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The journal represents the practice of a growing, diverse multidisciplinary field responsible for the development and application of devices and techniques to benefit patients by normalizing function and reducing suffering. In-depth reviews, original articles, national and international meeting abstracts, special focus editions and web based educational offerings help the reader to expand their knowledge and understanding of the interface between electrical stimulation, chemical neuromodulation, the nervous system and the patient. Our updates on past and future news of events and activities of the INS and its membership keep the reader abreast of issues related to professional education and development.

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The Effects of Anodal Transcranial Direct Current Stimulation on the Walking Performance of Chronic Hemiplegic Patients

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Objective: To evaluate the effect of a single session of tDCS over the primary motor cortex of the lower limb (M1-LL) vs. placebo on the walking performance in chronic hemiplegic patients.

Patients and Methods: Randomized, cross-over, double-blinded study. Eighteen patients with initially complete hemiplegia and poststroke delay >6 months were included. Each patient received a single session of anodal stimulation (2 mA, 20 min) over M1-LL (a-tDCS condition) and a pseudostimulation session (SHAM condition). The order of the two sessions was randomly assigned, with an 11-day interval between the two sessions. The anodal electrode was centered on the hotspot identified with Transcranial magnetic stimulation. The cathode was placed above the contralesional orbitofrontal cortex. Walking performance was evaluated with the Wade test and the 6-minute walk test (6MWT), gait parameters with GAITRite, and balance with posturography. These tests were performed during and 1 hour after the stimulation. Baseline assessments were performed the day before and 10 days after each session.

Results: The comparison between the 6MWT under a-tDCS vs. SHAM conditions demonstrated a nonsignificant positive effect of the stimulation by 15% during stimulation ($p = 0.360$) and a significant positive effect of 25% 1 hour after stimulation ($p = 0.038$). No significant differences were observed for the other evaluations.

Discussion: These results showed a significant positive effect of a single session of anodal tDCS of the M1-LL in chronic hemiplegic patients. This proof-of-concept study supports the conduct of clinical studies evaluating the effectiveness of a walking training program associated with iterative tDCS stimulation.

Keywords: Hemiplegia, neurostimulation, stroke, tDCS, walking

Conflict of Interest: The authors reported no conflict of interest.

INTRODUCTION

Stroke is the third cause for years of life lost (YLL) and the number of stroke survivors is still increasing, with a worldwide impact of three million years lived with disability (YLDs) in the 2015 (1–3). One of the main causes of disability is gait disorder (4). Although 70‐80% of patients recover the ability to walk after stroke (4,5), sequelae like reduced walking speed, balance disturbance or falls impact daily living activities and return home (5). New techniques in neurorehabilitation such as noninvasive brain stimulation (NIBS) can help to improve motor recovery after stroke (6,7). Among these techniques, transcranial direct current stimulation (tDCS) showed encouraging results regarding the enhancement of motor recovery for poststroke patients in rehabilitation (8).

Extensive research has been conducted to investigate the effects of tDCS on the upper limb (7,9), but few studies have evaluated its effects on the lower limb (LL) (5). Stimulation of the lower limb motor cortex (M1-LL) increases motor-evoked potential (MEP) amplitude of the LL muscles in the healthy subjects (10,11). The feasibility of M1-LL stimulation for motor recovery after stroke was lately evaluated (12–18). Positive effects of tDCS were observed on paretic quadriceps force, on motor control of the paretic ankle (12–14,18), on postural control (13,17,19), and on gait performance (timed up and go) (15) and suggest some improvement of the LL Fugl-Meyer assessment and LL motricity index (16).

These various results suggest that tDCS could be of potential interest for gait rehabilitation following stroke, but the effects of

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tDCS on gait parameters such as speed or endurance remain unknown. As a first approach, such stimulation should be evaluated on stable patients at a chronic stage, considering that motor recovery and gait capacities have reached a plateau (4,20). In the present study, a crossover design was implemented to minimize the effect of interindividual variability (21) and to facilitate intraindividual comparison in a small size sample (22).

The aim of this study was to evaluate the effects of a single anodal stimulation vs. SHAM stimulation (placebo) on quantitative gait parameters (speed and endurance) in chronic hemiplegic patients (at least 6 months). Balance and gait symmetry parameters were additionally evaluated as explanatory variables.

METHODS

Study Design

The investigation took place between January 2014 and April 2015, in the Department of Adult Physical Medicine and Rehabilitation (PM&R) of the University Hospital and in the Inter-University Laboratory of Human Movement Biology (LIBM) in Saint Etienne (France). To the authors' knowledge, no data were found in the literature to calculate the power of the effect. Thus, a two-step design (Gehan method) was used to determine the sample size of the study (23). Following this method, at least 17 patients had to take part in the study to observe an effect of 10% with a β error of 5%. To avoid confounding factors and to facilitate small design trial, a crossover study was conducted. Each patient received real tDCS stimulation (a-tDCS) and a placebo stimulation (SHAM-tDCS). The order of the stimulations (a-tDCS or SHAM-tDCS) was randomized with MATLAB (Mathworks Natick software, Natick, MA). Both stimulations were performed thanks to the Eldith DC-Stimulator Plus device (NeuroConn Gmbh, Ilmenau, Germany). The "study mode" of this device offered the possibility to blind the conditions (a-tDCS or SHAM-tDCS) for the experimenters and patients by the use of stimulation codes provided by the randomization software (24). A one-week washout was observed between the two sessions (i.e., time between the two sessions of tDCS), this duration being considered as long enough to avoid interferences (25). Considering the possibility that some patients might drop out early, difficulties with tDCS stimulation or evaluation tests, additional patients could be included in the study. The study was approved by the local institutional review board and conducted in compliance with the Declaration of Helsinki (26). Signed informed consent was obtained from each participant before his/her inclusion in the study. EudraCT number: 2009-A01244-53.

Participants

Among the 94 patients screened from the database of the PM&R department, 20 patients were included in the study. Hemiplegic patients (initially complete hemiplegia) had a first stroke before the previous past 6 months. They were between 18 and 75 years old, could walk more than ten meters, and were able to make an about-turn without any assistance. Patients with contraindications to magnetic resonance imaging (MRI) or tDCS (such as metallic implants, active implantable medical devices), neurological diseases other than their first stroke or serious medical comorbidity (cardiac, renal or respiratory failure, and active neoplasia) were excluded. Moreover, pregnant women were not being part in the study.

Among the 20 patients included in the study, 2 dropped out, one because of painful knee arthrosis and the other one because of a lack of motivation. In total, 18 hemiplegic patients (6 females/12 males, mean age 57.4 $\pm$ 3.6 years), whose stroke occurred 48 $\pm$ 17 months before their inclusion, were considered for statistical analysis (Fig. 1). Among these participants, 83% had ischemic strokes, 44% had subcortical lesions, and 61% had right-sided impairment (Table 1).

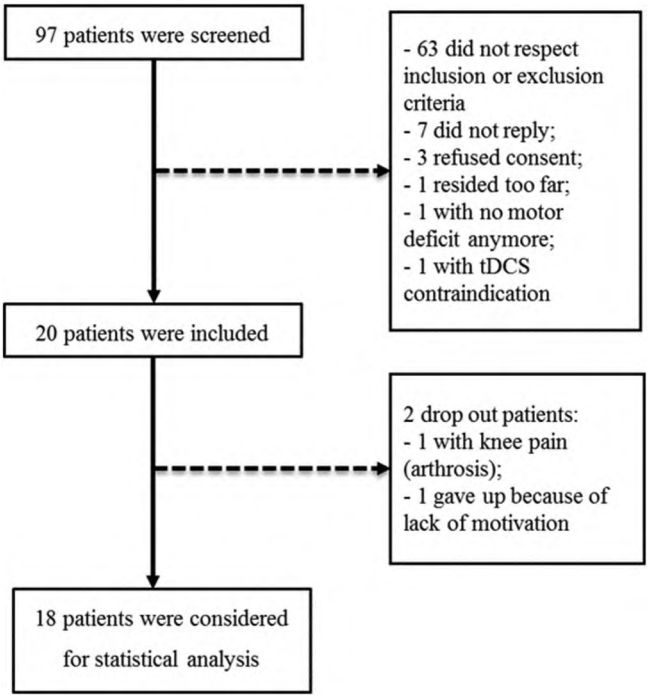

Figure 1. Flowchart.

Protocol

The complete protocol was performed in 22 days and consisted of 5 visits:

- Three evaluation visits: The patients performed the evaluation tests without tDCS. First at the inclusion visit (V_0), and then 10 days (V_2), and finally 22 days after the inclusion (V_4).
- Two stimulation visits (2 days and 11 days after the inclusion): During these sessions, the patients performed the tests with stimulation (a-tDCS or SHAM-tDCS). During 20 min of stimulation, patients were evaluated for all the gait and balance tests (V_1 or V_3). All the tests were repeated 1 hour later (V_{1+1h} or V_{3+1h}).

This protocol is summarized in Figure 2a and the evaluation sessions (Fig. 2b) are described in the following part.

Hotspot Determination

Transcranial magnetic stimulation was used to find the hotspot location on the paretic quadriceps by decreasing the stimulation intensity from 60% to 30% of the maximal stimulation output (MSO) of a Magstim 200 device (Magstim Company Limited, Whitland, Great Britain) with a double cone coil. The patient was sitting at rest. An electromyogram (8 channels, Medtronic, France) was used to detect the signal. Active and reference electrodes were placed on the belly of the vastus medialis of the paretic quadriceps. The ground electrode was on the bony part of the homolateral ankle. The hotspot location was measured as its distance to the nasion along the interhemispheric line. If no MEP was detected at 60% MSO, the nasion-M1 distance was estimated using the brain MRI (patient n°11).

Table 1. Description of the Population.

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Mean	Proportion n (%)
Age (years)	51	53	61	57	57	59	52	62	51	54	44	56	58	74	71	66	48	59	**57.4**	**NA**
Time since stroke (months)	23	50	65	84	16	34	38	99	128	16	28	17	12	19	25	35	53	118	**48**	**NA**
Etiology	I	I	I	H	I	I	I	I	I	I	H	I	I	I	H	I	I	I	**NA**	**15/3 (83/17)**
Hemiparetic side	R	L	L	R	L	R	L	L	R	R	R	R	R	R	R	L	R	L	**NA**	**11/7 (61/39)**
Location	S	S	G	G	C	S	G	G	G	S	S	G	S	C	S	S	C	G	**NA**	**S/G/C (8/7/3) (44/39/17)**

Abbreviations: C: cortical; G: global (cortical and subcortical); H: hemorragic; I: ischemic; L: left; NA: not available data; R: right; S: subcortical.

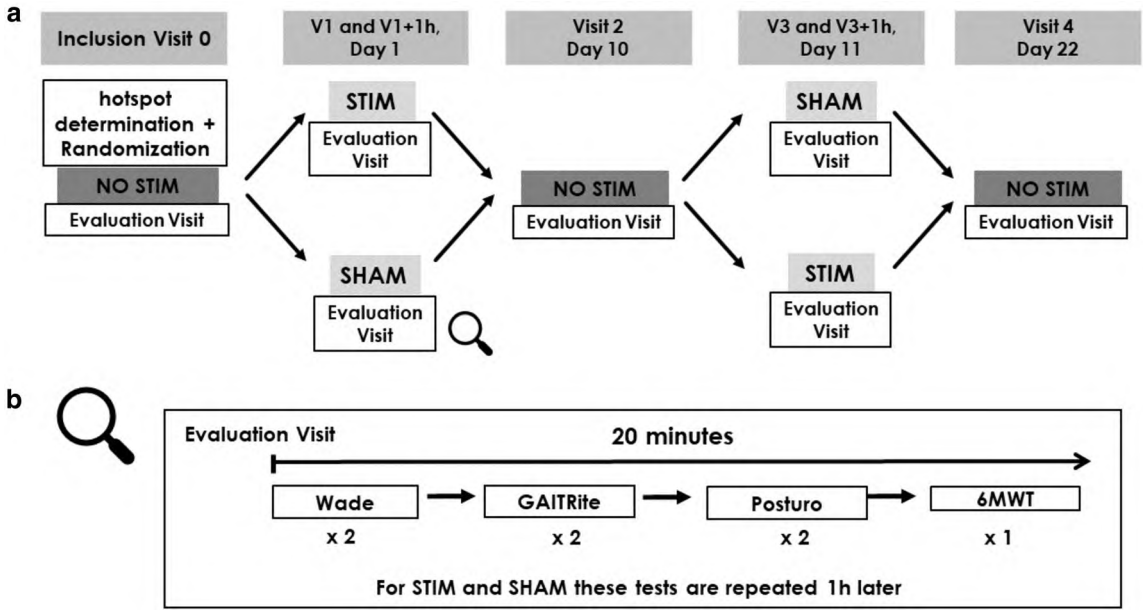

Figure 2. Procole. Abbrevations: SHAM: stimulation visit with placebo; STIM: stimulation visit with anodal tDCS.

tDCS

tDCS was delivered using a direct current stimulator (Eldith DC-Stimulator Plus, Neurconn society, Ilmenau, Germany) via a 25 cm^2 saline-soaked sponge anode located over the leg area of M1 at the location of the hotspot. The reference cathode (25 cm^2) was placed on the forehead above the contralateral orbit. During the tDCS session, the current was delivered for 20 min at 2 mA corresponding to a density of 0.08 mA/cm^2; the safety and efficiency of these parameters had already been proven in the previous studies (27,28). The same procedure was used for the SHAM session, but the current was only delivered for the first 30 sec to reproduce the tingling effect of real tDCS. The electrodes were also kept in place so that the participants did not know which stimulation they were receiving so that the double blind condition was respected (27).

Gait Evaluation

Two gait evaluations were performed: the Wade test for gait speed measurement and the 6-minute walk test (6MWT) for endurance evaluation. During the Wade test, patients had to walk 10 m and return as quickly as possible (23). Patients turned around at a line and were allowed to use walking aids. The results presented for this test are the mean performances of two consecutive evaluations. The walking speed was calculated by dividing the distance by the time taken. The 6MWT consisted of measuring the distance covered walking around a 72-meter long flat loop track during 6 min.

Step length and symmetry were assessed using a gait analysis system (GAITRite, 9 meters length, Biometrics SA; CIR Systems, Inc, Franklin, NJ, USA). Balance was evaluated with the feet together in eyes-open and eyes-closed conditions during a quiet stance of 30 sec for each condition. Recording was repeated twice with a posturography platform (200 Hz frequency; Winposturo, Medicapteurs, France) measuring the excursion of the center of pressure (COP) and the COP trajectory length.

Statistical Analysis

For the Wade test and the 6MWT, the normality of the distribution of the raw data was confirmed with the Shapiro–Wilk test. Parametric statistics were then used for raw data. A repeated measure ANOVA was performed on raw data (6MWT and Wade test) with XLSTAT software. A significant group effect (group starting with placebo stimulation vs. starting with STIM) was observed, as well as a time effect (learning effect) (Fig. 3). To remove these differences between the two groups, patients' performances were scaled on a 0–100 range of progression, 0 being the baseline performance (at V_0) and 100 being the maximum performance increase for the patient:

$$\text{Scaled Performance}(i) = (\text{Performance}(i)\text{-baseline performance})/(\text{maximal performance} - \text{minimal performance})$$

The analysis focused on the progression between groups (i.e., group SHAM-tDCS or a-tDCS), not the progression due the repetition of the tests (differences of performance between subjects who started with SHAM-tDCS or a-tDCS condition). Thus, statistical corrections were made to remove this learning effect. The progression trend over time was computed as the mean performances of all patients at the three evaluation sessions (V_0, V_2, and V_4) (Fig. 4). Finally, this bilinear progression trend (performance as a function of time) was subtracted from patients' performances (Fig. 4). Stimulation effect was computed as the difference between the performance during or 1 hour after the stimulation session and the performance at the baseline evaluation. (Fig. 4). All mean results are given with their standard error, and all bar graphs represent the mean value and the 95% confidence interval. Detrended data were tested as not normally distributed. Consequently, Figure 5 shows the detrended medians and a non-parametric statistical analysis (Wilcoxon paired test) was carried out to compare the detrended variables.

The same method was used for Wade test. The significance level was defined at $p \leq 0.05$. MATLAB (Mathworks) was used for the statistical analysis. After checking the normal distribution with the Shapiro–Wilk test, the effect of a-tDCS on postural evaluations (excursion of the center of pressure, trajectory length of center of pressure) and GAITrite evaluations (step length and duration) was assessed with a *t*-test. A repeated measure ANOVA was also performed on raw data with XLSTAT software. The mean value and 95% confidence interval were also estimated for each of these parameters.

RESULTS

A good tolerance of the stimulation associated with the gait tests was observed. Minor effects were reported by two patients: headache (patient n°9) and transient fatigue (patient n°11). Mean performances for Wade test and 6MWT were, respectively, 0.86 ± 0.22 meters per seconds and 335 ± 70 meters.

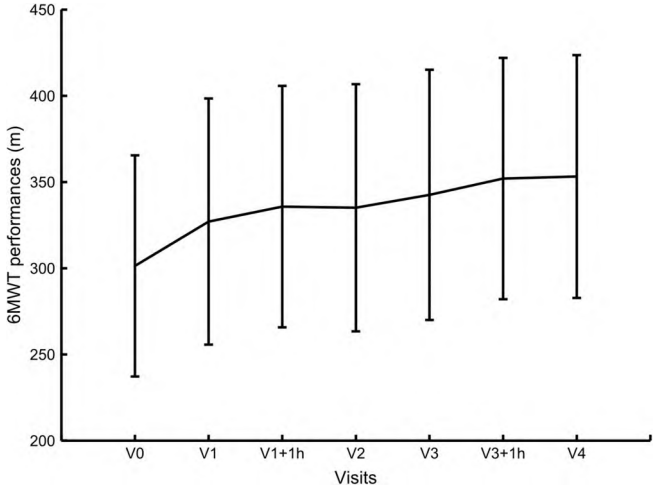

Figure 3. Mean progression of patients during 6MWT. Abbreviations: 6MWT: 6 minutes walking test; m: meters; V0: Visit 0; V1 + 1 h, Visit 1, evaluation test with 1 hour rest after the stimulation; the black line represents the mean value and 95% confidence interval.

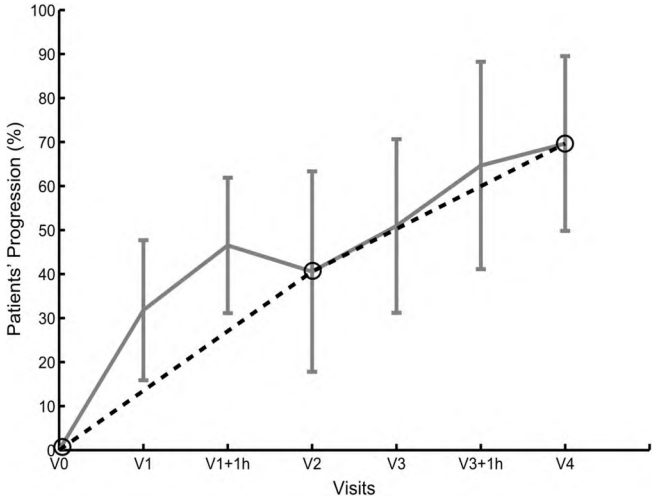

Figure 4. Mean patients' performances for 6MWT scaled to a 0-100 range of progression (plain line) and mean progression trend at the three evaluation sessions (dotted line). Abbreviations: 0: baseline performance; 100: maximum performance increased for the patient; V0: Visit 0; V1 + 1 h: Visit 1, evaluation test with 1 hour rest after the stimulation.

Independent of the condition of stimulation, a continuous improvement of the participants' performances was observed between the first and the last evaluation for both tests (i.e., learning effect): $21.3 \pm 8.7\%$ for Wade test and $18.3 \pm 5.7\%$ for 6MWT (Fig. 3 and 6). This learning effect was confirmed with a repeated measure ANOVA (rm-ANOVA), which showed significant time effect ($F_{4,116} = 25$, $p < 0.0001$ for the 6MWT and $F_{4,116} = 18$, $p < 0.0001$ for the Wade test). An additional group effect was also noticed ($F_{1,116} = 15$, $p < 0.0001$ for the 6MWT and $F_{1,116} = 13$, $p < 0.0001$ for the Wade test).

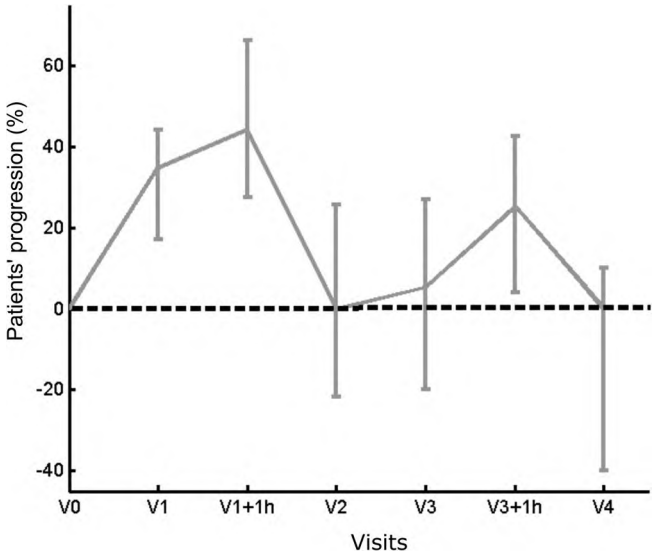

Figure 5. Patient's performances during 6MWT after subtracting the bilinear progression. Abbreviations: 0: baseline performance; 100: maximum performance increase for the patient; V0: Visit 0; V1 + 1 h: Visit 1, evaluation test with one hour rest after the stimulation; gray line is the median progression of all patients after subtracting the median progression trend at the three evaluation sessions (V0, V2, and V4). The gray line represents the median with the first and third quartiles.

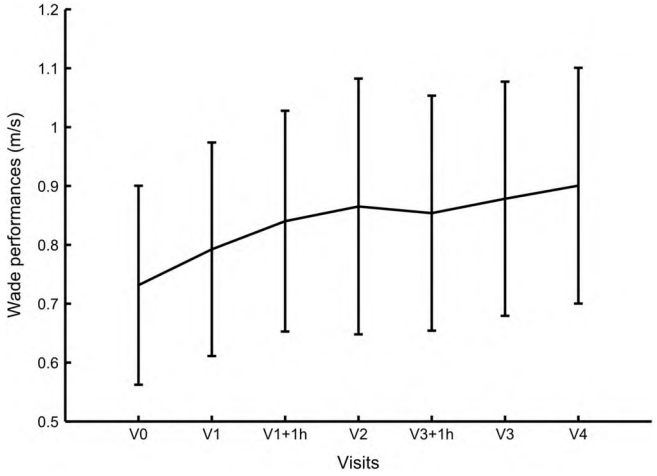

Figure 6. Mean progression of patients during Wade test. Abbreviations: m/s: meter per seconds; V0: Visit 0; V1 + 1 h: Visit 1, evaluation test with 1 hour rest after the stimulation; the black line represents the mean value and 95% confidence interval.

Regarding the 6MWT performances and the Wade test, the effect of a-tDCS or SHAM-tDCS was evaluated as the difference between the performance during or 1 hour after the stimulation and the performance at the baseline evaluation (V0 or V2 according to the order of the stimulation). Wilcoxon paired tests on the detrended data revealed a nonsignificant difference between a-TDCS and SHAM-tDCS effects during stimulation (+15%, $p = 0.360$) and a significant positive difference 1 hour after the stimulation (+25%, $p = 0.038$) (Fig. 7). For the Wade test, the same comparisons on the detrended data showed nonsignificant differences (+ 19.6% $p = 0.11$ during stimulation and + 12.1% $p = 0.23$ 1 hour poststimulation) (Fig. 8). The analysis of posturography (16 patients) and GAITRite (14 patients) with ANOVA for repeated measures showed insignificant group or time effect (excursion of COP: $F_{4,81} = 0$, $p = 1$; trajectory length of COP: $F_{4,81} < 2$, $p > 0.3$; step length GAITRITE: $F_{4,53} < 1.5$, $p > 0.5$; step duration GAITRITE: $F_{4,53} = 0$, $p = 1$). T-test on the raw data

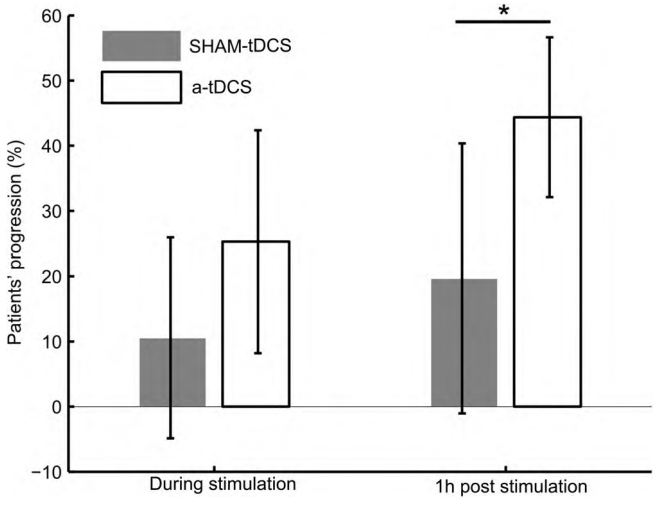

Figure 7. Comparison of the effect of a-tDCS and SHAM-tDCS conditions on 6MWT performance with Wilcoxon test. *: significant level, $p \leq 0.05$; gray bar plot corresponds to the session under placebo stimulation; white bar plot corresponds to the session under anodal tDCS stimulation; the black line represents the 95% confidence interval.

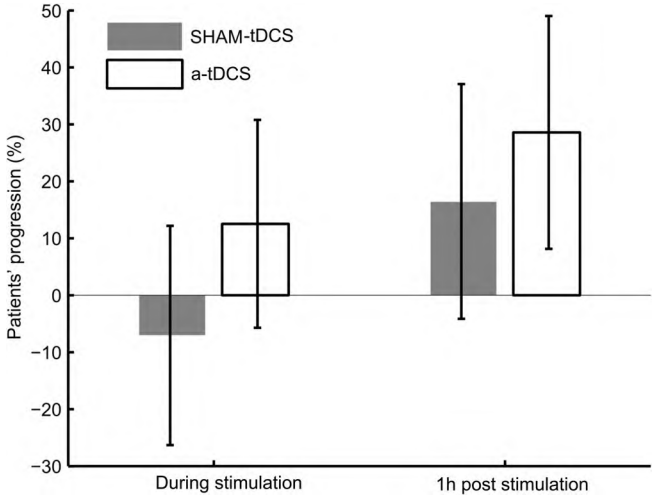

Figure 8. Comparison of the effect of a-tDCS and SHAM-tDCS conditions on the Wade test performance with Wilcoxon test. Description: gray bar plot corresponds to the session under placebo stimulation; white bar plot corresponds to the session under anodal tDCS stimulation; the black line represents the 95% confidence interval.

showed insignificant effect of a-tDCS vs. SHAM-tDCS for all posturography and GAITRite-evaluated parameters (Tables 2 and 3).

DISCUSSION

This study revealed a positive effect of anodal tDCS centered on the ipsilesional M1 of the LL (M1-LL) on gait performance of chronic hemiplegic patients. This effect was significant for endurance performances 1 hour after the stimulation (+25%, $p = 0.038$). A positive but nonsignificant effect was also observed for the Wade test (+ 19.6% $p = 0.11$ per stim and + 12.1% $p = 0.23$ 1 hour poststimulation). These results are the first proof of a beneficial effect of anodal tDCS on gait endurance. They complement the demonstration by Tahtis et al. of an improvement of the time up and go test (TUG) immediately following bi-hemispheric stimulation (2 mA, 15 min) in subacute stroke patients (16).

The potential mechanisms underlying the improvement of gait performances induced by tDCS applied to M1-LL remain mainly speculative. Even though an effect on balance and muscle strength was observed in some studies (13,14,17), no correlations between balance, gait function, and force improvement have been demonstrated for now (12,13,16). As large electrodes were used for the stimulation (5×5 cm in this study), tDCS delivered a nonfocal stimulation over several adjacent cortical areas especially on M1, the primary sensory cortex and the supplementary motor area (SMA). Previous fMRI studies, focused on the upper limb in stroke patients, concluded on a global action of tDCS on the sensorimotor network, including an increased excitability, changes in connectivity within the sensorimotor network of the affected side, and changes in the interhemispheric balance (24). An fMRI study on healthy subjects who underwent 4 sessions of anodal tDCS on M1-LL demonstrated increased activations after anodal tDCS (pre-post comparison and versus SHAM stimulation) regarding a large bilateral sensorimotor network (anterior cingulate gyrus, SMA and somatosensory cortices)

Table 2. Results of the Balance Assessment.

	Mean ± SD	[Minimum-Maximum]	Progression a-tDCS (%) ± SD	Progression SHAM (%) ± SD	*p*-value
Excursion of COP EO (mm^2)	56.3 ± 34.2	[5.5-149.3]	−11.4 ± 78.5	11.1 ± 32.1	0.32
Excursion of COP EC (mm^2)	56.3 ± 34.1	[7.8-149.2]	−4.3 ± 62.3	3.7 ± 32.6	0.67
COP trajectory length EO (mm)	556.0 ± 405.2	[161.5-2068.5]	−52.6 ± 164.6	−37.4 ± 91.4	0.76
COP trajectory length EC (mm)	815.8 ± 522.0	[195.8-3023.4]	−40.5 ± 167.2	−22.4 ± 90.0	0.72

Abbreviations: a-tDCS: anodal tDCS; COP: center of pressure; EC: eyes closed condition; EO: eyes open condition; mm: millimeter; *p*-value: significant difference $p < 0.05$; SD: standard deviation; SHAM: placebo stimulation.

Table 3. Results of the GAITRite Assessment.

	Mean ± SD	[Minimum-Maximum]	Progression a-tDCS (%) ± SD	Progression SHAM (%) ± SD	*p*-value
Step time difference (s)	0.2 ± 0.16	[0.01-0.7]	3.0 ± 29.3	14.0 ± 28.5	0.15
Step length difference (cm)	8.0 ± 5.3	[1.2-25.8]	8.6 ± 47.5	8.3 ± 40.0	0.21

Abbreviations: a-tDCS: anodal tDCS; cm: centimeter; *p*-value: significant difference $p < 0.05$; s: seconds; SD: standard deviation; SHAM: placebo stimulation.

(25). This transient overactivity of the sensorimotor network could support the improved gait endurance and possibly higher gait speed (15).

The positive effect of tDCS was larger and statistically significant 1 hour after stimulation compared to during stimulation. The mechanism of action of anodal tDCS is based on the depolarization of the neuronal membrane, which increases the neuronal excitability (29). The duration of this effect correlates with the duration of the tDCS stimulation, lasting up to 90 min for a 20 min stimulation of the upper limb M1 area (6,27). Specifically for the LL, anodal stimulation was shown to induce significant cortical excitability 20 min after the end of the stimulation which last until 60 min post-stimulation (28).

In the present study, the positive effect on gait endurance concerns chronic stroke patients and may not evidently extend to subacute stroke patients. Similar to our results, Danzl et al. used anodal tDCS on M1-LL and robotic gait training (12 sessions) and found significant enhancement of gait parameters (10MWT or TUG) (30). In contrast, Leon et al. combining anodal tDCS on M1-LL and gait robotic training (20 sessions) found no significant differences in subacute stroke patients (31). This negative result may be related to the very low gait performance at a subacute stage (gait speed <0.1 m/s in Leon et al vs. 0.86 m/s in the present study).

The present results also concern anodal tDCS and may not extend to alternative methods like bi-cephalic stimulation or tRNS. Although bi-hemispheric tDCS showed promising results on the upper limb for stroke patients (32), the median position of M1-LL implies a juxtaposition of both electrodes, which can prevent the current to reach the deep position of M1-LL. Therefore, a cautious approach was taken during this study. Studies should be conducted in stroke patients to compare the effectiveness of anodal, bi-hemispheric tDCS and tRNS (28).

Our sample of patients exhibits a large variability in walking performances and in the effect of tDCS on these performances. This variability was observed in numerous tDCS studies (14,17,27), but we also noticed a large progression across the seven repetitions of gait test. This continuous increase was not previously reported and was hence unexpected. In contrast, one study reported a stable single test–retest performance in stroke patients regarding the 6MWT (33). In this study, the test–retest interval was 30 min, shorter than the one-hour rest period of this study. As recommended by the American Thoracic Society (ATS) (34), a longer inter-test rest period prevents fatigue between two tests. In our study, the conditions of the 6MWT and Wade tests such as fixed starting point and regular spatial references may impact the linear improvement of the patient's performances (20,34). The high number of repetitions could also unmask this learning effect. Repetitive gait tests should hence be used with caution in stroke patients.

Regarding gait analysis and balance, we found no significant changes in explanatory variables that could explain the improvement in endurance 1 hour after the stimulation. To the authors' knowledge, only one previous study reported a significant improvement of balance parameters after anodal stimulation of M1-LL in stroke patients (14). Other studies observed a negative effect of tDCS on balance (16,17). An effect on balance may require more specific stimulation of cortical areas implied in balance control (e.*G. inferior* parietal areas) or the cerebellum (31–33). The transient modulation induced by a single 20 min stimulation session may also be too short to evoke a significant improvement of gait parameters such as gait symmetry (17). Such improvement may require multiple tDCS sessions coupled with intensive gait training (35).

CONCLUSIONS

The main purpose of this study conducted in a small sample was to demonstrate that a minimal 10% positive effect of tDCS, considered as clinically relevant, was required to conclude that further larger clinical studies should be conducted (36). This study reached its purpose, with a significant effect of 25% regarding the 6MWT (1 hour poststimulation). An insignificant effect size of 20% regarding the Wade test was also observed.

Further studies should be carried out to demonstrate a clinical benefit. They should combine motor training program with repeated tDCS (37,38).

Authorship Statement

All authors designed and conducted the study, including patient recruitment, data collection, and data analysis. Dr. E. Ojardias prepared the manuscript draft with important intellectual input from F. Chassagne, O. Azé, and Pr. Giraux and provided funding for editorial support. Dr E. Ojardias and F. Chassagne, O. Azé, and Pr. Giraux had complete access to the study data. We would like to thank Dr. D. Rimaud and M. Rimaud for their editorial support during preparation of this manuscript.

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