TRANSCRANIAL DIRECT CURRENT STIMULATION DOES NOT MODULATE MOTOR CORTEX EXCITABILITY IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

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ABSTRACT: *Introduction:* Amyotrophic lateral sclerosis (ALS) is a progressive disease caused by the degeneration of upper and lower motor neurons. The etiology of ALS is unclear, but there is evidence that loss of cortical inhibition could be related to motor neuron degeneration. We sought to determine whether cathodal transcranial direct current stimulation (tDCS) can reduce cortical excitability in patients with ALS. *Methods:* Three sessions of cathodal tDCS, lasting 7, 11, or 15 minutes, were performed in 10 patients and 10 healthy controls. Corticospinal excitability was measured before and after the tDCS. *Results:* Cathodal tDCS induced a consistent decrease in corticospinal excitability in healthy controls, but not in ALS patients. *Conclusions:* The failure of tDCS to produce an excitability shift in the patients supports the potential diagnostic value of tDCS as a marker of upper motor neuron involvement. However, variation in corticospinal excitability measurements both inter- and intraindividually will limit its usefulness.

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Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neurodegenerative disease caused by the degeneration of both the upper and lower motor neurons that control voluntary muscle movement. Although the exact etiology of ALS is unclear, loss of inhibition in motor cortex circuits has been described in patients with ALS, particularly early in the disease.[1] It is speculated that loss of inhibition not only causes central motor neuron loss but also drives anterior horn cells into metabolic deficit, a process called anterograde degeneration.[2]

A decade ago, a non-invasive tool to modulate cortical excitability, transcranial direct current stimulation (tDCS), was reintroduced.[3] With tDCS, a weak constant electrical current ($\leq$1 mA), which passes through the skull and underlying structures to the cortical structures, up- or downregulates cortical excitability depending on the stimulation polarity used. Cathodal tDCS over the motor cortex, where the cathode is placed over the primary motor cortex and the anode above the contralateral eyebrow, leads to decreased excitability of the motor cortex in healthy controls, evidenced by decreased muscle responses elicited by transcranial magnetic stimulation (TMS).[4–17] If tDCS is applied for several minutes, the changes can outlast the stimulation by up to 1 hour.[11,18] Given cortical disinhibition in patients with ALS, cathodal tDCS is considered a proposed treatment option. In healthy subjects, stimulation for at least 3 minutes at 1 mA already elicits an after-effect.[10] Stimulation for up to 15 minutes at 1 mA is without noticeable side effects.[19] Thus, stimulation for 3–15 minutes appears to be safe and effective.

Only one study has investigated the effects of tDCS stimulation in patients with ALS.[6] Anodal and cathodal tDCS, performed for 7 minutes, led to a consistent modification of cortical excitability in healthy subjects, but not in patients with ALS. However, in this study the duration of tDCS stimulation was not varied, even though studies of healthy individuals have shown that the duration of stimulation influences the extent and duration of cortical modulation.[11,18] The investigators suggested that tDCS might be useful as a diagnostic tool for ALS. They did not discuss the potential of tDCS as a therapeutic strategy. Obviously, to have a therapeutic effect on the continuous process of anterograde degeneration, cortical modulation needs to be present, but it also must be long-lasting.

The first aim of our study was to address the potential of tDCS as a therapeutic strategy. The second aim was to further investigate the diagnostic potential of short-duration tDCS, as reported by Quartarone et al.[6] For this purpose, we studied the effect of lengthening the tDCS stimulation up to 15 minutes in an attempt to induce lasting changes in cortical excitability.

METHODS

Subjects. Ten patients with sporadic ALS and 10 healthy controls participated in this study. All

Abbreviations: ADM, abductor digiti minimi; ALS, amyotrophic lateral sclerosis; ALS-FSR-R, ALS Functional Rating Scale, revised; ANOVA, analysis of variance; CMAP, compound muscle action potential; EMG, electromyography; ICF, intracortical facilitation; MEP, motor-evoked potential; $SI_{0.5mV}$, stimulator intensity to induce 0.5-mV MEPs; SI_{1mV}, stimulator intensity to induce 1-mV MEPs; SICI, short-latency intracortical inhibition; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation

Key words: amyotrophic lateral sclerosis, cortical excitability, paired-pulse TMS, transcranial direct current stimulation, transcranial magnetic stimulation

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