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Transcranial direct current stimulation associated with physical-therapy in acute stroke patients - A randomized, triple blind, sham-controlled study

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ABSTRACT

Background: Transcranial Direct Current Stimulation has been increasing in popularity in the last few years. Despite vast amounts of articles on the use of tDCS on stroke patients, very little has been done during the acute phase.
Objectives: Measure the effects of tDCS on functional and sensory outcomes throughout the first year post onset of stroke.
Methods: 50 acute stroke patients were randomized and placed into either the treatment or sham group. Anodal tDCS was applied (2 mA, 20 min) 5 times a week during the first month post stroke. Patients were evaluated with the Wolf Motor Function Test, the Semmes Weinstein Monofilament Test, the Upper Extremity section (UEFM), the Lower Extremity section (LEFM) and the Somatosensory section of the Fugl Meyer Test, the Tardieu Spasticity Scale, the Stroke Impact Scale (SIS), the Hospital Anxiety and Depression Scale (HADS) and the Barthel Index. Evaluations were held at 48 h post stroke, week 1, 2, 3, 4, 3 months, 6 months and 1 year.
Results: There were statistically and clinically significant improvements after tDCS in all functional motor outcomes, and somatosensory functions. Differences between both groups for the main outcome (WMFT time) were 51% ($p = 0.04$) at one month, and 57% ($p = 0.02$) at one year.
Conclusion: tDCS seems to be an effective adjuvant to conventional rehabilitation techniques. If applied in the acute stages of stroke, functional recovery is not only accelerated, but improved, and results are maintained up to one-year post stroke.

Introduction

In the past three decades, transcranial direct current stimulation (tDCS) has become an increasingly popular technique [1]. The use of tDCS in stroke research has gained particular interest, as both the online and offline effects tDCS can improve functional outcomes [2]. Among these effects, tDCS has been shown to improve inter-hemispheric inhibition (where the unrestricted inhibition from the healthy hemisphere further impedes the lesioned side) by modifying local cortical excitability [3] (either by improving the lesioned side's excitability, reducing the inhibition from the healthy side, or a combination of both) [4]. tDCS has also been shown to improve regional cerebral blood flow [5], which is beneficial by reducing inflammation and protecting neurons in the ischemic regions [6]. These online effects last throughout the stimulation, but the long-term or (offline) effects of tDCS are likely due to mechanisms similar to long-term potentiation or depression, where regular stimulation of a nerve ending can improve synaptic strength [7], as well as neurogenesis [8] and improved activation of supplementary cerebral areas [9].

The majority of papers focus on chronic stroke patients [10], most probably because there is relatively little variation in the evolution of chronic stroke recovery [11]. The overall effects of tDCS seem positive, as it promotes functional recovery [10]. Very few articles look at the effects of tDCS on acute stroke patients, and even fewer have a sufficient follow-up period [10]. This, despite the fact

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that it is now commonly accepted that the sooner rehabilitation is applied after stroke, the better the functional outcomes [12]. The available articles are contradictory, some portraying tDCS as beneficial in stroke recovery [13,14], others finding no effects at all [15,16]. Even less research has been done on the effects of tDCS on superficial somatosensory recovery in acute stroke patients.

The aim of this study was therefore to measure the effects of tDCS during the first month post onset of stroke on functional motor and somatosensory outcomes and to observe these outcomes during the first year post onset.

Materials and methods

Trial design

In this randomized, triple-blinded, sham controlled, parallel study, acute stroke patients received either 20 sessions of anodal tDCS or sham tDCS in addition to conventional rehabilitation, and were evaluated periodically throughout the first-year post onset. The allocation ratio was 1:1.

Participants

The stroke patients included in this study were consecutively recruited from the Liège University Hospital's Neurovascular Unit (Fig. 1). Patients aged between 18 and 80 years old, presenting their first ever symptomatic ischemic stroke confirmed by CT or MRI were eligible for the study. Patients were however excluded if they presented one of the following: inability to sign or understand the consent form, one "yes" in the high and relatively high risk sections of the TSST [17] (such as implants in their body that may be triggered or heated by electrical current, CNS-active medication, nicotine, alcohol or other substance use) or hemineglect. These exclusion criteria were similar to those found in other neuromodulation trials with stroke patients [10].

Intervention

Once randomized into one of the two groups, patients received intensive physiotherapy and occupational therapy for functional improvement in order to increase somatosensory functions, postural and motor control. Rehabilitation therapy was tailored to meet all patients' deficits, and lasted a total of 2 h per day, 5 days per week (Monday to Friday).

In addition to rehabilitation therapy, patients received either anodal tDCS or sham tDCS, starting 48 h post onset. The electrodes, both 25 cm^2, were placed on their head with the anode placed over the primary motor cortex of the lesioned side and the cathode over the contralesional eye (C3/Fp2 or C4/Fp1) (this model is the most frequently used in stroke research [10]. The electrodes were attached using a neoprene EEG cap, to deliver either a continuous current or no current and at a rate of 5 times per week for 4 weeks. tDCS lasted 20 min at 1 mA, with a 15 s ramp up and ramp down. Sham tDCS consisted of a 15 s ramp up followed by a 15 s ramp down of the current. This method has been shown to be efficient for blinding patients [18]. tDCS was applied systematically in the morning, prior to rehabilitation, so as to standardize the intervention and potentiate rehabilitation. The device used was a NE STARSTIM tCS® (Barcelona, Spain).

Outcome measures

Outcomes were measured at 48 h post stroke (T0), 1st week, 2nd week, 3rd week, 4th week, 3rd month, 6th month and 1 year, and were measured on two consecutive days, so as not to exhaust the patient.

The outcomes measured were the Wolf Motor Function Test (WMFT), the Semmes Weinstein Monofilament Test (SWMT), the Upper Extremity section (UEFM), the Lower Extremity section (LEFM) and the Somatosensory section of the Fugl Meyer Test, the Tardieu Spasticity Scale, the Stroke Impact Scale (SIS), the Hospital Anxiety and Depression Scale (HADS) and the Barthel Index.

Adverse effects were systematically measured after each tDCS session using a questionnaire similar to the one proposed by Brunoni [19].

Sample size

Sample size calculations were based on a pilot study [20] in order to achieve a clinically significant difference of 1,5 s [21] in the WMFT after one year when comparing anodal tDCS to the sham stimulation. A power analysis [22] revealed the necessary sample size to be $n = 21$ per group to achieve improvements with an $\alpha = 0.05$ and β at 95%. Based on our previous study, we compensated for a 15% drop-out rate, and a 5% decease rate at one year [23]. Therefore, a minimum of $n = 25$ patients per group were recruited. These results are the same as Rabadi et al. [24] and Rossi et al. [15] found in their sample size calculations.

Randomization

Patients were recruited by a third party physical therapist. Patients were randomly attributed to one of the two groups by using a system of shuffled opaque envelopes containing a code for the stimulator. The machine was programmed by a third party, to ensure that both patient, rehabilitation therapists, researchers who performed the stimulations and evaluators were all blinded.

Statistical analysis

The Shapiro-Wilk test was used to test normality. Data is presented as mean (±standard deviation). To compare the groups for baseline homogeneity and throughout the different evaluations, we used the Student *t*-test.

A 2-way ANOVA was applied to all outcome measures (WMFT time, WMFT Score, WMFT strength, WMFT hand dynamometer, UEFM, LEFM and the Somatosensory section of the Fugl Meyer, Barthel Index, HADS and the SIS). The "time" point is used as the within-patient factor, and the "Treatment" as between-patient measure.

Finally, Cohen's D was used to estimate the effect size of treatment.

Statistical significance was accepted at $p < 0.05$. Statistica (version 13.3 for Windows) software was used for statistical analysis.

Ethics committee

The study was approved by the institutional ethics committee (process number: B707201629972), and complied with the ethical standards of the World Medical Association (Declaration of Helsinki). Written informed consent was obtained from each of the subjects.

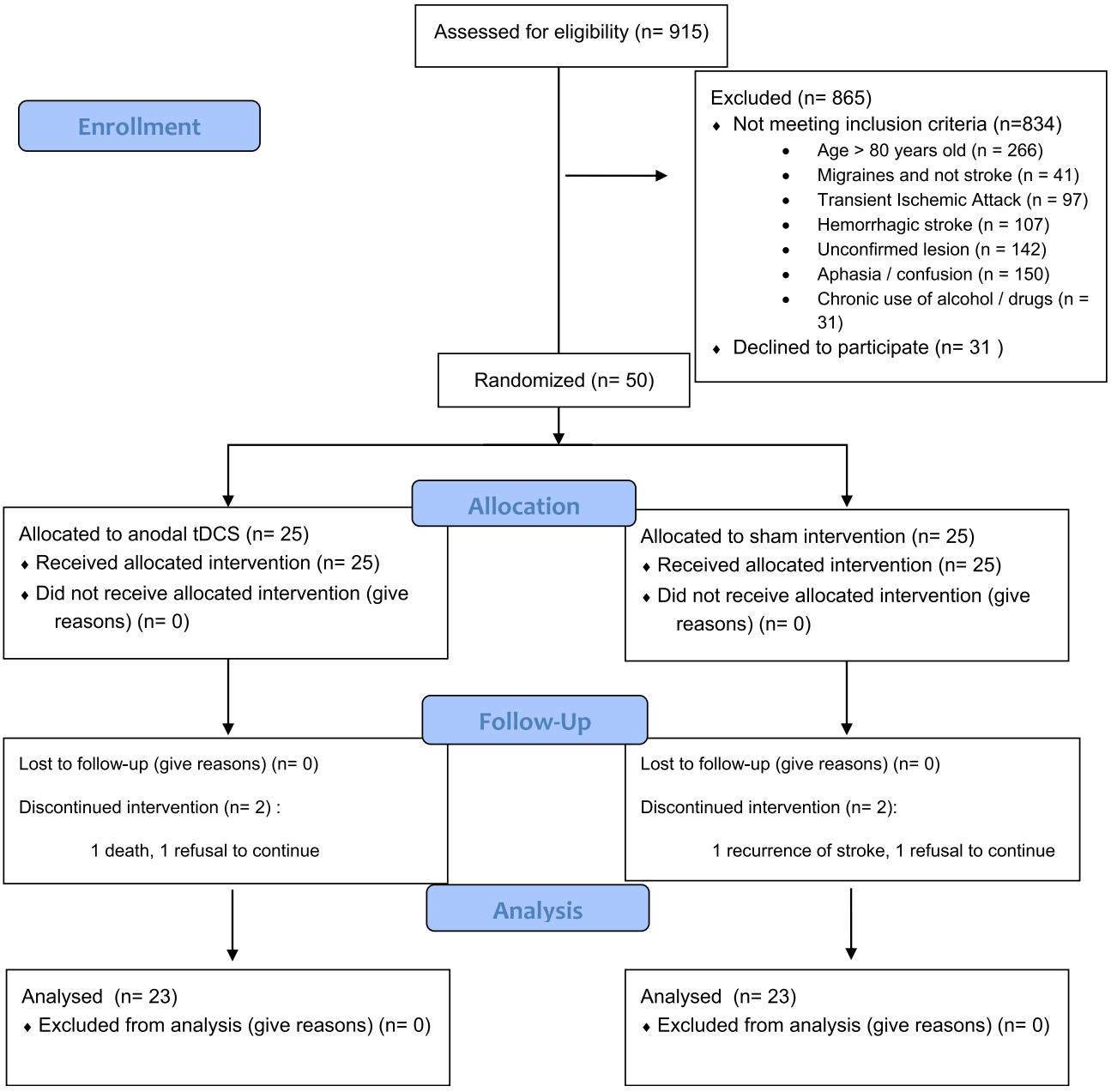

Fig. 1. Consort patient flow chart.

Results

Patient data

A total of 915 patients were screened for eligibility to achieve 50 that met our inclusion criteria, and were randomized into one of the two groups (Fig. 1). Both groups were similar in terms of age, lesion location, gender of patients and baseline treatment performances (Table 1). All patients were right handed.

All patients ($n = 50$) tolerated the treatment program, the side effects being similar between sham and the treatment group. Overall, 40 patients (80%) felt a slight tingling (22 in the tDCS group, and 18 in the sham group), 27 (54%) itching (15 in the tDCS group, and 12 in the sham group), 20 (40%) described a burning sensation (9 in the tDCS group, and 11 in the sham group) (but besides a slight local hyperaemia there was no signs of burns) and 2 (4%) patients (both in the treatment group) reported a slight headache, but estimated their discomfort at 2 and 3/10 on an EVA and did not require treatment to stop. No other serious side effects were noted. These results are similar to those found in other articles [25].

All patients underwent all stimulation sessions. Four patients dropped out of the study (two refused to continue (one in each group, both at 3 months post onset). One patient in the placebo group had a second stroke between 3- and 6-months post onset and was therefore excluded after the 3-month evaluations. One patient in the treatment group died (unrelated road accident) between the 6 month and one-year evaluation and was excluded after the former). Therefore, 46 patients were included in each analysis and have finished the study.

Primary functional outcome

Significant differences were seen in both groups when compared to baseline from the first week onwards ($p = 0.0004$ for

Table 1
Patient demographics and baseline assessments for both groups. Values are in mean (±SD) (range), MCA = Medial Cerebral Artery, ACA = Anterior Cerebral Artery, IC = Internal Capsule.

	Anodal tDCS	Sham tDCS	*P* value
Age (years)	62.48 (±11.86) (39–80)	63.48 (±12.94) (41–80)	0.78
Gender (males/females)	15/10	18/7	0.38
Stroke Location	10 ACA/7 MCA/8 IC	10 ACA/5 MCA/10 IC	0.47
Type of stroke	25 Ischemic	25 Ischemic	/
Handedness	25 Right Handed	25 Right Handed	/
Stroke Hemisphere	15 Right/10 Left	13 Right/12 Left	0.58
WMFT Time	229 (±235.38) (45–899)	233 (±260.36) (44–870)	0.95
WMFT Score	49.72 (±13.15) (24–70)	46.08 (±13.58) (2470)	0.96
WMFT weight (test #7) (kg)	4.76 (±2.33) (0–9)	4.4 (±2.69) (0–8)	0.61
WMFT handgrip strength (test #13)	18.2 (±8.24) (2–32)	17.92 (±9.7) (1–33)	0.91
Tardieu	0	0	/
Barthel index	61.6 (±21.3) (25–90)	64.4 (±19.54) (25–90)	0.63
HADS	18.4 (±10.02) (2–34)	18.12 (±9.16) (2–34)	0.92
SIS	176.12 (±95.79) (7–311)	190.84 (±93.34) (6–312)	0.58
Semmes Weinstein total (g)	110.17 (±196.79) (12.16–962.8)	99.78 (±182.48) (18.4–803.4)	0.85

the sham group and $p = 0.0001$ for the tDCS group). At the end of one year, there was a significant effect of "time" ($F = 35.65$, $p = 0.0001$) and "time by treatment" ($F = 7.83$, $p = 0.0001$) (Table 2). Significant differences between groups appeared only after week 4, where the average difference between treatment groups for the WMFT time was 100 s ($p = 0.04$) or a difference of 51%, and this difference was maintained until the end of the study (101 s ($p = 0.02$) or a difference of 57%) (Fig. 2). An *ad-hoc* analysis showed no significant correlation between age and improvements (at one-year $R = 0.05$ $p = 0.84$).

Secondary functional outcomes

At the end of follow-up (1-year post onset), the two-way ANOVA showed significant effects of "time" but also "time by treatment" for almost all outcomes at one year (except for the SWMT ($F = 0.93$, $p = 0.48$) and the somatosensory section of the FMMA ($F = 6.75$, $p = 0.09$) (Table 2). Significant differences between treatment groups are seen from week 2 (for the amount of weight lifted in the 7th item of the WMFT) but most of the significant results appear during weeks 3 and 4 (Fig. 2) and remain significantly different until the end of the study (except for the somatosensory section of the FMMA which is no longer significantly different at one year). Spasticity was similar throughout the tests for both groups.

Self-reported outcomes

The Barthel index showed a significant effect of "time" and "time by treatment", as did the HADS and SIS (Table 2). However, when comparing both groups at a given time, only significant differences were seen in the HADS from week 3 onwards. It should be of note that the Barthel Index scores hovered above the significance limit from week 4 ($p = 0.07$) to 1 year ($p = 0.06$) (Fig. 3).

Effect size

Cohen's *d* was calculated at 1 year for the main functional and somatosensory outcomes. The WMFT time and score's *d* was 1.1, the WMFT hand grip strength (HGS, item 14 of the WMFT) was 0.99, the WMFT weight lifted was 0.8, the SWMT was 0.69. These effect sizes are considered medium to high.

Lesion location

A retrospective analysis showed a significant effect ($F = 94.61$, $p = 0.00001$) of lesion location on the WMFT time recovery item, in favour of the middle cerebral artery. When analysed by group, the treatment group showed a significant effect ($F = 76.8$, $p = 0.000001$) in favour of the middle cerebral artery, similar to the sham group ($F = 172.48$, $p = 0.000001$). This significant effect is most probably due to the territory that this artery supplies (the face and upper limb), which could explain not only the higher initial deficit, but the proportionately faster recovery time.

Discussion

The aim of this study was to measure the effects of tDCS during the first month of stroke on functional motor and sensory outcomes, and to observe the effects during the first year post onset.

The primary finding of the present study is that tDCS, when applied during the acute stage of stroke, significantly improves functional outcomes, and that these improvements are maintained

Table 2
2-way ANOVA results for the different outcomes.

Outcome	Effect of « Time »	Effect of « Treatment »	Effect of « Time x Treatment »
WMFT time	$F = 35.65$, $p = 0.0001$	$F = 2.19$, $p = 0.146$	$F = 7.83$, $p = 0.0001$
WMFT score	$F = 358.8$, $p = 0.0001$	$F = 6.6$, $p = 0.015$	$F = 59.6$, $p = 0.0001$
WMFT weight	$F = 72.47$, $p = 0.0001$	$F = 4.42$, $p = 0.041$	$F = 17.88$, $p = 0.0001$
WMFT Handgrip Strength	$F = 143.3$, $p = 0.0001$	$F = 4.0$, $p = 0.051$	$F = 59.6$, $p = 0.0001$
Barthel Index	$F = 85.48$, $p = 0.0001$	$F = 1.44$, $p = 0.237$	$F = 11.67$, $p = 0.0001$
HADS	$F = 45.87$, $p = 0.0001$	$F = 4.81$, $p = 0.034$	$F = 3.46$, $p = 0.001$
SIS	$F = 92.21$, $p = 0.0001$	$F = 0.55$, $p = 0.464$	$F = 11.83$, $p = 0.0001$
SWMT (total)	$F = 11.24$, $p = 0.0001$	$F = 1.18$, $p = 0.282$	$F = 0.93$, $p = 0.481$
FM-UE	$F = 173.1$, $p = 0.0001$	$F = 2.5$, $p = 0.123$	$F = 28$, $p = 0.0001$
FM-LE	$F = 71.47$, $p = 0.0001$	$F = 3.79$, $p = 0.058$	$F = 9.74$, $p = 0.0001$
FM Sensitivity	$F = 55.24$, $p = 0.0001$	$F = 2.94$, $p = 0.094$	$F = 6.75$, $p = 0.094$

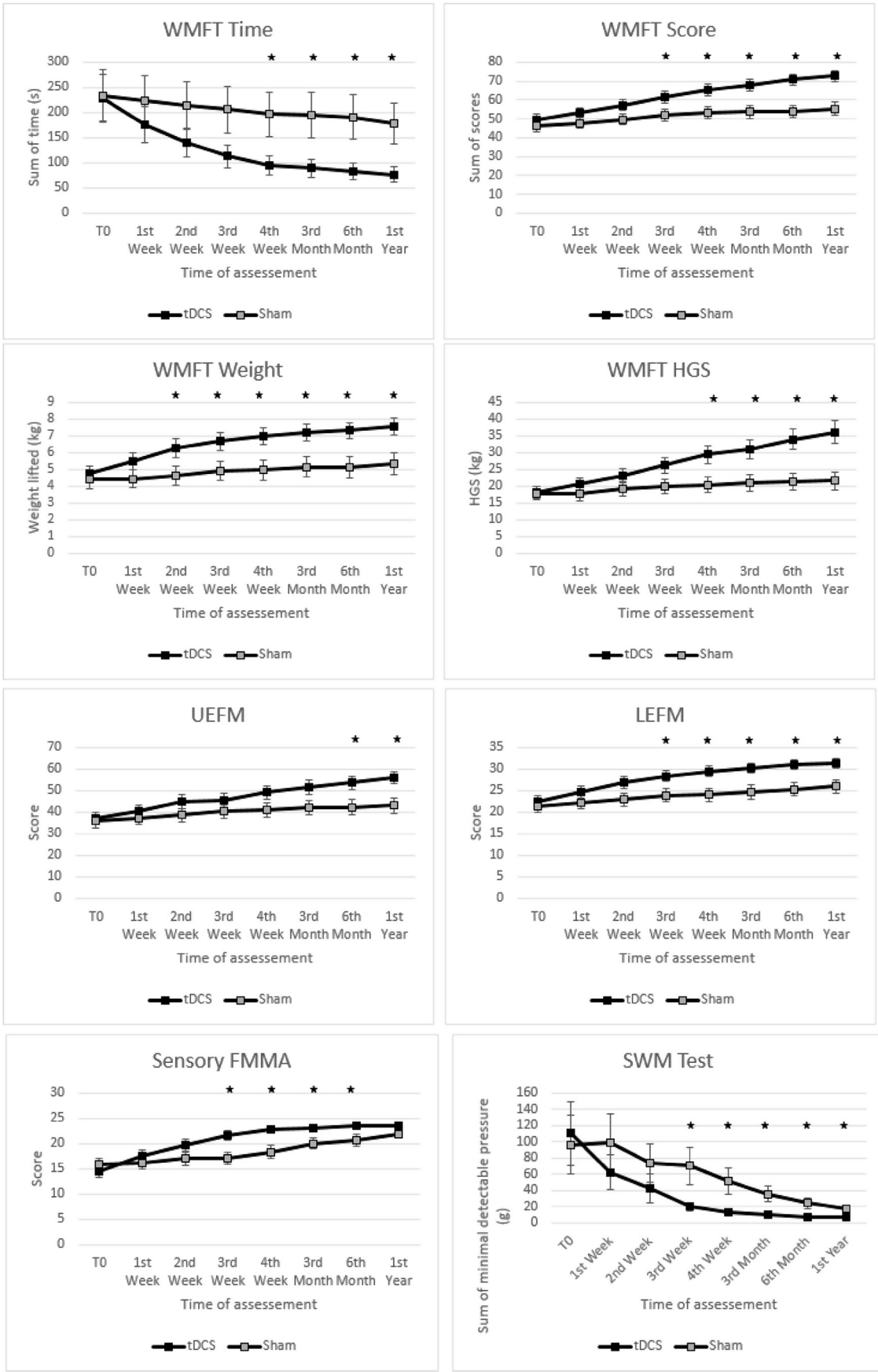

Fig. 2. Changes in functional outcomes over the course of one year. Data is expressed as mean ± SE. Asterisks indicate significance ($p < 0.05$).

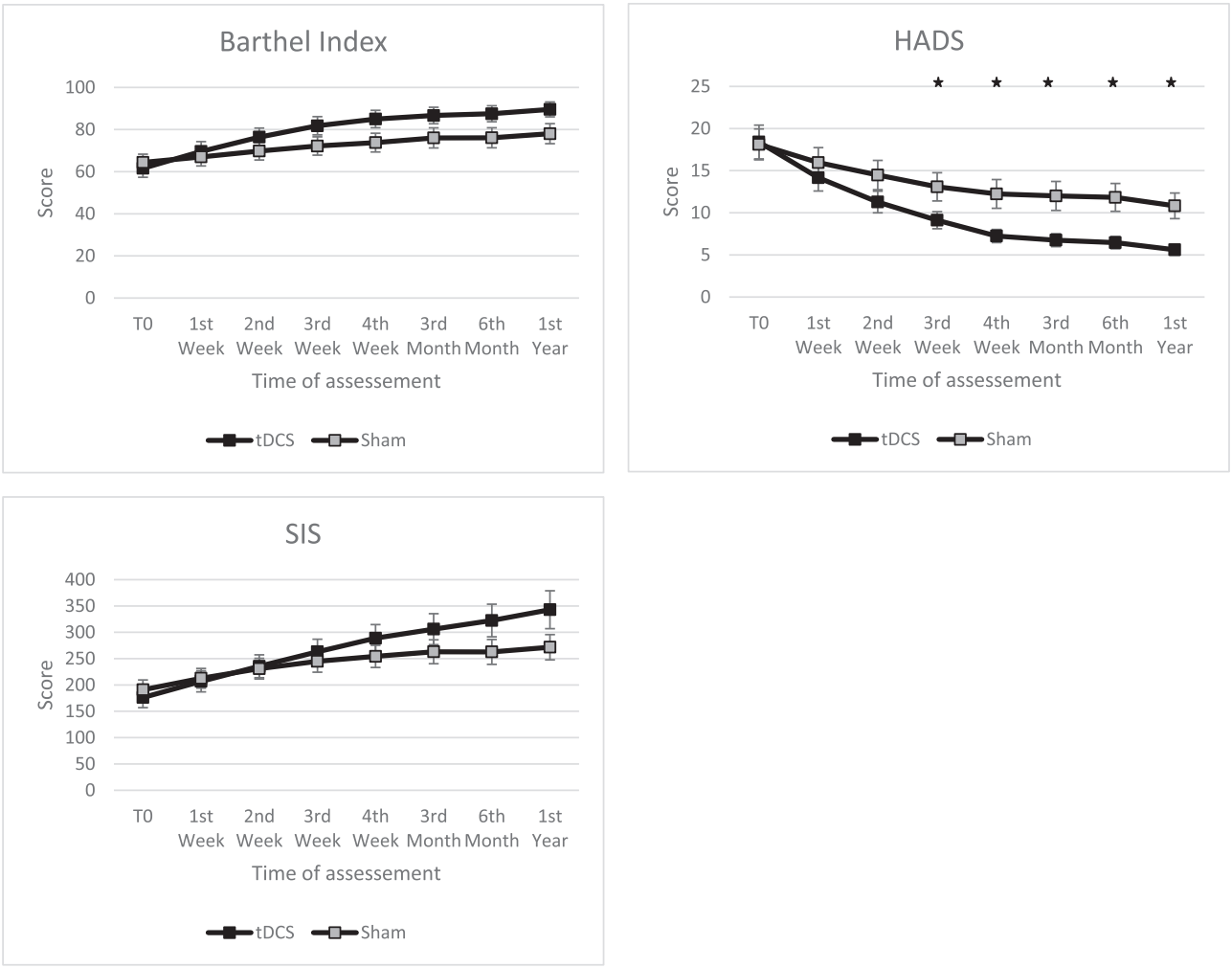

Fig. 3. Changes in self-reported outcomes over the course of one year. Data is expressed as mean ± SE. Asterisks indicate significance ($p < 0.05$).

for at least a year after onset. However, the degree of improvements was extremely surprising. Other authors have studied the effects of tDCS in the acute stages of stroke, such as Andrade et al. [13], who, at best, found a difference of around 34% after 10 sessions of tDCS. Sattler et al. [14], after 5 sessions, found similar effects to ours (53%). Other authors have not found any significant differences after 5 [15,16] or 10 [24] sessions of tDCS in the acute phase of stroke. The lack of results could, in part, be due to the limited number of sessions (significant differences in the current study were only seen after 3 weeks (or 15 sessions) of stimulation). The cumulative effect of tDCS sessions has previously been described [26], but not over as long of a period as our study did, and follow-up has never been for as long (some authors have looked at 6 months post stroke [27], but never a year).

Surprisingly, the somatosensory effects of tDCS weren't as pronounced as were hoped. Despite being placed over M1 of the affected side, the excitatory electrode overlapped S1, and therefore should have, to some degree, led to improved somatosensory outcomes. To the best of our knowledge, only one article analysed the effects of tDCS on somatosensory functions in the acute stroke setting [28], and they found that there were significant improvements to somatosensory outcomes. We found significant differences between the treatment and sham group in terms of somatosensory functions as measured by the SWMT, from the third week until the final evaluation. However, for the treatment group, the results remained stable after 3 months. This could be due to a ceiling effect, or that somatosensory functions were fully recovered, as the values at 3 months are considered normal sensory values. Another potential explanation could be the grading used in the devices: Between the thickest level and the second thickest level of the SWMT is a difference of 120 g, but only 80 g between the second and third thickest. The difference is reduced exponentially between each level, and this could reduce the precision of the measurement. An electronic version that measures the exact pressure threshold could have improved the precision of the results. There were also significant differences in the Somatosensory section of the FMMA from three weeks onwards, but the final 1-year evaluation found no differences between the group. It could be a ceiling effect of the evaluation, where the maximum score was reached by virtually all the patients by this time (but was reached at 6 months for the treatment group, and only at 1 year for the sham group).

Not only were the effects of tDCS objectively measured by an evaluator, but patient's self-reported outcomes were also significantly affected by tDCS. In part, this could simply be due to the natural evolution of stroke recovery, but it also could be due to frontal lobe effects of tDCS [29]. This is confirmed by the significant effects of tDCS on the HADS scale.

The Barthel Index almost reached statistical significance after the 4 weeks of stimulation, and the differences were maintained until the end of the study. There seemed to be a ceiling effect in the

treatment group, as most subjects reached the maximal score by week 4. This could potentially explain the lack of statistically significant differences between the groups. The SIS was not statistically significantly different between the sham and treatment groups. However, according to Lin et al. [21] we reached clinically significant differences from week 3 onwards.

As stated previously, the online (re-balancing interhemispheric inhibition [4], improving regional cerebral blood flow [5], and modifying local cortical excitability [3]) and offline effects (LTP and LTD-like effects [7], increasing activation of supplementary cerebral areas [9] and even neurogenesis [8]) of tDCS could contribute to the improved functional recovery post stroke.

The medium to high effect sizes are slightly higher than those summarised by Butler et al. [30], with a sample size of 25 subjects per group. According to Lin et al. [21], a minimal difference of 1,5 to 2 s is considered clinically significant. The significant difference of 100 s ($p = 0.04$) between the treatment and placebo groups after one year therefore hints at the clinical relevance of combining tDCS in the rehabilitation of acute stroke victims.

The screening criteria were similar to those found in other neuromodulation trials with stroke patients [10], however it should be noted that most of these screening criteria are based off of TMS protocols, and that the relevance could be different when applying tDCS, as there are no general exclusion criteria for tDCS [31].

The large standard deviations could, in part, be due to the heterogeneity of the lesion locations, but also due to the interindividual variability in responsiveness to tDCS. There seems to only be about 60% of subjects who respond to tDCS [32]. However, this variability decreases as time progresses, potentially due to a ceiling effect of the tests. The variability could be considered as a limitation of the current study. An *ad hoc* evaluation to see if tDCS affected patients differently depending on their age showed no correlation. This is interesting, as other authors have found that tDCS has different effects on elderly subjects when compared to younger subjects [33,34] (however these studies only look at healthy subjects). The choice was made to look at the effects of tDCS, indiscriminately of stroke lesion location, to best apply tDCS in a "real-world clinical setting" [15,35]. Another limitation was only stimulating M1 (and not specifically the region of the brain affected by the stroke) and only one type of current. There is a general lack of consensus on the most efficient montage [36] in stroke, and further research to compare the long-term differences of montages should be done. Future articles should also include neurophysiological data in the long term, to see if they follow the same trend as functional data.

Conclusion

This is the first study that looks at the effects of repetitive tDCS during the first month post onset of stroke and follows patients through the first year of their recovery. There is a statistically and clinically significant improvement after tDCS in all functional motor outcomes, and somatosensory functions are improved. However, it is the combination of tDCS with rehabilitation, and not simply the electrical stimulation, that allows for improved functional outcomes. If applied in the acute stages of stroke, functional recovery is not only accelerated, but improved, and results are maintained up to one-year post stroke.

Declaration of competing interest

The authors declare that there is no conflict of interest. The authors declare that the results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

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