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Long term clinical and neurophysiological effects of cerebellar transcranial direct current stimulation in patients with neurodegenerative ataxia

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ABSTRACT

Background: Neurodegenerative cerebellar ataxias represent a group of disabling disorders for which we currently lack effective therapies. Cerebellar transcranial direct current stimulation (tDCS) is a non-invasive technique, which has been demonstrated to modulate cerebellar excitability and improve symptoms in patients with cerebellar ataxias.
Objective: The present study investigated whether a two-weeks' treatment with cerebellar anodal tDCS could improve symptoms in patients with neurodegenerative cerebellar ataxia and could modulate cerebello-motor connectivity, at short and long term.
Methods: We performed a double-blind, randomized, sham controlled trial with cerebellar tDCS (5 days/week for 2 weeks) in twenty patients with ataxia. Each patient underwent a clinical evaluation pre- and post-anodal tDCS or sham stimulation. A follow-up evaluation was performed at one and three months. Cerebello-motor connectivity was evaluated using transcranial magnetic stimulation (TMS) at baseline and at follow-up.
Results: Patients who underwent anodal tDCS showed a significant improvement in all performance scores (scale for the assessment and rating of ataxia, international cooperative ataxia rating scale, 9-hole peg test, 8-m walking time) and in cerebellar brain inhibition compared to patients who underwent sham stimulation.
Conclusions: A two-weeks' treatment with anodal cerebellar tDCS improves symptoms in patients with ataxia and restores physiological cerebellar brain inhibition pathways. Cerebellar tDCS might represent a promising future therapeutic and rehabilitative approach in patients with neurodegenerative ataxia.
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1. Introduction

Neurodegenerative cerebellar ataxias represent a heterogeneous group of disabling disorders in which progressive ataxia of gait, limb dysmetria, oculomotor deficits, dysarthria and kinetic tremor are the prominent clinical manifestations [1]. Both the hereditary and sporadic forms usually present in young adulthood, and are characterized by atrophy of cerebellar or brainstem structures [2].

The most common forms of neurodegenerative ataxias include the autosomal dominant spinocerebellar ataxias (SCAs), Friedreich's ataxia, Fragile-X-associated tremor/ataxia syndrome (FXTAS), multiple system atrophy-cerebellar type (MSA-C), ataxia with oculomotor apraxia (AOA) and the sporadic adult-onset ataxia of unknown etiology (SAOA) [3,4].

Currently, cerebellar ataxias lack effective pharmacological interventions and there is growing interest in finding innovative therapeutic approaches to improve clinical symptoms in this spectrum of debilitating disorders.

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In this view, the field of cerebellar stimulation with transcranial direct current stimulation (tDCS) has recently gained much attention in the scientific community, in particular because these stimulation techniques are non-invasive, provide novel information on cerebellar physiology and might promote neural plasticity [5]. In particular, previous studies have demonstrated that cerebellar tDCS can modulate cerebellar excitability, by polarizing Purkinje cells [6], thus changing the pattern of activity in the deep cerebellar output nuclei [7].

A number of studies have demonstrated the efficacy of a single session of tDCS in improving symptoms in cerebellar disorders and in modulating locomotor adaptation in healthy subjects [8–11]. However, all of the studies to date have never explored the long-lasting effects of multiple sessions of cerebellar tDCS in neurodegenerative ataxias [5]. Indeed, tDCS determines a polarity-dependent modulation of cortical excitability, with effects that can last for up to a few hours after a single stimulation session [12], while multiple sessions are considered to induce cumulative and long-lasting after effects, mediated by the modulation of cortical plasticity [13].

tDCS effects on cerebellar function can be determined by assessing the modulation of cerebellar pathways using a transcranial magnetic stimulation (TMS) paired-pulse protocol known as cerebellar brain inhibition (CBI), which reflects the physiological inhibitory tone of the cerebellum on the contralateral motor cortex via the ventral thalamus [14,15]. CBI can thus be used as a neurophysiological technique to measure connectivity between the cerebellum and the motor cortex, reflecting the modulation of cerebellar excitability induced by cerebellar tDCS [7].

All the above observations defined the objective of this work, aimed at assessing long-term effects of multiple sessions of anodal cerebellar tDCS in patients with neurodegenerative cerebellar ataxia. To this, we assessed a) clinical outcomes and b) cerebello-cerebral connectivity (CBI) in a randomized, double-blind, sham-controlled study.

2. Methods

2.1. Subjects

Twenty patients with neurodegenerative ataxia, respectively five patients with SCA2 [16], two with SCA38 [17], one with SCA14 [18], one with Friedreich's ataxia [19], one with AOA type 2 [20], four with MSA-C [21], one with FXTAS [22] and five with SOAO [23], were consecutively recruited from the Centre for Ageing Brain and Neurodegenerative Disorders, Department of Clinical and Experimental Sciences, University of Brescia, Italy and from the Neurology Unit, University "La Sapienza", Rome, Italy. The number of included patients, corrected for possible drop-outs and patients in which a reliable motor cortex could not be elicited, was assessed using a power analysis, from results obtained from previous studies [11]. Each patient fulfilled current clinical criteria and genetic trait for the specific diagnosis. All enrolled patients shared a cerebellar syndrome and, as assessed by MRI, had quantifiable cerebellar atrophy.

For each patient, a review of past medical history, a semi-structured neurological examination and a standardized assessment of cerebellar functions was carried out. Moreover, each patient underwent brain structural imaging, to further confirm cerebellar atrophy.

Patients were evaluated free of sedative drugs or sodium- or calcium-channel blockers to avoid any interaction with the presumed neuromodulatory effects of tDCS.

In addition, ten age-matched healthy control subjects were recruited as reference group for TMS parameters.

Written informed consent was obtained from all patients. The study was approved by the ethics committee of the Brescia Hospital, Italy (NP1576 approved 12.01.16) in conformity with the Helsinki Declaration.

2.2. Study design

Patients were randomized into two groups: each group received anodal tDCS or sham stimulation for 5 days/week for 2 weeks, in a 3:2 ratio respectively (see Fig. 1).

At baseline, each patient underwent a clinical evaluation, according to a standardized assessment (see below, clinical assessment), and CBI evaluation by TMS when possible (see below, CBI assessment) (pre-stimulation, T0). The same work-up was carried out immediately after either sham or anodal tDCS (post-stimulation, T1), at one-month (T2) and at three-months follow-up (T3).

Two principal investigators were involved: one performing the clinical evaluation and CBI at baseline and at follow-up (A.B.) and one performing tDCS (V.D.). The patient and the examiner performing clinical ratings and TMS protocols were blinded to the type of stimulation.

2.3. Clinical assessment

At each time-point, the Scale for the Assessment and Rating of Ataxia (SARA) [24] and the International Cooperative Ataxia Rating Scale (ICARS) [25] were employed to evaluate cerebellar deficits.

SARA consists of eight items, including gait, stance, sitting, speech disturbance, finger chase, nose-finger test, fast alternating hand movements, and heel-shin slide. The higher the score, the worse is the patient's performance. ICARS is a semiquantitative 100-point scale consisting of 19 items, divided into four weighted sub-scores, namely posture and gait disturbances, limb kinetic function, speech disorder, and oculomotor deficits.

To evaluate finger dexterity and upper limb coordination, four timed trials of the 9-hole peg test (9HPT) [26] were performed separately for each hand. The 9HPT is a commonly used test to assess finger dexterity: the patient picks the pegs one at time and puts them in nine holes on a peg board until all holes are filled and then removes them one at a time, as quickly as possible. The total time to complete the task is recorded for each trial and for each separate hand (dominant and non-dominant).

To assess gait speed, we performed, four times for each session, the 8-m walking time (8 MW) [27], defined as the time needed to walk 8 m "as quickly as possible but safely", with any device but without help of another person or wall.

Finally, the Italian version of the Stroke and Aphasia Quality of Life Scale-39 (SAQOL-39), an interview-administered self-reported scale comprising 39 items assessing 4 subdomains (Physical, Communication, Psychosocial and Energy), was used to assess changes in the patient's quality of life [28].

2.4. Cerebellar brain inhibition (CBI)

TMS was performed with two figure-of-eight coils (each loop diameter 70 mm) connected to two Magstim stimulators (Magstim Company, Oxford, UK). The magnetic stimuli had a monophasic current waveform (rise time of 100 μs, decaying back to zero over 800 μs). Motor evoked potentials (MEPs) were recorded from the right first dorsal interosseous muscle (FDI) through surface Ag/AgCl electrodes placed in a belly-tendon montage and acquired using a Biopac MP-150 electromyograph (BIOPAC Systems Inc., Santa Barbara, CA, USA).

The TMS coil was held tangentially over the scalp region corresponding to the primary hand motor area contralateral to the

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