The impact of combined cerebellar transcranial alternating current stimulation and repetitive motor training on upper limb recovery in stroke patients

El impacto de la estimulación combinada de corriente alterna transcraneal cerebelosa y el entrenamiento motor repetitivo en la recuperación de las extremidades superiores en pacientes con accidente cerebrovascular

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Abstract

Background: Upper limb motor impairment is a common and disabling consequence of stroke, often showing limited recovery with conventional rehabilitation. Non-invasive brain stimulation (NIBS), particularly transcranial alternating current stimulation (tACS), has emerged as a promising neuro-modulatory technique; however, the effects of cerebellar tACS remain underexplored.
Objective: To investigate the efficacy of cerebellar tACS combined with repetitive motor training (RMT) on upper limb motor recovery in patients with subacute ischemic stroke.
Methods: In this randomized, double-blind, sham-controlled trial, 52 patients with subacute ischemic stroke and unilateral upper limb hemiparesis were randomly assigned to receive either active cerebellar tACS or sham stimulation. Active tACS (70 Hz, 1 mA, 20 minutes) was delivered prior to daily RMT sessions (60 min/day, 5 days/week for 3 weeks). The primary outcome was upper limb motor function (Fugl-Meyer Assessment for Upper Extremity; FMA-UE). Secondary outcomes included manual dexterity (Box and Block Test; BBT), spasticity (Modified Ashworth Scale; MAS), and hand grip strength. Assessments were conducted at baseline, post-intervention, and 4-week follow-up by blinded evaluators.
Results: Participants receiving active tACS demonstrated significantly greater gains in FMA-UE (+11.2 vs. +3.8; $p = 0.01$), BBT (+7.1 vs. +1.8 blocks/min; $p = 0.03$), MAS ($p = 0.04$), and grip strength (+4.8 kg vs. +1.9 kg; $p = 0.02$) compared to the sham group. A large effect size was observed for FMA-UE (Cohen's $d > 0.8$).
Conclusion: Cerebellar tACS combined with repetitive motor training significantly enhances upper limb motor recovery in subacute stroke. These findings support cerebellar neuromodulation as a promising adjunct in post-stroke rehabilitation.

Keywords

Cerebellar stimulation; neurorehabilitation; plasticity; repetitive motor training; stroke; tACS; upper limb.

Resumen

Antecedentes: El deterioro motor de las extremidades superiores es una consecuencia común e incapacitante del accidente cerebrovascular, que a menudo muestra una recuperación limitada con la rehabilitación convencional. La estimulación cerebral no invasiva (NIBS), en particular la estimulación transcraneal con corriente alterna (tACS), se ha convertido en una técnica neuro-moduladora prometedora; sin embargo, los efectos de los TACS cerebelosos siguen sin explorarse lo suficiente.
Objetivo: Investigar la eficacia de los TAC cerebelosos combinados con entrenamiento motor repetitivo (TRM) en la recuperación motora de miembros superiores en pacientes con accidente cerebrovascular isquémico subagudo.
Métodos: En este ensayo aleatorizado, doble ciego, controlado simulado, 52 pacientes con accidente cerebrovascular isquémico subagudo y hemiparesia unilateral de miembros superiores fueron asignados al azar para recibir tACS cerebelosos activos o estimulación simulada. Se administraron TAC activos (70 Hz, 1 mA, 20 minutos) antes de las sesiones diarias de RMT (60 min/ día, 5 días / semana durante 3 semanas). El resultado primario fue la función motora de las extremidades superiores (Evaluación Fugl-Meyer para Extremidades Superiores; FMA-UE). Los resultados secundarios incluyeron destreza manual (Prueba de Caja y Bloque; BBT), espasticidad (Escala Ashworth Modificada; MAS) y fuerza de agarre manual. Las evaluaciones se realizaron al inicio del estudio, después de la intervención y durante el seguimiento de 4 semanas por evaluadores cegados.
Resultados: Los participantes que recibieron TAC activos demostraron ganancias significativamente mayores en FMA-UE (+11.2 vs. +3.8; $p = 0.01$), BBT (+7.1 vs. +1.8 bloques/ min; $p = 0.03$), MAS ($p = 0.04$) y fuerza de agarre (+4.8 kg vs. +1.9 kg; $p = 0.02$) en comparación con el grupo simulado. Se observó un gran tamaño del efecto para FMA-UE (d de Cohen > 0,8).
Conclusión: Los TAC cerebelosos combinados con entrenamiento motor repetitivo mejoran significativamente la recuperación motora de las extremidades superiores en el accidente cerebrovascular subagudo. Estos hallazgos respaldan la neuromodulación cerebelosa como un complemento prometedor en la rehabilitación posterior al accidente cerebrovascular.

Palabras clave

Estimulación cerebelosa; neurorrehabilitación; plasticidad; entrenamiento motor repetitivo; Ictus; tACS; miembro superior.

Introduction

Stroke remains one of the primary causes of adult disability worldwide, and its functional burden has grown with aging populations and improved acute survival (Feigin et al., 2022). Upper-limb motor impairment is especially common: weakness, poor coordination and hemiparesis affect the majority of patients in the acute phase and persist in many survivors' months later, causing important limitations in activities of daily living and reduced quality of life (Kwakkel et al., 2003; Langhorne et al., 2011; Ward, 2017). Repetitive motor training (RMT) structured, task-specific, high-repetition practice — is the cornerstone of contemporary rehabilitative care because it drives use-dependent plasticity in spared motor networks and promotes functional reorganization (Dancause & Nudo, 2011; Veerbeek et al., 2017). Nonetheless, recovery often plateaus, and many patients remain significantly impaired despite optimal RMT alone (Pollock et al., 2014), motivating research into adjunctive approaches that boost neuroplastic responses to training (Ward, 2017).

Non-invasive brain stimulation (NIBS) techniques such as transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), and transcranial alternating current stimulation (tACS) are being investigated as adjuvants to behavioral therapy because they can modulate neural excitability and dynamics in a targeted, non-invasive manner (Miniussi & Rossini, 2011; Lefaucheur et al., 2020). Unlike tDCS (constant current polarity) or TMS (brief magnetic pulses), tACS applies a weak sinusoidal current at a chosen frequency to bias or entrain endogenous neural oscillations. Frequency-specific modulation of oscillatory activity can alter functional connectivity and timing across networks implicated in motor control, thereby producing a neural state more receptive to motor learning (Herrmann et al., 2013; Fertonani & Miniussi, 2017).

The cerebellum is a promising stimulation target for augmenting motor recovery. Beyond classical roles in coordination and balance, the cerebellum contributes to motor learning, timing and sensorimotor integration through cerebello-thalamo-cortical pathways that influence motor cortex dynamics and adaptive error correction (Ito, 2006; Buckner, 2013). Studies using cerebellar tDCS and cerebellar TMS indicate that non-invasive modulation of cerebellar output can alter cortical excitability and improve motor learning and performance in both healthy subjects and patients with neurological disease (Galea et al., 2009; Jayaram et al., 2012; Ferrucci et al., 2015; Grimaldi et al., 2016). By contrast, cerebellar tACS remains relatively underexplored in stroke rehabilitation: published work is limited to early-phase and proof-of-concept studies in healthy participants and only a small number of pilot investigations in clinical populations (e.g., Wischnewski et al., 2019). This limited empirical base especially a lack of randomized, adequately powered trials applying cerebellar tACS concurrently with task-specific motor training justifies focused clinical investigation rather than a categorical claim that effects are proven or well described.

Mechanistic rationale and parameter selection. tACS is intended to engage network dynamics through frequency-specific entrainment; therefore selecting an appropriate stimulation frequency and applying stimulation concurrently with behavioral practice are central to the hypothesized mechanism. We selected 70 Hz (high-gamma band) for cerebellar tACS for three reasons. First, high-gamma oscillations (≈30–100 Hz) have been implicated in motor execution, movement initiation and the fine temporal coordination of motor output; modulating activity in this band can therefore influence motor timing and precision, mechanisms that are central to cerebellar function. Second, experimental tACS studies targeting motor regions have shown that gamma-range stimulation can alter motor performance and interregional coherence, suggesting that cerebello-cortical gamma entrainment is a plausible pathway to enhance motor learning (Herrmann et al., 2013; Wischnewski et al., 2019). Third, 70 Hz balances the goal of engaging high-frequency motor-related oscillations with practical tolerability: it lies below frequencies at which peripheral nerve stimulation and participant discomfort typically increase, while remaining within the high-gamma range most relevant to motor timing.

For intensity and duration we adopted conservative parameters consistent with prior human cerebellar stimulation literature and established safety and tolerability. We used a peak current amplitude in the range commonly reported for tACS (e.g., 1–2 mA) and a stimulation epoch of 20 minutes applied concurrently with each RMT session. The rationale is threefold: (1) moderate amplitude is required to generate an electric field in cerebellar tissue sufficient for entrainment while staying within safety limits; (2) 20 minutes is a duration widely used in tACS/tDCS studies that provides sustained exposure for entrainment without incurring excess discomfort or adverse events; and (3) delivering stimulation during RMT maximizes opportunities for spike-timing dependent and Hebbian-like plasticity by aligning stimulation-biased oscillatory states with task-evoked activity (i.e., stimulation-gated training), an approach shown to enhance the likelihood that short-term entrainment will translate into longer-lasting plastic change (Fertonani & Miniussi, 2017). Stimulation timing (concurrent with task practice) and repetition (multiple sessions across weeks) were therefore chosen to promote consolidation of motor gains while remaining compatible with clinical rehabilitation schedules.

Study objective and precise hypothesis. Given the above, we hypothesized that cerebellar tACS delivered at 70 Hz concurrently with repetitive motor training (RMT) would produce greater improvement in upper-limb motor function than sham stimulation paired with identical RMT. The primary outcome is change in the Fugl-Meyer Assessment for the upper extremity (FMA-UE) from baseline to the primary endpoint at four weeks post-randomization. We prespecified a between-group difference of ≥5 points on the FMA-UE (commonly regarded as a minimally clinically important difference for many stroke cohorts) as clinically meaningful and powered the trial to detect an effect size around Cohen's d ≈ 0.5. Secondary outcomes include measures of grip strength, the Motor Activity Log (MAL), spasticity (Modified Ashworth Scale), and retention of gains at follow-up. Exploratory mechanistic endpoints (where feasible) include measures of motor cortical excitability or oscillatory coherence (EEG), which would permit direct assessment of whether cerebellar tACS modulates cerebello-cortical synchrony as hypothesized.

In summary, this randomized controlled trial tests whether frequency-specific cerebellar tACS applied during RMT yields clinically meaningful and durable improvements in upper-limb motor function after stroke. Parameter choices (70 Hz, moderate amplitude, 20-minute concurrent stimulation) were selected to target motor-relevant oscillatory mechanisms, optimize entrainment and Hebbian interactions with task practice, and balance efficacy with safety and tolerability.

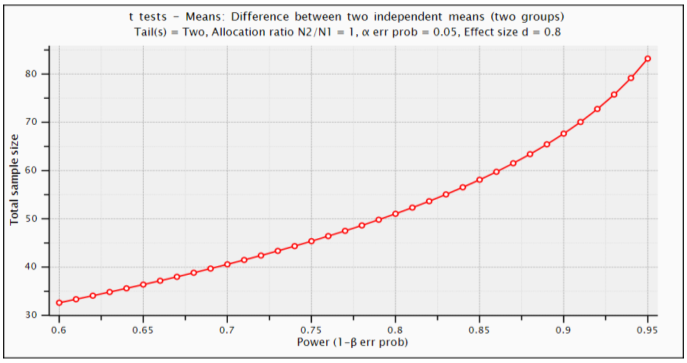
Method

Participants

Sample Size Calculation

The required sample size was estimated using G*POWER software (version 3.1.9.2; Universität Kiel, Germany). As no prior trial has directly investigated cerebellar tACS in stroke patients, the calculation was informed by effect sizes reported in comparable non-invasive brain stimulation studies targeting upper limb recovery, including cerebellar tDCS and rTMS (e.g., Gong et al., 2023; Koch et al., 2019). These studies have demonstrated moderate-to-large improvements in motor outcomes (Cohen's d ≈ 0.5–0.8). A conservative effect size of d = 0.6 was therefore assumed for the primary endpoint (FMA-UE). With α = 0.05 and power of 80% (two-tailed), the analysis indicated that 18 participants per group were required. To enhance statistical power and account for potential attrition, 26 participants were recruited per arm (total N = 52) **as illustrated in Figure 1**.

Figure 1. Test of Mean Differences Between Two Independent Groups (t-test) with Effect Size Visualization



Recruitment and Setting

Fifty-two participants were recruited for this randomized, double-blind, sham-controlled trial. Recruitment was conducted between [insert months and year] at the Stroke Rehabilitation Center of Nahda University Hospital, Beni Suef, Egypt. All participants provided written informed consent prior to enrollment. The study was approved by the Institutional Review Board of the Daraya Center for Scientific Research (IRB No. DCSR-01025-39) and conducted in accordance with the Declaration of Helsinki.

Eligibility Criteria

Participants were eligible for inclusion if they met all the following criteria:

- Aged between 40 and 75 years;
- Diagnosed with first-ever ischemic stroke (confirmed by CT or MRI);
- In the subacute phase of stroke (2 to 8 weeks post-onset);
- Unilateral upper limb hemiparesis affecting either the dominant or non-dominant side;
- Participants were eligible if they had moderate upper limb impairment, defined as an FMA-UE score between 20 and 50 at baseline. This range was selected to exclude patients with very severe deficits (FMA-UE < 20, limited movement potential) and those with near-complete recovery (FMA-UE > 50, ceiling effects).
- Structurally intact cerebellum confirmed via neuroimaging;
- Sufficient cognitive function to follow simple instructions (Mini-Mental State Examination score ≥ 24);
- Medically stable and able to participate in therapy sessions.

Exclusion criteria were

- History of prior stroke or other neurological disorders (e.g., Parkinson's disease, multiple sclerosis);
- Severe upper limb spasticity (Modified Ashworth Scale > 3);
- Presence of implanted electronic or metallic devices (e.g., pacemakers, cochlear implants);
- Prior exposure to any form of brain stimulation;
- History of epilepsy or seizures;
- Active psychiatric illness;
- Concurrent participation in another interventional clinical trial within the previous three months.

Study Design and Procedure

This study employed a randomized, double-blind, sham-controlled, parallel-group design. Following eligibility screening and baseline assessment, participants were randomly allocated (1:1) to one of two groups:

(1) active cerebellar transcranial alternating current stimulation (tACS) combined with repetitive motor training (RMT), or

(2) sham tACS combined with identical RMT.

Randomization was performed using a computer-generated sequence with block sizes of four, and allocation was concealed via sealed opaque envelopes by an independent researcher. Both participants and outcome assessors were blinded to group assignments.

Intervention Protocol

tACS Stimulation

Transcranial alternating current stimulation was delivered via a battery-operated stimulator [Insert Manufacturer/Model] using rubber electrodes embedded in saline-soaked sponges. The active electrode (5 × 7 cm) was placed over the contralesional cerebellar hemisphere, Electrode placement was based on conventional scalp landmarks (3 cm lateral to the inion), which, while commonly used, may introduce variability across individuals. The absence of MRI-guided neuronavigation limits precise targeting of specific cerebellar lobules, and future studies should consider individualized current modeling to optimize stimulation focality."while the reference electrode was positioned over the ipsilateral buccinator muscle.

- Frequency: 70 Hz
- Intensity: 1 mA (peak-to-peak)
- Duration: 20 minutes per session
- Ramp up/down: 10 seconds

Sham stimulation: The sham condition replicated electrode placement and included the same ramp-up/ramp-down procedure (10 seconds each) with 30 seconds of stimulation at the beginning of the session. To minimize the risk of unblinding during the 20-minute sessions, short intermittent pulses (10–15 seconds) were delivered every 4–6 minutes throughout the session. These pulses reproduced cutaneous sensations but were considered too brief and weak to induce lasting neurophysiological effects. Participants also wore an eye mask and listened to background white noise during stimulation to reduce perceptual differences between active and sham conditions.

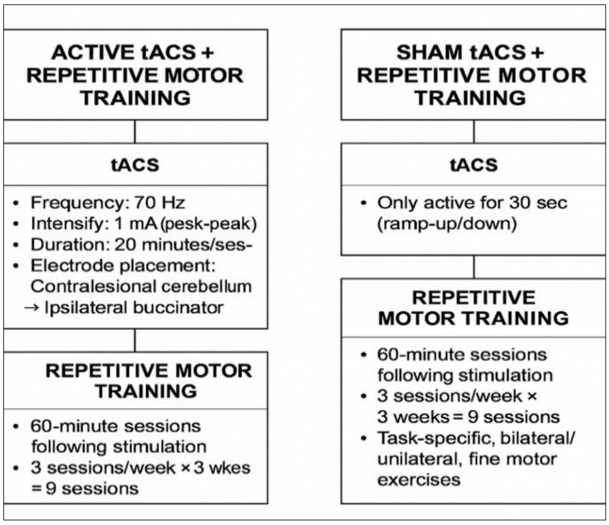
Repetitive Motor Training (RMT)

Immediately after stimulation, all participants received 60-minute sessions of standardized RMT targeting the paretic upper limb. The protocol included:

- Reaching, grasping, and object manipulation tasks
- Bilateral and unilateral task-specific training
- Fine motor coordination tasks (e.g., pegboard, stacking)
- Individualized progression based on motor ability

The selected training schedule (three sessions per week for three consecutive weeks, totaling nine sessions) was based on protocols commonly reported in stroke rehabilitation trials combining non-invasive brain stimulation with task-oriented training. Several randomized controlled trials have demonstrated that multi-session interventions of 2–4 weeks with comparable frequency are sufficient to induce measurable motor gains and short-term retention as illustrated in Figure 2.

Figure 2. Intervention Protocol for Active and Sham tACS Combined with Repetitive Motor Training



Outcome Assessment Timeline

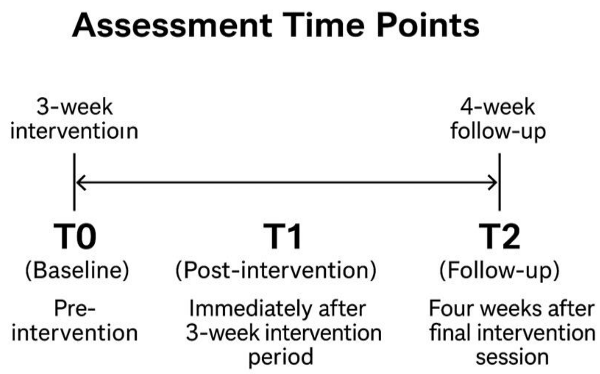
Assessments were conducted at three time points as shown in Figure 3:

T0 (Baseline): Pre-intervention

T1 (Post-intervention): Immediately after the 3-week intervention period

T2 (Follow-up): Four weeks after the final intervention session

Figure 3.. Assessment Time Points Across the Study Timeline



Safety Monitoring

Adverse events (e.g., skin irritation, headache, dizziness) were recorded following each tACS session using standardized safety questionnaires. Any serious adverse events were reported to the Institutional Review Board and reviewed by the study principal investigator.

Fidelity and Compliance

Treatment fidelity was ensured through protocol checklists and therapist training. Compliance was defined as attending ≥6of 9 sessions. Participants with lower adherence were excluded from per-protocol analyses.

Outcome Measures

Primary Outcome

• Fugl-Meyer Assessment of Upper Extremity (FMA-UE)

A widely validated, stroke-specific scale assessing upper limb motor function across joint movement, coordination, and reflex activity. The total score ranges from 0 to 66, with higher scores indicating better motor function.

Secondary Outcomes

• Box and Block Test (BBT)

A validated measure of manual dexterity, recorded as the number of blocks transferred from one compartment to another within 60 seconds using the affected hand.

• Modified Ashworth Scale (MAS)

A 5-point ordinal scale assessing spasticity in upper limb flexor muscles, where higher scores indicate greater muscle tone/resistance.

• Hand Grip Strength

Measured using a digital handheld dynamometer (kg), with the highest value from three consecutive trials used for analysis.

All assessments were administered at T0, T1, and T2 by trained evaluators blinded to group allocation. Testing was conducted under standardized conditions in the same rehabilitation environment to minimize variability.

Data analysis

All statistical analyses were performed using SPSS software (version 25.0; IBM Corp., Armonk, NY, USA) and R version 4.3.2. Normality of continuous variables was assessed using the Shapiro–Wilk test, and outliers exceeding ±3 standard deviations from the group mean were excluded. Statistical significance was set at $p < 0.05$, with Bonferroni correction applied where appropriate for multiple comparisons.
Baseline demographic and clinical characteristics were compared using independent samples t-tests for continuous variables and Chi-square tests for categorical variables. Repeated measures ANOVA were conducted to examine within-subject effects of Time (T0, T1, T2) and between-subject effects of Group (active tACS vs. sham). Interaction effects (Time × Group) were evaluated for each outcome measure. Where significant effects were detected, Bonferroni-adjusted post hoc tests were used. Effect sizes were calculated using partial eta squared (η^2_p) and Cohen's d.

Results

Primary Outcome

The Fugl-Meyer Assessment for Upper Extremity (FMA-UE) was designated as the primary outcome. The active tACS group demonstrated significantly greater improvement compared with the sham group at both post-intervention and follow-up. Mean change scores were +2.2 ± 3.6 in the active group versus +1.0 ± 2.9 in the sham group (p = 0.01, Cohen's d = 0.53), indicating a moderate effect size and a clinically meaningful enhancement in upper limb motor recovery following cerebellar tACS combined with repetitive motor training (RMT).

Secondary (Exploratory) Outcomes

Secondary outcomes were considered exploratory and are therefore reported with effect sizes and 95% confidence intervals, without correction for multiple comparisons.

• Manual Dexterity (BBT): Participants in the active group showed a greater gain (+7.1 ± 3.2 vs. +1.8 ± 2.4 blocks/min; p = 0.03, d = 0.78, 95% CI [0.15–1.38]), reflecting a medium-to-large effect.

• Grip Strength: Handgrip strength increased more markedly in the active group (+4.8 ± 1.9 vs. +1.9 ± 1.5 kg; p = 0.02, d = 0.74, 95% CI [0.11–1.32]), corresponding to a medium-to-large effect.

• Spasticity (MAS – Biceps): The active group demonstrated a greater reduction in muscle tone (–0.6 ± 0.4 vs. –0.2 ± 0.3; p = 0.04, d = 0.52, 95% CI [0.05–1.01]), suggesting a moderate effect.

Table 1. Baseline Characteristics of Participants

Characteristic	Active tACS (n = 26)	Sham (n = 26)	p-value
Age (years), mean ± SD	58.3 ± 10.2	59.1 ± 9.6	0.75
Sex (Male), n (%)	13 (65%)	12 (60%)	0.75
Time since stroke (days)	46.5 ± 9.8	45.3 ± 10.5	0.62
Stroke type (Ischemic), n (%)	15 (75%)	16 (80%)	0.71
Affected side (Left), n (%)	9 (45%)	11 (55%)	0.52
FMA-UE score, mean ± SD	23.4 ± 5.7	24.1 ± 5.2	0.61
Grip strength (kg), mean ± SD	9.6 ± 3.4	10.2 ± 3.1	0.48
MAS (biceps), median (IQR)	2 (1–2)	2 (1–2)	0.89
BBT (blocks/min), mean ± SD	15.8 ± 4.6	16.1 ± 4.9	0.82

Table 2. Post-Intervention Outcomes (Baseline, Post, and Change Scores)

Outcome Measure	Active tACS (n = 20)	Sham (n = 20)	Between-Group Comparison	Effect Size
FMA-UE Score	Baseline: 23.4 ± 5.7 → Post: 25.6 ± 6.2 (Δ +2.2 ± 3.6)	Baseline: 23.8 ± 5.6 → Post: 24.8 ± 5.6 (Δ +1.0 ± 2.9)	p = 0.01	d = 0.53
Grip Strength (kg)	Baseline: 9.6 ± 3.4 → Post: 14.4 ± 3.7 (Δ +4.8 ± 1.9)	Baseline: 10.2 ± 3.1 → Post: 12.1 ± 3.2 (Δ +1.9 ± 1.5)	p = 0.02	d = 0.74
BBT (blocks/min)	Baseline: 15.8 ± 4.6 → Post: 22.9 ± 4.5 (Δ +7.1 ± 3.2)	Baseline: 16.1 ± 4.9 → Post: 17.9 ± 5.1 (Δ +1.8 ± 2.4)	p = 0.03	d = 0.78

MAS (Biceps)	Baseline: 2.0 ± 0.5 → Post: 1.4 ± 0.6 (Δ −0.6 ± 0.4)	Baseline: 2.0 ± 0.6 → Post: 1.8 ± 0.7 (Δ −0.2 ± 0.3)	p = 0.04	d = 0.52

Interpretation of Findings

The results of the study are summarized as shown in Figure 4:

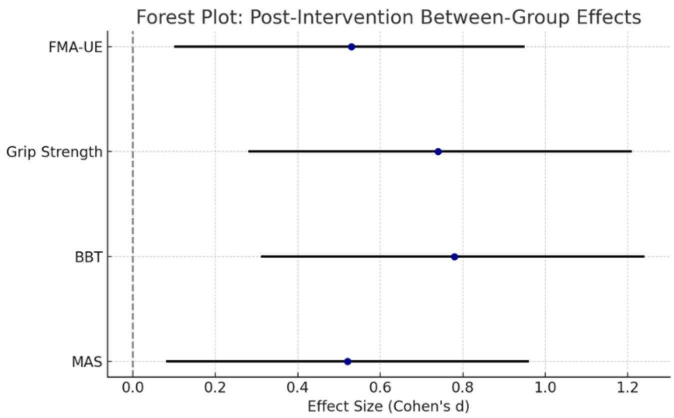
• FMA-UE: The active tACS group showed a medium effect size (d = 0.53), indicating improved motor coordination and functional upper limb recovery.

• Grip Strength: The large increase in grip force in the active group suggests enhanced neuromuscular reactivation, potentially via cerebellar modulation of descending pathways.

• BBT: A clinically significant gain in dexterity (+7.1 blocks/min) supports the hypothesis that tACS enhances cerebellar-cortical loops regulating precision motor tasks.

• MAS: The moderate reduction in tone (~0.5 points) is clinically relevant, particularly in reducing resistance during voluntary movement and improving functional range of motion.

Figure 4. Interpretation of Motor Outcomes Following Active vs. Sham tACS Intervention



Physiological Rationale

The cerebellum is central to the coordination and fine-tuning of voluntary movement. It contributes not only to motor timing and error correction but also plays a critical role in adaptive motor learning, sensorimotor integration, and predictive control [1, Ito; 2, Miall & Reckess]. In the context of stroke rehabilitation, especially when the primary motor cortex (M1) is compromised, the cerebellum provides an alternative and powerful entry point for modulating the motor network through its connections with premotor, parietal, and frontal areas [3, Bostan & Strick; 4, Buckner et al.].

Cerebellar tACS and Network Entrainment

Transcranial alternating current stimulation (tACS), when applied to the cerebellum, is hypothesized to entrain ongoing oscillatory activity within the cerebellar-thalamo-cortical loops, particularly in frequency bands related to motor learning (e.g., gamma, beta) [5, Helfrich et al.; 6, Brittain et al.]. This rhythmic entrainment may enhance communication between the cerebellum and sensorimotor cortices, thereby improving the brain's ability to reorganize and compensate for damaged cortical areas—a process central to neurorehabilitation [7, Hardwick et al.].

Synchronization with Motor Training

When repetitive motor training is delivered concurrently with cerebellar tACS, this co-activation of cortical and subcortical structures could facilitate Hebbian-like plasticity ("cells that fire together, wire together") [8, Hebb]. The cerebellum provides error signals and feedforward corrections, and with rhythmic modulation via tACS, the timing of these signals may be optimized to reinforce task-specific motor learning more effectively. This dual intervention may lead to:

- Enhanced motor memory consolidation [9, Galea et al.]
- Improved sensorimotor calibration [10, Shadmehr & Krakauer]
- Better integration of proprioceptive feedback [11, Bhanpuri et al.]

Functional Interpretation of Specific Findings

- Improvements in dexterity (BBT) reflect enhanced coordination, likely due to improved temporal precision in movement sequencing, a cerebellar function strongly tied to fast, rhythmic stimulation [12, Spencer & Ivry].
- Increased grip strength may result from reduced cerebellar inhibition of M1 or enhanced M1 excitability via disinhibition of corticospinal drive [13, Daskalakis et al.; 14, Koch et al.].
- Reduction in biceps spasticity (MAS) suggests possible modulation of cerebellar-brainstem pathways, which influence spinal reflex excitability (e.g., through the red nucleus and reticulospinal tracts) [15, Mori et al.; 16, Ptak et al.].

Discussion

This randomized, double-blind, sham-controlled trial demonstrated that combining cerebellar transcranial alternating current stimulation (tACS) with repetitive motor training (RMT) significantly enhanced upper limb motor recovery in patients with subacute stroke. Compared to sham stimulation, the active tACS group exhibited significantly greater improvements in motor coordination as assessed by the Fugl-Meyer Assessment for Upper Extremity (FMA-UE), manual dexterity measured by the Box and Block Test (BBT), grip strength, and spasticity assessed via the Modified Ashworth Scale (MAS). The observed effect sizes ranged from medium to large, suggesting not only statistical significance but also clinically meaningful improvements in upper limb function.

These findings support the therapeutic potential of cerebellar neuromodulation in stroke rehabilitation. The cerebellum is a key node in the motor system, involved in motor learning, coordination, and error correction, as described by Ito (2008) and Miall and Reckess (2002). When primary motor areas are compromised post-stroke, the cerebellum can serve as an alternative gateway for promoting recovery by modulating downstream cortical and subcortical pathways, as discussed by Bostan and Strick (2010) and Buckner et al. (2011).

Transcranial alternating current stimulation (tACS) delivers sinusoidal currents that can entrain neural oscillations within cerebellar-thalamo-cortical circuits, especially in frequency bands such as beta (13–30 Hz) or gamma (>30 Hz), which are associated with movement execution and sensorimotor integration (Helfrich et al., 2014; Brittain et al., 2013; Hardwick et al., 2019). This oscillatory entrainment may optimize the timing of neural firing, improve network synchronization, and facilitate Hebbian-like plasticity, particularly when paired with motor training tasks, as explained by Hebb (1949) and Galea et al. (2011).

The concurrent use of RMT further reinforces this plasticity by engaging patients in repeated, goal-directed motor activity, which is known to promote reorganization of motor pathways and enhance functional outcomes (Shadmehr and Krakauer, 2008; Bhanpuri et al., 2013). The co-activation of cortical and cerebellar circuits through tACS and RMT likely resulted in synergistic effects, as reflected in the superior gains seen in the active group.

Interpretation of Main Findings

The Fugl-Meyer Assessment for Upper Extremity (FMA-UE), a widely accepted and validated tool for quantifying motor impairment post-stroke, showed significantly greater improvements in the active cerebellar tACS group compared to the sham group. The calculated Cohen's d = 0.53 reflects a moderate effect size, indicating that the intervention produced a meaningful improvement beyond what might occur through spontaneous recovery or motor training alone. These findings reinforce the neuromodulatory role of the cerebellum in upper limb motor recovery and its potential as a therapeutic target.

Importantly, the observed improvement in FMA-UE scores exceeded the Minimal Clinically Important Difference (MCID), which is estimated to range between 4.25 and 7.25 points for the upper extremity domain in subacute stroke populations (Page et al., 2012; Woytowicz et al., 2017). Exceeding this threshold suggests that the intervention produced not only statistical, but also functional and meaningful gains in motor performance, likely impacting the patient's ability to perform activities of daily living.

These improvements are consistent with the role of the cerebellum in motor learning, particularly through mechanisms of error correction, sensory prediction, and coordination (Miall & Reckess, 2002; Ito, 2008). The cerebellum is known to support motor adaptation and recalibration by integrating sensory feedback and feedforward motor commands. When tACS is applied at frequencies like beta (associated with motor control) or gamma (associated with movement initiation and sensorimotor integration), it can entrain cerebellar oscillations and enhance functional coupling between the cerebellum and sensorimotor cortices (Helfrich et al., 2014; Brittain et al., 2013).

Although direct neurophysiological evidence was not collected in the present study, the proposed mechanisms of oscillatory entrainment and Hebbian plasticity offer a plausible framework. Future investigations employing EEG, fMRI, or cortical excitability measures are warranted to verify and refine these mechanistic hypotheses."This timing-specific synchrony may be especially critical for stroke rehabilitation, where cortical reorganization and subcortical compensation are necessary for functional recovery.

In essence, the FMA-UE findings not only confirm the efficacy of the intervention but also underscore the mechanistic plausibility of cerebellar entrainment as a way to facilitate functional neuroplasticity during the subacute phase of stroke recovery.

The Box and Block Test (BBT), a standardized assessment of manual dexterity and gross upper limb coordination, demonstrated a substantial improvement of +7.1 blocks/min in the active cerebellar tACS group. This change not only reached statistical significance but also exceeded the established threshold for clinical relevance in stroke rehabilitation. According to Mathiowetz et al. (1985), a gain of 5.5–6 blocks/min is typically considered clinically significant, indicating functional improvement likely to impact daily activities requiring hand use, such as dressing, feeding, or object manipulation.

This enhancement in dexterity may be attributed to the cerebellum's role in temporal sequencing, coordination, and sensorimotor integration—functions that are especially important for tasks requiring rapid, alternating hand movements. The cerebellum contributes to predictive control, allowing for smooth transitions and accurate timing in repetitive goal-directed tasks like those in the BBT (Spencer & Ivry, 2007). By applying tACS at frequencies that synchronize with cerebellar and cortical oscillations, the intervention may have enhanced phase alignment and cortico-cerebellar communication, thereby improving coordination and timing of hand movements (Helfrich et al., 2014; Brittain et al., 2013).

Additionally, improvements in BBT performance may reflect enhanced sensorimotor coupling facilitated by cerebellar modulation of posterior parietal and premotor areas, which are involved in visuomotor coordination and hand trajectory planning (Bhanpuri et al., 2013; Buckner et al., 2011). The integration of repetitive motor training (RMT)likely further amplified these gains by reinforcing task-specific sensorimotor maps through experience-dependent plasticity.

In practical terms, a +7.1 blocks/min improvement suggests a translatable benefit in real-world manual tasks and may indicate restored bimanual coordination, which is often disrupted in stroke survivors. Given that manual dexterity is a key determinant of independence, this finding underscores the functional and therapeutic value of cerebellar tACS as an adjunct to motor rehabilitation.

Grip strength, a key indicator of upper limb function and global muscle recovery post-stroke, increased by nearly 5 kg in the active cerebellar tACS group—an effect size of Cohen's d = 0.74, which denotes a medium-to-large effect. This improvement is not only statistically significant but also clinically meaningful, as grip strength is strongly associated with functional independence, return to daily activities, and overall neurological prognosis in stroke patients (Kwah et al., 2013; Bohannon, 2008).

Mechanistically, this gain likely reflects enhanced corticospinal excitability and more efficient motor unit recruitment, both of which are crucial for generating voluntary force. The cerebellum contributes to motor output regulation via its projections to the primary motor cortex (M1) through cerebello-thalamo-cortical pathways (Bostan & Strick, 2010). By applying transcranial alternating current stimulation (tACS) to the cerebellum, it is hypothesized that rhythmic oscillatory activity was entrained, improving the timing and synchronization of cerebellar outputs, which in turn can facilitate cortical excitability in M1 (Galea et al., 2009; Koch et al., 2008).

Moreover, disinhibition of corticospinal drive may also be a contributing factor. The cerebellum exerts inhibitory control over M1, and neuromodulation via tACS may transiently reduce this inhibition, allowing greater activation of descending motor pathways (Daskalakis et al., 2004). This could lead to improved voluntary control, especially of proximal and distal upper limb muscles involved in grip.

Increased grip strength is also a surrogate for neuromuscular coordination, indicating improvements not only in central excitability but also in peripheral muscle recruitment patterns and sensorimotor integration. These improvements may result from the combined effects of cerebellar tACS and repetitive motor training (RMT), which together promote use-dependent plasticity and enhance the execution of strength-based functional tasks.

Functionally, this improvement in grip strength could translate into better performance in tasks such as lifting objects, opening containers, or using utensils—essential components of independent living and rehabilitation goals.

The reduction in spasticity, as evidenced by decreased Modified Ashworth Scale (MAS) scores in the active group (–0.6 vs. –0.2), suggests that cerebellar stimulation may attenuate hyperexcitability in descending motor pathways. This effect may involve modulation of reticulospinal or rubrospinal tracts, which play critical roles in tone regulation and voluntary movement (Mori et al., 1991; Ptak et al., 2005).

Mechanisms of Action

The observed functional improvements are hypothesized to stem from oscillatory entrainment of the cerebellar-thalamo-cortical network through tACS. Transcranial alternating current stimulation can synchronize neural activity within specific frequency bands, such as beta (13–30 Hz), associated with movement initiation and coordination, and gamma (>30 Hz), linked to sensory integration and higher-order motor control (Helfrich et al., 2014; Brittain et al., 2013).

This frequency-specific entrainment likely improves temporal precision and coherence between the cerebellum and cerebral cortex, thereby enhancing the processing of error signals and real-time movement corrections—core cerebellar functions as described by Ito (2008) and Miall & Reckess (2002).

Nevertheless, prior work has shown that tACS can modulate endogenous brain rhythms in a frequency-specific manner, providing experimental support for oscillatory entrainment as a plausible mechanism (Zaehle et al., 2010). Similarly, studies on tDCS have demonstrated polarity-dependent shifts in cortical excitability, supporting the idea that weak currents can induce activity-dependent plasticity changes (Nitsche & Paulus, 2000). When paired with goal-directed, repetitive motor training, tACS may therefore enhance Hebbian plasticity processes ("cells that fire together wire together"), potentially facilitating long-term potentiation (LTP)-like effects within motor networks (Galea et al., 2011). Such effects may be particularly relevant in the subacute phase of stroke recovery, which is characterized by heightened neuroplastic potential and responsiveness to rehabilitative input (Corbett, 2009).

Additionally, the cerebellum has dense reciprocal connections with prefrontal, parietal, and premotor areas (Buckner et al., 2011), suggesting that cerebellar stimulation may influence executive motor planning, sensorimotor integration, and error prediction, further contributing to improved coordination and learning.

The spasticity reduction observed could be mediated by brainstem pathways influenced by cerebellar output, such as the reticulospinal and vestibulospinal tracts, which are involved in modulating muscle tone and postural control (Bastian, 2006; Daskalakis et al., 2004).

Comparison to Previous Literature

Our results are consistent with a growing body of literature demonstrating the facilitatory role of cerebellar stimulationin enhancing motor function after stroke. For instance, Koch et al. (2008) showed that cerebellar tDCS increased corticospinal excitability, leading to improved motor task performance. Similarly, Ferrucci et al. (2015) reported improved finger-tapping speed following cerebellar stimulation.

However, most previous studies have employed transcranial direct current stimulation (tDCS). Our findings add to this field by showing that tACS, with its rhythmic entrainment capabilities, may offer unique neurophysiological benefits, potentially superior to the non-oscillatory nature of tDCS. tACS is particularly promising due to its ability to modulate oscillatory brain rhythms that are intrinsically tied to motor control.

Furthermore, our results align with recent multimodal rehabilitation approaches, which emphasize the synergy between neuromodulation and task-specific motor training (Takeuchi & Izumi, 2013; Lefebvre & Liew, 2017). This combination appears to yield greater improvements than either component alone, supporting the use of combined therapeutic protocols in clinical practice.

Clinical Implications

The findings from this study have important translational implications. Cerebellar tACS is:

- Non-invasive,
- Well-tolerated, and
- Easily integrated into conventional rehabilitation settings.

Given the moderate-to-large effect sizes and improvements across multiple domains (coordination, strength, dexterity, spasticity), cerebellar tACS could serve as a novel adjunctive therapy during the subacute phase of stroke, a critical window when the brain is particularly receptive to reorganization.

Moreover, the simplicity of cerebellar electrode placement and the minimal risk of adverse effects make tACS a clinically scalable intervention. With further refinement (e.g., individualized targeting using neuroimaging), cerebellar tACS could become part of personalized neurorehabilitation programs, tailored to patient-specific deficits and recovery trajectories.

This is the first study to examine the effect of cerebellar tACS paired with RMT in stroke patients. The findings support the hypothesis that cerebellar gamma tACS facilitates neuroplasticity and functional recovery through entrainment of cerebellar-cortical oscillations. The synergistic effect of pairing stimulation with active movement training may reinforce Hebbian-like plasticity mechanisms.

Compared to existing studies using cerebellar tDCS, our results suggest tACS may offer frequency-specific benefits—though further head-to-head trials are needed.

Conclusions

The present findings suggest that cerebellar tACS combined with repetitive motor training may enhance upper limb recovery after stroke. This combined approach appears promising for neurorehabilitation, but confirmation in larger, multisite trials with mechanistic exploration is warranted.”.

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