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Home-Based Tele-tDCS in Amyotrophic Lateral Sclerosis: Feasibility, Safety, and Preliminary Efficacy

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ABSTRACT

Objective: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease with limited treatment options. Transcranial direct current stimulation (tDCS) shows promise as a neuromodulatory intervention in various neurological disorders, but its application in ALS, particularly in a remote, home-based format, remains underexplored. This study investigates the feasibility, safety, and preliminary efficacy of remotely supervised tele-tDCS in ALS patients.

Methods: This double-blinded pilot study included 14 spinal-onset ALS participants randomized into two groups: the intervention group received 72 tele-tDCS sessions over 24 weeks, and the delayed-start group received 36 sham sessions followed by 36 tele-tDCS sessions. Stimulation was delivered at 2 mA for 20 min 3 times a week. Primary outcomes included feasibility, safety, and disease progression measured by the ALS Functional Rating Scale-Revised (ALSFRS-R). Adherence and adverse effects were monitored throughout.

Results: Ten participants completed the study, with an overall compliance rate of 98.3%. No serious adverse events were reported, and mild side effects, like itching and tingling, were consistent with tDCS literature. The intervention group demonstrated a significantly slower decline in ALSFRS-R scores than the delayed-start group. At 24 weeks, the intervention group had a mean ALSFRS-R change of −1.7, compared to −13.6 in the delayed-start group ($p = 0.0018$). Additionally, the change in ALSFRS-R between pre- and mid-intervention significantly differed between groups ($p = 0.0071$).

Interpretation: Tele-tDCS was feasible, safe, and well-tolerated in individuals with ALS. Preliminary efficacy results suggest that tele-tDCS may slow disease progression, underscoring the potential of tele-tDCS as a promising home-based neuromodulatory intervention in ALS management.

Trial Registration: Clinical trial registration: NCT04866771

1 | Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative condition that leads to the degeneration of cortical, brainstem, and spinal motoneurons, affecting approximately 30,000 individuals in the United States [1, 2]. There is currently no cure or treatment to halt the progression of ALS. In the U.S., four drugs have been approved: riluzole (Rilutek, Tiglutik, Exservan) in 1995, offering a modest survival benefit; tofersen (Qalsody) in 2023, targeting SOD1 mutations in a small subset of patients; edaravone (Radicava) in 2017; and RELYVRIO in 2022. However, in 2024, the ADORE trial of oral edaravone was halted, and RELYVRIO was withdrawn due to poor trial outcomes, highlighting the urgent need for more effective treatments [3, 4]. This challenge has spurred the exploration of innovative approaches like neuromodulation, which may complement conventional drug therapies. These emerging strategies aim to slow disease progression, improve quality of life, and extend survival for ALS patients [5].

Early-stage ALS often manifests as altered motor cortex excitability, possibly due to changes in the properties of motoneuronal membranes [6–9]. This characteristic presents a target for interventions such as transcranial direct current stimulation (tDCS), which modulates neural excitability and could potentially influence ALS symptoms and disease progression. tDCS has been increasingly investigated to modulate neural excitability, improve motor learning, and enhance motor behavior [10–13]. tDCS involves applying a weak electric current (≤ 2 mA) to the skull and underlying cortical structures, with anodal stimulation increasing excitability and cathodal stimulation leading to inhibition [14]. Its effects are mediated by various mechanisms, possibly involving N-methyl D-aspartate (NMDA) receptors [15]. Given its efficacy as a neuromodulatory adjunct in stroke, Parkinson's disease, multiple sclerosis, and other neurological disorders, tDCS presents a promising avenue for symptomatic treatment of ALS, warranting further investigation into its specific benefits for this condition [16].

Although tDCS has shown potential in other neurodegenerative diseases, its application in ALS remains underexplored, particularly for long-term, home-based interventions [5, 17–22]. Two studies reported no changes in corticomotor excitability in ALS patients following single sessions of tDCS, and another investigation revealed that disease progression remained unchanged after a regimen of 12 monthly cathodal tDCS sessions over a year in a single patient [17–19]. Clinical trials suggest multiple tDCS sessions are necessary for significant benefits in clinical outcomes and neuroplasticity, typically administered over 4 weeks (three times a week for at least 12 sessions) [23–28]. Madhavan et al. (2019) examined the long-term efficacy of anodal and cathodal tDCS (three times a week for 12 sessions) in ALS. They observed a modest enhancement in gait speed with anodal tDCS, highlighting its potential for symptomatic improvement in ALS patients. These studies were conducted in laboratory environments, limiting participation due to the considerable burden ALS places on patients and their caregivers [29]. As a result, intervention studies in progressive neurological disorders like ALS often face higher dropout rates, leading to challenges in data collection and the potential for studies to be underpowered. Such constraints may reduce the broader applicability and practical value of these interventions [30–32].

To address these challenges, research across various neurological conditions, including stroke, multiple sclerosis, depression, and vascular dementia, has demonstrated the feasibility and effectiveness of remotely administered tDCS [33–42]. Implementing remotely supervised tDCS or "tele-tDCS" in ALS presents a promising strategy to mitigate the logistical and physical demands on patients and caregivers. By enabling patients to undergo treatment in the comfort of their own homes under remote supervision, tele-tDCS promises to enhance patient independence, safety, and quality of life and aims to minimize travel-related barriers. This approach could lead to improved participation rates and data quality in studies, offering a more accessible and patient-friendly intervention method. Sivaramakrishnan et al. [22] explored the safety and viability of a rigorous tele-tDCS regimen in two patients—administered thrice weekly over 8 weeks, totaling 24 sessions—and reported no significant adverse events, alongside preliminary evidence affirming its safety and practicality for ALS patients. Given its low-risk profile, portability, and user-friendly design, tele-tDCS emerges as an attractive option for home-based therapy under remote guidance. Nonetheless, the necessity for extended research, characterized by longer treatment periods and stringent adherence to protocols, remains to establish its clinical effectiveness in ALS management conclusively. This study thoroughly examines the safety and feasibility of a 24-week anodal tele-tDCS protocol. Beyond assessing these fundamental aspects, our research also explored the intervention's potential to slow down the progression of ALS, focusing on key metrics such as motor function, quality of life, and survival rates as an exploratory aim to understand the broader impact of this extended-term treatment on patient outcomes.

2 | Methods

This study is a randomized, double-blinded clinical trial (NCT04866771) approved by the institutional review board at the University of Illinois Chicago. It was conducted in the Brain Plasticity Lab at the University of Illinois Chicago, IL. All measures were collected between August 2021 and June 2024. Primary clinical outcomes are reported in this paper.

2.1 | Participants

Inclusion criteria included individuals aged between 18 and 80 years with a diagnosis of possible, probable, or definite ALS (as identified by the revised El-Escorial criteria) within 5 years of diagnosis, experiencing spinal-onset ALS with initial weakness in the upper or lower extremity, stable dose of Riluzole, Edaravone, Relyvrio, or no ALS medications, score ≥ 2 for "swallowing" and ≥ 1 for "walking" on the ALS Functional Rating Scale-Revised (ALSFRS-R), and availability of a caregiver for remote administration of the protocol. Exclusion criteria included those with bulbar-onset ALS, any neurological diagnosis other than ALS, psychiatric disorders,

any other significant concomitant disease such as systemic/cardiovascular/renal/hepatic disorders, tracheostomy, noninvasive ventilation for more than 12 h per day, enrollment in an ongoing ALS pharmaceutical trial, and those planning on moving within 6 months. Initial participant contact was by telephone, and their written informed consent was obtained on inclusion.

2.2 | Study Design

This study includes two groups, the intervention and delayed-start group, randomized through stratified sequential randomization (Figure 1). The stratification of participants into the two groups was based on their progression rate, which was calculated using their ALSFRS-R score (see clinical outcomes for more information). Participants were randomized using computer-generated block randomization, and both participants and researchers were blinded to group allocation. The tele-tDCS devices were preprogrammed to ensure the blinding of the assessor, trainer, and participant. The intervention group received 72 sessions of tele-tDCS, while the delayed-start group received 36 sessions of sham-tDCS, followed by 36 sessions of tele-tDCS. We conducted six evaluations to monitor changes in disease progression over time, consisting of one pre-testing, up to three mid-testing visits, one post-testing, and a 3-month follow-up session. At each of these sessions, functional outcomes and neurophysiological testing were performed. Each mid-testing session also included a clinical and scalp integrity check, restocking of supplies, and reprogramming the tDCS device for additional codes. The study intervention included remotely supervised tele-tDCS, administered thrice a week for 72 sessions (approximately 24 weeks). During each session, side effects were monitored and recorded using a custom-developed questionnaire (see Supporting Information).

2.3 | Stimulation Parameters

A portable tDCS device (Soterix Medical 1X1 tDCS mini-CT Stimulator, NY) was used in this study. This device included a stimulator, a customized head strap for secure placement, and designated positions for active (anodal current over the lower limb motor cortex) and inactive electrodes (cathodal current over the contralateral supraorbital region). It featured built-in programmable codes, allowing for controlled session-specific settings under the remote supervision of a researcher. The stimulation dosage of 2 mA for 20 min was preprogrammed into the device by research personnel before being provided to participants. The stimulation intensity of 2 mA for 20 min was chosen based on previous tDCS studies in neurodegenerative diseases, which have shown this dose to be effective and well-tolerated [43–45]. The preprogramming ensured neither participants nor caregivers could alter the stimulation intensity or duration.

2.4 | tDCS Tolerability and Training

During the initial visit, research personnel tested the participant's tolerability to tDCS stimulation. This involved placing electrodes on the participant's scalp, administering a 15-min stimulation, and monitoring for any side effects. Following this assessment, the participant and caregiver were introduced to the device and given hands-on training on correctly positioning the headset and operating the device. The precise location for the active electrode placement was marked on the participant's scalp by the researcher using a surgical skin marker to ensure consistent placement. Caregivers were instructed to regularly re-mark this spot to maintain visibility, taking special care to preserve the mark during activities like showering. In case the mark faded or became invisible, caregivers were also trained to measure and re-mark the stimulation spot. We supplemented these instructions with demonstrative pictures and detailed measurements for home reference. Participants were provided with an information guide, which included a device information booklet, tDCS session logs, electrodes, and all necessary supplies for measurement, ensuring they were fully equipped to continue the process at home. Following the training, participants were assessed using a tDCS self-administration and computer aptitude checklist to ensure both participants and caregivers were competent in all aspects of remote tDCS use (see Supporting Information).

2.5 | Remotely Supervised Sessions

All intervention sessions were facilitated via ZoomPHI, allowing the participant and the researcher to see each other throughout the process. A caregiver was required always to be present to start and stop the session as instructed, ensuring

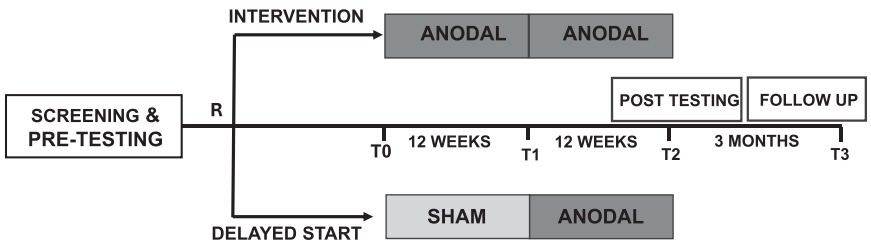

FIGURE 1 | Study design overview. Participants were randomized (R) into intervention or delayed-start groups following screening and pre-testing. The intervention group received two 12-week sessions of anodal stimulation, while the delayed-start group received 12 weeks of sham stimulation followed by 12 weeks of anodal stimulation. Post-testing was conducted after 24 weeks (T2), with follow-up assessments occurring 3 months later (T3).

safety and proper operation. Each session began with a comprehensive pre-session checklist to confirm safety and accuracy. This checklist covered verifying the marked stimulation point on the scalp, confirming the correct side for stimulation and electrode placement, and checking the fit of the head strap. Once the setup was confirmed, the researcher provided the caregiver with a unique, preprogrammed code to activate the tDCS device. A reliable connection, classified as moderate or good, indicated on the device, was required to proceed with the stimulation. Detailed session logs were kept, recording the session number, duration, any side effects experienced, and additional observations. The device signaled the end of stimulation with a beeping sound, after which a side effects questionnaire was completed to capture feedback on the participant's experience (see Supporting Information).

2.6 | Study Stop Criteria

Study stop criteria were established based on predetermined safety protocols to ensure participant well-being throughout the study. These criteria included inability to pass a tDCS aptitude test, intolerance to tDCS, failure to initiate video conferencing for three consecutive sessions, inability to correctly place the headset within 15 min in more than one session, and the occurrence of any adverse events. Study cessation would occur if an adverse event resulted in a life-threatening situation, necessitated initial or prolonged hospitalization, caused disability or permanent damage, or required intervention to prevent permanent impairment or damage as a direct consequence of the research study. In addition, a prespecified interim analysis was conducted for the continuation of the entire study, where the adverse events and mean change in ALSFRS-R between the two groups were compared after the first six participants had completed the study. The stop criteria were defined as a mean difference between groups exceeding two standard deviations. If this occurred, the study would be stopped for full review by the medical monitor, or the protocol would be revised before proceeding.

2.7 | Safety and Feasibility

Safety monitoring was conducted using a custom-designed, structured tDCS adverse event questionnaire administered at the end of each session (see Supporting Information). This questionnaire collected information on symptoms directly related to the electrode placement on the scalp and forehead, such as itching, tingling, burning, skin redness, or injury. It also assessed broader potential side effects, including headache, neck pain, scalp pain, sleepiness, difficulty concentrating, acute mood changes, and seizures. Participants were asked to rate the intensity of any symptoms they experienced on a scale of 0–4 (0 = none, 1 = mild, 2 = moderate, 3 = considerable, and 4 = strong) if they responded affirmatively.

Feasibility was evaluated using compliance, recruitment, randomization, recruitment, and adherence metrics. The completion rate of scheduled sessions determined compliance. Recruitment effectiveness and the randomization process were assessed by comparing the number of participants approached for screening to those enrolled. Retention was determined by the proportion of enrolled participants who completed the study.

2.8 | Clinical Outcomes

Disease severity was assessed using the ALSFRS-R, which includes questions related to daily functioning like speech, salivation, swallowing, breathlessness, and activities utilizing mobility [46, 47]. The progression rate was calculated by dividing the difference between the ALSFRS-R score obtained from the participant and the total score (48 points) by disease duration (in months) at the time of evaluation ((48 − ALSFRS-R score at the last visit)/duration in months between symptom onset and last visit) [48, 49]. Progression rates at the initial visit were used to subgroup participants into slow, intermediate, and fast progressors (Slow; rate < 0.5, Intermediate; rate 0.5–1, Fast; rate > 1) [48].

2.9 | Statistical Analyses

Statistical analyses were conducted using SAS (version 9.4), with statistical significance considered at a p-value < 0.05. Standard descriptive statistics were calculated using an intent-to-treat analysis at four time points: At entry (T0), 12 weeks (T1), 24 weeks (T2), and 3-month follow-up (T3). These descriptive statistics provided means for both the intervention and delayed-start groups at each time point, as well as mean change scores (post-minus-pre) for both groups.

Baseline characteristics were compared between the groups using chi-square tests for categorical variables and independent t-tests for continuous variables. A one-sided equivalence test was used to compare the rates of serious adverse events between the intervention and delayed-start groups at T1, T2, and T3.

Recruitment and retention rates, as well as the success of randomization, were assessed using frequency analyses. Linear mixed-effects models, with random intercepts to account for repeated measures within participants, were used to evaluate changes in ALSFRS-R scores over time. Time was treated as a categorical variable with three contrasts to capture sequential changes between time points (T0 to T1, T1 to T2, and T2 to T3). Interaction terms between group and time were included in the models to test treatment effects compared to sham, the sustainability of treatment effects, and longer-term outcomes.

Bonferroni corrections were applied to adjust for multiple comparisons. No significant differences were observed between groups in baseline covariates such as age, sex, time since diagnosis, or ALSFRS-R scores, ensuring comparability between the groups. Missing data due to dropouts were assumed to be missing at random and handled using the last observation carried forward.

3 | Results

We screened 70 individuals diagnosed with ALS for eligibility. Fourteen individuals (7 males, 7 females) were enrolled in the study, with 10 completing it (Figure 2). The reasons for dropout among the four participants were not directly related to study procedures. Two participants were unable to begin the remote sessions. For one person, this was due to a decline in symptoms, leading to multiple hospitalizations and prolonged delays in ALS medication approval. Scheduling conflicts coupled with unresponsiveness contributed to the second withdrawal. One participant discontinued after completing 14 sessions due to hospitalization for pre-existing pain management and subsequent transition to palliative care. Another participant, after completing 13 sessions, withdrew following hospital admission for a leg fracture, which resulted in excessive missed sessions. There were no significant differences in demographic or outcome measures between the groups at baseline. Descriptive statistics summarizing the demographic and clinical characteristics of the study participants are presented in Table 1.

3.1 | Safety and Feasibility

No serious adverse effects were reported in either the delayed-start or intervention groups. While a difference in the occurrence of side effects was seen between the groups, this difference did not reach significance ($p = 0.16$). Itching and tingling were the most common side effects reported across all sessions, with no significant differences in the incidence of itching ($p = 0.06$) or tingling ($p = 0.15$) between the groups (Figure 3). In terms of study compliance, seven out of the 10 participants who completed the study attended all 72 training sessions. Two intervention group participants missed one session each, while another delayed-start group participant missed 10 sessions, resulting in an overall compliance rate of 98.3%. The recruitment rate was 30%, with 21 of the 70 screened individuals meeting the study criteria. Of those eligible, 14 were enrolled, resulting in an enrollment rate of 64%. Retention rates were 100% for the intervention group and 57% for the delayed-start group, indicating a high level of participant commitment in the intervention group.

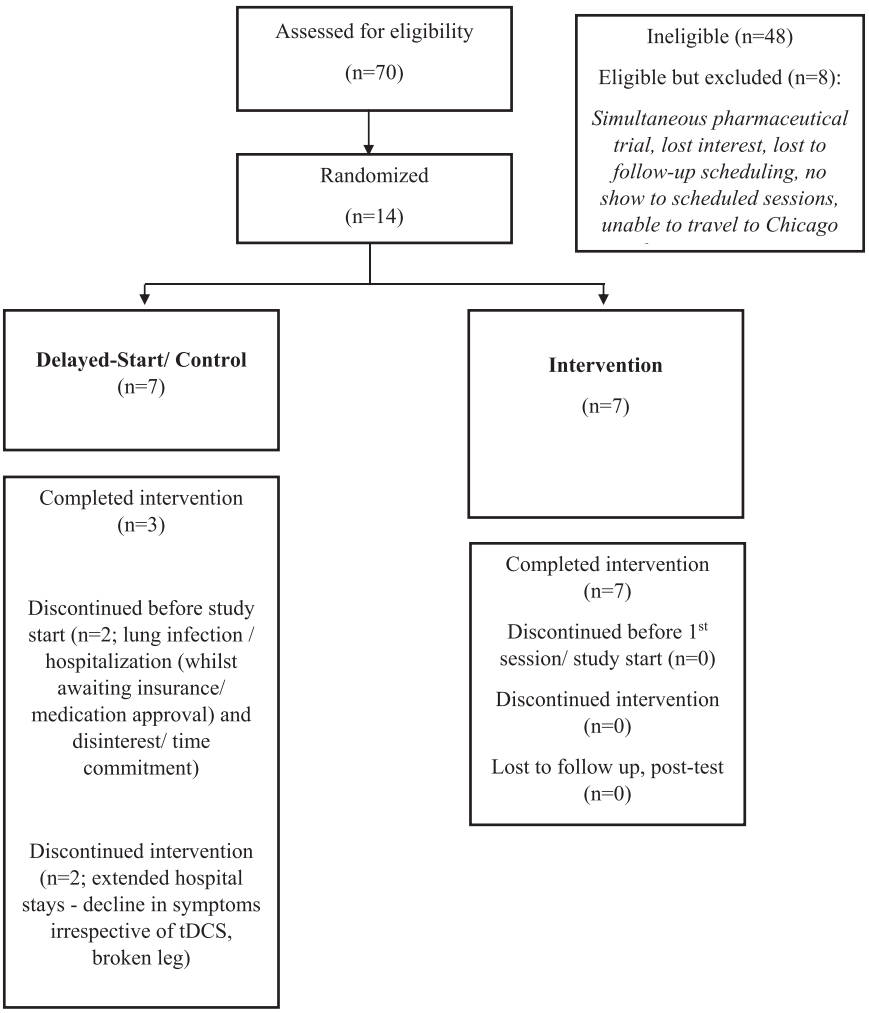

FIGURE 2 | CONSORT flow diagram of participant enrollment and study completion. Out of 70 individuals assessed for eligibility, 14 were randomized (7 to the intervention group and 7 to the delayed-start/control group). Forty-eight were ineligible, and 8 were excluded due to reasons like participation in another trial, loss of interest, or logistical challenges. All participants in the intervention group completed the study. In the delayed-start group, 3 completed the intervention, while 4 discontinued due to medical or logistical issues.

TABLE 1 | Baseline characteristics of the intervention and delayed-start groups.

	Intervention group	Delayed-start group
	Mean (SD)	Mean (SD)
Age (years)	53 (9)	55 (10)
Sex (male/female)	3/4	4/3
Time since onset (months)	29 (22)	26 (13)
Onset side (left/right)	4/3	3/4
Onset limb (upper/lower)	4/3	5/2
ALSFRS-R	39 (7)	31 (4)
Riluzole use (yes/no)	5/2	6/1
Progression subgroup		
Slow	4	2
Medium	2	3
Fast	1	2

Note: Baseline demographics and clinical features of the intervention and delayed-start groups are shown as mean (SD) or counts.

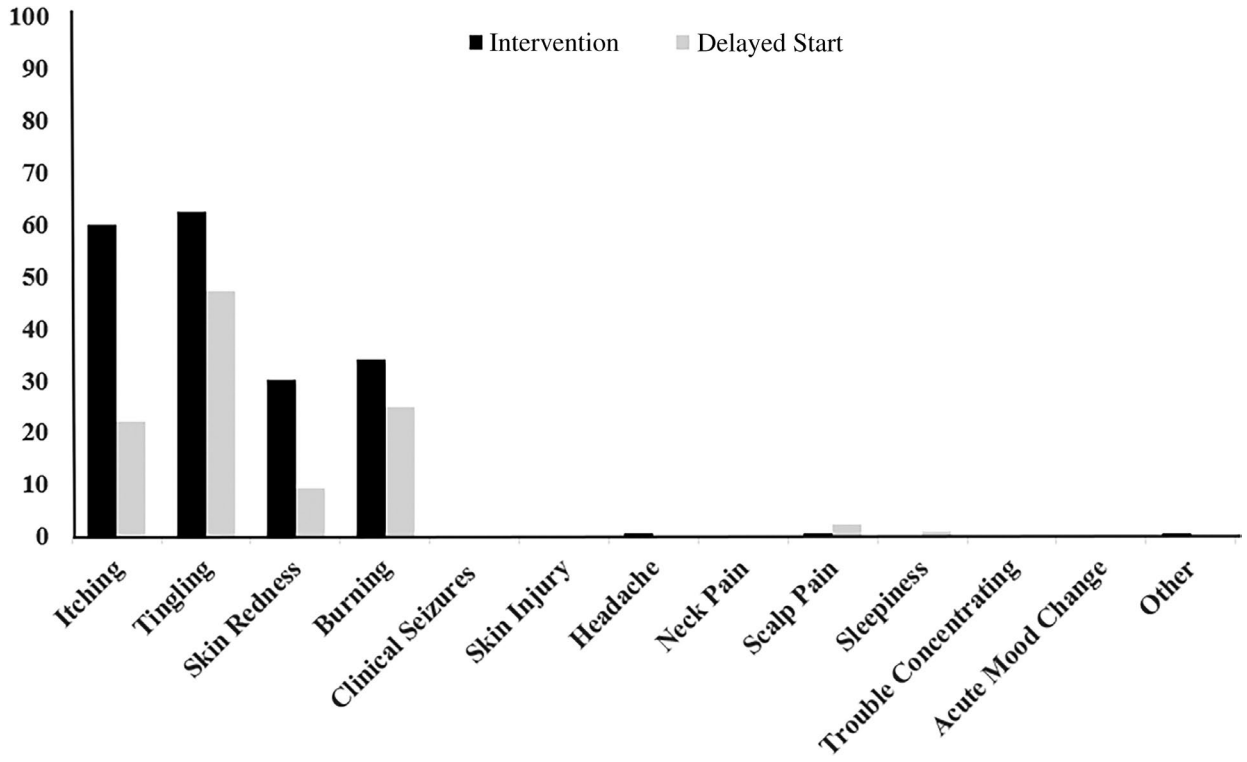

FIGURE 3 | Side effects in intervention and delayed-start groups. Percentage of participants reporting anticipated side effects at the end of each session is displayed for the intervention group (black bars) and the delayed-start group (gray bars). Common events like itching, tingling, skin redness, and burning occur more frequently in the intervention group.

3.2 | Clinical Outcomes

Baseline ALSFRS-R scores did not differ between groups ($p = 0.12$). Repeated measures linear regression revealed a statistically significant difference in ALSFRS-R score changes between the intervention and delayed-start groups from T0 to T1 (SE = 1.88, df = 12, t value = 3.24, $p = 0.0071$) and T1 to T2 (SE = 2.98, df = 12, t value = 4.00, $p = 0.0018$), as shown in Table 2. This finding highlights a distinct pattern of disease progression between both groups. Specifically, the intervention group demonstrated a mean ALSFRS-R change score of 1 from T0 to T1, whereas the delayed-start group showed a mean score change of 7.1. From T0 to T2, the intervention group had a mean change of 1.7, compared to a mean change of 13.6 in the

TABLE 2 | Repeated measures mixed model results for ALSFRS-R scores.

	Repeated measures mixed model results (14 subjects, 34 measurements)										
	Intervention group ($n=7$)			Delayed-start group ($n=7$)			Comparisons between groups				
	Mean	SD	p	Mean	SD	p*	Interaction	SE	df	t value	p*
ALSFRS scores											
At T0	38.6	3.50		32.0	4.40						
At T1	37.6	7.00		26.0	2.65						
At T2	36.9	7.71		19.3	0.58						
		SE			SE						
Change T0 to T1	−1.0	1.06	0.3624	−7.1	1.56	0.0007*	6.1	1.88	12	3.24	0.0071*
Change T0 to T2	−1.7	1.70	0.3250	−13.60	2.47	0.0001*	11.9	2.98	12	4.00	0.0018*

Note: ALSFRS-R scores are presented for the intervention and delayed-start groups ($n=7$ each) across time points (T0, T1, T2). Mean scores, standard deviations (SD), and p-values are shown for within-group changes. Comparisons between groups indicate significant differences in score changes from T0 to T1 ($p=0.0071$) and T0 to T2 ($p=0.0018$). The intervention group showed smaller declines compared to the delayed-start group, as reflected in interaction effects and group differences. *$p < 0.05$ representing statistical significance.

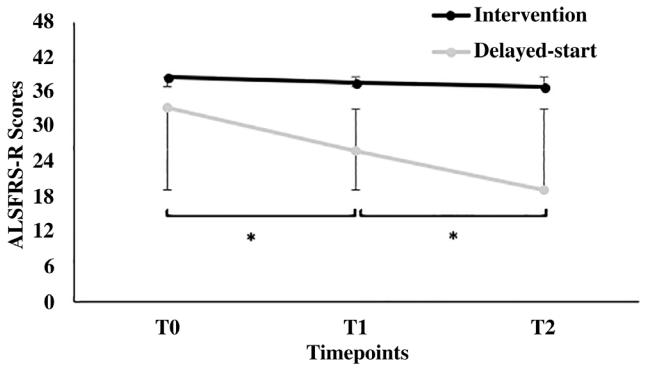

FIGURE 4 | ALSFRS-R scores over time for intervention and delayed-start groups. ALSFRS-R scores were assessed at three time points: Baseline (T0), 12 weeks (T1), and 24 weeks (T2). The intervention group (black line) maintained relatively stable scores over time, while the delayed-start group (gray line) exhibited a significant decline in ALSFRS-R scores between T0 and T1 and continued to decline through T2. Asterisks (*) indicate significant differences between groups at respective time points ($p<0.05$). Error bars represent standard deviations.

delayed-start group. We could not obtain T3 scores from all participants in the delayed-start group, so these data were excluded from statistical comparisons between the two groups. The intervention group showed a mean change of 1.5 from T0 to T3. These results suggest that the delayed-start group experienced a more pronounced disease progression than the intervention group, as illustrated in Figure 4.

4 | Discussion

This study explored the safety, feasibility, and preliminary efficacy of a 24-week tele-tDCS protocol in individuals with ALS, offering novel insights into the potential for remotely supervised neuromodulation to impact disease progression. To the best of our knowledge, this is the first study to investigate the long-term application of tele-tDCS in persons with ALS. The findings underscore the potential of tele-tDCS to offer a viable solution for delivering neuromodulatory interventions remotely, addressing the limitations imposed by ALS progression, which often precludes patients from accessing in-person therapies or experimental studies.

4.1 | Safety and Feasibility

Our results align with prior studies on the safety profile of tDCS, with no serious adverse effects reported in either the intervention or delayed-start groups. The most common side effects, mild itching and tingling, are consistent with existing literature on tDCS in both healthy and clinical populations. For example, Fertonani et al. and Poreisz et al. found mild tingling and itching to be the most frequent side effects, occurring in over 70% and 30% of sessions, respectively [50, 51]. Similarly, Nitsche et al. [52] established safety guidelines for tDCS in humans, noting that side effects like itching and tingling are typical and transient, further corroborating the minimal risk profile of this intervention. In our study, the slightly higher incidence of these effects in the intervention group likely reflects the active stimulation during the initial 12 sessions, though this difference did not reach statistical significance. These findings reinforce the overall safety and tolerability of long-term tele-tDCS in ALS patients, making it a feasible option for future clinical applications.

4.2 | Efficacy of Tele-tDCS

One of the most significant advantages of tele-tDCS is its ability to reach patients in geographically diverse locations within the United States, as demonstrated by our participants from states including Florida, Minnesota, Missouri, and Michigan. This highlights the potential for tele-tDCS to expand access to therapeutic interventions, particularly for rural or underserved patients who may otherwise struggle to participate in clinical

trials. The significant difference in disease progression between the intervention and delayed-start groups offers preliminary evidence for the potential efficacy of tele-tDCS in ALS. The slower decline in ALSFRS-R scores in the intervention group suggests that tele-tDCS may have a clinically meaningful impact on patients' functional abilities. Previous studies have shown that even small changes in ALSFRS-R scores can translate to significant differences in patient quality of life and independence in activities of daily living [53]. Therefore, these preliminary results are promising, although more studies are needed to confirm these effects.

4.3 | Mechanisms of Action

The efficacy of tDCS in potentially slowing ALS progression may be attributed to several mechanisms of action. tDCS likely exerts its effects by modulating glutamatergic cortical circuits, which play a key role in neuroplasticity. Studies suggest that tDCS can enhance synaptic plasticity by increasing the expression of neuroprotective factors and modulating excitability in the motor cortex [54]. Additionally, facilitatory tDCS might increase connectivity between cortical and subcortical structures, particularly from the M1 motor cortex to regions like the caudate nucleus and thalamus [55–57]. A compensatory increased subcortical structure activation occasionally accompanies cortical degeneration in ALS [58]. Madhavan et al. [20] discussed the possibility of anodal tDCS facilitating this compensatory subcortical connectivity increase, leading to functional improvements. While these mechanisms offer promising insights into the potential efficacy of tele-tDCS, they remain largely hypothetical, and further research is needed to substantiate their role in ALS progression and treatment outcomes.

4.4 | Limitations, Challenges, and Future Opportunities

As with many ALS studies, challenges with recruitment and retention were encountered. While the dropout rate is not directly related to the study protocol, it reflects the inherent difficulties of conducting clinical trials in progressive neurodegenerative diseases. The unpredictable nature of ALS progression often makes it difficult for patients to maintain long-term participation, even with remote supervision [59]. Interestingly, all study dropouts occurred in the delayed-start group, which raises important considerations for future research. Despite participants being blinded to their group allocation, the higher dropout rate in the delayed-start group suggests that factors unrelated to the knowledge of treatment timing may influence adherence. This phenomenon may be tied to the psychological burden of participation in long-term clinical trials or external factors such as health complications, as observed in our study [60]. Further investigation into the psychological impacts of clinical trial participation and methods to optimize retention, particularly in delayed-intervention groups, is warranted.

The variability in individual disease trajectories and the uneven distribution of progression rates between the groups limit the generalizability of these findings. ALS progression is notoriously heterogeneous, with some patients experiencing rapid decline while others progress more slowly. Future studies should also consider stratifying participants based on disease stage or progression rate to account for individual variability in response to tDCS. Predictive biomarkers, such as neurofilament light chain (NFL) levels, serum cardiac troponin T, or genetic markers, could provide valuable tools for stratification, allowing for a more personalized approach to treatment [61]. Furthermore, this study's relatively short follow-up period limits the ability to draw conclusions about the long-term effects of tele-tDCS. Future research should aim for longer follow-up assessments, at least 12 months, to determine whether the benefits of tele-tDCS persist beyond the active intervention phase.

One potential limitation of tele-tDCS is the variability introduced by home-based, remotely supervised administration. Differences in electrode placement, session adherence, and stimulation intensity could influence the consistency of treatment effects. Charvet et al. [62] highlighted the need for standardized protocols and real-time feedback mechanisms to ensure proper electrode positioning and dosage adjustments during home use. Future studies should incorporate these improvements to minimize variability and maximize the efficacy of tele-tDCS.

Another limiting factor could be the possibility of participant unblinding due to the participants in the intervention group experiencing greater side effects than those in the delayed-start group. While both groups experienced itching, tingling, skin redness, and burning, the percentage experienced in the intervention group was greater. However, it is important to note that the delayed-start group also reported similar sensations (itching: 22%, tingling: 47%), with some individuals experiencing these effects at high frequencies (e.g., one participant reported tingling during 60% of sessions, while another experienced itching in 71% and tingling in 72% of sessions). This suggests that these sensations were not exclusive to the intervention group, potentially reducing the risk of immediate unblinding. To mitigate expectation bias, participants were informed that both the intervention and control conditions could elicit sensations. Additionally, outcome assessors remained blinded to group allocation to prevent bias in evaluations. Importantly, previous studies have shown that well-designed sham-tDCS protocols can effectively maintain blinding. Palm et al. [63] demonstrated that participants could not reliably distinguish between active and sham stimulation, supporting the validity of our blinding approach. Furthermore, Kessler et al. [64] found that while sensory side effects were more frequent in active tDCS sessions compared to sham, their severity was typically low, suggesting that expectation bias can be minimized with proper participant information and study design. These findings align with our approach to controlling for expectation effects and reinforce the reliability of our study outcomes. Future studies should incorporate participant feedback on their perceived treatment group in questionnaires to assess the extent of potential unblinding during the intervention.

While our study primarily relied on clinical outcome measures, future studies may benefit from incorporating objective biomarkers such as NFL to assess potential neuroprotective or neurodegenerative effects and troponin T to rule out systemic or cardiac involvement. These biomarkers could provide additional

physiological validation of the intervention's effects and further mitigate concerns regarding placebo-driven outcomes.

Additionally, the small sample size in our study, coupled with the relatively short follow-up period, constrains the ability to draw definitive conclusions about the long-term efficacy of tele-tDCS in ALS management. Long-term follow-up is essential to fully understand the sustained impact of tele-tDCS on ALS progression. Studies in other neurodegenerative conditions, such as Alzheimer's disease, have shown that neuromodulatory interventions may have cumulative and lasting effects on cognition and memory over extended periods [65, 66]. Future trials should include follow-up assessments at 12 months or longer to assess whether the benefits of tele-tDCS persist beyond the active intervention phase. In addition, the tele-supervised nature of the intervention may introduce variability in electrode placement and session adherence, which could impact the consistency of tDCS effects. Ensuring proper home use remains a challenge in telehealth-based interventions [62]. Future protocols should include mechanisms for real-time feedback on correct electrode positioning and dosage adjustments by clinicians to minimize these issues. Future studies should also focus on developing personalized tele-tDCS protocols that account for individual disease characteristics, such as bulbar versus limb onset ALS, to optimize treatment outcomes. Tailoring stimulation parameters to specific patient needs may enhance the efficacy of tele-tDCS and improve patient adherence. Nevertheless, our findings are consistent with the growing body of literature that suggests tDCS can modulate neural excitability and slow functional decline in neurodegenerative diseases [67, 68].

4.5 | Clinical Implications

The ability of tele-tDCS to mitigate disease progression, even modestly, holds significant clinical implications. Current pharmacological treatments for ALS, such as Riluzole, Edaravone, and Relyvrio, offer limited improvements in survival and symptom management, highlighting the need for complementary therapies that can provide additional benefits. While the evidence supporting repetitive transcranial magnetic stimulation (rTMS) for slowing disease progression in ALS is still inconclusive due to limited and methodologically varied studies, the cost-effectiveness and accessibility of tele-tDCS make it a promising alternative [69]. This is especially true for patients in remote or underserved areas, where in-person rTMS treatments are less feasible. Tele-tDCS can be administered at home, reducing the logistical burden on patients and providing more consistent access to treatment.

5 | Conclusion

In conclusion, this study demonstrates the feasibility, safety, and potential efficacy of tele-tDCS in ALS, providing a strong foundation for future exploration of this promising intervention. The remote administration of tele-tDCS presents a substantial advantage by reducing the physical and logistical burden on patients while expanding access to treatment, particularly for those in geographically diverse or underserved areas. Our findings suggest that tele-tDCS holds promise as a complementary therapy to existing pharmaceutical treatments, with the potential to slow disease progression and improve quality of life.

However, to confirm these early findings, future research should focus on larger clinical trials with more diverse patient populations and longer follow-up periods to assess the long-term impact of tele-tDCS. Further, stratifying participants by disease stage or individual progression rates will allow for more nuanced analyses, helping to identify which patients might benefit most from the intervention. Developing adaptive trial designs and personalized stimulation protocols tailored to specific ALS subtypes (e.g., bulbar vs. limb onset) will be crucial in optimizing treatment outcomes.

Ultimately, this study highlights the importance of personalized, home-based interventions as a viable and accessible complement to conventional ALS therapies. With continued research, tele-tDCS could play a critical role in improving functional outcomes and enhancing the quality of life for individuals living with ALS.

Author Contributions

S.M. designed and conceptualized the study, had a major role in data collection, analyzed the data, and drafted the manuscript for intellectual content. S.D. had a major role in data collection, analysis, and drafting the manuscript for intellectual content. M.C. had a major role in data collection, analyzing the data, and revising the manuscript for intellectual content. A.D. had a major role in data collection, analyzing the data, and revising the manuscript for intellectual content. K.R. designed and conceptualized the study and revised the manuscript for intellectual content. S.F. designed and conceptualized the study, performed statistical analyses, and revised the manuscript for intellectual content. G.S. had a major role in data collection and revised the manuscript for intellectual content.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Deidentified data that underlie study results will be shared by the corresponding author upon reasonable request from qualified investigators immediately following publication.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.