241247746:383–93:.
21 Richard A, Van Hamme A, Drevelle X, *et al*. Contribution of the supplementary motor area and the cerebellum to the anticipatory postural adjustments and execution phases of human gait initiation. *Neuroscience* 2017;358:181–9.
22 Neige C, Massé-Alarie H, Mercier C. Stimulating the Healthy Brain to Investigate Neural Correlates of Motor Preparation: A Systematic Review. *Neural Plast* 2018;2018:5846096.
23 Qanbari S, Khanmohammadi R, Olyaei G, *et al*. Effects of combining sensory-motor exercises with transcranial direct current stimulation on cortical processing and clinical symptoms in patients with lumbosacral radiculopathy: An exploratory randomized controlled trial. *PLoS ONE* 2024;19:e0314361.
24 Hou Z-C, Huang H-S, Ao Y-F, *et al*. The effectiveness and sustainability of supervised balance training in chronic ankle instability with grade III ligament injury: a one-year prospective study. *J Foot Ankle Res* 2022;15:9.
25 Hertel J, Corbett RO. An Updated Model of Chronic Ankle Instability. *J Athl Train* 2019;54:572–88.
26 Thair H, Holloway AL, Newport R, *et al*. Transcranial Direct Current Stimulation (tDCS): A Beginner's Guide for Design and Implementation. *Front Neurosci* 2017;11:641.
27 Conceição JS, Schaefer de Araújo FG, Santos GM, *et al*. Changes in Postural Control After a Ball-Kicking Balance Exercise in Individuals With Chronic Ankle Instability. *J Athl Train* 2016;51:480–90.
28 Carlsen AN, Eagles JS, MacKinnon CD. Transcranial direct current stimulation over the supplementary motor area modulates the preparatory activation level in the human motor system. *Behav Brain Res* 2015;279:68–75.
29 Hupfeld KE, Ketcham CJ, Schneider HD. Transcranial direct current stimulation (tDCS) to the supplementary motor area (SMA) influences performance on motor tasks. *Exp Brain Res* 2017;235:851–9.
30 Bolzoni F, Bruttini C, Esposti R, *et al*. Transcranial direct current stimulation of SMA modulates anticipatory postural adjustments without affecting the primary movement. *Behav Brain Res* 2015;291:407–13.
31 Nomura T, Kirimoto H. Anodal Transcranial Direct Current Stimulation Over the Supplementary Motor Area Improves Anticipatory Postural Adjustments in Older Adults. *Front Hum Neurosci* 2018;12:317.
32 Olyaei G, Khanmohammadi R, Talebian S, *et al*. The effect of exergaming on cognition and brain activity in older adults: A motor-related cortical potential study. *Physiol Behav* 2022;255:113941.
33 Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods* 2004;134:9–21.
34 Khanmohammadi R, Olyaei G, Talebian S, *et al*. The effect of video game-based training on postural control during gait initiation in community-dwelling older adults: a randomized controlled trial. *Disabil Rehabil* 2022;44:5109–16.
35 Khanmohammadi R, Talebian S, Hadian MR, *et al*. Time and Frequency Domain Analysis of Gait Initiation in Younger and Older Adults. *J Aging Phys Act* 2017;25:212–7.
36 Mirshahi M, Halabchi F, Golbakhsh M, *et al*. Reliability and Recalibration of the Persian Version of Cumberland Ankle Instability Tool Cut-off Score in Athletes with Functional Ankle Instability. *Adv J Emerg Med* 2019;3:e26.
37 Evans JD. *Straightforward statistics for the behavioral sciences*. Thomson Brooks/Cole Publishing Co, 1996.
38 Penzer F, Duchateau J, Baudry S. Effects of short-term training combining strength and balance exercises on maximal strength and upright standing steadiness in elderly adults. *Exp Gerontol* 2015;61:38–46.

39 Sefton JM, Yarar C, Hicks-Little CA, *et al*. Six weeks of balance training improves sensorimotor function in individuals with chronic ankle instability. *J Orthop Sports Phys Ther* 2011;41:81–9.
40 Taube W, Gruber M, Gollhofer A. Spinal and supraspinal adaptations associated with balance training and their functional relevance. *Acta Physiol (Oxf)* 2008;193:101–16.
41 Kubica J, Szymura J, Domagalik A, *et al*. Systematic Balance Exercises Influence Cortical Activation and Serum BDNF Levels in Older Adults. *J Clin Med* 2019;8:1910.
42 Yoshida N, Kobayashi N, Masunari A, *et al*. Changes in the muscle reaction time of ankle periarticular muscles by balance training. *JPFSM* 2013;2:493–500.
43 Plangtaisong P, Shen W, Wheeler PC, *et al*. Effect of exercise interventions and prophylactic devices on reducing peroneal muscle reaction time by sudden ankle perturbation: A systematic review and meta-analysis. *Medicine in Novel Technology and Devices* 2021;11:100082.
44 de Vasconcelos GS, Cini A, Sbruzzi G, *et al*. Effects of proprioceptive training on the incidence of ankle sprain in athletes: systematic review and meta-analysis. *Clin Rehabil* 2018;32:1581–90.
45 Jacobs JV, Lou JS, Kraakevik JA, *et al*. The supplementary motor area contributes to the timing of the anticipatory postural adjustment during step initiation in participants with and without Parkinson's disease. *Neuroscience* 2009;164:877–85.
46 Kanekar N, Aruin AS. Improvement of anticipatory postural adjustments for balance control: effect of a single training session. *J Electromyogr Kinesiol* 2015;25:400–5.
47 Laddawong T, Saito H, Soga T, *et al*. Acute Effects of a Hop-Stabilization Warm-Up Program on Dynamic Balance, Ground Reaction Force, and Muscle Activity During Cutting Movements in Collegiate Athletes with Chronic Ankle Instability. *Int J Exerc Sci* 2024;17:343–58.
48 Mckeon PO, Ingersoll CD, Kerrigan DC, *et al*. Balance Training Improves Function and Postural Control in Those with Chronic Ankle Instability. *Medicine & Science in Sports & Exercise* 2008;40:1810–9.