No add-on effects of Unilateral and Bilateral Transcranial Direct Current Stimulation on Fine Motor Skill Training Outcome in Chronic Stroke. A Randomized Controlled Trial

Benedikt Taud
Charité Universitätsmedizin, Neurocure Cluster of Excellence, Berlin

Robert Lindenberg
Department of History, Philosophy and Ethics of Medicine, Heinrich Heine University, Düsseldorf

Robert Darkow
Charité Universitätsmedizin, Neurocure Cluster of Excellence, Berlin

Jasmin Wevers
Charité Universitätsmedizin, Neurocure Cluster of Excellence, Berlin

Dorothee Höflin
Charité Universitätsmedizin, Neurocure Cluster of Excellence, Berlin

Ulrike Grittner
Charité Universitätsmedizin, Institute of Biometry and Clinical Epidemiology, Berlin

Marcus Meinzer
Universitätsmedizin, Department of Neurology, Greifswald

Agnes Flöel (✉ agnes.floel@med.uni-greifswald.de)
Universitätsmedizin, Department of Neurology, Greifswald

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Abstract

**Background:** Transcranial direct current stimulation (tDCS) may improve motor recovery after stroke. This study investigated if uni- and bihemispheric tDCS of the motor cortex can enhance fine motor training outcome and transfer to clinical assessments of upper motor function.

**Methods:** In a randomized, double-blinded, sham-controlled trial, forty chronic stroke patients underwent five days of fine motor skill training of the paretic hand with either unilateral or bilateral (N=15/group) or placebo tDCS (N=10). Immediate and long-term (three months) effects on training outcome and motor recovery (Upper Extremity Fugl-Meyer, UE-FM, Wolf Motor Function Test, WMFT) were investigated.

**Results:** Trained task performance significantly improved independently of tDCS in a curvilinear fashion. Anodal, but not dual tDCS resulted in a steeper learning curve on the UE-FM. Neither training nor combined training-tDCS improved WMFT performance.

**Conclusions:** Fine motor skill training can facilitate recovery of upper extremity function. Minimal add-on effects of tDCS were observed.

**Clinical Trial Registration-URL:** NCT01969097 retrospectively registered on 25/10/2013.

Background

Transcranial direct current stimulation, a non-invasive brain stimulation technique, can improve motor training outcome in stroke\(^1\). So far, few studies have investigated the effects of unilateral and bilateral tDCS on fine motor skill training outcome. This training may be particularly suited to improve motor function in severely impaired patients lacking preserved extensor muscle function for more complex training paradigms\(^2,^3\). A previous study that administered unilateral M1-tDCS concurrently with four weeks of daily grip force training failed to show stimulation effects. However, tDCS was administered at a very low current intensity (0.5mA). The present study aimed to address three open questions: (1) Does fine motor skill training improve trained motor function, and/or generalize to clinical assessments of upper extremity function in chronic stroke?; (2) If immediate and long-term training gains occur, are they enhanced by concurrent unilateral or bilateral M1-tDCS?; (3) Does unilateral or bilateral tDCS result in differential transfer effects? We hypothesized that both anodal and dual tDCS would enhance motor training outcome and transfer to clinical assessments of upper motor function\(^4,^5\).

Materials And Methods

Forty patients with chronic (> 6 months post-stroke; Table 1 for details) right or left hemispheric ischemic or hemorrhagic stroke participated in a randomized, double-blind, sham-controlled study. Inclusion criteria consisted of occurrence of ischemic or hemorrhagic stroke at least 6 month prior to enrollment; ability to complete the motor training; no previous or subsequent strokes; no additional neurologic, medical or psychiatric disorders; and no concurrent use of CNS-affecting drugs. Patients were stratified to the
stimulation groups by baseline UE-FM score to receive five consecutive days of fine motor skill training with anodal (N = 15), dual (N = 15) or sham (N = 10) tDCS. Patients, care providers and investigators collecting the data were blinded to the stimulation conditions. The study was approved by the ethics committee of the Charité Universitätsmedizin Berlin (Protocol: EA1/026/11), where all data was collected. Participants gave written informed consent prior to study inclusion. Sample size calculations were based on previous uni- and bihemispheric tDCS studies. Due to the small expected effect of sham stimulation we proposed an unbalanced group size for the power analysis, which revealed the necessary group size for the stimulation group n = 15 and for the sham group n = 10 to achieve a statistical power of at least 95% (2-tailed, alpha = 0.05). Figure 1 displays the flow-chart of the study.

Table 1
Demographic information and baseline motor performance.

| Group | Age, years | Time post stroke, month | Sex (M/F) | Baseline UE-FM | Baseline WMFT | Affected Hemisphere (right/left) |
|-------|------------|-------------------------|-----------|----------------|---------------|----------------------------------|
| Dual  | 58.3 ± 12.8 | 21.9 ± 17.2             | 11/4      | 47.1 ± 17.9    | 0.7 ± 0.6     | 8/7                              |
| Anodal| 60.3 ± 10.3 | 28.8 ± 35.3             | 12/3      | 46.9 ± 15.0    | 0.6 ± 0.6     | 8/7                              |
| Sham  | 60.6 ± 12.9 | 28 ± 25.1               | 8/2       | 43.6 ± 20.7    | 0.8 ± 0.7     | 6/4                              |

Legend: Values are reported as mean ± standard deviation. Stimulation groups were comparable regarding age, onset, and baseline motor function (all p > 0.05.)

Primary and secondary research question

The primary research question was whether unilateral or bilateral tDCS in combination with a fine motor skill training improves UE-FM scores in stroke patients. Changes in training performance and WMFT score were secondary outcomes.

Clinical assessment

Subjects underwent standardized motor function and impairment assessments using UE-FM and WMFT prior to and immediately after the intervention. The UE-FM examines multi-joint movements of the upper limb (max. score = 66, lower scores = greater impairment). The WMFT comprises 15 time-based items ranging from whole arm movements to fine finger control. WMFT completion times were logarithmized to account for skewed data distribution. This score has a maximum value of 2.08s[log] with lower values reflecting better arm function. All tests (including the training task without-tDCS) were repeated three
months later to investigate potential long-term effects of tDCS on motor function. Assessments were videotaped and analyzed by two independent raters.

One participant (anodal-group) was excluded from UE-FM/WMFT follow-up assessments (shoulder luxation). Five participants (2 dual, 2 anodal, 1 sham) did not complete the motor task follow-up assessments for non-medical reasons.

Motor Training

Similar to a previous study, the training consisted of isometric abductions with the paretic thumb, which was placed in a sling attached to a Grass® Force-Displacement-Transducer FT10 (Grass Instruments). Velcro straps fixated the forearm to minimize unwanted movement. Signal software (Cambridge Electronic Design Ltd.) was used for data acquisition and task presentation. Force displacement was amplified and digitized using a CPT22 AC/DC Straining Gage Amplifier (Grass® Technologies; amplification: 2000Hz, high filter: 3Hz). Each training day consisted of eight blocks of 30 trials, four seconds/trial. A target force window was defined between 30–40% of the individual maximum force output on the y-axis and 2800-3200ms on the x-axis. Abductions in the target window were considered “hits”.

tDCS Stimulation

tDCS was administered using a battery driven direct current stimulator (DC-Stimulator PLUS, NeuroConn). The anode (5x7cm²) was placed above the ipsilesional M1 (C3/C4 of the international 10–20 EEG-system, depending on the lesion). The cathode was placed above the contralesional supraorbital ridge (anodal, size 10x10cm²) or the contralesional M1 (dual, size 5x7cm²). The current was increased to 1mA over 10 seconds and lasted for 25 minutes. The sham group was pseudo-randomly assigned to a montage (50% anodal/dual) and received 30 seconds of tDCS to ensure the typical initial tingling sensation. A second investigator configured DC-Stimulator to ensure investigator blinding.

Statistical Analysis

SPSS 22 (IBM Corp. Released 2013) and a two-sided significance level ($\alpha = 0.05$) was employed. Separate linear mixed models investigated effects of tDCS on performance (motor task, UE-FM, WMFT). Time points (motor task: training-days$_{1-5}$, follow-up; UE-FM/WMFT: baseline, post, follow-up) were level-one units nested in different individuals (level-two units). Random intercept models tested differences between the stimulation conditions. A squared centered time variable ($\text{TIME}^2$) tested for curvilinear learning effects. The Time x Stimulation interaction assessed whether the learning curve slopes differed between groups. Baseline UE-FM scores and training blocks were covariates in the motor task analysis. There was no adjustment for multiple testing and p-values. Model parameters for motor tasksday1-5 and follow-up: $N = 40$ participants, 1864/1920 test values. Model parameters for UE-FMtime-points1-3: $N = 40$
Results

Motor Training

There was no overall difference between the groups with regard to hits (reference sham: dual $\beta$ = -0.72, $p = 0.64$, $R^2=0.01$, 95%-CI = 0.00-0.01; anodal $\beta$ = 0.88, $p = 0.58$, $R^2=0.01$, 95%-CI = 0.00-0.02). There was a curvilinear improvement in performance ($\text{TIME}^2 \beta = -0.28$, $p < 0.001$, $R^2=0.03$, 95%-CI = 0.02–0.05, $\text{TIME}\beta = 0.50$, $p < 0.001$, $R^2=0.01$, 95%-CI = 0.00-0.02), but no differences between the groups (dual x time, $\beta = 0.17$, $p = 0.18$, $R^2=0.00$, 95%-CI = 0.00-0.01; anodal x time, $\beta = 0.25$, $p = 0.06$, $R^2=0.00$, 95%-CI = 0.00-0.01). Performance declines during the follow-up were comparable between groups (Fig. 2A).

UE-FM

There was no overall difference between the stimulation groups in the UE-FM (reference sham: dual $\beta = 4.27$, $p = 0.55$, $R^2=0.15$, 95%-CI = 0.01–0.28; anodal $\beta = 5.07$, $p = 0.20$, $R^2=0.20$, 95%-CI = 0.09–0.33). There was a curvilinear improvement in the UE-FM ($\text{TIME}^2 \beta = -0.86$, $p = 0.004$, $R^2=0.01$, 95%-CI = 0.00-0.08, $\text{TIME}\beta = 0.70$, $p = 0.04$, $R^2=0.01$, 95%-CI = 0.000-0.06). Improvement in the dual and sham groups was almost parallel, performance gains in the anodal group were steeper and additional gains were observed throughout the follow-up period (dual x time, $\beta = 0.60$, $p = 0.17$, $R^2=0.00$, 95%-CI = 0.00-0.05; anodal x time, $\beta = 1.37$, $p = 0.002$, $R^2=0.01$, 95%-CI = 0.00-0.08, Fig. 2B).

Legend: (A) The graph depicts the mean number of hits per block for each group across the training and follow-up period based on the linear mixed model. Vertical bars represent model based 95% confidence intervals. (B) The graphs depict the mean UE-FM score for each group across the training and follow-up period based on the linear mixed model. Vertical bars represent model based 95% confidence intervals.

WMFT

Neither training nor tDCS affected the WMFT (supplementary information).

Discussion

Previous studies with comparable isometric pinch tasks demonstrated better trained task performance and UE-FM improvements, but not WMFT$^2$, and improvements in the Jebsen-Taylor hand function and Grooved-Pegboard tests$^{10}$. In line with these findings, our study demonstrated long-term improvements of trained task performance and functionally relevant recovery of upper extremity function.

However, the present study did not confirm substantial add-on effects of unilateral or bilateral tDCS. Previous studies had only investigated effects of unilateral tDCS on fine motor skill training and reported...
mixed results. While beneficial effects of anodal tDCS on the shoulder-elbow-subscale of the UE-FM have been demonstrated, no effects on trained task performance were reported\(^2\). In contrast another study reported improved trained task performance with anodal tDCS, but not enhanced functional recovery\(^10\). Both studies report no long-term effect of anodal tDCS on task performance, but beneficial effects on the shoulder-elbow-subscale lasting up to two months\(^2\). Hence, the mainly weak effects of tDCS reported previously, and the results of our study, question the utility of tDCS to enhance the outcome of this particular type of training.

Due to the small sample size, low statistical power, heterogeneity of the sample and drop-outs in the training task the results should be interpreted with caution. However, smaller proof-of-principle studies are imperative prior to investing limited resources into larger randomized control trials and our results in combination with previous studies do not encourage large follow-up trials. The sample comprised patients with left or right hemispheric ischemic or hemorrhagic lesions, which may have been suboptimal. Yet the sample accurately represents the general patient population and beneficial training effects were found despite variable lesion types, sizes and locations. Nonetheless a more homogeneous sample would be preferable with regard to tDCS. Furthermore, missing data was balanced across groups and the mixed effects models used are robust regarding missing data. Nonetheless, while there were no substantial effects at the group level, individual participants may have benefited from tDCS and future studies are needed to include individualized modeling of current flow and functional imaging to investigate characteristics of potential responders.

**Conclusion**

We confirm significant performance improvements due to the fine motor skill training in patients with chronic stroke. Only limited add-on effects were induced by tDCS.

**List Of Abbreviations**

CNS central nervous system

M1 primary motor cortex

mA milliamps

tDCS transcranial direct current stimulation

UE-FM Upper Extremity Fugl-Meyer

WMFT Wolf Motor function Test

**Declarations**
Ethics approval and consent to participate

The study was approved by the ethics committee of the Charité Universitätsmedizin Berlin in accordance with the Declaration of Helsinki. Participants gave written informed consent prior to study inclusion.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors’ contribution

AF and RL conceived the study. BT, RD, DH and JW processed the data. BT and UG performed the statistical analysis. BT wrote the manuscript, AF and MM revised the manuscript.

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