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Motor and cognitive outcomes of cerebello-spinal stimulation in neurodegenerative ataxia

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Cerebellar ataxias represent a heterogeneous group of disabling disorders characterized by motor and cognitive disturbances, for which no effective treatment is currently available.

In this randomized, double-blind, sham-controlled trial, followed by an open-label phase, we investigated whether treatment with cerebello-spinal transcranial direct current stimulation (tDCS) could improve both motor and cognitive symptoms in patients with neurodegenerative ataxia at short and long-term. Sixty-one patients were randomized in two groups for the first controlled phase. At baseline (T0), Group 1 received placebo stimulation (sham tDCS) while Group 2 received anodal cerebellar tDCS and cathodal spinal tDCS (real tDCS) for 5 days/week for 2 weeks (T1), with a 12-week (T2) follow-up (randomized, double-blind, sham controlled phase). At the 12-week follow-up (T2), all patients (Group 1 and Group 2) received a second treatment of anodal cerebellar tDCS and cathodal spinal tDCS (real tDCS) for 5 days/week for 2 weeks, with a 14-week (T3), 24-week (T4), 36-week (T5) and 52-week follow-up (T6) (open-label phase). At each time point, a clinical, neuropsychological and neurophysiological evaluation was performed. Cerebellar-motor cortex connectivity was evaluated using transcranial magnetic stimulation.

We observed a significant improvement in all motor scores (scale for the assessment and rating of ataxia, international cooperative ataxia rating scale), in cognition (evaluated with the cerebellar cognitive affective syndrome scale), in quality-of-life scores, in motor cortex excitability and in cerebellar inhibition after real tDCS compared to sham stimulation and compared to baseline (T0), both at short and long-term. We observed an add-on-effect after two repeated treatments with real tDCS compared to a single treatment with real tDCS. The improvement at motor and cognitive scores correlated with the restoration of cerebellar inhibition evaluated with transcranial magnetic stimulation.

Cerebello-spinal tDCS represents a promising therapeutic approach for both motor and cognitive symptoms in patients with neurodegenerative ataxia, a still orphan disorder of any pharmacological intervention.

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Abbreviations: CCAS = cerebellar cognitive affective syndrome; CCASS = cerebellar cognitive affective syndrome scale; ICARS = international cooperative ataxia rating scale; MEP = motor evoked potential; RMT = resting motor threshold; SARA = scale for the assessment and rating of ataxia; SCA = spinocerebellar ataxia; SF-36 = short-form health survey 36; tDCS = transcranial direct current stimulation; TMS = transcranial magnetic stimulation

Introduction

Neurodegenerative ataxias represent a heterogeneous group of disabling progressive diseases characterized by limb and gait ataxia, oculomotor deficits, dysarthria, and kinetic tremor.¹⁻³ Often these disorders result in the cerebellar cognitive affective syndrome (CCAS), whose hallmark features include deficits in executive function, visual spatial processing, linguistic skills and emotion regulation.^{4,5} The genetic causes of ataxias involve a growing list of over 100 genes whose products are implicated into mitochondrial dysfunction, oxidative stress, abnormal mechanisms of DNA repair, possible protein misfolding, and abnormalities in cytoskeletal proteins.⁶

No effective treatment is currently available for most of these diseases, with the exception of the symptomatic, physical and occupational therapies, treatments in immune-mediated cerebellar ataxias, and specific supplementation as in vitamin E deficiency and spinocerebellar ataxia 38 (SCA38).^{7,8} For this reason, there is an increasing interest in finding innovative approaches to reduce clinical symptoms. In this view, cerebellar transcranial direct current stimulation (tDCS) is a non-invasive treatment which promotes neuroplasticity and has been shown to improve motor symptoms in patients with neurodegenerative cerebellar ataxias.⁹⁻¹⁹

Our previous pilot study has supported the clinical efficacy of cerebello-spinal tDCS in these disorders.²⁰ The results were accomplished by the restoration of cerebellar inhibition, a neurophysiological measure which reflects the modulation of cerebellar excitability, using a transcranial magnetic stimulation (TMS) paired-pulse protocol.²⁰

Despite the fact our findings were promising, several unmet issues still need to be addressed, and were the objective of this work: (i) to evaluate if treatment with cerebello-spinal tDCS may also improve cognitive symptoms, such as those related to CCAS; (ii) to verify whether two repeated tDCS treatments are superior to a single tDCS treatment in improving both motor and cognitive symptoms; (iii) to study when the effects tDCS treatments wane over time to define the best timing for repeated tDCS treatments;

(iv) to evaluate if the effects on cerebellar excitability are long-lasting and if they correlate with motor and cognitive improvement; and (v) to increase sample size in order to improve generalizability of these results to specific groups of ataxias.

To perform these tasks, we conducted a double-blind, randomized, sham-controlled tDCS trial (5 days/week for 2 weeks) followed, after a 3-month washout period, by an open-label phase (5 days/week for 2 weeks).

Materials and methods

Standard protocol approvals, registrations, and patient consents

Written informed consent was obtained from all participants according to the Declaration of Helsinki. The study protocol was approved by the local ethics committee (Brescia Hospital), #NP3244. This trial has been registered at ClinicalTrials.gov (NCT04153110).

Participants

Sixty-one patients with neurodegenerative ataxia were recruited from the Centre for Ageing Brain and Neurodegenerative Disorders, Neurology Unit, University of Brescia, Italy and entered the study. Inclusion criteria consisted of: patients ≥ 18 years old with a cerebellar syndrome and quantifiable cerebellar or spinal cord atrophy on MRI. We excluded cases with severe head trauma in the past, history of seizures, stroke or intracranial haemorrhage, intracranial expansive process, pacemaker, metal implants in the head/neck region, severe comorbidity (i.e. cancer in the past 5 years, non-controlled hypertension), use of illegal drugs, or pregnancy.

Twenty-four had a genetic form of spinocerebellar ataxia (five SCA1, 12 SCA2, one SCA14, one SCA28, five SCA38),²¹ 10 had multiple system atrophy with cerebellar phenotype (MSA-C),²² seven had Friedreich's ataxia,²³ 17 had a sporadic adult-onset ataxia (SAOA),³ and three had cerebellar ataxia with neuropathy and

vestibular areflexia syndrome (CANVAS).²⁴ The classification in each subgroup fulfilled current clinical criteria, with a genetic mutation for all except SAOA. For each patient, we reviewed past medical history and performed a semi-structured neurological examination and a standardized assessment of cerebellar functions. Patients were evaluated free of sedative drugs or sodium- or calcium-channel blockers to avoid any interaction with the presumed neuromodulatory effects of tDCS.

Study design

Patients were randomized in two groups for the first controlled phase. At baseline (T0), Group 1 received placebo stimulation (sham tDCS) while Group 2 received anodal cerebellar tDCS and cathodal spinal tDCS (real tDCS) for 5 days/week for 2 weeks (T1), with a 12-week (T2) follow-up (randomized, double-blind, sham controlled phase). At the 12-week follow-up (T2), all patients (Group 1 and Group 2) received a second treatment of anodal cerebellar tDCS and cathodal spinal tDCS (real tDCS) for 5 days/week for 2 weeks, with a 14-week (T3), 24-week (T4), 36-week (T5) and 52-week follow-up (T6) (open-label phase) (Fig. 1A). Summarizing, Group 1 underwent sham stimulation followed by real stimulation (sham/real tDCS), while Group 2 underwent real stimulation both times (real/real tDCS).

At each time point (T0–T6), every patient underwent a clinical and cognitive evaluation, assessment of quality of life, according

to a standardized protocol, and cerebellar inhibition evaluation using TMS (see ‘Clinical assessment’ and ‘Cerebellar inhibition’ sections below) (Fig. 1A).

The patient and the examiners were blinded to the type of stimulation when applying tDCS (V.C.), performing clinical ratings (I.L., M.M.) and TMS protocols (V.C., V.D.). The tDCS device was previously set to real or sham stimulation by a different researcher (A.Be.). To ensure blindness also in the open-label phase of the study, the neurological examination was video-recorded and analysed retrospectively by a blinded neurologist (A.A.), who was unaware of the time point (T0–T6), as the videos were presented randomly.

B.B. was responsible for random allocation sequences, enrolment of participants, and assigned participants to specific interventions. A computer-assisted randomization was used to randomize subjects into groups.

Because of the Covid-19 pandemic, we adopted telemedicine to remotely assess patients at follow-up visits during the lockdown in Italy (March–May 2020).²⁵

Clinical assessment

At each time point, the cerebellar motor condition was evaluated by means of the scale for the assessment and rating of ataxia (SARA)²⁶ and the international cooperative ataxia rating scale (ICARS)²⁷; cognitive deficits were assessed with the cerebellar

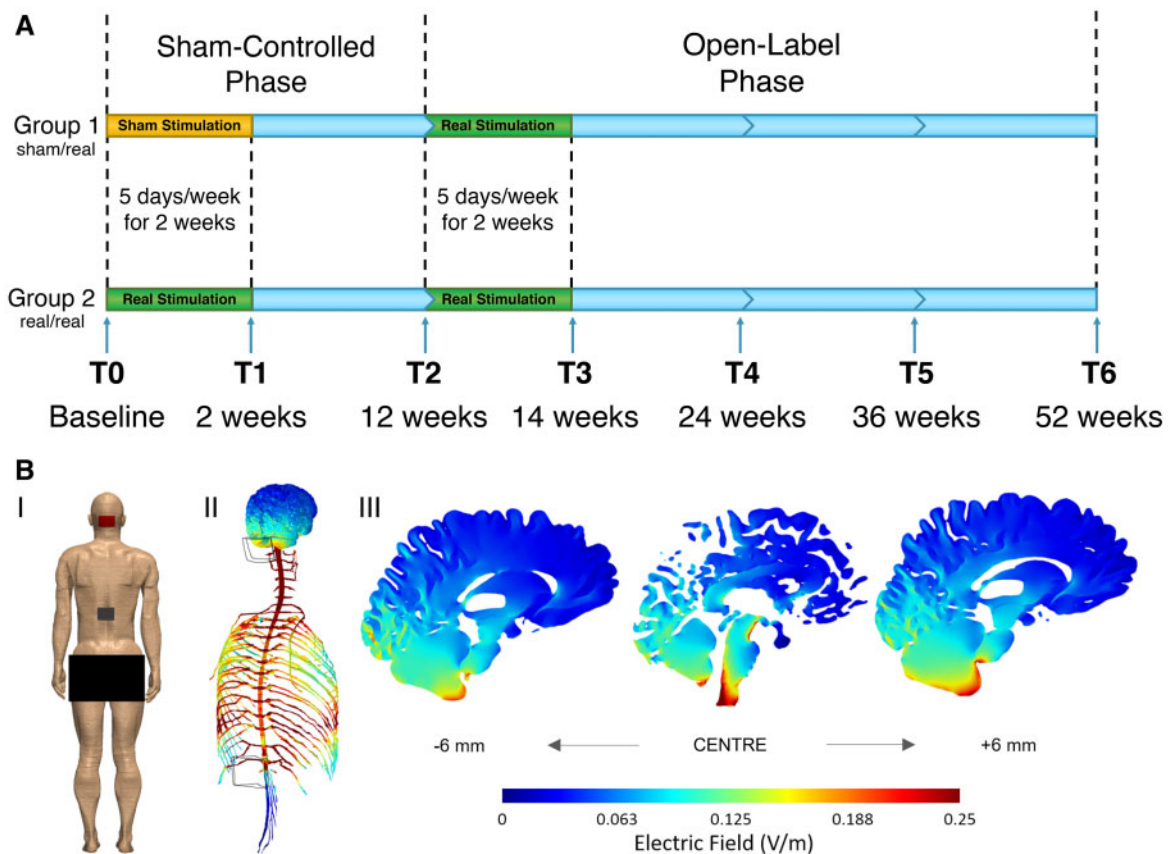


Figure 1 Study design and computational modelling of electric field distribution. (A) Schematic representation of the study design. Our clinical trial was divided into a sham-controlled phase (T0–T2) where 61 patients were divided into Group 1 (sham stimulation, $n = 28$) and Group 2 (real stimulation, $n = 33$). Following this phase all patients received real tDCS and were evaluated at T3, T4, T5 and T6. Weeks from the recruitment are indicated below each time point. (B) Computer simulation of current density distribution in the brain and spinal cord. (i) A full body MRI derived model was used to mimic the exact clinical experiment from electrode placement, electrode size and current intensity delivered; (ii) posterior-lateral view of the induced current flow or electric field magnitude; (iii) cortical cross-section slice electric field plot to demonstrate current flow through the cerebellum and the brainstem.

cognitive affective syndrome scale (CCASS),⁵ and quality of life was evaluated with the Italian version of the short-form health survey 36 (SF-36).²⁸

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 subscores, namely posture and gait disturbances, limb kinetic function, speech disorder, and oculomotor deficits.

CCASS is a 10-item series that measures semantic and phonemic fluency, category switching, digit span forward and backward, cube draw or cube copy, delayed verbal recall, similarities, go/no-go, and assessment of neuropsychiatric domains. The total score (0–120, the higher the score, the better is the patient's performance) or the total number of failed tests (0–10) may be considered. A diagnosis of possible CCAS is made with one failed test, a diagnosis of probable CCAS is made with two failed tests, and a diagnosis of definite CCAS is made with three failed tests.⁵

Finally, the SF-36, an interview-administered self-reported scale consisting of 36 scaled scores assessing eight subdomains (physical functioning, bodily pain, social role functioning, mental health, emotional role functioning, vitality, general health perceptions, physical role functioning), was used to assess changes in the patient's quality of life.²⁸

Cerebellar inhibition

Two Magstim TMS stimulators connected with two 70 mm figure-of-eight coils (Magstim Company) were used to evaluate cerebellar inhibition, as previously published.²⁹ The current waveform for the magnetic stimuli had a monophasic configuration, with a rise time of 100 μ s and decaying back to zero in 800 μ s.

Surface Ag/AgCl electrodes positioned in a belly-tendon montage on the right first interosseous muscles were used to record motor evoked potentials (MEPs), using a Biopac MP-150 electromyograph (BIOPAC Systems Inc). Responses were amplified and filtered at 20 Hz and 2 kHz with a sampling rate of 5 kHz.

The stimulation coil was positioned with the handle directed 45° angle laterally and posteriorly to the sagittal plane, over the region corresponding to the primary motor cortex (hand area), contralateral to the target first interosseous muscle. The 'hot spot' was defined as the point in which magnetic stimulation resulted in the maximum MEP amplitude with the minimum stimulator intensity, which was marked with a felt-tip pen on the scalp to ensure constant placement of the coil throughout the experiment.

Resting motor threshold (RMT) was defined as the minimal stimulus intensity needed to produce MEPs with an amplitude of at least 50 μ V in 5 of 10 consecutive trials during complete muscle relaxation (expressed as percentage of maximum stimulator output), which was controlled by visually checking the absence of EMG activity at high-gain amplification.³⁰

Cerebellar inhibition was assessed using previously described techniques.^{29,31–33} Briefly, the second coil was used to deliver the conditioning stimuli which was placed over the contralateral cerebellar hemisphere³⁴ (1 cm inferior and 3 cm right to the inion), a site corresponding to the posterior and superior lobules of the lateral cerebellum.³⁵ For cerebellar stimulation, the handle was positioned upward with the coil placed tangentially to the skull. The cerebellar conditioning stimulus intensities were set at 110% RMT obtained in the contralateral motor cortex.²⁹ Conditioning stimuli preceded the test stimuli by 5 ms interstimulus intervals (ISI). Ten responses were collected for 5 ms ISI and 15 for the test stimuli alone in a pseudorandomized sequence. The amplitude of the

conditioning MEPs was expressed as a ratio of the mean unconditioned response. The intertrial interval was set at 5 s ($\pm 10\%$).

Transcranial direct current stimulation

Transcranial DCS was delivered by a battery-driven constant current stimulator through a pair of saline-soaked (0.9% NaCl) surface sponge electrodes ($7 \times 5 \text{ cm}^2$, current density 0.057 mA/cm² for the anodal cerebellar electrode; $8 \times 6 \text{ cm}^2$, current density 0.042 mA/cm² for the cathodal spinal electrode) (Fig. 1B). The anode was placed on the scalp over the cerebellum area (2 cm under the inion) and the cathode over the spinal lumbar enlargement (2 cm under T11). This particular montage, with a concurrent cerebellar and spinal stimulation, was chosen to target both of these structures, that are discretely involved in different types of ataxia.

The electrodes were secured using elastic gauzes and an electroconductive gel was applied to electrodes to reduce contact impedance ($< 5 \text{ k}\Omega$ for all sessions).

During anodal stimulation a constant current of 2 mA was applied for 20 min, as suggested by recently published consensus recommendations^{36,37} and based on computation modelling studies (see 'Computational modelling of electric field distribution' section).^{38–40}

For the sham condition, the electrode placement was the same, but the electric current was ramped down 10 s after the beginning and at the end of the stimulation to make this condition indistinguishable from the experimental stimulation. To detect differences in the perception of the stimulation, we asked the patients whether they thought they were receiving real or sham stimulation, and if they perceived tingling cutaneous sensations, which were rated on a scale from 0 to 4, with 0 = no sensations reported, 1 = mild, 2 = moderate, 3 = strong, 4 = very strong sensations reported.

Computational modelling of electric field distribution

Based on the methods developed previously by our group,^{41–43} we performed computational modelling of electric field distribution for cerebello-spinal tDCS (real tDCS). As shown in Fig. 1B, the current effectively reaches the cerebellum, brainstem and spinal cord.

Outcome measures

The co-primary end points were defined as a significant change from baseline in: (i) SARA; (ii) ICARS; and (iii) CCASS scores. The secondary end points were defined as significant changes from baseline in (iv) cerebellar inhibition; and (v) SF-36 quality of life scale.

Statistical analyses

We used a power analysis to determine the necessary sample size, based on previously published work on tDCS in ataxia^{9,10,44}; considering power ($1 - \beta = 0.80$) and $\alpha = 0.05$, we calculated that 61 patients would be needed, correcting also for possible drop-outs, with an estimated drop-out rate of 10% observed in similar studies in the same setting.^{44,45} Intention-to-treat analyses were performed. For patients with missing values at follow-up (Fig. 2), data were assigned using mixed effects models for repeated measures without any *ad hoc* imputation for both clinical and neurophysiological measures.

Cohen's κ was run to determine if there was agreement between the type of sensation perceived and the type of stimulation received. An unpaired t-test was used to evaluate differences in

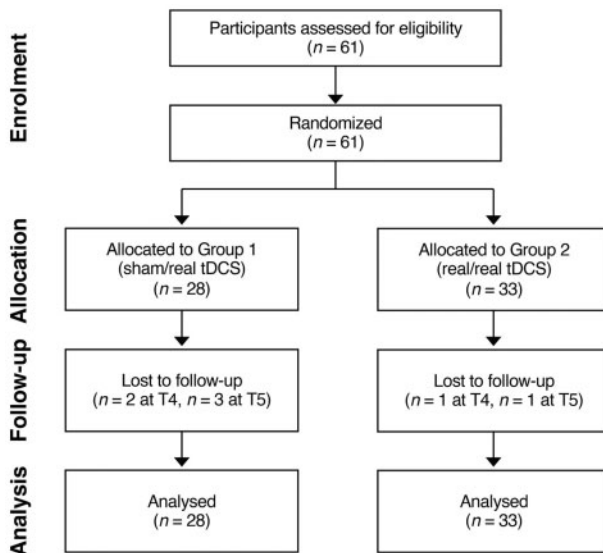


Figure 2 Flow chart of the study. We recruited 61 patients with primary neurodegenerative ataxia. Patients were randomly divided into two groups (Group 1, $n = 28$; Group 2, $n = 33$) for the first phase. During the course of the study, seven cases interrupted the trial between T3 and T5 (lost at follow-up).

perception of cutaneous sensation during real and sham stimulation in both groups.

To assess the effect of tDCS treatment on clinical scores and neurophysiological measures over time, we used a two-way mixed analysis of covariance (ANCOVA) with Time as within-subject factors and Treatment (real/real stimulation versus sham/real stimulation) as between-subject factors. Baseline values of each score were used as covariates, to reduce possible effects of baseline characteristics on clinical score changes over time. Moreover, we separately evaluated effects of Time and Treatment in the randomized, double-blind phase and in the open-label phase.

We reported marginal mean differences with 95% confidence intervals (95% CIs) for relevant comparisons (i.e. differences between groups in the randomized, double-blind phase and differences between time points and groups for the open-label phase). Only when ANCOVA significant effects were reached, *post hoc* testing with Hochberg's step-up procedure⁴⁶ to control the familywise error rate (FWR) was conducted to analyse group-differences at respective time points (for clinical and neurophysiological scores all P -values are reported after adjustment for multiple comparisons). Mauchly's test was used to assess for assumption of sphericity, while Greenhouse-Geisser ϵ determination was used to correct in case of sphericity violation.

As an exploratory analysis, Spearman rank-order correlations were used to assess associations between the improvement in functional scores, neurophysiological parameters, and demographic or clinical characteristics.

Statistical analyses were performed using SPSS version 25 (SPSS, Inc., Chicago, IL, USA).

Data availability

All data, including outcome measure results, study protocol and statistical analysis plan, will be shared through ClinicalTrials.gov via public access (<https://clinicaltrials.gov/ct2/show/NCT4153110>).

Results

Participants

Sixty-one participants were initially enrolled and randomized into Group 1 and 2 to receive sham ($n = 28$) or real stimulation ($n = 33$), respectively, in the initial controlled phase, which was followed by an open-label phase after 12-week follow-up. Demographic and clinical characteristics of patients are reported in Table 1.

We performed 410 evaluations, 16 of which were carried out by telemedicine (without the TMS measures) because of the Covid-19 pandemic. All patients completed at least four evaluations; three patients dropped out from the study at T4 (two for Covid-19 lockdown in Group 1, one for a foot fracture in Group 2), four patients at T5 (one for lumbar fracture, one for worsening of symptoms and one for Covid-19 lockdown in Group 1, one for Covid-19 lockdown in Group 2).

There was no statistically significant association between the type of stimulation and patients' perception, as assessed by Cohen's κ ($\kappa = 0.03$, $P = 0.839$); tingling cutaneous sensations were equally perceived in both groups ($t = -0.32$, $P = 0.751$ at unpaired t -test), suggesting that real tDCS could not be distinguished from sham stimulation.

Measure reliability

To evaluate intra-rater variability on SARA and ICARS scores throughout evaluations, considering that video-recordings were shown randomly to ensure blindness also in the open-label phase, 20 video-recordings were shown twice to A.A. Intraclass correlations coefficients for single measures were high for both measures: SARA = 0.97 (95% CI: 0.92 to 0.99), $P < 0.001$; ICARS = 0.97 (95% CI: 0.91 to 1.00), $P < 0.001$.

Motor assessment

We observed a significant Time $\times$ Treatment interaction for SARA ($P = 0.004$, partial $\eta^2 = 0.08$) and ICARS ($P < 0.001$, partial $\eta^2 = 0.11$). Mean changes over time are reported in Table 2, Fig. 3A and B. In the randomized, double-blind phase, we observed a marginal mean difference between groups (sham versus real) of +4.1 (95% CI: +3.5 to +4.7, $P < 0.001$) points for SARA, and of +11.0 (95% CI: +9.3 to +12.7, $P < 0.001$) points for ICARS (Table 3). In the open-label phase, we observed a mean difference between T3 and T2 for SARA and ICARS, with a still significant difference at T5 for SARA and at T6 for ICARS (Supplementary Table 1). We still observed a significant marginal mean difference between groups for SARA and ICARS in the open-label phase (Table 3), suggesting an add-on effect of multiple stimulations.

The exploratory analysis performed on the four weighted subscores of the ICARS scale showed that there was a statistically significant main effect of Treatment in the posture and gait ($P < 0.001$, partial $\eta^2 = 0.30$), in the kinetic limb coordination ($P < 0.001$, partial $\eta^2 = 0.44$) and in the oculomotor movement subscores ($P = 0.015$, partial $\eta^2 = 0.10$), but not in the dysarthria subscores ($P = 0.076$, partial $\eta^2 = 0.05$).

We did not observe a significant effect of diagnosis on SARA or ICARS score, highlighting how results were not influenced by the type of ataxia (see Supplementary Table 2 for individual scores in each separate group of ataxias).

A Spearman rank-order correlation was run to assess the relationship between the percentage of average change in functional scores (SARA and ICARS) after the trial in which both groups performed real stimulation (T3 compared to T2), and demographic or clinical characteristics. There was a negative correlation between the improvement at SARA scores and baseline SARA ($r_s = -0.64$,

Table 1 Demographic and clinical characteristics of included patients

Variable	All patients	SCA	MSA-C	SAOA	Mixed
Patients, n	61	24	10	17	10
Age, years	56.9 ± 13.9	49.0 ± 10.3	67.9 ± 8.8	61.3 ± 14.8	57.7 ± 14.8
Age at onset, years	43.6 ± 18.4	35.1 ± 11.6	63.2 ± 7.2	48.7 ± 20.1	36.0 ± 20.0
Disease duration, years	13.3 ± 12.7	13.9 ± 11.6	4.7 ± 4.4	12.6 ± 13.0	21.0 ± 15.7
Sex, % female	55.7	58.3	60.0	52.9	50.0
Education, years	11.1 ± 3.8	12.3 ± 3.8	9.1 ± 4.4	10.6 ± 3.9	11.1 ± 2.3
SARA	19.5 ± 9.3	18.8 ± 9.7	24.7 ± 8.2	14.6 ± 6.1	24.5 ± 9.8
ICARS	47.6 ± 21.6	47.7 ± 22.6	56.9 ± 19.1	35.4 ± 16.0	59.1 ± 21.4
CCASS	72.9 ± 20.5	79.3 ± 18.7	57.4 ± 25.5	71.6 ± 17.0	75.4 ± 19.0
SF-36	481.8 ± 140.8	523.24 ± 132.4	359.2 ± 124.1	483.9 ± 150.0	501.2 ± 101.0
CBI	0.96 ± 0.07	0.10 ± 0.09	0.94 ± 0.07	0.96 ± 0.07	0.96 ± 0.05
RMT	39.1 ± 8.4	38.3 ± 8.1	39.3 ± 8.8	39.2 ± 9.5	41.0 ± 8.1

Values are expressed as mean ± standard deviation. CBI = cerebellar inhibition (ISI 5 ms) expressed as ratio of mean MEP amplitude related to the control MEP; Mixed = Friedreich's ataxia and cerebellar ataxia with neuropathy and vestibular areflexia syndrome; MSA-C = cerebellar variant of multiple system atrophy; RMT = resting motor threshold expressed as % of maximum stimulator output; SAOA = sporadic adult-onset ataxia.

Table 2 Clinical and neurophysiological parameters (mean ± standard deviation) of included patients

	Randomized double-blind phase			Open-label phase			
	T0	T1	T2	T3	T4	T5	T6
Group 1 (sham/real tDCS)							
Primary outcomes							
SARA	19.8 ± 10.6	19.1 ± 10.5 [*]	19.7 ± 10.6	15.4 ± 9.5 ^{**}	16.2 ± 9.4 ^{**}	17.6 ± 9.9 ^{**}	18.9 ± 10.3
ICARS	48.5 ± 24.0	47.0 ± 24.2	48.7 ± 24.0	37.3 ± 21.6 ^{**}	39.8 ± 22.8 ^{**}	42.4 ± 23.0 ^{**}	43.8 ± 23.0 ^{**}
CCASS	72.7 ± 22.5	77.6 ± 20.4 [*]	76.1 ± 18.6	86.0 ± 19.5 ^{**}	83.4 ± 17.5 ^{**}	82.8 ± 21.1 ^{**}	82.6 ± 19.0 ^{**}
Secondary outcomes							
SF-36	467.3 ± 144.6	491.6 ± 139.3 [*]	469.6 ± 152.4	569.8 ± 132.7 ^{**}	548.5 ± 132.5 ^{**}	542.5 ± 112.7 ^{**}	537.2 ± 137.5 ^{**}
CBI	0.95 ± 0.09	0.97 ± 0.06	0.95 ± 0.06	0.64 ± 0.11 ^{**}	0.78 ± 0.12 ^{**}	0.87 ± 0.08 [*]	0.97 ± 0.05
Group 2 (real/real tDCS)							
Primary outcomes							
SARA	19.2 ± 8.1	14.4 ± 7.8 [†]	15.0 ± 7.6 [†]	12.3 ± 7.5 ^{††}	13.2 ± 7.1 ^{††}	14.6 ± 7.7 [†]	15.7 ± 8.0 [†]
ICARS	46.9 ± 19.6	33.7 ± 18.8 [†]	37.0 ± 18.2 [†]	28.4 ± 15.7 ^{††}	31.1 ± 15.5 ^{††}	33.2 ± 15.2 ^{††}	35.3 ± 15.4 [†]
CCASS	73.1 ± 18.9	84.0 ± 16.8 [†]	84.3 ± 19.6 [†]	90.5 ± 16.4 ^{**}	89.0 ± 16.3 ^{**}	89.0 ± 17.6 ^{**}	89.0 ± 15.9 ^{††}
Secondary outcomes							
SF-36	466.6 ± 140.6	592.8 ± 123.7 [†]	572.4 ± 131.0 [†]	647.1 ± 89.5 ^{††}	634.7 ± 96.1 ^{††}	622.1 ± 105.1 ^{††}	618.3 ± 96.0 ^{††}
CBI	0.97 ± 0.06	0.65 ± 0.11 [†]	0.78 ± 0.13 [†]	0.61 ± 0.09 ^{**}	0.76 ± 0.13 [*]	0.81 ± 0.09 [*]	0.90 ± 0.06 ^{††}

Clinical assessment and neurophysiological parameters at T0: baseline; T1: after 2 weeks treatment of randomized sham (Group 1) or real (Group 2) tDCS; T2: at 12-week follow-up; T3: after 2 weeks open-label real tDCS treatment; T4: at 24-week follow-up; T5: at 36-week follow-up; T6: at 52-week follow-up. CBI = cerebellar inhibition (ISI 5 ms) expressed as ratio of mean MEP amplitude related to the control MEP.

*Significant difference compared to T0 (randomized, double-blind phase); ^{*}significant difference compared to T2 (open-label phase); [†]significant difference compared to Group 1 (sham/real tDCS); significance levels are corrected for multiple comparisons with Hochberg's step-up procedure.⁴⁶

$P < 0.001$), with average disease duration ($r_s = -0.37$, $P = 0.003$), with the number of basic activities of daily living ($r_s = -0.50$, $P < 0.001$) and instrumental activities of daily living lost ($r_s = -0.55$, $P < 0.001$). Also, for ICARS we observed a negative correlation between the improvement at ICARS scores and baseline ICARS ($r_s = -0.61$, $P < 0.001$), with average disease duration ($r_s = -0.72$, $P = 0.035$) with the number of basic activities of daily living ($r_s = -0.56$, $P < 0.001$) and instrumental activities of daily living lost ($r_s = -0.55$, $P < 0.001$).

There was no significant association between the percentage of improvement in SARA or ICARS and sex, age at evaluation, age at disease onset and disease subtype.

Considering that each disease subtype may have different rates of disease progression, we observed a significant negative correlation between disease duration and the improvement at SARA ($r_s = -0.54$, $P = 0.007$) and ICARS scores ($r_s = -0.58$, $P = 0.003$) only in patients with SCA, but not in SAOA, MSA-C, Friedreich's ataxia or CANVAS.

Cognitive assessment

For CCASS we did not observe a significant Time × Treatment interaction (Table 2 and Fig. 3C). In the randomized, double-blind phase, the main effect of Treatment showed a significant difference (sham versus real) in main mean scores of -7.0 (95% CI: -10.4 to -3.5 , $P < 0.001$) (Table 3), while in the open label phase the main effect of Time showed a significant difference between T3 and T2 with a still significant difference at T6 (Supplementary Table 1). As for motor outcomes, we still observed a significant marginal mean difference between groups also in the open-label phase (Table 3).

We assessed the number of failed tests for each group and at each time point to define possible (one failed test), probable (two failed tests), definite (three failed tests) CCAS or absent CCAS (no failed tests). We did not observe a significant difference between the distribution of diagnosis between groups at T0, while we observed an increase in absent/possible CCAS at T1 only in Group 2 (real/real tDCS) and at T3 in both groups (Fig. 4).

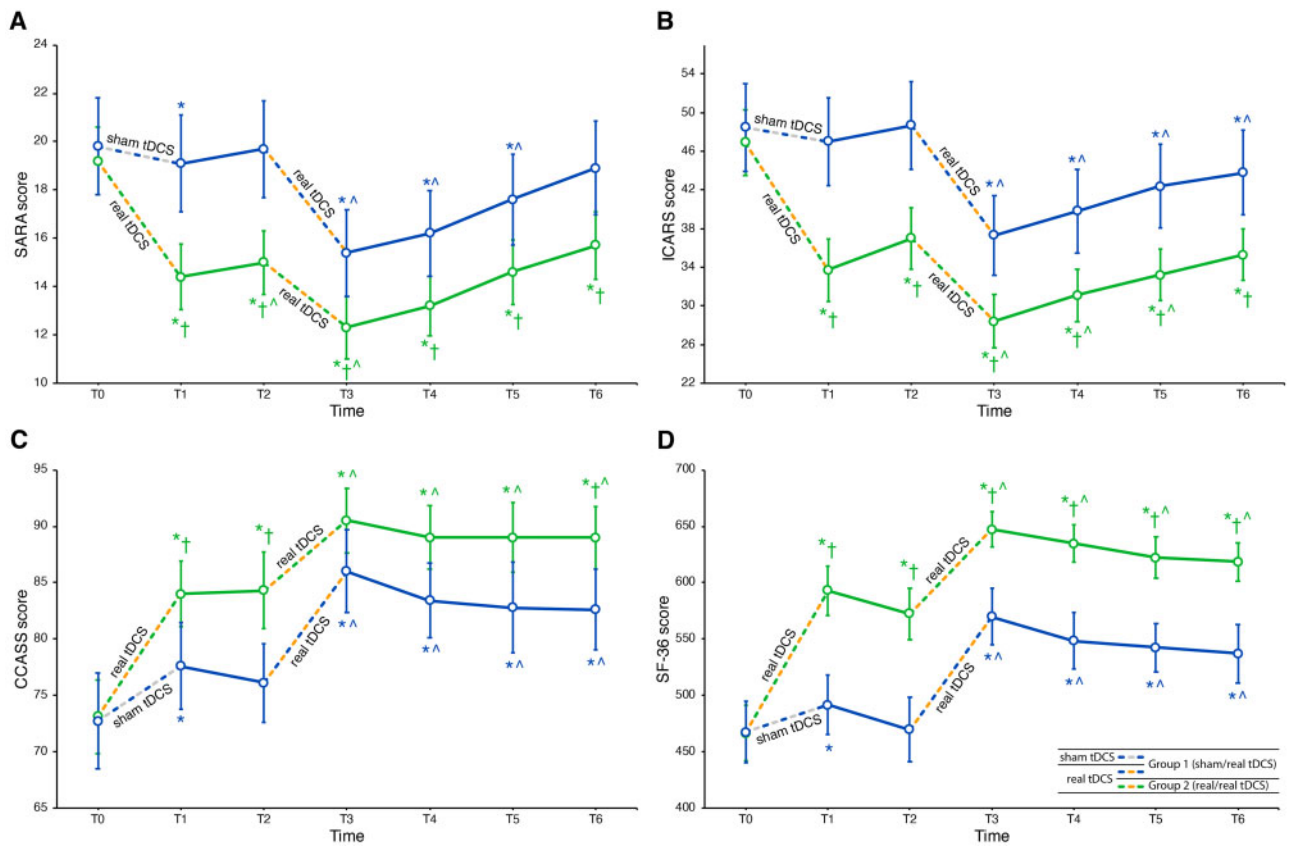


Figure 3 Clinical measures of analysed patients at different time points. The panels show (A) SARA, (B) ICARS, (C) CCASS scale, and (D) SF-36 scores at different time points [T0: baseline; T1: after 2 weeks treatment of randomized sham (Group 1) or real (Group 2) tDCS; T2: at 12-week follow-up; T3: after 2 weeks open-label real tDCS treatment; T4: at 24-week follow-up; T5: at 36-week follow-up; T6: at 52-week follow-up]. Blue lines represent Group 1 (sham/real tDCS), green lines represent Group 2 (real/real tDCS); dashed lines represent the intervention (grey = sham tDCS; orange = real tDCS); error bars represent standard errors. *Significant difference compared to T0 (randomized, double-blind phase); ^Significant difference compared to T2 (open-label phase); +Significant difference compared to Group 1 (sham/real tDCS); significance levels are corrected for multiple comparisons with Hochberg's procedure.⁴⁶

Quality of life assessment

For SF-36 we did not observe a significant Time $\times$ Treatment interaction (Table 2 and Fig. 3D). In the randomized, double-blind phase, the main effect of Treatment showed a significant difference (sham versus real) in main mean scores of -103.1 (95% CI: -133.7 to -72.4 , $P < 0.001$) (Table 3), while in the open label phase the main effect of Time showed a significant difference between T3 and T2 with a still significant difference at T6 (Supplementary Table 1). As for primary outcomes, we still observed a significant marginal mean difference between groups also in the open-label phase (Table 3).

Cerebellar inhibition

Forty-five patients underwent cerebellar inhibition assessment with a TMS paired-pulse protocol. We observed a significant Time $\times$ Treatment interaction for cerebellar inhibition ($P < 0.001$, partial $\eta^2 = 0.29$). Mean changes over time are reported in Table 2 and Fig. 5. In the randomized, double-blind phase, we observed a marginal mean difference between groups (sham versus real) of $+0.24$ (95% CI: $+0.19$ to $+0.30$, $P < 0.001$) (Table 3), while in the open-label phase we observed decreasing mean differences from T2 over time, with a still significant difference at T4 (Supplementary Table 1).

To evaluate if motor cortex excitability changed after restoring cerebellar inhibition, we exploratorily analysed the effects on

RMT, in which we observed a significant main effect of Time ($P < 0.001$, partial $\eta^2 = 0.13$) and Treatment ($P = 0.001$, partial $\eta^2 = 0.23$) (see Fig. 5 for individual comparisons).

A significant correlation was observed between the percentage of restoration of cerebellar inhibition and the improvement at SARA ($r_s = 0.42$, $P = 0.004$) and CCASS ($r_s = 0.52$, $P < 0.001$) scores, but not at ICARS ($r_s = 0.25$, $P = 0.092$) or SF-36 ($r_s = 0.15$, $P = 0.334$) scores.

Discussion

Clinical treatments for neurodegenerative ataxias are hampered by the heterogeneity of the underlying pathogenetic mechanisms and the various disease presentations even in independent subjects with the same pathogenetic variant. Most neurodegenerative ataxias remain orphan of disease-modifying treatments, and rehabilitative interventions have focused exclusively on motor symptoms, somewhat neglecting the frequently concomitant cognitive decline and behavioural symptoms observed in the CCAS.^{47,48}

In this randomized, double-blind, sham-controlled trial, followed by an open-label phase, performed on 61 patients with different forms of neurodegenerative ataxia, we observed a significant improvement in motor and cognitive symptoms after treatment with cerebello-spinal tDCS, independently of disease subtype. We showed an improvement in SARA and ICARS scores,

Table 3 Marginal means (95% CI) of treatment

Outcome	Mean Group 1 (sham/real tDCS)	Mean Group 2 (real/real tDCS)	Mean difference	P-value*
Overall				
Primary outcomes				
SARA	17.5 (16.9 to 18.1)	14.4 (13.9 to 14.9)	3.1 (2.3 to 3.9)	<0.001
ICARS	42.4 (40.8 to 44.0)	33.8 (32.3 to 35.2)	8.7 (6.5 to 10.8)	<0.001
CCASS	81.6 (79.1 to 84.1)	87.5 (85.2 to 89.8)	-5.9 (-9.3 to -2.5)	0.001
Secondary outcomes				
SF-36	526.1 (502.1 to 550.1)	614.9 (592.8 to 637.1)	-88.8 (-121.5 to -56.2)	<0.001
CBI	0.86 (0.84 to 0.88)	0.76 (0.74 to 0.77)	0.11 (0.08 to 0.14)	<0.001
Randomized, double-blind phase				
Primary outcomes				
SARA	19.1 (18.7 to 19.5)	15.0 (14.6 to 15.4)	4.1 (3.5 to 4.7)	<0.001
ICARS	47.0 (45.8 to 48.3)	36.0 (34.9 to 37.2)	11.0 (9.3 to 12.7)	<0.001
CCASS	77.0 (74.5 to 79.6)	84.0 (81.7 to 86.4)	-7.0 (-10.4 to -3.5)	<0.001
Secondary outcomes				
SF-36	480.0 (457.5 to 502.6)	583.1 (562.3 to 603.8)	-103.1 (-133.7 to -72.4)	<0.001
CBI	0.96 (0.92 to 1.00)	0.72 (0.68 to 0.75)	0.24 (0.19 to 0.30)	<0.001
Open-label phase				
Primary outcomes				
SARA	17.3 (16.6 to 17.9)	14.4 (13.8 to 15.0)	2.9 (2.0 to 3.7)	<0.001
ICARS	41.7 (39.9 to 43.5)	33.6 (32.0 to 35.3)	8.0 (5.6 to 10.5)	<0.001
CCASS	82.3 (79.6 to 85.0)	88.2 (85.8 to 90.7)	-5.9 (-9.6 to -2.2)	0.002
Secondary outcomes				
SF-36	533.1 (506.6 to 559.7)	619.3 (594.8 to 643.7)	-86.2 (-122.2 to -50.1)	<0.001
CBI	0.84 (0.82 to 0.86)	0.78 (0.76 to 0.80)	0.07 (0.03 to 0.09)	<0.001

CBI = cerebellar inhibition (ISI 5 ms) expressed as ratio of mean MEP amplitude related to the control MEP.

*P-value for main effects of Treatment.

particularly in posture and gait and in the kinetic limb coordination subscores, which correlated inversely with disease duration and impairment in activities of daily living. Cognitive scores, evaluated with the CCASS, were also improved after cerebello-spinal tDCS, with a significant number of patients reverting from probable and definite CCAS to possible or no CCAS after real stimulation.

The recovery in motor and cognitive domains was further supported by an improvement in patients' self-reported quality of life and the restoration of neurophysiological measures of motor cortex excitability and cerebellar-cerebral connectivity.

Previous pilot studies have already reported long lasting beneficial effects on motor scores after repeated sessions of cerebellar or cerebello-spinal tDCS.^{10,44} A recent meta-analysis indicated a ~26% improvement in ataxia immediately after tDCS with sustained efficacy over months (~28% improvement after 3 months) when compared with sham stimulation.¹⁵ However, these studies were hindered by small sample sizes, the effects of tDCS on cognition were not assessed, and the effects of cumulative treatments was not considered.

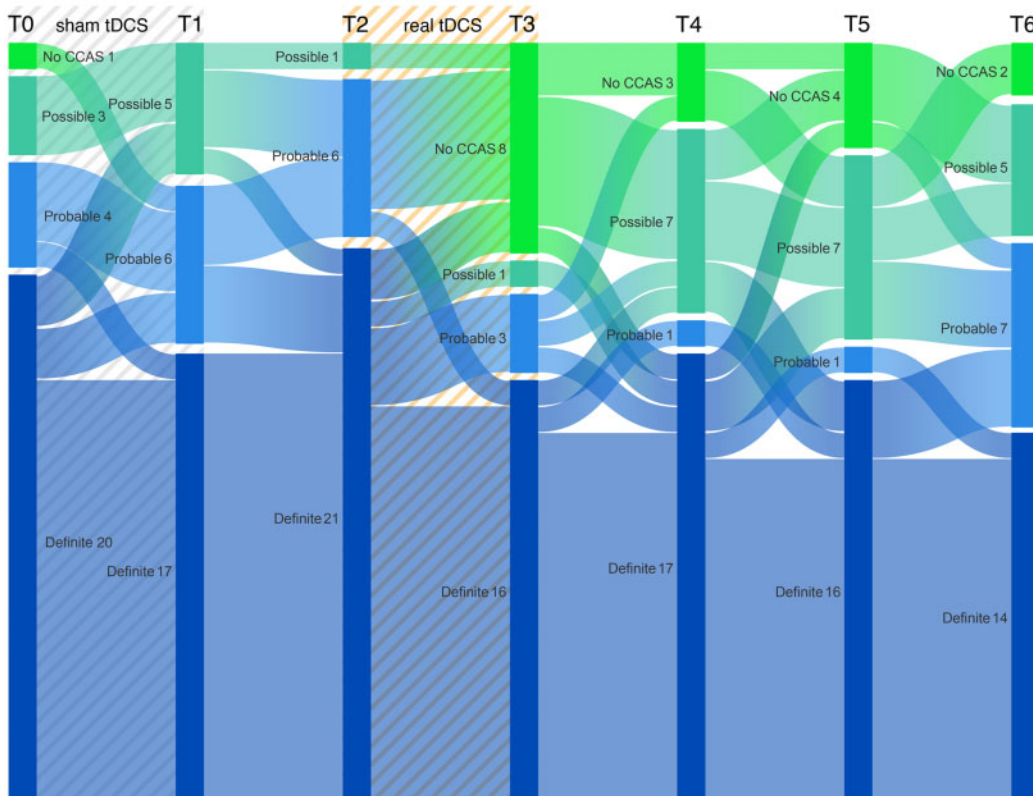
In this study, we tried to overcome these shortcomings, designing a clinical trial with a double-blind, randomized, placebo-controlled phase followed by an open-label phase, which allowed us to determine if the repetition of multiple sessions of tDCS over time may further increase both the entity and duration of the observed effects. Indeed, at 52 weeks after enrolment (T6), along with an overall improvement in motor and cognitive scores as compared to baseline, patients undergoing two repeated sessions of tDCS (real/real stimulation) had a significant improved outcome compared to patients undergoing only one session of tDCS (sham/real stimulation) (Fig. 3). The same effect was observed for neurophysiological measures of cerebellar-motor cortex connectivity (Fig. 5). We also applied a strict methodology for motor

assessments with randomly presented video recordings for clinical evaluation, which allowed for a rigorous blinding of data analysis during all phases.

Compared to previous studies, we have increased the strength of our observations by including a larger sample of subjects, not observing a significant effect of diagnosis on clinical outcomes, suggesting that the treatment was evenly effective on genetically determined SCAs, MSA-C and SAOA. We confirmed that patients who were less affected clinically and functionally showed the greatest improvement in motor scores, suggesting that the earlier the intervention is applied, the better the outcome. Moreover, cerebello-spinal tDCS was able to improve CCAS (Figs 3 and 4), also referred to as Schmahmann's syndrome, which reflects a constellation of deficits in executive functions, visuospatial abilities, language and emotion, and which has been attributed to the disruption of pathways connecting the cerebellum with limbic circuits and prefrontal, temporal and parietal association cortices.^{4,48,49} CCAS has been variably described in genetically defined SCAs, in autosomal recessive ataxias, and in MSA-C⁴⁸ and the current literature suggests that it should be treated in a specific way depending on the subtype, beyond motor impairment rehabilitation.^{48,50} Interestingly, the present findings might argue that tDCS may have a dual effect on both cognitive performances and motor functions in neurodegenerative ataxias; thus, tDCS may be proposed as a combination therapy in these cases. This dual effect may also be deduced by computational modelling studies (Fig. 1B), which show a widespread activation of cerebellar structures, thus comprehensively affecting different cerebellar functions.

The pathophysiological mechanisms underlying the effects of non-invasive stimulation of the cerebellar cortex are still not completely understood. Cerebellar tDCS seems to exert its effects by inducing an excitatory tone on Purkinje cells and changing the pattern of activity in the deep cerebellar output nuclei, with anodal

A Group 1 (sham/real tDCS)



B Group 2 (real/real tDCS)

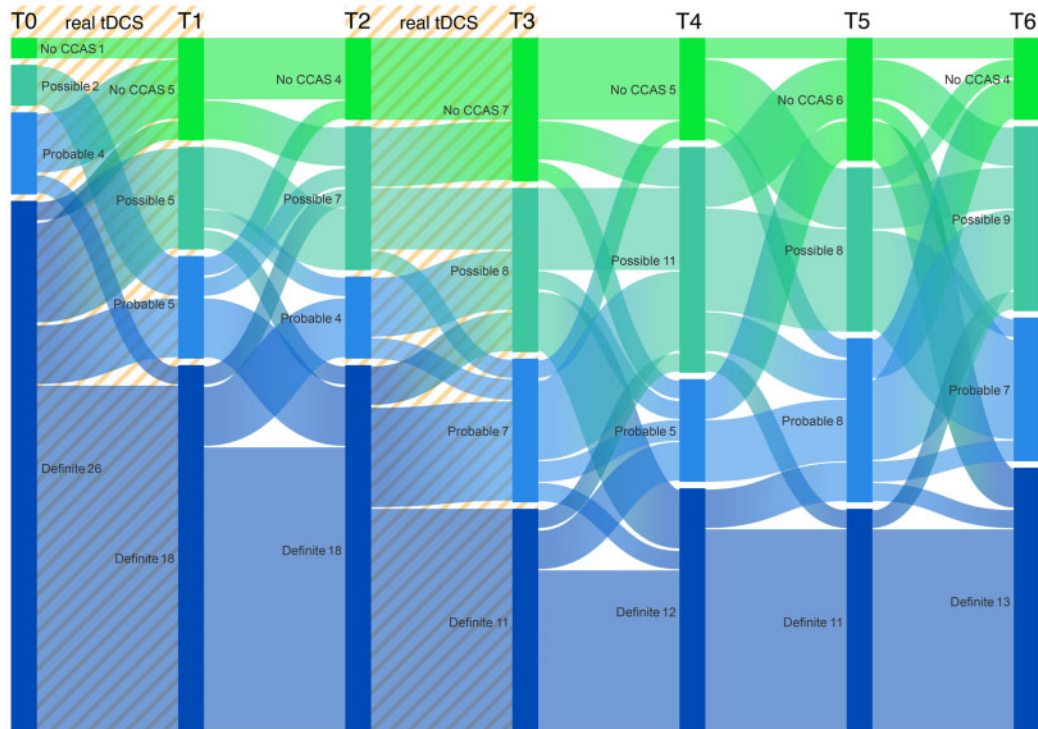


Figure 4 Sankey diagram showing the evolution of patients in different CCAS groups. The changes of patients over time at different time points is presented, T0: baseline; T1: after 2 weeks treatment of randomized sham (Group 1) or real (Group 2) tDCS; T2: at 12-week follow-up; T3: after 2 weeks open-label real tDCS treatment; T4: at 24-week follow-up; T5: at 36-week follow-up; T6: at 52-week follow-up in (A) Group 1 and (B) Group 2. The height of the boxes and the thickness of the stripes are proportional to the number of patients belonging to each CCAS group and moving from each group, respectively. Each patient was classified in a CCAS group as: possible (one failed test at the CCAS), probable (two failed tests), definite (three failed tests) CCAS or absent CCAS (no failed tests). Dashed lines represent the intervention (grey = sham tDCS; orange = real tDCS).

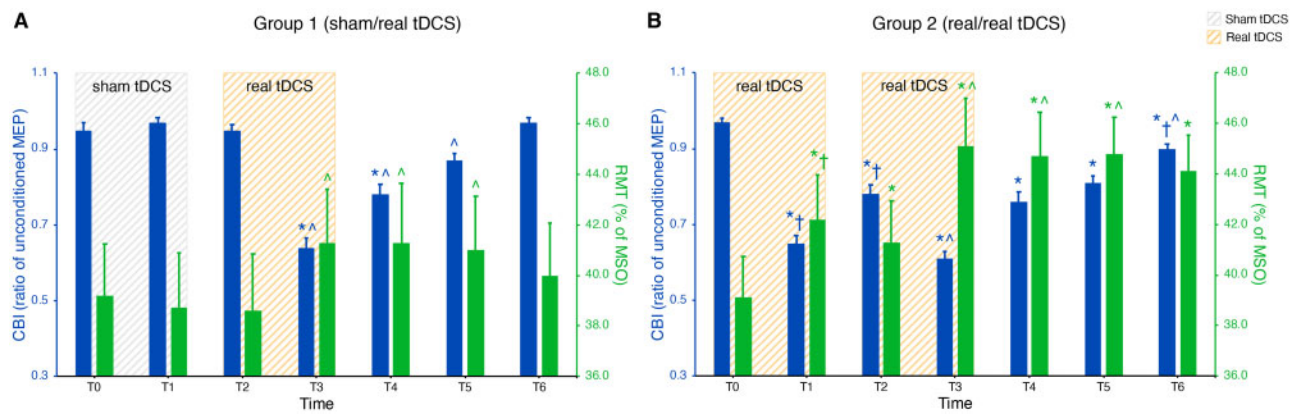


Figure 5 Neurophysiological measures at different time points. The panels show cerebellar inhibition (CI) (A) and RMT (B) assessed by TMS at different time points [T0: baseline; T1: after 2 weeks treatment of randomized sham (Group 1) or real (Group 2) tDCS; T2: at 12-week follow-up; T3: after 2 weeks open-label real tDCS treatment; T4: at 24-week follow-up; T5: at 36-week follow-up; T6: at 52-week follow-up]. For cerebellar inhibition, data are plotted as a ratio to the unconditioned motor evoked potential amplitude; for RMT data are plotted as percentage of the maximum stimulator output (MSO). Dashed lines represent the intervention (grey = sham tDCS; orange = real tDCS); error bars represent standard errors. *Significant difference compared to T0 (randomized, double-blind phase); ^significant difference compared to T2 (open-label phase); †significant difference compared to Group 1 (sham/real tDCS); significance levels are corrected for multiple comparisons with Hochberg's step-up procedure.⁴⁶

tDCS increasing the excitability of the cerebellar cortex,^{51,52} enhancing the physiological inhibitory tone over the primary motor cortex, through the inhibition of the dentate nucleus, which has an excitatory effect on the ventrolateral motor thalamus and eventually, on the motor cortex.^{33,53} The long-lasting changes in neurophysiological measures observed in the present study seem to reflect these mechanisms, with the increase of cerebellar inhibition associated with a decrease in motor cortex excitability (increased RMT). Interestingly, the rate of restoration of cerebellar-cerebral connectivity, as measured with cerebellar inhibition, correlated with the rate of motor and cognitive improvement, as measured with SARA and CCASS, respectively, further proving the strict correlation between neurophysiological and clinical parameters.

We observed that the improvement in clinical and neurophysiological measures persisted on average between 3 and 6 months, suggesting that tDCS treatment could be repeated every 3 months to maintain clinical benefit.

We acknowledge that the present study entails some limitations: even though this is one the largest groups of neurodegenerative cerebellar ataxias considered so far, different diseases were included and heterogeneous groups were relatively small, so clear-cut associations need to be made with caution even though analysis excluded a major effect of diagnosis on outcomes measures; multicentre studies are also needed to further prove the clinical efficacy of tDCS and future studies should be devoted to assess its efficacy in at-home settings.

In conclusion, multiple sessions of cerebello-spinal tDCS repeated every 3 months, are an effective, non-invasive, painless, and easy to perform treatment to be considered in the spectrum of neurodegenerative ataxias, capable of improving both motor and cognitive functions with long-lasting effects.

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Competing interests

The authors report no competing interests.

Supplementary material

[Supplementary material](#) is available at *Brain* online.

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