# Safety and Feasibility of Transcranial Direct Current Stimulation in Amyotrophic Lateral Sclerosis – A pilot study with a single subject experimental design.

Single Subject Research Article

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**Conflicts of Interest**

We have no conflicts of interest to disclose.

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**Abstract**

Introduction: Transcranial direct current stimulation (tDCS) has been explored as a neuromodulatory tool to prime motor function in several neurological disorders. Studies using tDCS in amyotrophic lateral sclerosis (ALS) are limited. We investigated the safety, feasibility and effects of long term tDCS in an individual with ALS.

Methods: A 36 year old male diagnosed with clinically definite ALS received twelve sessions each of anodal, sham and cathodal tDCS. Outcome measures included disease progression (revised ALS functional rating scale (ALSFRS-R)), clinical measures of endurance and mobility, and corticomotor excitability.

Results: No adverse events or change in disease progression were noticed during the study. Small improvement in gait speed (15% increase) was noticed with anodal tDCS only.

Conclusions: This case study demonstrates the safety and feasibility of long term facilitatory and inhibitory tDCS on a single participant with ALS. This study serves as a guideline for implementing tDCS in future ALS trials.

Keywords: amyotrophic lateral sclerosis, transcranial direct current stimulation, transcranial magnetic stimulation, cortical excitability, neurodegenerative disease

# INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive disease characterized by degeneration and death of motor neurons in the brain and spinal cord, leading to loss of voluntary movement and respiratory compromise, resulting in early death. Currently there is no cure for ALS. Riluzole, the only FDA approved drug for ALS, increases survival time only minimally creating an urgent need to explore alternative treatments. The pathophysiology leading to ALS is still unclear. Several studies have implicated cortical dysfunction and altered neurotransmission as possible causes for neurodegeneration in ALS (Boillée, Velde,Cleveland 2006;Rothstein et al. 1995).

Non-invasive transcranial direct current stimulation (tDCS) has emerged as a promising experimental tool to promote neuromodulation of cortical circuits in numerous neurological and neuropsychiatric populations (Flöel 2014;Madhavan and Shah 2012). tDCS modulates short term and long term corticomotor excitability via alteration of neuronal membrane potential and synaptic transmission respectively. Only three studies have investigated the effects of tDCS on patients with ALS. Quartarone et al. (2007) and Munneke et al. (2011) reported no changes in corticomotor excitability to single sessions of tDCS on patients with ALS. Di Lazzaro et al. (2013) examined the efficacy of long term cathodal tDCS (1 session/month for 12 months) in one individual with ALS, and reported no changes in disease progression. Given the varied clinical and complex pathology of ALS, further long term tDCS studies in larger cohorts, especially examining the role of facilitatory and inhibitory stimulation, are needed. As a first step towards this process, in this single subject experimental design, we aimed to investigate the safety, feasibility and effects of long term treatment with facilitatory and inhibitory tDCS on disease progression, corticomotor excitability and motor function in ALS.

# METHODS

This was a sham-controlled single subject study conducted in the Brain Plasticity Laboratory at the University of Illinois at Chicago. A schematic design of the study is shown in Figure 1.

## Participant

The participant was a 36-year-old Hispanic man, with no other known past medical history, 7 months post diagnosis of ALS, and 1 year after the onset of symptoms. The participant was not on any prescription medications due to lack of insurance coverage.

At the time of an initial visit to the laboratory, a neurological examination revealed bilateral atrophy in the thenar, hypothenar muscles and deltoid muscles. Fasciculations were noted in the right arm, abdomen, and both legs. Strength testing results, using Kendall's (Kendall et al. 1993) manual muscle testing grades are reported in Table 1. Strength testing showed mild decrease in strength at the ankles and knees with a somewhat pronounced decrease at the hips. Strength in the arms was also affected, with greater weakness in the shoulder muscles, and mild weakness in elbow and hand muscles. The weakness was more prominent on the right side than the left. The participant was unable to stand from sitting without using his arms for support, but was able to walk unassisted. There were no deficits in sensation, cranial nerves, co-ordination or speech. Muscle tone was increased in bilateral upper extremities and lower extremities (Table 1). Reflexes were 3+ in bilateral biceps, triceps, knee, and 4+ at ankle. Babinski's sign was absent.

The participant was independent in most activities of daily living and was ambulatory with an ankle foot orthosis. The participant's functional walking distance was 355 meters as measured by the 6 minute walk test. The participant was informed of the research procedures and risks, and a

signed informed consent was obtained. The study was approved by the institutional review board at University of Illinois at Chicago.

**Intervention - Transcranial direct current stimulation**

tDCS was delivered using a constant current stimulator (Chattanooga Ionta, TN, USA). Since the participant presented with a predominant right sided weakness, we targeted the left lower limb motor cortex representation. An oblong saline-soaked surface sponge electrode (Iogel® Iontophoresis; 3.5 cc) was placed on the left lower limb motor cortex. The leg motor representation was anatomically identified to be located 1 cm posterior and 1 cm lateral to the vertex based on previous studies in our lab (Sivaramakrishnan, Tahara-Eckl,Madhavan 2016). The reference electrode (7 cm × 5 cm) was placed over the right supraorbital region. A current of 2 mA was delivered for 20 minutes. We chose a stimulation intensity of 2 mA for our 34.71 $cm^2$ electrode giving a current density of 0.057 $mA/cm^2$, and applied the current for 20 minutes yielding a total charge of 19 $\mu C/cm^2$. These density and charge values are well within the limits (28.57 $\mu A/cm^2$ - 80 $\mu A/cm^2$) reported in tDCS-related safety studies and other clinical interventions (Iyer et al. 2005;Munneke et al. 2011;Poreisz, Boros, Antal,Paulus 2007;Quartarone et al. 2007). The polarity was switched for anodal and cathodal stimulation. The electrodes were placed in the same configuration as anodal/cathodal stimulation for the sham (placebo) tDCS stimulation. The current was initially increased in a ramp like fashion for 30 seconds and then the machine was turned off. These parameters were chosen for sham stimulation based on previous reports that the perceived sensations such as tingling and itching typically fade out in the first 30 seconds of tDCS (Nitsche et al. 2003).

tDCS was performed 3 times a week for 4 weeks, with a washout time of 2 weeks between the three conditions. Hence, 12 sessions each of anodal, sham and cathodal stimulation were administered. An interval of 2 weeks was provided between each treatment condition to minimize carryover effects of tDCS (Figure 1). To minimize diurnal variations, tDCS was administered in the morning for all sessions.

## Outcome measures

### Clinical Tests

Disease progression was measured using the ALS Functional Rating Scale – Revised (ALSFRS-R). Other clinical tests included the 6 minute walk test (6MWT) to estimate the aerobic capacity, the timed up and go test (TUG) to assess fall risk, and the 10 meter walk test to assess gait speed. The participant was instructed to walk at his self-selected (SS) speed and fast speed (FS) for the 10 MWT. Two trials of each condition were conducted, and the mean of these trials was calculated. All the clinical tests and TMS sessions were conducted in the mornings (preferred time for the participant) to minimize the possible influences of fatigue.

### TMS

Corticomotor excitability (CME) of bilateral first dorsal interosseous (FDI) muscles, and bilateral tibialis anterior (TA) muscles was measured with single pulse TMS (Magstim 200 stimulator (Magstim, Dyfed, Wales UK)) with a double cone coil (diameter 110 mm) for the lower limb and figure of eight coil (diameter 70 mm) for the upper limb using a posterior-anterior cortical current orientation. Electromyography (EMG) data were collected bilaterally from the TA and FDI muscles. Surface Ag/AgCl electrodes were placed over the muscle belly of

the TA and FDI. The reference electrode was placed over the spinous process of the seventh cervical vertebra. EMG data were sampled at 2000Hz, amplified (1000X) and band pass filtered (10-500Hz) with a Delsys EMG system (Bagnoli 8, MA USA).

TMS elicited motor evoked potentials (MEPs) were recorded bilaterally with the participant seated comfortably on a chair, with his knees flexed to 90°. During TMS, the participant was instructed to maintain a weak tonic contraction approximately 10% of the maximum voluntary contraction (MVC). Spike2 software (Cambridge Electronic Design 1401, London, UK) was used to provide the target level of EMG, and trigger the stimulator at 0.25 Hz. We planned to record 10 MEPs at 120% active motor threshold (AMT) from each muscle. During the experiment, the coil was initially placed over the vertex (Cz) and then the double cone coil was moved in small increments to find the location for producing the maximum MEP response for the contralateral TA muscle at the lowest stimulator intensity. For obtaining the location of the FDI muscle, we placed the figure of eight coil tangentially to the scalp by moving it in small increments around the hand area of the M1.

The active motor threshold was defined as the lowest stimulator intensity at which the response to TMS was considered absent when no MEPs were observed even after stimulating at 90-100 % machine stimulator output (MSO). The EMG was monitored for fasciculation responses during the TMS. These responses were not considered as MEPs during the analysis. Spike2 was used to analyze all the data.

## RESULTS

The participant did not report any tDCS-related adverse effects (including clinical seizures, skin injury, neurological deterioration, unpleasantness, and headaches) during/after the intervention. The participant adhered to the entire intervention without any drop-out.

All clinical data are shown in Table 2.

**ALSFRS-R**

The ALSFRS-R showed minimal to no change in disease progression throughout the course of the study. A one-point increase was observed post anodal stimulation; however the increment was observed in the swallowing subsection of the ALSFRS-R.

**10MWT**

The gait speeds increased by 14.6% (SS), and 5.95% (FS) post anodal stimulation. There was a decrease of 10.4% (SS), and 7.38% (FS) following cathodal stimulation. Gait speeds decreased by 0.99 % (SS) and 0.69% (FS) post sham stimulation.

**Timed up and go (TUG)**

The total time for TUG reduced by 6.2% post anodal tDCS. It increased by 4% post cathodal tDCS and by 15.3% post sham tDCS.

**Six minute walk distance (6MWD)**

The 6MWD reduced by 1.4% post anodal tDCS, increased by 2.97% post cathodal tDCS and reduced by 2.96% post sham tDCS. It was observed that the 6MWD showed a progressive decline during the course of the study.

**Corticomotor excitability**

MEPs were absent at baseline and post tDCS stimulation at 100% MSO for TA and FDI muscle representations of both hemispheres. Hence, corticomotor excitability was not further quantified.

## DISCUSSION

In this pilot study, we report for the first time the safety and feasibility of long term anodal and cathodal stimulation of the lower limb M1 in an individual with ALS. The participant completed 24 sessions of stimulation (12 anodal and 12 cathodal) without any adverse events. This stimulation protocol was safe and well tolerated. Our results support that tDCS did not advance disease progression (ALSFRS-R), as evidenced by no changes in ALSFRS-R scores. Furthermore, our study suggests that anodal stimulation, may elicit small benefits in walking outcomes such as 10MWT and TUG. The minimal clinically important difference (MCID) for the 10MWT has not been established in individuals with ALS. However a change of 0.06 m/s in individuals with spinal cord injury (Musselman 2007), and 0.16 m/s in individuals with stroke (Tilson et al. 2010) is considered to be clinically meaningful. Since slower gait speeds and increased stride time have been documented with disease progression in ALS (Goldfarb and Simon 1984;Hausdorff et al. 2000), this modest increase in gait speed after anodal tDCS, may have the potential to translate to clinical improvements in functional ability. Comparable improvements were not elicited by cathodal or sham tDCS.

Although our participant did not present with advanced progression of the disease (ALFRS-R score 41/48), he showed no response to TMS. A reduced MEP or inability to elicit one is most likely suggestive of a significant loss of cortical motor neurons or increased cortical inhibition (Floyd et al. 2009). We expected to see lower thresholds and larger MEPs, in line with the

cortical hyperexcitability documented in many TMS studies in ALS patients (Floyd et al. 2009;Menon, Kiernan,Vucic 2015;Vucic, Nicholson,Kiernan 2008). However, our results favor others that have reported hypoexcitability in ALS (Attarian, Vedel, Pouget,Schmied 2006, 2008;Khedr, Ahmed, Hamdy,Shawky 2011).

Typically, brain stimulation studies in ALS have proposed or used inhibitory stimulation to counter the effects of glutamate hypertoxicity observed in ALS (Angelucci et al. 2004;Di Lazzaro et al. 2006;Munneke et al. 2011;Quartarone et al. 2007). However, new animal studies have suggested that hyperexcitability observed during early ALS may be critical for preservation of function, questioning the premise of testing inhibitory stimulation only (Angelucci et al. 2004;Di Lazzaro et al. 2006;Munneke et al. 2011;Quartarone et al. 2007) . In this case report, we examine the safety and feasibility of anodal tDCS, and illustrate a hypothetical model for the role of facilitatory stimulation in ALS, especially in the later stages of the disease (Figure 2). Neurodegenerative diseases such as ALS present with pathological changes that include reduced neurotrophic support and decreased expression of neuronal growth factors (Dawbarn and Allen 2003). Anodal tDCS has the potential to stimulate glutamatergic cortical circuits (Purpura and McMurtry 1965), modulate regional increases in synaptic plasticity (Podda et al. 2016), and thereby increase expression of neuronal protection factors such as brain derived neurotrophic growth factor (BDNF) (Podda et al. 2016) which can be critical for preservation of function in ALS. In addition to regional effects, remote effects of tDCS on distant cortical and subcortical areas, such as increased connectivity from the M1 to ipsilateral caudate nucleus and thalamus, have been reported in neuroimaging studies (Boros et al. 2008;Polanía, Paulus,Nitsche 2012a, b). Long term tDCS to the M1 has been shown to improve gait and bradykinesia in patients with Parkinson’s disease (Benninger et al. 2010), where the underlying subcortical pathways were

hypothesized to be modulated by tDCS. The degeneration of cortical motor neurons in ALS has been reported to be accompanied by a compensatory increase in activation of subcortical structures in individuals with ALS (Konrad et al. 2006). It is possible that anodal tDCS may facilitate this compensatory increase in subcortical connectivity, leading to improvements in function. However, it would be cautious to presume that this hypothetical model supporting facilitation of neuronal excitability in ALS may be limited to individuals who show neurophysiological damage such as decreased responses to TMS.

## CONCLUSIONS

This case study reports the safety and feasibility of long term tDCS in an individual with ALS and serves a guideline for implementing tDCS in larger randomized controlled trials.

**List of abbreviations**

ALS: Amyotrophic Lateral Sclerosis

TMS: Transcranial Magnetic Stimulation

MEP: Motor Evoked Potential

tDCS: Transcranial Direct Current Stimulation

BDNF: Brain Derived Neurotrophic Factor

EMG: Electromyography

FDI: First Dorsal Interossei

TA: Tibialis Anterior

ALSFRS-R: ALS Functional Rating Scale – Revised

CME: Cortico-Motor Excitability

10 MWT: 10 Meter Walk Test

6MWT: 6 minute Walk test

6MWD: 6 Minute Walk Distance

TUG: Timed Up and Go test

MVC: Maximum Voluntary Contraction

MSO: Maximum Stimulator Output

AMT: Active Motor Threshold

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Table 1: Muscle strength and spasticity measurements

| **Muscle Strength** | | |
|---|---|---|
| | Right | Left |
| Shoulder flexors | 2+ | 3- |
| Shoulder extensors | 3 | 3 |
| Shoulder abductors | 3- | 3- |
| Elbow flexors | 3 | 3 |
| Elbow extensors | 2+ | 3 |
| Grip strength | Good | Good |
| Hip flexors | 3 | 3+ |
| Hip extensors | 2+ | 3- |
| Hip abductors | 3 | 3 |
| Knee flexors | 4 | 4 |
| Knee extensors | 4 | 5 |
| Ankle dorsiflexors | 4 | 4 |
| Ankle plantar flexors | 3+ | 4 |
| **Spasticity** | | |
| Shoulder adductors | 0 | 0 |
| Elbow flexors | 1+ | 1 |
| Elbow extensors | 0 | 0 |
| Knee flexors | 2 | 3 |
| Knee extensors | 1+ | 2 |

Table 2: Change in clinical outcomes with tDCS

| | **Anodal** | **Cathodal** | **Sham** |
|---|---|---|---|
| | ALSFRS-R | | |
| Pre-tDCS | 40 | 41 | 41 |
| Post-tDCS | 41 | 41 | 41 |
| | **Gait speed (Self-selected speed, m/s)** | | |
| Pre-tDCS | 0.89 | 0.95 | 1.01 |
| Post-tDCS | 1.02 | 0.85 | 1 |
| | **Gait speed (Fast speed, m/s)** | | |
| Pre-tDCS | 1.12 | 1.15 | 1.16 |
| Post-tDCS | 1.19 | 1.07 | 1.15 |
| | **TUG (seconds)** | | |
| Pre-tDCS | 12.41 | 12.44 | 11.64 |
| Post-tDCS | 11.64 | 12.94 | 13.43 |
| | **6MWD (m)** | | |
| Pre-tDCS | 355 | 303 | 337 |
| Post-tDCS | 350 | 312 | 327 |

**Figure 1. Schematic of the study design**

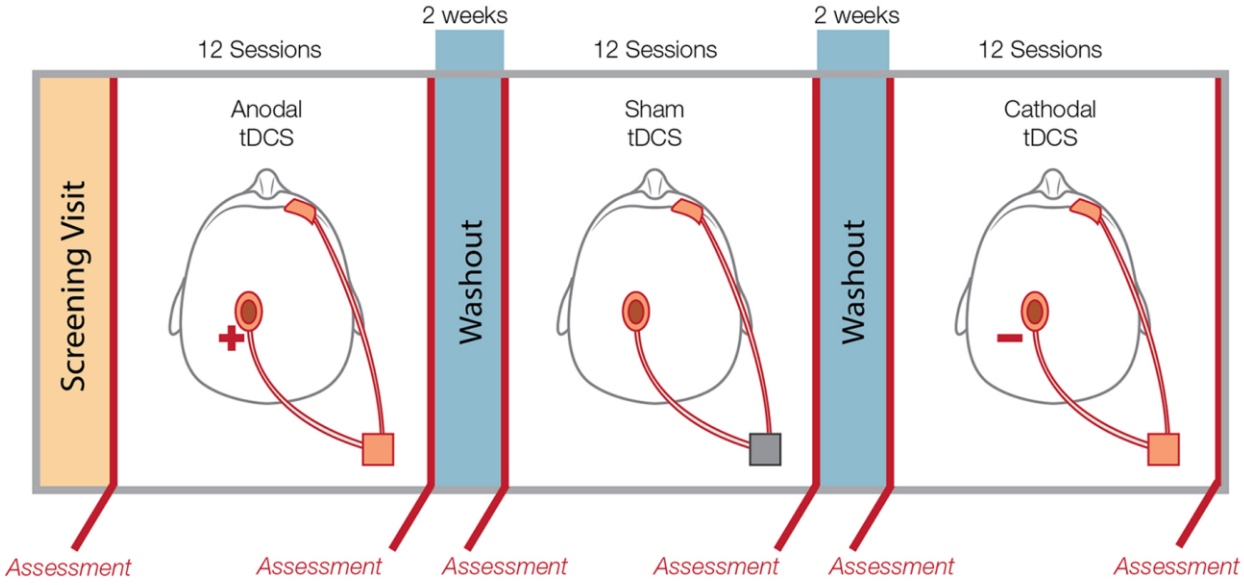
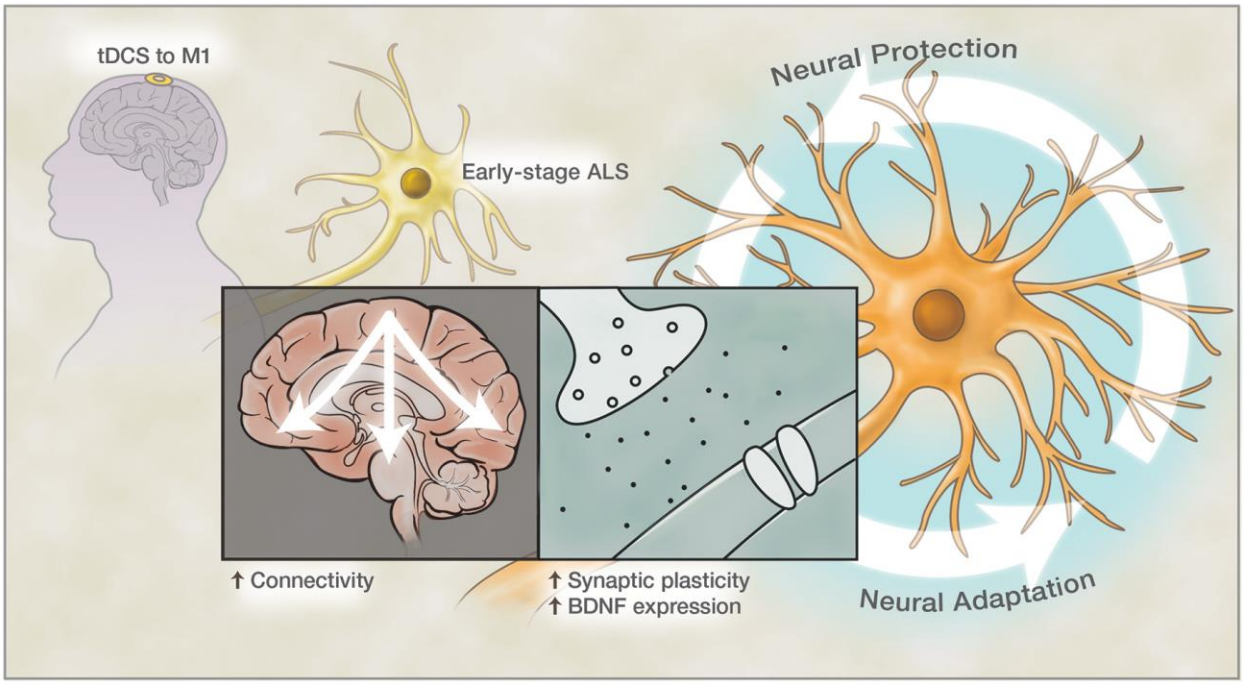


Figure 2


tDCS to M1
Early-stage ALS
Neural Protection
↑ Connectivity
↑ Synaptic plasticity
↑ BDNF expression
Neural Adaptation