Safety and efficacy of transcranial direct current stimulation in addition to constraint-induced movement therapy for post-stroke motor recovery (TRANSPORT2): a phase 2, multicentre, randomised, sham-controlled triple-blind trial

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Summary

Background Motor impairments contribute substantially to long-term disability following stroke. Studies of transcranial direct current stimulation (tDCS), combined with various rehabilitation therapies, have shown promising results in reducing motor impairment. We aimed to evaluate the safety and efficacy of three doses of tDCS in combination with modified constraint-induced movement therapy (mCIMT) in people who have had their first ischaemic stroke in the preceding 1–6 months.

Methods We conducted a phase 2, multicentre, randomised, triple-blind, sham-controlled study with a blinded centrally scored primary outcome. The trial was conducted at 15 medical centres in the USA. Eligible participants were enrolled between 1 month and 6 months after their first ischaemic stroke. Inclusion criteria required participants to have a persistent motor deficit, defined as a Fugl–Meyer Upper-Extremity (FM-UE) score of 54 or lower (out of 66), and two consecutive baseline visits (separated by 7–14 days) with an absolute difference of 2 or fewer points on the FM-UE scale. Participants were randomly assigned to treatment groups by an adaptive randomisation algorithm hosted on the TRANSPORT2 WebDCU study website. Participants received either sham, 2 mA, or 4 mA of bi-hemispheric tDCS for the first 30 min and mCIMT with 120 min of active therapy time per session, administered over ten sessions during a 2-week period. The primary endpoint was the change in FM-UE score from baseline to day 15, which was analysed in all participants who have data both at baseline and post-baseline (modified intention-to-treat group). Safety outcomes were analysed in all participants. TRANSPORT2 is registered at clinicaltrials.gov (NCT03826030) and its status is completed.

Findings 129 participants were recruited between Sept 9, 2019, and June 14, 2024, and 43 participants were randomly assigned to each group. 54 (42%) of 129 participants were female, and 69 (53%) were White. Two participants in the sham plus mCIMT group withdrew consent before the day 15 assessment and were excluded from the primary analysis. The median baseline FM-UE score was 39·0 (IQR 30·0–46·0) in the sham plus mCIMT group, 39·0 (27·0–48·0) in the 2 mA plus mCIMT group, and 40·0 (27·0–48·0) in the 4 mA plus mCIMT group. For the primary outcome, the adjusted mean change from baseline to day 15 in FM-UE was 4·91 (3·00–6·82) for sham plus mCIMT, 3·87 (2·00–5·74) for 2 mA plus mCIMT, and 5·53 (3·64–7·42) for 4 mA plus mCIMT (p=0·39). No clinically important adverse events were observed in any group and no deaths were reported.

Interpretation tDCS at doses of 2 mA or 4 mA, in addition to mCIMT, did not lead to further reduction in motor impairment in patients 1–6 months after stroke, but it was safe, well tolerated, and feasible for clinical practice. tDCS at higher doses (ie, >4 mA) might be a consideration for future trials in addition to balancing known covariates affecting stroke recovery during the group allocation.

Funding National Institute of Neurological Disorders and Stroke.

Introduction

Advances in reperfusion therapies and acute stroke care have improved survival and functional outcomes after stroke, but increasing numbers of individuals are surviving with persisting disabilities. Motor impairment, particularly upper-extremity weakness (ie, affecting the arms and hands), is the most common long-term disability after a stroke.[1] One intervention that has proven efficacy in people with residual distal hand muscle movement after stroke is constraint-induced movement therapy (CIMT), either in the original[2] or modified (mCIMT)[3,4] format. CIMT has two major components: restraining the

Research in context

Evidence before this study

We searched PubMed and Embase using the terms "transcranial direct current stimulation" AND "stroke" AND "sham" AND "motor" AND "upper extremity" AND "Fugl-Meyer", from Jan 1, 2000, to June 30, 2024, for English-language publications only. There were 62 initial records, which were then manually screened. We identified 12 clinical trials on transcranial direct current stimulation (tDCS) for stroke upper-extremity recovery that included the Fugl–Meyer Upper-Extremity (FM-UE) scale as an outcome measure, had a sham-control group, included five or more stimulation sessions, and enrolled 15 or more participants in each treatment group. Most of these trials were underpowered, conducted at a single centre, and showed variable and inconsistent results. Only a tDCS current level of 2 mA or lower had been tested.

Added value of this study

TRANSPORT2 is a multicentre trial with adequate statistical power to evaluate overall treatment differences in three tDCS dosing groups (4 mA *vs* 2 mA *vs* sham stimulation). This trial is one of a few large studies that systematically collected neurophysiology and neuroimaging assessments of corticospinal tract integrity in addition to clinical outcomes. All three groups received simultaneous structured, high-intensity rehabilitation therapy (ie, modified constraint-induced movement therapy [mCIMT] for 120 min), which has been proven to be effective for a defined stroke population with preserved distal muscle movement. Furthermore, to the best of our knowledge, TRANSPORT2 is the first stroke recovery trial in which the primary outcome (ie, FM-UE score) was rated both in-person locally as well as by a single central rater.

Implications of all the available evidence

Although participants in all three dosing groups showed improvement, there was no statistical difference in the primary outcome between groups. The combined intervention was found to be safe, well tolerated, and feasible to implement in a multicentre trial setting. Adding tDCS up to 4 mA to a structured high-intensity therapy (ie, mCIMT) for patients with persistent upper extremity weakness 1–6 months post-stroke did not result in further reduction in motor impairment. Future research might consider testing tDCS current higher than 4 mA, balancing known covariates affecting stroke recovery during the randomisation process, and investing more efforts in stroke recovery trial enrolment and outcome standardisation.

less-affected or unaffected upper extremity; and training the affected upper extremity by first practising skills appropriate for current motor capacity and then using more difficult tasks as the patient improves. Despite the growing need for new rehabilitative therapies, controlled trials to assess whether post-stroke upper extremity motor impairment can be improved during the rehabilitation phase, beyond the outcomes obtained with guideline-recommended standard or usual care interventions, are rare.[5,6] Developing new effective therapies that enhance recovery and reduce disability beyond intensive and structured forms of rehabilitation therapy remains an important research priority.[7]

Over the past two decades, both invasive and non-invasive brain stimulation interventions have emerged as promising approaches to affect cortical excitability and improve outcomes in individuals who have had strokes, by making use of brain plasticity.[8] Transcranial direct current stimulation (tDCS) is a non-invasive easy-to-use tool that can modulate stroke-induced atypical interhemispheric imbalance and increase synaptic plasticity when paired with rehabilitation therapy.[9–11] Although several single-centre proof-of-concept tDCS studies have shown encouraging results at reducing motor impairment and improving motor function in people after stroke, most studies were underpowered, paired tDCS with varied forms of rehabilitation therapy, and were limited to a maximum current of 2 mA.[12,13] Since outcomes across these studies have been variable, a multicentre validation study with high scientific rigor would be needed to provide a definitive result.[14] Findings of a meta-analysis revealed a dose–response relationship between current density (ie, current/electrode pad size, typically measured in mA/cm²) and motor impairment reduction, as measured by the Fugl–Meyer Upper-Extremity (FM-UE) scale.[15] These studies have indicated that stimulation dose is a crucial variable in tDCS research. A phase 1 trial assessing escalating current showed that up to 4 mA was safe and tolerable in individuals who have had an ischaemic stroke.[16] Two additional healthy human studies have shown that higher-dose tDCS (ie, 3 mA or 4 mA) has better effects on behavioural performance, amplitude of motor evoked potentials, and imaging measures of brain activity as compared to the lower dose.[17,18]

We designed a phase 2 multicentre study (TRANSPORT2) with the aim to test whether there is an overall treatment effect between three tDCS dose groups when combined with rehabilitation therapy. To control for the effect of adjunctive rehabilitation therapy, mCIMT was selected due to its proven efficacy and the availability of a quantified protocol.[2,3] We also aimed to confirm that the proposed intervention is safe, tolerable, and feasible to administer within a multicentre trial setting.

Methods

Study design

TRANSPORT2 was a phase 2, multicentre, randomised, sham-controlled triple-blinded trial conducted at 15 medical centres in the USA (four sites terminated

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early during the COVID-19 pandemic). A centralised institutional review board based at the University of Cincinnati approved the study (central institutional review board approval number 2018-4092C). The study protocol and statistical analysis plan are provided in the appendix (pp 12–84).

See Online for appendix

Participants

Eligible participants were enrolled between 1 month and 6 months after their first ischaemic stroke, which was defined clinically as a neurological deficit that lasted over 24 h and was confirmed by CT, MRI, or both. Inclusion criteria required participants to have a persistent motor deficit, defined as a FM-UE score of 54 or lower (out of 66), and two consecutive baseline visits (separated by 7–14 days) with an absolute difference of 2 or fewer points on the FM-UE scale. Key exclusion criteria include taking medications at the time of study that might affect tDCS, having moderate to severe cognitive impairment, the presence of any risk factors for MRI, tDCS, or transcranial magnetic stimulation, and concurrent enrolment in another investigational stroke recovery study. Full eligibility criteria are provided in the appendix (p 5). Data on sex was collected by self-report, with the provided options of male and female. Written informed consent was obtained from participants at the time of enrolment.

Randomisation and masking

Participants were randomly assigned through a web-based central randomisation system to receive either sham, 2 mA (low dose), or 4 mA (high dose) tDCS. The randomisation system was installed on the TRANSPORT2 WebDCU study website and the randomisation method was designed to prevent serious imbalances in the distribution of known prognostic variables. All randomisation and data management was centrally controlled by The National Data Management Center for StrokeNet studies (Medical University of South Carolina, Charleston, SC, USA). The adaptive randomisation algorithm targeted equal allocation among the three treatment arms, controlling for overall treatment imbalances and serious imbalances in covariates considered to affect outcome: specifically, study site, time from stroke (1–3 months or 3–6 months), and baseline motor impairment measured using the second qualifying FM-UE measurement. The first 30 participants were randomly assigned in a 1:1:1 ratio; for the remaining participants (ie, 31st to 129th), serious imbalances overall and in the prespecified covariates were accounted for using the minimal sufficient balance approach.[19]

For the **TRANSPORT2 WebDCU study website** see https://webdcu.musc.edu

Randomisation was triggered via WebDCU after all required baseline information was entered. Six-character unique tDCS treatment activation codes, which corresponded to the randomly assigned treatment group for a given participant, were obtained at the beginning of each session via WebDCU and were entered into a laptop connected to the tDCS device that translated the code into the assigned stimulation current using a pre-loaded script. At the end of the last session, participants and outcome raters were asked to guess the dose group to which they believed participants had been assigned (appendix p 79).

TRANSPORT2 was triple-blinded. The investigators, trainers (ie, therapist delivering mCIMT), and tDCS operators; the local or central raters; and the participants were all masked to treatment assignment. The participants were typically enrolled by the clinical study coordinator, who could also participate in other study procedures (eg, as the tDCS operator). The trainer of each participant was not allowed to be their outcome rater. Two statisticians were assigned to the TRANSPORT2 study: one masked, the other unmasked.

Procedures

Direct current was delivered using a Chattanooga dual-channel iontophoresis device (Chattanooga Group, Hixson, TN, USA). A bi-hemispheric montage was used, with the centre of the electrodes placed by the tDCS operator at C3/C4 positions, according to the 10/20 EEG cap (Rhythmlink International, Columbia, SC, USA). The electrode pads were saline-soaked sponges (with dimensions 5 cm × 7 cm) impregnated with biocarbon material (Soterix Medical, Woodbridge, NJ, USA); pads were placed by the tDCS operator in the craniocaudal direction with a centre of C3/C4. The anodal electrode was positioned on the lesional hemisphere and the cathodal electrode on the contralesional hemisphere (appendix pp 85–102). The current density was 0·057 mA/cm² for the 2 mA group and 0·114 mA/cm² for the 4 mA group.

Participants received the randomly assigned dose of tDCS for the first 30 min of each of the ten sessions over a 2-week period. All participants also received mCIMT, with a goal of 120 min of active therapy time per session. For mCIMT, participants wore a mitt (ie, a glove that has a single compartment for all fingers) on the less affected hand to constrain its use (appendix pp 126–253). Trainers selected tasks from a menu of approved activities, focusing on promoting increased use of the more affected upper extremity during functional activities. All trainers passed ongoing fidelity checks via a central trainer to deliver mCIMT. Sham stimulation consisted of increasing current from 0 mA to 2 mA over 30 s only, but leaving the electrodes in place for 30 minutes. After each session, the trainer reminded participants of their behavioural contract, which included wearing a mitt on the unaffected hand for at least 6 h per day and practising specific tasks. Participants had MRI and transcranial magnetic stimulation assessments of corticospinal structure and function before and after the 2-week intervention (ie, at the second baseline measurement and day 15; details of the protocol for these assessments are in the appendix, pp 103–25 and 397–402). Follow-up

sessions were held on day 15 (± 2 days), day 45 (±5 days), and day 105 (±10 days) for assessment of both immediate and long-term effects.

Outcomes

The primary outcome was the mean change in centrally rated FM-UE scale from the second qualifying baseline (hereafter, baseline) to day 15 (±2 days). The FM-UE is a 33-item motor impairment scale (0 to 66 points, with higher points indicating less impairment). Secondary efficacy outcome measures were the mean change from baseline to day 15 in the Wolf motor function test time score (a measure of functional motor activity) and the mean change from baseline to day 15 in the hand subscale of the stroke impact scale (version 3.0; a measure of quality of life). The Wolf motor function test time score is a median score of 15 in hierarchically arranged timed arm movements and hand dexterity tasks, each to be completed in 120 s. If a task could not be completed in 120 s, a score of 121 s was assigned. A decrease in the Wolf motor function test time score means improved functional motor performance. The stroke impact scale is a self-report questionnaire that evaluates disability and health-related quality of life after a stroke. The hand subscale has five items and each item is rated using a five-point Likert scale (5 is the best score). An increase in this score indicates improved quality of life.

FM-UE scale was assessed both by site raters (who were masked to the intervention) and by a central rater (who was masked to timepoint and intervention), by watching video recordings. The centrally rated score only was used for the primary outcome analysis. Primary and secondary outcome measures were also collected at the follow-up sessions (days 45 and 105) to assess the long-term effects. Extensive training and standardisation procedures for administration of all outcome measures were implemented for site raters and required periodic certification (ie, every fourth participant) via the central rater to assure the accuracy and reliability of each assessment delivery.

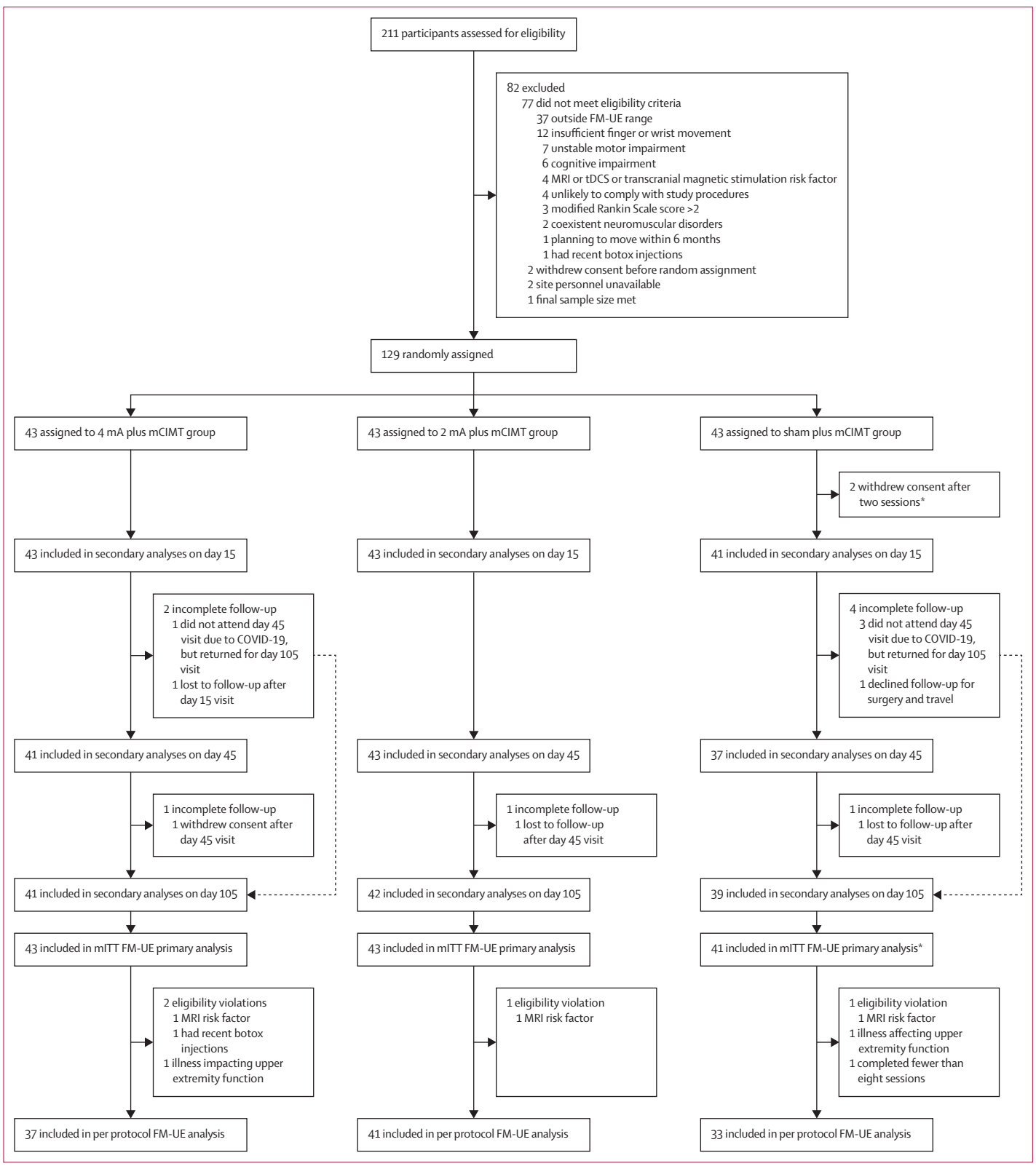
We prespecified subgroup analyses of the primary outcome by sex (male *vs* female) and race or ethnicity (Non-Hispanic White *vs* other; appendix p 77). We also did post-hoc subgroup analyses of the primary outcome by median age (<59 years *vs* ≥59 years), motor evoked potential status (presumed positive, yes *vs* no), affected side (left *vs* right), and time from stroke (30–90 days *vs* 91–180 days).

Safety, tolerability, and feasibility outcomes were also assessed. Safety was defined as the rate of prespecified clinically important adverse events occurring during the 2-week intervention period, including severe headache, second-degree skin burn, clinical seizure, and neurological deterioration (ie, ≥4-point increase in National Institutes of Health stroke scale). Adverse events and serious adverse events were first assessed at the participating sites by a local investigator; an independent medical safety officer then reviewed all serious adverse events and, when need was determined by sites, some adverse events (appendix pp 7–9). Tolerability of the intervention was assessed with a visual analogue scale at the end of the last session. The visual analogue scale is a numeric scale from 0 to 10, with 0 being no discomfort and 10 being extreme discomfort. Feasibility was defined as at least 80% of participants who had at least eight (≥80%) of ten intervention sessions.

Statistical analysis

A change of 4·25–7·25 on the FM-UE scale was considered a clinically meaningful difference, in line with published literature.[20] Our study was powered under the assumption that mCIMT alone would achieve a score change on the FM-UE scale of at least 4·5 and that additional treatment with either 2 mA or 4 mA tDCS would increase the FM-UE score change by an additional 4·5 points, giving a total score change of 9·0. Furthermore, a meta-analysis of previous trials assessing the effects of tDCS in individuals who had had a stroke conservatively estimated the treatment variability to have an SD of 7.[15] With a sample size of 31 participants per treatment group, a two-sided type 1 error rate of 10%, and an SD of 7, if the true mean score change was 4·5 for the sham group, 9·0 for the 2 mA group, and 9·0 for the 4 mA group, our study would have 83% power to reject the null hypothesis that the three-arm means are equivalent, using ANOVA. To account for incomplete sessions and loss to follow-up, the sample size was inflated in two ways. Based on a conservative estimate from the EXCITE and VECTOR trials,[2,3] 8% of participants were expected to complete fewer than ten full sessions of tDCS plus mCIMT in the specified window. Thus, the sample size was inflated for the dilution in treatment effect using an inflation factor of $1/(1–0·08)^2$ or n=37. Additionally, to account for up to 15% participant loss to follow-up before collecting the primary and secondary outcome measures (on days 45 and 105), an inflation of 115% was used to account for the missing samples in the intention-to-treat analyses. As a result, the final sample size was 43 participants per treatment group or 129 participants in total.

The primary outcome analysis was conducted in the modified intention-to-treat population—ie, we excluded participants who had no post-baseline measure. The primary null hypothesis tested was no overall difference in FM-UE scale change between the three treatment groups on day 15 (ie, after the 2-week intervention). The null hypothesis was tested at a type 1 error rate of 10% against the alternative that at least one pair of means was not equal. The change in FM-UE in each treatment group was modelled using a linear mixed-effects repeated measures model of the change from baseline in FM-UE, adjusted for each visit (ie, day 15, day 45, and day 105),



treatment group, interaction term for treatment group by visit, baseline FM-UE, time from stroke in a dichotomous manner (30–90 days *vs* 91–180 days), and enrolment site. An AutoRegressive AR(1) autocorrelation structure was used to model the correlations across visits for the same participant, and variance components structure for sites. For each element of the FM-UE scale, if the centrally rated score could not be determined (due to video errors), the site-rater score was substituted. For secondary outcomes, we planned to conduct formal statistical tests only if the primary null hypothesis was rejected, as prespecified in the statistical analysis plan (appendix pp 76, 77).

Sensitivity of the primary findings was assessed using a per-protocol sample, which was defined as participants who: completed at least eight intervention sessions; completed the FM-UE at each of the three post-intervention visits (ie, day 15, day 45, and day 105); did not have recurrent clinical stroke or other prespecified illness known to affect upper extremity motor functioning during the study period; did not receive any other forms of rehabilitation therapy targeting the weak arm after the intervention; and did not have any eligibility violations. The intention of the per-protocol analysis was to assess the maximum possible treatment effect achievable. Less than 50% of participants were anticipated to receive additional forms of rehabilitation therapy after the intervention; however, the analysis plan stipulated if this percentage exceeded 50%, the per-protocol sample would exclude the criterion that participants did not receive any other forms of rehabilitation therapy targeting the weak arm after the intervention.

Statistical analyses were conducted with SAS (version 9.4, SAS Institute, Cary, NC, USA). A data safety monitoring board, independently appointed by the National Institute of Neurological Disorders and Stroke, oversaw this trial.

Role of the funding source

The funder provided input regarding the study design during the grant review process; the independently appointed data safety monitoring board provided input regarding the study design during the active recruitment period. One representative of the study sponsor was on the executive committee and participated in oversight of the trial. The funder had no involvement in data collection, data analysis, data interpretation, and manuscript writing.

Results

Between Sept 9, 2019, and June 14, 2024 (the study was put on hold for 3 months during the COVID-19 pandemic in 2020), 211 participants consented and were assessed for eligibility at 15 study sites. 82 (39%) participants were excluded and 129 (61%) were

	Sham tDCS plus mCIMT (n=43)	2mA tDCS plus mCIMT (n=43)	4mA tDCS plus mCIMT (n=43)
Age, years	56·0 (46·0–66·0)	62·0 (51·0–67·0)	60·0 (51·0–67·0)
Sex			
Male	21 (49%)	30 (70%)	24 (56%)
Female	22 (51%)	13 (30%)	19 (44%)
Race			
White	23 (53%)	25 (58%)	21 (49%)
Asian	0	3 (7%)	1 (2%)
Black or African American	20 (47%)	14 (33%)	19 (44%)
Multiple	0	1 (2%)	0
Unknown or not reported	0	0	2 (5%)
Ethnicity			
Hispanic or Latino	3 (7%)	3 (7%)	5 (12%)
Not Hispanic or Latino	40 (93%)	40 (93%)	38 (88%)
Time since first ever ischaemic stroke to random assignment			
30–90 days	11 (26%)	12 (28%)	11 (26%)
91–180 days	32 (74%)	31 (72%)	32 (74%)
Pre-stroke dominant side			
Left	3 (7%)	4 (9%)	3 (7%)
Right	40 (93%)	39 (91%)	40 (93%)
Side of the body made weak by first ever ischaemic stroke			
Left	23 (53%)	30 (70%)	17 (40%)
Right	20 (47%)	13 (30%)	26 (60%)
Pre-stroke modified Rankin Scale			
0 (no symptoms at all)	39 (91%)	35 (81%)	35 (81%)
1 (no significant disability despite symptoms)	1 (2%)	4 (9%)	5 (12%)
2 (slight disability)	3 (7%)	4 (9%)	3 (7%)
Fugl–Meyer upper extremity scale (site assessed, second qualifying score)	39·0 (30·0–46·0)	39·0 (27·0–48·0)	40·0 (27·0–48·0)
National Institutes of Health stroke scale score	3·0 (2·0–4·0)	3·0 (2·0–4·0)	3·0 (2·0–4·0)
Montreal cognitive assessment score	27·0 (25·0–29·0)	27·0 (24·0–29·0)	26·0 (23·0–28·0)
Wolf motor function test time score	3·9 (2·4–11·8)	4·0 (2·1–22·2)	3·3 (2·3–11·5)
Log(Wolf motor function test time score)	1·4 (0·9–2·5)	1·4 (0·7–3·1)	1·2 (0·8–2·4)
Stroke impact scale (hand subscale) score	25·0 (10·0–30·0)	30·0 (15·0–55·0)	30·0 (15·0–40·0)
Lesion volume, affected side (cm³, centrally assessed)*	1·4 (0·8–15·8)	2·5 (1·2–12·4)	1·5 (0·9–11·8)
Weighted corticospinal tract lesion load, affected side (cm³, centrally assessed)*	0·5 (0·3–0·7)	0·5 (0·3–0·8)	0·6 (0·2–0·8)
Presumed MEP positive, affected side (site assessed)*†			
Yes	32 (76%)	31 (72%)	27 (63%)
No	10 (24%)	12 (28%)	16 (37%)

Data are median (IQR) or n (%). tDCS=transcranial direct current stimulation. mCIMT=modified constraint-induced movement therapy. MEP=motor-evoked potential. *Missing for one participant randomly allocated to the sham tDCS plus mCIMT group. †MEP was presumed to be positive if an MEP of 50 μV could be induced from a hand muscle on the affected side in 50% of trials.

Table 1: **Baseline characteristics**

Figure 1: **Trial profile**
The mITT group included all participants who have data both at baseline and post-baseline. FM-UE=Fugl–Meyer Upper-Extremity assessment. tDCS=transcranial direct current stimulation. mCIMT=modified constraint-induced movement therapy. mITT=modified intention-to-treat. *Two participants in the sham plus mCIMT treatment group who withdrew consent after two sessions are not included in the primary FM-UE analysis or the secondary analyses on day 15.

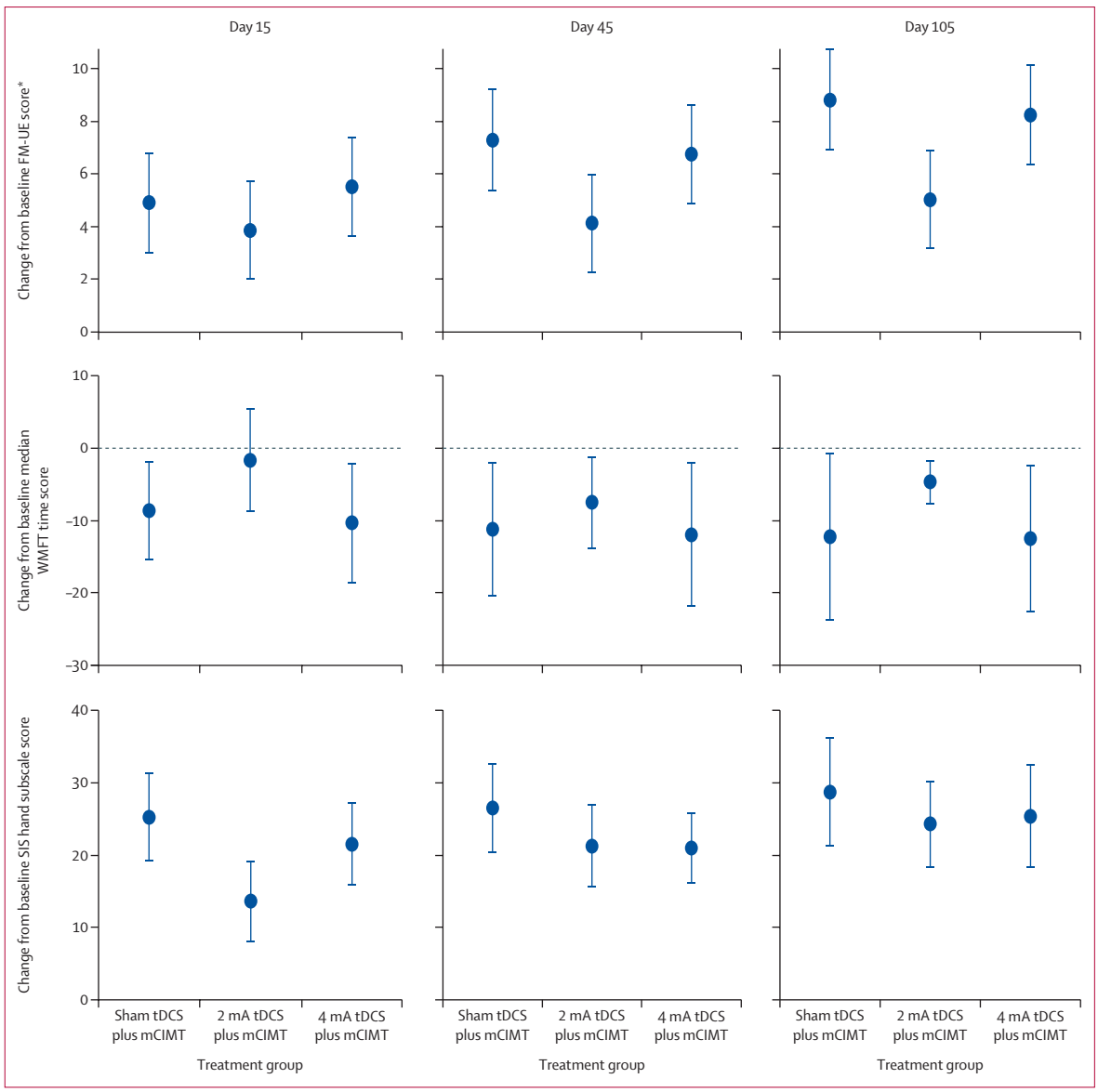


Figure 2: **Primary outcomes and secondary outcomes**
Data are adjusted mean group value with 95% CI for FM-UE score changes, and unadjusted mean group value with 95% CI for the median WMFT time score and SIS hand subscale. FM-UE=Fugl–Meyer Upper-Extremity. SIS=stroke impact scale (version 3.0). WMFT=Wolf Motor Functional Test. *For FM-UE score, the p value for the primary null hypothesis that all three groups are equal at day 15 is 0·39; the p value for two-factor interaction between the treatment arm and visit day is 0·23.

randomly assigned to treatment groups, 43 in each group (figure 1, table 1). One participant in each treatment group was lost to follow-up after day 45, two participants in the sham plus mCIMT group and one in the 4 mA plus mCIMT group withdrew consent, one participant in the sham plus mCIMT group terminated early for other reasons, and no participants died (figure 1). The last participant visit was completed in September, 2024.

The median age at randomisation was 59 years (IQR 50–66). 54 (42%) of 129 participants were female, and 69 (53%) were White. The mean baseline (second qualifying) FM-UE score was 37 (SD 11·1) and the median score was 39 (IQR 27–47), as assessed by the site rater. 34 (26%) of 129 participants were randomly assigned to a treatment group at 30–90 days after stroke. The proportion of right-sided weakness and of female individuals appeared to vary between groups (table 1).

43 participants in the 4 mA plus mCIMT group, 43 in the 2 mA plus mCIMT group, and 41 in the sham plus mCIMT group were included in the primary analysis. The adjusted mean change from baseline to day 15 in FM-UE score was 4·91 (95% CI 3·00–6·82) for the sham plus mCIMT group, 3·87 (2·00–5·74) for the 2 mA plus mCIMT group, and 5·53 (3·64–7·42) for the 4 mA plus mCIMT group

	Treatment	N	Least squares mean (95% CI)	Least squares mean difference (95% CI)		$p_{interaction}$
Sex						0·40
Male	Sham	20	4·57 (2·13 to 7·00)			
	2 mA	30	2·75 (0·79 to 4·70)	2 mA-Sham	−1·82 (−4·83 to 1·19)	
	4 mA	24	3·77 (1·55 to 6·00)	4 mA-Sham	−0·79 (−3·93 to 2·35)	
Female	Sham	21	5·05 (2·30 to 7·80)			
	2 mA	13	6·09 (2·61 to 9·58)	2 mA-Sham	1·05 (−3·27 to 5·36)	
	4 mA	19	7·25 (4·39 to 10·10)	4 mA-Sham	2·20 (−1·66 to 6·06)	
Race or ethnicity						0·65
Non-Hispanic White	Sham	20	4·10 (1·45 to 6·75)			
	2 mA	22	3·67 (1·21 to 6·13)	2 mA-Sham	−0·43 (−3·96 to 3·10)	
	4 mA	18	4·11 (1·39 to 6·84)	4 mA-Sham	0·01 (−3·68 to 3·70)	
Other	Sham	21	5·61 (2·99 to 8·22)			
	2 mA	21	4·06 (1·47 to 6·66)	2 mA-Sham	−1·54 (−5·07 to 1·98)	
	4 mA	25	6·49 (4·10 to 8·88)	4 mA-Sham	0·88 (−2·51 to 4·28)	
Age group						0·55
<59 years	Sham	24	5·55 (2·90 to 8·20)			
	2 mA	17	5·07 (1·88 to 8·26)	2 mA-Sham	−0·48 (−4·42 to 3·46)	
	4 mA	20	6·42 (3·57 to 9·27)	4 mA-Sham	0·88 (−2·88 to 4·63)	
≥59 years	Sham	17	4·04 (1·47 to 6·61)			
	2 mA	26	3·04 (0·99 to 5·08)	2 mA-Sham	−1·00 (−4·21 to 2·21)	
	4 mA	23	4·38 (2·12 to 6·65)	4 mA-Sham	0·35 (−2·95 to 3·64)	
Affected side of the body						0·56
Left	Sham	21	5·60 (3·05 to 8·14)			
	2 mA	30	4·45 (2·31 to 6·59)	2 mA-Sham	−1·15 (−4·38 to 2·09)	
	4 mA	17	5·62 (2·78 to 8·46)	4 mA-Sham	0·02 (−3·69 to 3·73)	
Right	Sham	20	4·10 (1·38 to 6·83)			
	2 mA	13	2·40 (−0·89 to 5·70)	2 mA-Sham	−1·70 (−5·80 to 2·40)	
	4 mA	26	5·35 (2·98 to 7·71)	4 mA-Sham	1·24 (−2·19 to 4·67)	
Time from first ischaemic stroke						0·69
30–90 days	Sham	10	5·70 (1·50 to 9·90)			
	2 mA	12	3·98 (0·27 to 7·69)	2 mA-Sham	−1·73 (−7·39 to 3·94)	
	4 mA	11	5·52 (1·62 to 9·41)	4 mA-Sham	−0·19 (−6·03 to 5·65)	
91–180 days	Sham	31	3·74 (1·80 to 5·67)			
	2 mA	31	3·29 (1·35 to 5·22)	2 mA-Sham	−0·45 (−3·20 to 2·29)	
	4 mA	32	4·89 (2·99 to 6·79)	4 mA-Sham	1·15 (−1·57 to 3·87)	
Presumed motor evoked potential positive						0·78
Yes	Sham	30	4·88 (2·57 to 7·19)			
	2 mA	31	3·62 (1·43 to 5·80)	2 mA-Sham	−1·26 (−4·34 to 1·81)	
	4 mA	27	6·07 (3·73 to 8·41)	4 mA-Sham	1·19 (−2·02 to 4·40)	
No	Sham	10	3·72 (0·73 to 6·71)			
	2 mA	12	4·55 (1·70 to 7·39)	2 mA-Sham	0·83 (−3·29 to 4·95)	
	4 mA	16	4·25 (1·71 to 6·80)	4 mA-Sham	0·53 (−3·32 to 4·39)	

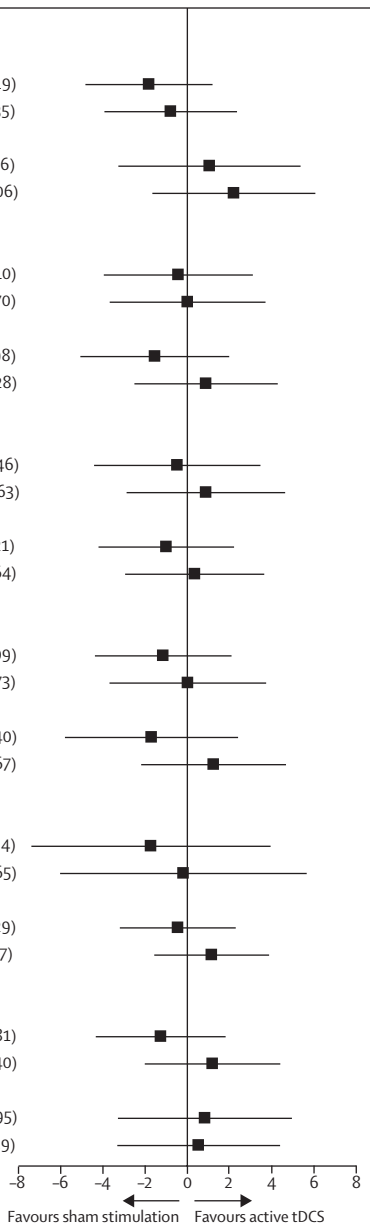


Figure 3: **Subgroup analysis**
Data compare the primary outcome of change in FM-UE score between baseline (second qualifying FM-UE score) and day 15. Prespecified subgroup analyses were sex and race or ethnicity; all other data are post-hoc subgroup analyses. Data are shown as the adjusted mean group differences and 95% CI, as calculated by stratified linear mixed-effects repeated measures models. The stratified models were adjusted for visit, treatment arm, baseline FM-UE, and time from stroke (except in the time from first ischaemic stroke subgroup analysis). Tests of interaction were performed using mixed models that included visit by treatment arm by subgroup indicator interactions (and all lower level terms) as well as baseline FM-UE, and time from stroke. An AR(1) autocorrelation structure was used for visits within the same subject. Time from stroke used the same definition as the randomisation (30–90 days; 91–180 days). Due to convergence issues, these models did not include a random effect for site.

(figure 2). The primary null hypothesis was not rejected (p=0·39). All three groups sustained improvement through to day 105 (3 months after the intervention period), reaching a change in FM-UE of 8·82 (95% CI 6·89–10·75) in the sham plus mCIMT group, 5·04 (3·16–6·92) in the 2 mA plus mCIMT group, and 8·24 (6·33–10·16) in the 4 mA plus mCIMT group. 420 (2%) of 20121 FM-UE items could not be centrally scored.

The number of participants who received usual rehabilitation therapy targeting the weak arm after the

	Sham tDCS plus mCIMT (n=43)	2 mA tDCS plus mCIMT (n=43)	4 mA tDCS plus mCIMT (n=43)	p value*
Safety				
Clinically important adverse events	0	0	0	..
Severe headache	0	0	0	..
Second-degree skin burn	0	0	0	..
Clinical seizure	0	0	0	..
Neurological deterioration (≥4-point increase in NIHSS score)	0	0	0	..
Death	0	0	0	..
Any serious adverse event†	2 (5%)	0	5 (12%)	0·069
Tolerability				
Visual analogue scale‡ (0–10 equivalent to no to extreme discomfort)	1·0 (0·0–2·0)	0·0 (0·0–2·0)	1·0 (0·0–4·0)	0·56
Feasibility				
At least eight treatment sessions completed	40 (93%)	43 (100%)	43 (100%)	0·11

Data are n (%) or median (IQR). All 129 participants randomly assigned to treatment groups were included in the safety analysis. All adverse events are listed in the appendix (pp 7–9). NIHSS=National Institutes of Health stroke scale. tDCS=transcranial direct current simulation. mCIMT=modified constraint-induced movement therapy. *Serious adverse events and feasibility were compared using Fisher's exact test and tolerability was compared using the Kruskal–Wallis test. †None of the serious adverse events were possibly or definitely related to the intervention. ‡A local investigator forgot to assess the visual analogue scale for one participant who was randomly allocated to the sham tDCS plus mCIMT group.

Table 2: **Safety, tolerability, and feasibility**

2-week TRANSPORT2 intervention was balanced across the three groups: 25 (58%) of 43 in the sham group, 27 (63%) of 43 in the 2 mA group, and 26 (61%) 43 (60.5%) in 4 mA group. As such, the per protocol sample did not exclude participants on the basis of additional post-treatment therapy alone. Ten (23%) participants in the sham plus mCIMT group, two (5%) in 2 mA plus mCIMT group, and six (14%) in the 4 mA plus mCIMT group were excluded from the per-protocol analysis. The most common reason for exclusion was incomplete follow-up. The primary findings were supported by the per-protocol analysis (p=0·21, appendix p 10).

In the prespecified subgroup analyses of the primary outcome by sex and race or ethnicity, the treatment effect did not differ (figure 3). No significant differences were observed in any post-hoc subgroups (ie, median age, motor evoked potential status, affected side, and time from stroke).

No formal statistical tests were performed for the Wolf motor function test time score or the stroke index scale hand subscale, since the primary null hypothesis was not rejected. The raw mean change in median Wolf motor function test time score from baseline to day 15 was –8·67 (95% CI –15·50 to –1·84) in the sham plus mCIMT group, –1·65 (–8·76 to 5·46) in the 2 mA plus mCIMT group, and –10·37 (–18·64 to –2·11) in the 4 mA plus mCIMT group. A similar decrease was seen over the next two follow-up visits (ie, at day 45 and day 105; figure 2).

The raw mean change in the stroke index scale hand subscale from baseline to day 15 was 25·24 (19·13 to 31·36) in the sham plus mCIMT group, 13·60 (8·01 to 19·20) in the 2 mA plus mCIMT group, and 21·51 (15·77 to 27·25) in the 4 mA plus mCIMT group. A similar increase was seen over the next two follow-up sessions, up to day 105 (figure 2).

No clinically important adverse events or deaths occurred during the intervention period in any group (table 2). Serious adverse events occurred in two (5%) participants in the sham plus mCIMT group, no participants in the 2 mA plus mCIMT group, and five (12%) participants in the 4 mA plus mCIMT group (p=0·069). No serious adverse events were determined to be possibly or definitely related to the intervention. The median visual analogue scale score for tolerability assessment was 1·0 (IQR 0·0–2·0) for the sham plus mCIMT group, 0·0 (0·0–2 ·0) for the 2 mA plus mCIMT group, and 1·0 (0·0–4·0) for the 4 mA plus mCIMT group. No significant difference in tolerability between the three groups was observed (p=0·56). Trial adherence (measuring feasibility) was good, with 40 (93%) participants in the sham plus mCIMT group, 43 (100%) in the 2 mA plus mCIMT group, and 43 (100%) in the 4 mA plus mCIMT group having at least eight treatment sessions. No difference in feasibility was noted between the three groups (p=0·11). Site raters were not able to guess whether the participant was assigned to active tDCS more accurately than by chance (p=0·12), nor were the participants themselves (p=0·17, appendix pp 6, 7).

Discussion

This phase 2, randomised, triple-blind, sham-controlled multicentre trial investigated the effects of tDCS applied over the motor regions of the affected hemisphere (anodal stimulation) and unaffected hemisphere (cathodal stimulation) at three different doses (sham, 2 mA, and 4 mA). Stimulation was administered for 30 min, combined with 120 min of a standardised and structured intensive form of rehabilitative therapy for ten sessions over a 2-week period. No significant difference was observed across the three treatment groups in the primary outcome, which was the mean change in FM-UE score from baseline to day 15. The FM-UE score did improve at day 15, and was sustained at the day 45 and day 105 follow-up assessments, but there was no statistical difference in score improvement between the treatment groups. The combined tDCS and mCIMT intervention was safe, well tolerated, and feasible for implementation in a multicentre trial setting.

To the best of our knowledge, TRANSPORT2 is the first stroke recovery study to test tDCS at 4 mA with a corresponding current density of 0·114 mA/cm² using a 5×7 cm electrode pad. Our trial did not show an effect of tDCS (either at 2 mA or 4 mA) versus sham treatment. A higher current (or current density) might lead to stronger effects, and current at 4 mA or higher has been applied

safely in recent studies. Chhatbar and colleagues[21] measured intracranial voltage gradient using deep brain stimulation electrodes in three individuals with Parkinson's disease, reporting a value of 0·19–0·26 mV/mm when 4 mA with an electrode pad of 5×7 cm was applied with a bitemporal montage. These values are still below the 1 mV/mm threshold that is necessary to influence neuronal spiking and subthreshold currents in animal studies. Other research involving both animals and humans indicates that 4·5 mA current or higher is likely to be required to reliably modulate the occipital α wave amplitude in humans.[22] In a concurrent tDCS–functional MRI and behaviour study of 32 healthy participants, testing doses of 0·1 mA, 2 mA, and 4 mA with a 12·56 cm² electrode pad, a linear tDCS dose response was shown for a finger sequence task; functional MRI results showed more consistent increases in regional cerebral blood flow at 4 mA.[17] Robust enhancement of motor sequence learning in 108 healthy participants was shown using anodal 4+4 montage at 4 mA (current density of 0·41 mA/cm² and estimated electrical field magnitude of 0·47 mV/mm).[23] Additionally, in a meta-analysis, a positive dose–response relationship was noted between current density and motor impairment reduction in individuals who have had a stroke, further supporting current density increases.[15] The strategy for increasing current density can be achieved in three ways: increasing the current while maintaining the same pad size, keeping the current constant while reducing the pad size, or using different electrode placement (ie, montage). Under-dosing could be an issue, as brain injury based on a rat model occurs at a current density of 14·3mA/cm², which is more than an order of magnitude higher than the human protocols.[24] Because the 4 mA current with a pad size of 35 cm² was shown to be safe and tolerable in individuals who had had a stroke in TRANSPORT2, we believe that future investigations into the efficacy of higher current or current density are justified.

In TRANSPORT2, mCIMT was selected as an intensive, structured rehabilitative therapy, consisting of 120 min of active therapy per session for ten sessions over a 2-week period (20 h of therapy time in total). Additionally, participants were required to adhere to a home contract, which included wearing a mitt on the unaffected hand for 6 h per day and practising specific tasks outside the intervention sessions, as prescribed by the trainer. This therapy regimen represents a level of intensity that is four-times or more than what is typically provided in standard rehabilitation care in real-world practice. Therefore, mCIMT alone for ten sessions could have been a strong driver of the induced recovery in all treatment groups, and adding tDCS at 4 mA or lower current might not have yielded additional benefits. Whether adding more sessions of tDCS could amplify the effect from mCIMT is still unknown.

Findings from animal stroke models suggest that there might be a time-sensitive window when the brain is especially responsive to rehabilitation therapy.[25,26] These findings were replicated in the CPASS study of patients with stroke, which showed that task-specific motor intervention was most effective within the first 2–3 months after stroke.[27] In TRANSPORT2, we specifically stratified enrolment time by 30–90 days and 91–180 days following first ever ischaemic stroke, and we also balanced the time from stroke between the treatment groups during the randomisation process. However, a post-hoc subgroup analysis did not show a differential treatment response on the primary outcome based on enrolment time. Only 34 (26%) of 129 participants were randomly allocated 30–90 days post-stroke, so these results should be interpreted with caution. Two other large stroke recovery trials had similar findings to ours. In the EXCITE trial, which had similar enrolment criteria as TRANSPORT2, CIMT was delivered to eligible participants 3–9 months or 15–21 months after stroke, and both groups had approximately the same level of change in arm motor function 24 months after the intervention.[28] In the LEAPS trial that studied lower extremity recovery after stroke, one group received training on a treadmill with the use of bodyweight support 2 months after stroke (early locomotor training) and the other group received this training 6 months after stroke (late locomotor training). There was no statistically significant difference in changes in walking speed between the two groups at one year after stroke.[29]

The VNS-REHAB study has similarities with TRANSPORT2, as it combined invasive vagus nerve stimulation with 90 min of rehabilitation therapy for 18 sessions over a 6-week period (27 h of therapy).[30] Participants in the VNS-REHAB study had a longer time between their stroke and the intervention (9 months to 10 years post-stroke; 3·2 years on average) compared with the subacute population in TRANSPORT2 (1–6 months post-stroke; 3·8 months on average). However, the two trials were comparable in terms of age and baseline impairments. In VNS-REHAB, the active arm showed an improvement of 5·0 points on the FM-UE scale and the control arm improved by 2·4 points. The magnitude of improvement over 2 weeks observed from the three groups of TRANSPORT2 was comparable to that of the active arm over 6 weeks in VNS-REHAB. This observation shows that the time from stroke and the intensity and duration of rehabilitation therapy probably have important implications for the design of future brain stimulation stroke recovery trials.

The NETS trial is possibly the most comparable in design to TRANSPORT2, in that it investigated tDCS (including a sham group) in addition to rehabilitative therapy in a multicentre setting in patients after first-ever ischaemic stroke, using the FM-UE scale as the primary outcome.[31] However, notable differences include the dose of stimulation (1 mA in NETS), participant characteristics (more acute strokes in NETS; 5–45 days post-stroke, 20 days on average since stroke), and the type of

rehabilitative therapy (less intensive in NETS; applied for 45 min per session for ten sessions). In NETS, the mean change in FM-UE was 8·76 for active stimulation compared with 9·07 for sham stimulation at 1–7 days after the 2-week intervention. A further small increase in FM-UE was reported at 1-month follow-up, but no further change at the 3-month follow-up. In TRANSPORT2, with mean time from stroke of 116 days, participants achieved slightly more than half of the change in FM-UE compared with the primary outcome in NETS right after the intervention. However, in TRANSPORT2, the mean estimates of change in FM-UE increased over time in the sham plus mCIMT and the 4 mA plus mCIMT groups (not in the 2 mA plus mCIMT), reaching 8–9 points at 3 months. NETS revealed a significant interaction between treatment group and sex, with FM-UE scores improving more in female participants than male participants. In TRANSPORT2, the estimated mean differences for female participants were numerically larger than male participants, but they were not statistically significant. Possible explanations include variability in subgroups due to chance or physiological or functional differences in brain organisation that might be favourable to female participants. For example, females have a relatively larger midsagittal corpus callosum size, resulting in more interhemispheric connections; bi-hemispheric stimulation could have more of an effect for those that already have more pronounced structural and functional connectivity between the hemispheres. Furthermore, old-aged female participants (ie, individuals aged 64–87 years) receive higher current density than male participants due to sex differences in brain torque.[32] Overall, this possible differential response to brain stimulation by sex warrants further investigation in future trials.

Single-pulse transcranial magnetic stimulation is widely used to elicit motor evoked potentials, which can serve as a biomarker for corticospinal tract integrity.[33] Motor evoked potentials have been found to be valuable in predicting both natural recovery and therapeutic response. For example, in the EVEREST trial involving invasive epidural motor cortex stimulation, participants with motor evoked potential positive status had better responses to brain stimulation than those without motor evoked potential.[34] Similarly, in a tDCS robotic trial, the presence of motor evoked potentials at baseline was associated with a higher proportion of participants achieving a clinically meaningful improvement (ie, ≥5 point change on the FM-UE scale) compared with those without motor evoked potentials.[35] In TRANSPORT2, 90 (70%) participants had motor evoked potential positive status at baseline. Our inclusion criteria required participants to have preserved distal muscle movements, similar to the EXCITE trial.[2] However, we did not observe a differential response with regard to motor evoked potential status between the three treatment groups in TRANSPORT2.

TRANSPORT2 has several strengths. This trial is the first brain stimulation stroke recovery study funded and conducted through StrokeNet in the USA.[36] Despite challenges posed by the COVID-19 pandemic, the trial maintained high performance, achieving a high retention rate of 98% for the primary endpoint at day 15 visit. The loss-to-follow-up rate was also lower than initially estimated in the sample size calculation. The study enrolled a diverse population, including 47% non-White and 42% female participants, both groups that have been historically under-represented in stroke trials.[37] Substantial efforts were dedicated to initial and ongoing training of site study teams in intervention protocols, outcome assessments, neurophysiology evaluations (ie, transcranial magnetic stimulation assessment of motor evoked potentials), and standardised neuroimaging data collection to ensure scientific rigor and data quality. Additionally, TRANSPORT2 appointed one central rater to blindly assess the primary outcome measures, effectively eliminating inter-rater variability. Our eligibility criteria required participants to show an absolute change of 2 or fewer points on the FM-UE scale between two consecutive baseline visits, thereby excluding participants with rapid ongoing spontaneous motor recovery. We also conducted blindness assessments with both raters and participants at the end of the last session by asking them to guess the group assignment, with the results indicating successful blinding of group assignments. These methodological approaches underscore the crucial steps necessary to enhance the design and execution of future stroke recovery trials.

TRANSPORT2 had several limitations that highlight opportunities to improve future stroke recovery trials. First, TRANSPORT2 balanced several important covariates—including baseline FM-UE, time from stroke, and enrolment site—during the randomisation process, but we did not balance sex. As observed in the NETS study, as well as in our prespecified subgroup analysis, sex might have a differential effect on stroke motor recovery. The imbalance of female participants might partly account for the performance of the 2 mA plus mCIMT group. Sex should be balanced in future trials. Second, the use of a blinded central rater for the primary outcome measure was one of the innovative and scientifically rigorous aspects of TRANSPORT2. However, the central rater did not complete scoring in real-time and, as a result, 2% of items in total on the FM-UE were unable to be centrally scored (due to video recording errors, partly because of COVID-19 restrictions). Additionally, seven participants deemed eligible by the local rater were later found to have FM-UE scores higher than 54 by the central rater. Real-time administration and rating of the FM-UE by a central rater might improve this process in future trials, eliminating issues with scale administration and video capture. Third, a modelling-based dosing approach rather than one-dose-fits-all

approach could be considered and tested in future trials; however, several positive brain stimulation stroke recovery trials have used the one-dose-fits-all-approach.[13,30,38] Lastly, due to COVID-19, StrokeNet was shut down for 3 months. Although the network resumed enrolment after this period, it took the TRANSPORT2 team longer than expected to restart trial enrolment at study sites due to various local COVID-19 policies. The top three sites enrolled 50% of participants and the remaining 11 sites contributed the remaining 50%, which shows variation in site enrolment. These limitations and challenges highlight the need to establish robust infrastructure for stroke recovery trials, enabling more efficient and expedited execution of multicentre studies.

In summary, this multicentre tDCS stroke recovery trial involved participants who have had a first-ever ischaemic stroke with persistent upper-extremity motor deficits between 1–6 months after stroke. TRANSPORT2 showed that adding bi-hemispheric tDCS at 2 mA or 4 mA to intensive rehabilitation therapy, such as mCIMT, did not lead to further improvement for post-stroke motor recovery. Currents of 2 mA and 4 mA were safe and well tolerated, and the intervention combined with mCIMT was feasible in the multicentre trial setting. In future trials, we might consider testing tDCS at higher current or current density, balancing known covariates affecting stroke recovery during the randomisation, and investing more efforts into trial enrolment and outcomes standardisation.

Contributors

GS, CC, and WF contributed to trial conceptualisation and methodology. WF, GS, and JPB contributed to funding acquisition. GS, JAF, SLW, VTR, SF, JPB, RZ, OA, PYC, AS, DE, CL, GEF, GFW, SP, CG, MRB, and WF contributed to data collection, resource and project administration. CC, ZS, and VR contributed to data curation, software, validation, and statistical analysis. GS, WF, CC, and JPB contributed to writing the original draft. CC and ZS directly accessed and verified the underlying data reported in the manuscript. All authors had full access to all the data, contributed to reviewing and editing, and had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

WF received grant funding from the US National Institute of Health (NIH) for the present study as the contact Principal Investigator and other grants from the NIH and American Heart Association for other brain stimulation stroke recovery studies. He also received consulting fees from serving as the chair of the Data Safety Monitoring Board for North American Science Associates and being a scientific advisory member for Burke Rehabilitation Institute and California Institute of Regenerative Medicine. GS received grant support for the present study as a Multiple Principal Investigator from the NIH, grant support from the NIH for other brain stimulation recovery studies, and also received honorarium for grand rounds from academic institutions. JAF, SLW, VTR, SF, JPB, RZ, OA, PYC, AS, DE, CL, GEF, GFW, SP, CG, MRB, CC, ZS, and VR received grant support for their efforts as site Principal Investigators or co-investigators or key team members for the present study from the NIH since 2018. PYC also received other grant support from NIH (an R03 early career award). JPB received financial support and study medication from Novo Nordisk for an NIH-sponsored FASTEST study; consulting fees from Roche–Genentech, Brainsgate, and Basking Biosciences Department; and fees from his role on the Pharmacy and Therapeutics Committee for Kroger Prescription Plans. DE also received travel reimbursement from the American Academy of Neurology, Rehabilitation Medicine Society of Australia and New Zealand and Villa Beretta Rehabilitation Hospital, and Milan Polytechnic University; participated in data safety monitoring board or scientific advisory board for the Harvard Medical School, and served as an unpaid robotics special interest group co-chair for the World Federation of Neurorehabilitation. SF received grant support from the NIH for the present work as well as other grant support from the National Science Foundation and the NIH; consulting fees for participating in another NIH grant; and travel support for conferences from University of South Carolina. CG and CC also received other grant support from the NIH for other stroke recovery projects. CL acknowledged grant support from the Veteran Administration. GFW received travel reimbursement from NIH, National Science Foundation, and the Veterans Health Administration and served on advisory boards for two stroke rehabilitation product companies (NeuroInnovators and Myomo).

Data sharing

In accordance with National Institutes of Health StrokeNet data-sharing policies, anonymised individual data with a data dictionary (which does not include identifiers) will be made publicly available in the National Institute of Neurological Disorders and Stroke (NINDS) data repository within 1 year after this primary manuscript has been accepted for publication for the foreseeable future via https://www.ninds.nih.gov/current-research/research-funded-ninds/clinical-research/archived-clinical-research-datasets. Requests for data access should be made by submitting the NINDS data request form (available via the previous website) to the NINDS Clinical Research liaison at CRLiaison@ninds.nih.gov. The study protocol, statistical analysis plan, and manuals of procedures are available in the appendix (pp 12–401).

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