


# Transcranial Direct Current Stimulation to Optimise Participation in Stroke Rehabilitation – A Sham-Controlled Cross-Over Feasibility Study

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Neuroscience Insights  
Volume 15: 1–4  
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DOI: 10.1177/2633105520922181



## ABSTRACT

**BACKGROUND:** Fatigue and attentional decline limit the duration of many therapy sessions in older adults poststroke. Transcranial direct current stimulation (tDCS) may facilitate participation in rehabilitation, potentially via reduced fatigue and improved sustained attention poststroke.

**OBJECTIVE:** To evaluate whether tDCS results in an increase in the number of completed rehabilitation therapy sessions in stroke survivors.

**METHODS:** Nineteen participants were randomly allocated to receive 10 sessions of 2-mA anodal (excitatory) tDCS, or sham tDCS, applied to the left dorsolateral prefrontal cortex (DLPFC) for 20 minutes within 1 hour prior to the first rehabilitation therapy session of the day. After a 2-day washout period, participants then crossed-over. Researchers applying the tDCS, and those recording measures were blinded to group allocation. The number of first rehabilitation therapy sessions completed as planned, as well as the total duration of rehabilitation therapy, were used to determine the influence of tDCS on participation in stroke rehabilitation.

**RESULTS:** The total number of first therapy sessions completed as planned did not vary according to group allocation (111 of 139 sessions for tDCS, 110 of 147 sessions for sham treatment; chi-square 1.0;  $P = .31$ ).

**CONCLUSIONS:** Our results suggest that, while tDCS to the DLPFC was well tolerated, it did not significantly influence the number of completed rehabilitation therapy sessions in stroke survivors.

**KEYWORDS:** Stroke rehabilitation, transcranial direct current stimulation, fatigue, attention, noninvasive brain stimulation

**RECEIVED:** October 25, 2019. **ACCEPTED:** February 10, 2020.

**TYPE:** Brief Report

**FUNDING:** The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by a Small Project Research Grant from the Stroke Foundation–Australia.

**DECLARATION OF CONFLICTING INTERESTS:** The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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## Introduction

Attention deficits may affect the ability of older adults to engage in rehabilitation poststroke.<sup>1</sup> In addition, fatigue is very common poststroke. Fatigue is a complex impairment. Reduced cortical excitability is postulated to be one factor contributing to poststroke fatigue.<sup>2</sup> Thus, fatigue and attentional decline may limit rehabilitation therapy session duration in older adults poststroke.<sup>1,2</sup> Because rehabilitation is typically offered only in the initial months poststroke, it is critical that stroke survivors engage in as much therapy as possible during this time. The mean physiotherapy session treatment duration in a large published series was  $38 \pm 17$  minutes.<sup>3</sup> We identified that many patients, particularly those with severe stroke, are not able to stay alert for the duration of their therapy sessions and often cannot complete their therapy due to fatigue, attentional decline, or loss of concentration. In local audit data, the mean session duration of therapy

sessions among 14 stroke survivors in the Bentley Hospital Stroke Rehabilitation Unit (SRU) was  $34 \pm 23$  minutes. These published international data, and our local data, are both far below the recommended durations of rehabilitation therapy (at least 3 hours a day of scheduled therapy)<sup>4</sup> suggesting the importance of investigating interventions that can improve duration and the number of therapy sessions.

There is preliminary evidence that noninvasive brain stimulation (NIBS) can enhance alertness and attention poststroke.<sup>5,6</sup> Compared with other NIBS techniques such as repetitive transcranial magnetic stimulation, transcranial direct current stimulation (tDCS) offers a reliable safety profile,<sup>7</sup> affordability, ease of application, and sophisticated sham mode which allows for blinded control in clinical trial settings.<sup>8</sup> Transcranial direct current stimulation is one of the most commonly used adjuvant NIBS techniques and has been shown to augment the recovery of upper limb movement and function



and to assist in the management of dysphasia, visual neglect, and language dysfunction poststroke.<sup>9</sup>

Transcranial direct current stimulation acts to modulate cortical excitability by application of weak electrical currents (up to 2 mA)<sup>10</sup> via electrodes applied to the scalp. Depending on the current polarity, neuronal firing rates increase or decrease due to changes in resting membrane potentials, with anodal tDCS increasing the likelihood of neuronal firing and cathodal tDCS decreasing the likelihood of neuronal firing.<sup>11</sup> It has been shown to be safe even when applied acutely (within two days) to the stroke-affected cortex.<sup>12</sup> Previous research has shown stroke survivors demonstrated greater accuracy, but not speed, on a test of executive attention following one session of tDCS compared with sham stimulation.<sup>5,6</sup> The application of tDCS to the DLPFC has been shown to enhance cognitive functions including working memory, visuomotor coordination, and decision-making in healthy individuals,<sup>13,14</sup> and in people with dementias or Parkinson disease.<sup>15-17</sup> The after-effects of tDCS on cortical excitability are likely modulated by *N*-methyl-D-aspartate (NMDA) receptor-dependent processes, and a number of investigations have shown that longer term changes can be induced in neuronal networks, including cognitive-attentional networks.<sup>9</sup>

The main adverse effect of tDCS which has been documented include a mild tingling or itching sensation, usually at the site of the cathodal electrode, which is common at the beginning of stimulation.<sup>7</sup> An expert panel have provided recommendations for clinical and research use which clearly set out safety parameters.<sup>18</sup>

The available data suggest that tDCS may reduce fatigue and improve sustained attention poststroke. However, there are no data on longer term effects of tDCS with regard to sustained attention or clinical benefits, such as improved participation in rehabilitation, in older stroke survivors. We, therefore, designed the present study to test the hypothesis that tDCS applied to the DLPFC, compared with sham treatment, would be associated with an increase in the duration of rehabilitation therapy sessions in stroke survivors.

## Materials and Methods

The study was approved by the Royal Perth Hospital Human Research Ethics Committee (2016-027) and prospectively registered (ACTRN12616000254493). An investigator provided all participants with a written information sheet, a simplified written summary of the information sheet designed for people experiencing communication impairments, and verbal information about the study. All participants provided written informed consent.

Older adults (60+ years) admitted to the Bentley Hospital SRU with a diagnosis of ischaemic stroke, who clinical staff judged were likely to be inpatients  $\geq 1$  month, were eligible to participate. Exclusion criteria included prestroke history of fatigue-related syndromes, unstable comorbid medical or psychiatric disease, history of seizures or metallic foreign body

implant, and use of NMDA receptor antagonists or calcium channel blockers (which limit the beneficial effect of tDCS). Participants were randomly allocated to receive 10 sessions (ie, each weekday for 2 weeks) of 2-mA anodal (excitatory) tDCS or sham tDCS, applied to the left DLPFC for 20 minutes. After a 2-day washout period, participants then crossed-over to the other study condition.

Transcranial direct current stimulation was applied within 1 hour prior to the first daily therapy session. Transcranial direct current stimulation was applied in accordance with published guidelines for the safe use of tDCS.<sup>5,18</sup> Transcranial direct current stimulation was delivered by a constant current electric stimulator via a pair of rubber surface electrodes overlying a saline infused pad. The anode was applied to the left DLPFC (according to the International EEG 10/20 System),<sup>19</sup> and the cathode was applied to the contralateral supraorbital area. Anodal stimulation consisted of a 30-second current ramp up followed by 19 minutes of constant current stimulation (2 mA) and a 30-second ramp down to zero current (20-minute total protocol)<sup>10,20,21</sup>; sham stimulation consisted of a 30-second current ramp up (2 mA) followed immediately by a 30-second ramp down to zero current. Researchers applying the tDCS and those recording measures were blinded to group allocation. Outcome measures were (a) whether the first rehabilitation therapy session of the day immediately following application of tDCS was completed as planned and (b) the cumulative duration (in minutes) of rehabilitation sessions.

We aimed to enrol at least 18 participants to provide 0.8 power at the 0.05 level to detect a treatment effect of an increase in 17 minutes of therapy time with anodal tDCS compared with sham. Categorical frequency data (ie, sessions completed as planned) were categorised as 'completed' or 'not complete' and compared using the chi-square statistic. A paired sampled *t* test was used to determine within-subject differences in total therapy time according to group allocation.

## Results

One hundred seventy consecutive patients were screened. The reasons for screen failure were length of stay anticipated to be  $\leq 1$  month ( $n=64$ ), diagnosis not ischaemic stroke ( $n=48$ ), treatment with calcium channel blockers ( $n=16$ ), which interfere with tDCS effects, and other ( $n=13$ ). Ten patients declined participation. The 19 remaining participants (13 female; 6 male; median age 79 [70.5, 82.5] years) were recruited.

The total number of planned first therapy sessions completed did not vary according to group allocation (111 of 139 therapy sessions completed as planned following tDCS cf 110 of 147 therapy sessions completed as planned in the sham condition; chi-square 1.0;  $P=.31$ ). Similarly, the proportion of patients completing all first therapy sessions of the day was not different according to group allocation (4 of 16 participants receiving tDCS; 8 of 18 participants receiving sham;

chi-square=1.4;  $P=.24$ ). The within-subject difference in therapy time according to sequence allocation was 25 minutes (95% confidence interval [CI] -80, 130;  $P=.61$ ).

## Discussion

This research evaluated a novel use of an established therapeutic intervention (tDCS) to address an area of high clinical need, namely optimising the ability of older adults to engage in rehabilitation poststroke. We found that use of tDCS is feasible in a clinical setting of subacute stroke rehabilitation but did not find evidence of increased engagement in therapy in this clinical population. There are a number of potential reasons for this finding. Stroke is a heterogeneous disease, and it is possible that subgroups of stroke survivors may have benefited from the intervention, but this was not able to be identified due to the small sample size of this feasibility study. Individuals who were in the subacute recovery phase poststroke who were anticipated to be able to complete the intervention as an inpatient (minimum 1-month length of stay) were recruited. These patients tend to have severe lesions and poststroke deficits; consequently, the findings may not be generalisable to other stroke survivors, or to stroke survivors earlier in the course of their recovery. We did not specify inclusion of patients with a specific aetiology of ischaemic stroke; however, none of the included patients had a diagnosis of haemorrhage. It could also be the case that the dose of treatment (10 sessions, which we judged would be feasible in a cross-over design) in our study was insufficient, given that some previous studies have used up to 30 sessions, and that there are some data<sup>10</sup> supporting a dose-response relationship. Similarly, we chose a 2-day washout, which may have been insufficient. Future studies may consider use of a higher numbers of sessions over a longer time period or tDCS applied simultaneously with rehabilitation intervention. Finally, we used a clinical endpoint (duration of rehabilitation sessions) as the primary outcome. More sensitive measures of sustained attention, fatigue, and other factors limiting participation in therapy, including self-report measures, may be required to demonstrate benefits in subgroups of stroke survivors with fatigue/attention deficits.

The strengths of our study are that participants and assessors were blinded to group allocation, and the inclusion of a sham condition, so that participants acted as their own control. The major limitation of our study is the potential for random error, and limited generalisability, because of the small number of participants. These limitations are unfortunately common in many of the studies in this field. There were also methodological limitations; eg, we did not confirm successful blinding. Further studies with carefully selected subgroups of stroke survivors should be considered. Measurement of fatigue and attention at multiple time points in each 24-hour period would have been desirable, but was not possible in this feasibility study. This study shows that tDCS is feasible for in-patients, and future work should directly measure fatigue and attention

to understand whether tDCS can increase engagement in therapy via reduction in fatigue and increase in attention.

In conclusion, to our knowledge, this is the first study to explore the use of tDCS to specifically improve attention and reduce the effect of fatigue on treatment tolerance in older stroke survivors. Our results suggest that, while tDCS to the DLPFC was feasible to apply during subacute stroke rehabilitation, and was well tolerated, it did not significantly influence fatigue or alertness which are major contributors to a patient's engagement in therapy. Larger studies are needed to make definitive conclusions about any potential benefit of tDCS to the DLPFC on alertness poststroke in older stroke survivors.

## Acknowledgements

Helen Singer was employed as a research assistant on the study and assisted with literature review and proposal drafting.

## Author Contributions

All authors contributed to study design and acquisition of data. CEB analysed the data and drafted the manuscript, with critical revision by all authors.

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