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Spinal direct current stimulation (tsDCS) in hereditary spastic paraplegias (HSP): A sham-controlled crossover study

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Objective: Hereditary spastic paraplegia (HSP) represents a heterogeneous group of neurodegenerative diseases characterized by progressive spasticity and lower limb weakness. We assessed the effects of transcutaneous spinal direct current stimulation (tsDCS) in HSP.

Design: A double-blind, randomized, crossover and sham-controlled study.

Setting: Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, Milan.

Participants: eleven patients with HSP (six men, mean age ± SD: 37.3 ± 8.1 years), eight affected by spastin/SPG4,¹ by atlastin1/SPG3a, 1 by paraplegin/SPG7 and 1 by ZFYVE26/SPG15.

Interventions: tsDCS (anodal or sham, 2.0 mA, 20’, five days) delivered over the thoracic spinal cord (T10-T12).

Outcome measures: Motor-evoked potentials (MEPs), the H-reflex (Hr), F-waves, the Ashworth scale for clinical spasticity, the Five Minutes Walking test and the Spastic Paraplegia Rating Scale (SPRS) were assessed. Patients were evaluated before tsDCS (T0), at the end of the stimulation (T1), after one week (T2), one month (T3) and two months (T4).

Results: The score of the Ashworth scale improved in the anodal compared with sham group, up to two months following the end of stimulation (T1, P = .0137; T4, P = .0244), whereas the Five Minutes Walking test and SPRS did not differ between the two groups. Among neurophysiological measures, both anodal and sham tsDCS left Hr, F-waves and MEPS unchanged over time.

Conclusions: Anodal tsDCS significantly decreases spasticity and might be a complementary strategy for the treatment of spasticity in HSP.

Keywords: Hereditary spastic paraplegias, Movement disorders, Spasticity treatment, Transcutaneous spinal direct current stimulation, Non-invasive spinal stimulation

Introduction

Hereditary spastic paraplegias (HSP) represent a heterogeneous group of neurodegenerative diseases characterized by progressive spasticity and lower limb weakness, rarely involving all four limbs and variably associated with non-motor symptoms, ranging from sensory disturbances to cognitive impairment, epilepsy and cerebellar dysfunction.¹,² HSP may be inherited by an autosomal or X-linked modality. Approximately 50 loci have been mapped so far; three of them representing approximately 50% of all mutations, SPG4 being the cause in 40%, SPG3 in 10% and SPG31 in 5% of all families studied. There were no significant associations between disease progression with genotype, but with the age at onset: in particular, for patients with SPG4...
mutations, disease progression was worst in late-onset disease.

Specifics of the study, disease progression was least in late-onset disease.
evaluated (six sub-items: hip extension, leg abduction, knee flexion, knee extension, ankle flexion and ankle extension). The Five Minutes Walking Test (5MWT) and Spastic Paraplegia Rating Scale (SPRS) were also assessed. For 5MWT participants walked back and forth along a 30-m hallway, turning around cones at each end for five minutes. They were allowed to use their habitual assistive devices at each testing session. Walking improvement on the 5MWT is indicated by positive change scores (in meters). SPRS efficiently reflects the severity of functional problems, comprising also non-motor symptoms, and correlates with disease duration.29 For both Walking Test and SPRS scores, the best results reached by each patient entered the analysis.

H-reflex
H reflex was obtained by delivering rectangular pulses through Ag-AgCl electrodes (10-mm diameter) placed over the tibial nerve at the popliteal fossa (interelectrode distance 20 mm) and recorded from the soleus muscle through Ag-AgCl surface electrodes (10-mm diameter) placed 2 cm apart over the muscle belly. The hip was kept semiflexed (∼110°), the knees slightly flexed (∼150°), and the ankles in ∼10° plantar flexion.25 The current intensity was gradually enhanced to achieve the H-reflex threshold (the minimum stimulation intensity that evoked a reproducible response higher than 50 µV), maximal H reflex (Hmax), and maximal compound muscle action potential (CMAPmax). In order to minimize post-activation inhibition, the pulses were delivered at random time points, ranging from 10 to 20 s. Stimulation began at 0-mA intensity and grew in 1-mA steps up to the intensity reaching the maximal H reflex.25 The signals were amplified and bandpass filtered (3 Hz–3 kHz). We assessed the H-reflex size (peak-to-peak amplitude, mV), and we calculated the Hmax - to - CMAPmax ratio.

F-waves
F waves were elicited with a 25% supramaximal stimulation applied to the tibial nerve and recorded from the AH muscle through a pair of 10-mm surface Ag-AgCl electrodes in a belly-to-tendon configuration. F waves from the abductor hallucis (AH) muscle were obtained by 20 stimuli delivered to the ankle (1 Hz repetition rate).30 In order to prove the absence of muscular activity, we recorded the audio EMG feedback from the same muscles used for MEP recording. The F-wave mean latency (milliseconds), minimal latency (milliseconds), mean amplitude (mV), and mean temporal dispersion (milliseconds) were assessed. The filter setting was 15–1500 Hz, and the skin temperature at the ankle kept above 32°C.

Motor-evoked potentials (MEPs)
A detailed description of the methods used for MEPs recording has been extensively reported elsewhere.25 Transcranial Magnetic Stimulation (TMS) was delivered by a Novametrix Magstim 200 stimulator (Magstim, Whitland, UK) using a flat coil (outer diameter 13.5 cm). The coil was ensured in a constant position over the vertex. MEPs were recorded at rest by two standard, non-polarizable Ag-AgCl surface electrodes (diameter 10 mm; Technomed Europe), one placed over the belly of the abductor hallucis (AH) muscle and the other on the first metatarsophalangeal joint of the toe. Because the AH has been used in many TMS studies both in health and disease, we selected this muscle for our experiments. As reported in previous studies, both legs were evaluated separately, beginning from the right side.29 The stimulation intensity was kept at 120% of resting motor threshold (RMT).34,35 The threshold was set differently for each side and was analyzed at each time point. The current direction was adjusted, with current flowing in the coil anticlockwise for right AH and clockwise for the contralateral side.30 In order to assess MEP changes among different time points, we delivered the stimulation intensity used at baseline; for the assessment of MEP area and amplitude, the stimulator output was the same at each time point. Eight MEPs were collected at 10-second intervals and averaged at each time point. MEPs were amplified and filtered (bandwidth 3 Hz–3 kHz; Nicolet Viking IV P). Different variables were studied: RMT (% of stimulator output), onset latency (milliseconds) and area under the curve (mVms) of the motor response. RMT was measured immediately at the end of stimulation week and at each time interval (T2, T3, T4; see below); the MEP area and latency were assessed offline on MEPs averaged from eight sweeps.

Experimental design
Subjects were studied before and after anodal and sham tsDCS. Every patient received both the treatment named anodal (A) or sham (S) session in a cross-over design (AS or SA sequence) To assign patients to the treatment sequence, we used an alternating allocation design. All patients carried out two experimental conditions held at least three months apart, to avoid carry-over effects. Each session, either anodal or sham, lasted five days a week (20’ twice a day).
scores were assessed by a neurologist, while the electrophysiological recordings were made by a neurologist and technicians and their off-line evaluation by a third examiner, all blinded to the tsDCS polarity. MEPs, H-reflex and F-waves were derived from both sides. Clinical scores, MEPs, H-reflex and F-waves were assessed before tsDCS (T0), immediately at the end of stimulation week (i.e. within few minutes following the final tsDCS session, T1), after one week (T2), one month (T3) and two months (T4).

No pharmacological modification was performed during the week of tsDCS and during the three months between the two experimental conditions. Moreover, no other therapeutic interventions (i.e. physical therapy) were performed during the three months.

Statistical analysis
Values are reported as the mean ± standard error (S.E.). MEP amplitudes were measured peak-to-peak. Nonparametric analyses were used, as all data sets did not pass the Shapiro-Wilk test for normality (P < .05). tsDCS-induced changes in each variable were then assessed with a Friedman test (non-parametric analysis on paired data) with the main factor “time” (four levels: T1, T2, T3 and T4). In order to disclose significant changes at each time point between anodal and sham tsDCS (T1, T2, T3, T4), a Wilcoxon matched-pairs signed test was then applied. Both the electrophysiological measures and clinical scores were normalized to baseline before entering the analysis (according to the formula (T1 - T0)/T0 * 100 + 100). Statistical significance was set at P < 0.05. The data were analyzed using SPSS v. 21.0 for Windows (SPSS Inc.).

Results
Electrophysiology
All patients tolerated the procedure well, without adverse effects. They rarely reported a slight tingling or itching sensation below the stimulating electrodes lasting only a few seconds or disappearing just after wetting the electrode sponges.

All patients completed the neurophysiological assessment. Baseline values did not change among the different experimental sessions (P > 0.2 for all the comparisons made, Wilcoxon test with “stimulation” as factor).

Anodal tsDCS did not statistically modify the MEP variables when compared to sham group, although the anodal polarization leads to a slight reduction in MEP area over time (Table 1; threshold: P = 0.23; onset latency: P = 0.27; area: P = 0.16, Friedman’s test).

None of the remaining electrophysiological measures assessed were significantly changed following tsDCS (P > 0.35, Friedman’s test, for all the comparisons made: relative raw data are reported in Table 2).

Clinical evaluation
The baseline values did not change among different experimental sessions (P > 0.2 for all the comparisons made; Table 3).

The score of the Ashworth scale for lower limbs improved in the anodal compared with sham group, in particular up to two months following the end of stimulation, at T1 (P = 0.0137, Wilcoxon matched-pairs signed test) and T4 (P = 0.0244). Among the sub-items, patients showed a significant improvement in hip flexion (T4: P = 0.016, Wilcoxon matched-pairs signed test) and knee extension (T2: P = 0.0156; T3: P = 0.0078; T4: P = 0.0039, Fig. 1).

Nine patients only completed the clinical evaluation by performing also the Five Minutes Walking Test and the SPRS. No significant change was found when the scores were compared, although there was a general tendency toward improvement in the anodal group (Five Minutes Walking test: P = 0.072, Friedman analysis); no improvement in non-motor symptoms was found, as assessed by the Spastic Paraplegia Rating Scale (P = .83), the Wilcoxon matched-pairs signed test did not reveal significant differences between anodal and sham tsDCS at any time point (P > .1).

Discussion
Thoracic tsDCS improved the Ashworth score in HSP patients. To the best of our knowledge, this study is
the first to investigate the effects of tsDSCS in patients with HSP.

Although tsDSCS mechanisms of action still remain debated, a growing body of evidence suggests that tsDSCS interferes with cortical, corticospinal, and spinal motor output in humans. Since spinal stimulation modulates both alpha and gamma motor neuron activity in animals, anodal tsDSCS could directly inhibit gamma system in humans. In addition, the pre-synaptic inhibition and post-activation depression induced by tsDSCS could reduce spasticity by modulating interneuronal excitability. Spasticity is known to be associated with abnormally strong pre-synaptic inhibition, as well post-activation depression of synaptic actions of group Ia afferents. This activity changes after tsDSCS in the F-waves and H-reflex are in line with those reported in healthy volunteers; the absence of H-reflex changes suggests no modification in small motor neurons, whereas the lack of F-wave effects rules out changes both in large motor neurons and postsynaptic excitability. Among neurophysiological measures, the lack of changes after tsDSCS in the F-waves and H-reflex are in line with those reported in healthy volunteers; the absence of H-reflex changes suggests no modification in small motor neurons, whereas the lack of F-wave effects rules out changes both in large motor neurons and postsynaptic excitability.

Cortical networks could be additional targets of tsDSCS in spasticity. The modulation of cortical GABAergic activity by tsDSCS could improve spasticity dampening the GABAergic tone, at a spinal as well as cortical level. Further support for a combined cortico-spinal modulation comes from a recent study showing that anodal tsDSCS depresses both M1- and peripheral-evoked local field potentials (LFP) in the dorsal horn, possibly reducing maladaptive plasticity that contributes to muscle afferent fibers sprouting and hyperreflexia.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Changes over time in F-waves and H-reflex parameters between anodal and sham tsDSCS. Results are reported as raw data ± S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>F-waves</strong></td>
<td><strong>H-reflex</strong></td>
</tr>
<tr>
<td>Threshold (mA)</td>
<td>Minimal latency (ms)</td>
</tr>
<tr>
<td><strong>Anodal</strong> (mean ± SE)</td>
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</tr>
<tr>
<td>$T_0$</td>
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<tr>
<td>$T_4$</td>
<td>25.0 ± 2.0</td>
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<tr>
<td><strong>Sham</strong> (mean ± SE)</td>
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<td>$T_0$</td>
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<td>20.5 ± 1.8</td>
</tr>
<tr>
<td>$T_4$</td>
<td>21.3 ± 3.8</td>
</tr>
</tbody>
</table>

| Table 3 | Changes in total Ashworth score, 5MWT and SPRS, at baseline and at different time points after tsDSCS, following anodal and sham tsDSCS. Because the raw data did not assume normality, the results are reported here as mean values and interquartile range (IQR). 5MWT: the 5 Minutes Walking Test; SPRS: Spastic Paraplegia Rating Scale. |
|-----------------|----------|----------|----------------|
| Ashworth score  | 5MWT     | SPRS     |
| **Anodal (mean and interquartile)** | | |
| $T_0$ | 21.4 ± 10.5 | 18.6 ± 13.6 | 17.0 ± 12.4 |
| $T_1$ | 17.8 ± 9.5 | 19.5 ± 12.2 | 18.8 ± 12.6 |
| $T_2$ | 19.7 ± 10.0 | 18.6 ± 5.4 | 15.2 ± 5.4 |
| $T_3$ | 17.9 ± 7.5 | 17.8 ± 13.8 | 18.6 ± 13.4 |
| $T_4$ | 16.9 ± 6.5 | 18.6 ± 13.6 | 15.9 ± 11.0 |
| **Sham (mean and interquartile)** | | |
| $T_0$ | 21.3 ± 5.5 | 22.3 ± 15.5 | 20.2 ± 13.3 |
| $T_1$ | 20.1 ± 7.5 | 22.8 ± 17.8 | 19.8 ± 12.1 |
| $T_2$ | 19.6 ± 5.5 | 23.0 ± 17.8 | 18.1 ± 9.8 |
| $T_3$ | 19.8 ± 5.0 | 19.1 ± 16.5 | 17.0 ± 12.4 |
| $T_4$ | 20.0 ± 8.0 | 21.0 ± 14.8 | 18.3 ± 13.5 |
large deletions to nonsense and missense mutations, associated with different disease courses. This heterogeneity could explain the relative increase in Ashworth scores at T₁ and T₄, as observed in the sham group compared with anodal polarization, due to some patients worsened faster than others. Finally, the effects of direct spinal polarization on non-motor features were not assessed in our study; it is important especially in complex recessive spastic paraplegias, as spatacsin/SPG11, ZFYVE26/SPG15 and paraplegin/SPG7.47 From a statistical point of view, although a crossover study does not require a specific number of patients in each group, it was not possible to counterbalance for eleven patients as this number is not a multiple of the two experimental conditions.

Conclusions
This study is the first to investigate the effects of tsDCS in patients with HSP. The results are in line with previous data on spinal cord injuries20 and chronic stroke,21 thereby confirming the efficacy of tsDCS for the treatment of spasticity. Our results may, therefore, contribute to the design of more specific applications in clinical practice; in particular, the use of a combined transcranial and spinal stimulation strategy would be of interest in the wide field of movement disorders, possibly improving motor recovery, as seen in animals.48 Moreover, as the improvement lasts up to two month (T₄) with a subsequent worsening of clinical scores, future studies should provide more frequent stimulation cycles. Another critical point to be assessed in future studies is the target of tsDCS; a combined spinal and cortical stimulation protocol to improve the clinical outcome should be evaluated. Lastly, as in other human diseases, the optimal tsDCS repetition rate and duration to promote clinical improvements remains unknown.

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**Disclaimer statements**

**Contributors** None.

**Declaration of interest** None.

**Conflicts of interest** The authors have no conflict to declare.

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