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Transcranial direct current stimulation for upper and lower limb motor function in young people with Cerebral Palsy: a randomised controlled pilot study

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ABSTRACT

Purpose: Cerebral Palsy (CP) is the commonest cause of childhood motor disability. Transcranial direct current stimulation (tDCS) is a promising adjuvant therapy, but research targeting upper and lower limbs simultaneously is needed. We aimed to pilot tDCS with upper/lower limb motor training, estimate the potential effect on motor function, and investigate brain imaging correlates of function.

Materials and methods: Participants (10–16 years) with CP affecting upper and/or lower limbs were randomised (online software) to 10 sessions of active ($n=14$) or sham ($n=13$) tDCS combined with motor training. The primary outcomes were upper and lower limb function assessed at 1-week post-intervention using the Jebson Taylor hand function (JTT) and Timed Up and Go (TUG) tests. Secondary, imaging outcomes included baseline tractography, grey matter volume, and resting state connectivity.

Results: Adherence was good: 74% completed all intervention sessions, 100% completed the primary outcome assessment. There were no between-group differences (1-week post-intervention, intention-to-treat; group-by-time JTT: $F(1,25)=1.189, p=0.286$, partial-eta-squared = 0.05; TUG: $F(1,25)=1.605, p=0.217$, partial-eta-squared = 0.06). Imaging showed subtle associations between better JTT at baseline and higher grey matter volume (caudate nucleus) and stronger sensorimotor resting state connectivity.

Conclusions: The trial was well tolerated, but effect sizes were small. Larger studies are needed to further explore tDCS for CP.

IMPLICATIONS FOR REHABILITATION

- Cerebral Palsy (CP) commonly affects upper and lower limb motor function in children.
- Transcranial direct current stimulation (tDCS) is a promising adjunct therapy, but research combining tDCS with both upper and lower limb training in CP is needed.
- We found that 10 sessions of combined tDCS and training was well tolerated in children aged 10–16 with CP.
- There was no clear indication of motor improvements following tDCS compared to sham.
- Brain imaging revealed subtle associations between brain structure/function and baseline function, but no clear relationship with intervention response
- Further research and evidence is needed before tDCS can be recommended clinically for children with CP.

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Introduction

Cerebral Palsy (CP) is a significant contributor to paediatric morbidity/mortality and is the most common cause of motor disability in childhood [1]. A recent stakeholder engagement process proposed to define CP as *an early-onset lifelong neurodevelopmental condition characterised by limitations in activity due to impaired development of movement and posture, manifesting as spasticity, dystonia, choreoathetosis, and/or ataxia* [2]. They further highlighted that *the phenotype of CP is complex and heterogeneous, with each person experiencing a unique presentation*.

It is well documented that children with CP have impaired motor skills arising from the neurological damage (in some cases some motor skills may never be acquired), and more difficulty in performing activities of daily living (ADLs), than typically developing children [3]. Despite an initial upward trajectory in motor skill function early in childhood for some, young people with CP experience an overall decline in function and mobility from adolescence into adulthood and onwards [4–6]. This affects numerous areas of daily life and participation, as defined in the International Classification of Functioning, Disability and Health (ICF) [5,7]. While there is an extensive scope of research looking at ways to prevent CP, the prevalence over the last 20 years has remained fairly static in developed countries [8]. It is therefore critical to pursue interventions to improve motor function and increase the independence of young people with CP.

Non-invasive brain stimulation (NIBS) techniques, which have gained increasing favour over the last two decades, offer the potential to modulate neural activity following an acquired brain injury [9]. One such technique is transcranial direct current stimulation (tDCS). Although there has been considerable investigation of tDCS for adult stroke [10–17], the findings are mixed and cannot be assumed to translate directly to CP. The application of tDCS in young people with CP appears to be safe [18] and guidelines have been developed to ensure appropriate use [19]. However, research on the effectiveness of tDCS on motor function is limited [20]. For the upper limb, single session studies delivering anodal tDCS to increase cortical excitability have reported improvements in reaching movement duration [21] and grasp and release [22]. Randomised controlled trials (RCTs) administering multiple days of anodal tDCS found improvements in spasticity and passive range of movement [23], as well as motor function [24]. Studies delivering 10 days of anodal tDCS to target the lower limb are generally promising, with improvements in balance [25,26], walking velocity and cadence [27] and the timed up and go [26]. However, studies often limit to specific subtypes of CP such as perinatal stroke or those with unilateral impairment. Given that approximately two-thirds of children with CP have motor deficits in more than one limb [28], it is of value to investigate whether combining tDCS with therapy involving both upper and lower limb training would be feasible and have the potential to be effective. To our knowledge, no studies have evaluated the use of tDCS at improving both upper and lower limb function in the same session.

Therefore, to contribute evidence and inform future study design (including sample size calculations for larger trials), we aimed to conduct a pragmatic pilot study to 1) estimate the size of the potential effect on upper and lower limb motor function, and 2) use brain imaging (tractography, grey matter volume and resting state connectivity) to explore potential correlates of baseline function and response to tDCS in this population. Young people with CP were randomised to 10 sessions of active or sham tDCS combined with motor training for the upper and lower limb. Function was assessed at baseline and at follow-up assessments 1, 6 and 12-weeks post-intervention. We hypothesised that 1) there would be an indication of improvements in motor function for active tDCS compared to sham, and 2) measures of brain imaging would correlate with motor function at baseline and changes in function at 1-week post-intervention.

Methods

Study design

This was a two-arm parallel group, randomised controlled pilot study, designed following CONSORT guidelines. The study was approved by the United Kingdom National Research Ethics Service (West Midlands - Edgbaston Research Ethics Committee, approval reference 20/WM/0046) and registered as a clinical trial on the ISRCTN registry, prior to enrolment of the first participant (reference ISRCTN74235136).

Participants

To be eligible, participants had to be 10–16 years of age (at time of recruitment), with a diagnosis of CP. This age group was chosen to ensure engagement and compliance with the trial procedures, while also capitalising on the capacity for motor skill development and neural plasticity during this critical developmental period. As a pragmatic trial, we wanted to include people with a range of upper and/or lower limb impairments, therefore we included participants with gross motor function classification score (GMFCS) I-III and manual ability classification score (MACS) I-III. Participants needed to be able and willing to follow instructions, able and willing to provide informed consent (if 16 years of age) or with a parent/guardian to provide informed consent on their behalf (if under 16 years of age). Participants were excluded if they had contraindications to tDCS, including seizures within the previous 2 years, pacemakers, or metal implants in the head [19]. We relied on parent/guardian report as to whether the child had experienced seizures in the past 2 years. Given that tDCS does not elicit action potentials in the cortical neurons, the risk of serious adverse events such as seizures is low [18]. We therefore felt this risk-based approach to screening to be appropriate, rather than relying on a thorough review of medical records which was deemed disproportionate to the risk. Whist it is theoretically possible that this introduces bias to the sample, it also ensures a more inclusive recruitment strategy. We did not exclude participants based on previous surgery or Botulinum Toxin treatments. Additional exclusion criteria applied for the optional magnetic resonance imaging (MRI) sub-study, such as MR non-compatible metallic implants. Participants who were unable or unwilling to undergo MRI were still able to participate in all other aspects of the trial.

All participants (regardless of group allocation) received £15 per session as compensation for their time and were reimbursed for travel expenses.

Setting, recruitment, and consent

Participants were recruited through UK NHS trusts, schools and online advertisement between September 2021 and October 2023. For potential participants identified through NHS trusts, clinical staff obtained verbal consent for contact details to be passed to the research team (or potential participants could contact the researchers directly if preferred) who then provided the participant information sheet. For school recruitment, following agreement to study involvement from the head teacher, a school staff member sent a letter of invitation and participant information sheet to parents/guardians. Parents/guardians were asked to complete a screening consent form and return it to the school. In all cases, researchers then contacted interested parents/guardians to complete screening and recruitment processes. Parents/guardians of children aged under 16 years provided written informed consent and children provided written assent. Participants aged 16 years provided written informed consent. Testing and intervention sessions took place at University, school and NHS site settings, depending on recruitment route and participant residence (*see supplementary methods for site details*).

Intervention

The intervention was 10 sessions of tDCS combined with motor training (active stimulation group), in comparison to sham stimulation combined with motor training (control group). We chose 10 sessions as this is consistent with previous studies in adult stroke [16] and input from parents of young people with CP felt this would be appropriate to fit in around other time commitments. Intervention sessions took place over approximately 2 weeks.

The active stimulation group received anodal tDCS (1 mA; Nurostym, Brainbox Ltd, UK) for the first 20 min of each 90 min training session (alongside motor training) [20]. The anode (35 cm^2) was placed over the primary motor cortex contralateral to the more-affected upper/lower limb (C3/C4; located using the 10–20 EEG system [29]), as close to the sagittal midline as possible (with the intent of covering upper and lower limb cortical motor representations). The cathode (35 cm^2) was placed over the contralateral supraorbital ridge [30]. For the control group, electrodes were placed in the same manner, but to deliver sham stimulation, the current was ramped up over 30s then turned off, as is standard practice. Electrodes were removed after 20 min.

All participants, regardless of group allocation, were scheduled to receive 10 motor training sessions of 90 min each (15-h total), in groups of up to five participants. This programme was delivered by a qualified physiotherapist, trained in the necessary protocols prior to starting the study. Progressive upper and lower limb exercises were conducted in a "circuit-style" session, whereby exercises were practiced for 2–5 min. Each activity had a fixed time and increasing difficulty levels through repetitions, distance and complexity. These exercises incorporated principles of motor learning [31], of the Hand Arm Bimanual Intensive Therapy (HABIT) [32], the upper limb intensive (Magic) camp programme [33] and the HABIT Including Lower Extremities (HABIT-ILE) programme [34]. Individualised prescription/progression was based upon achievement within sessions, and activities were delivered in a fun and engaging manner, with the participants' goals incorporated wherever possible. Training activities were developed with input from a young person with impairments in upper and lower limb motor function, their parent, physiotherapists, occupational therapists and movement neuroscientists (*see supplementary methods for examples)*.

Outcomes

Assessments were conducted, by trained assessors (FM, BG) blinded to group allocation, at baseline, 1-week following the end of the intervention period (herein termed 1-week) and at 6- and 12-weeks follow-up. Assessments took place at university or school sites, depending on recruitment route and participant residence.

The primary upper limb outcome was the change in time for the Jebson Taylor hand function test (JTT, in seconds) [35], for the most affected upper-limb, at 1-week post-intervention. Participants were familiarised with the tasks prior to assessment at the baseline session. At each assessment session, participants completed each task three times. They were instructed to perform the activity as quickly and accurately as possible. The maximum time allowed for each subtask was 120 s, and participants were given the maximum time if they were unable to complete the task. A total time (in seconds) was calculated by summing the best repetition time for each of the 6 subtasks.

The primary lower limb outcome was the change in time for the Timed Up and Go (TUG, in seconds) [36] at 1-week post-intervention. Participants were allowed to use any walking aids they typically required and were instructed to perform as quickly and safely as they could. The best of three repetitions was used.

Secondary outcomes

To better understand the longitudinal effects on motor function, JTT and TUG were assessed across all timepoints.

Gait data were assessed with the instrumented 10 m walk [37], using an inertial measurement unit (IMU) (LPMS-B, Life Performance Research, Japan) attached to the skin over the fourth lumbar area, according to [38–40] (see supplementary methods for details). Participants performed the exercise at their self-selected walking pace.

Spasticity was assessed with the Modified Ashworth Scale (MAS) [41], across key joints bilaterally. Given that we were targeting both upper and lower limbs, this resulted in 12 joints assessed at each timepoint. To reduce the number of statistical comparisons performed, rather than testing for changes in individual joint MAS scores, at each follow-up timepoint for each joint we assigned a score of 1 if the MAS increased from baseline, −1 if it decreased, and 0 if it was unchanged. By summing across the joints, we thus calculated a score out of 12, where positive values are indicative of increasing spasticity. We also analysed data for the most-affected side only (i.e., the limb contralateral to the stimulated hemisphere).

To detect the presence of mirror movements we used the Woods and Teuber scale. Participants performed three unilateral movements: finger tapping, fist rotation, alternate finger touching. Mirror movements of the resting hand were scored from 0 (no clear movements) to 4 (movements equal to those observed in the active hand).

We also used the Functional Assessment Questionnaire (FAQ) [42], and Functional Mobility Scale (FMS) [43]. For the FAQ, for each subsection we assigned +1 if the score improved from baseline, −1 if it got worse or 0 if it stayed the same then summed the subsections, such that positive values are indicative

of a greater number of subsections improving than getting worse. Similarly, for the FMS, for each distance (5 m, 50 m, 500 m) we assigned +1 if the score improved, −1 if it got worse or 0 if it stayed the same.

We also included patient reported outcome measures. The Children's hand use experience questionnaire (CHEQ, v2.0, www.cheq.se) [44] was used to evaluate the participant's experience in using their more affected hand in activities where two hands are needed. The automated calculations were used to quantify unit scores for hand use, time required and feeling bothered, which were summed to create a total value. The parent/guardian and child reported Gait Outcomes Assessment List (GOAL) [45] was used to assess gait function, priorities, and expectations. The GOAL questionnaires (v5.0; parent and child versions) were completed with children and parents separated and the researcher supporting as needed. GOAL scores were automatically calculated using a formula-protected analysis sheet provided by the GOAL developers.

Additionally, a process evaluation questionnaire was completed to understand participant's experience of the intervention. To explore the occurrence of side effects from the brain stimulation, participants and their parents were asked to identify whether they experienced commonly found sensations or effects.

Brain structure and function

A baseline magnetic resonance imaging (MRI) scan was an optional component, conducted at the University of Oxford. MRI sub-study participants underwent a scan lasting approximately 45 min, including T1- and T2-weighted anatomical scans, diffusion imaging, and resting state functional MRI. Details of acquisition parameters are in supplementary materials. Brain imaging data were analysed using tools from the FMRIB Software Library [46]. Full details can be found in the supplementary materials, but briefly: Diffusion data were processed using FMRIB's Diffusion Toolbox to calculate the corticospinal tract fractional anisotropy. T1-weighted images were analysed using voxel-based morphometry [47] to generate measures of grey matter volume. Resting state FMRI was processed using MELODIC [48] to estimate functional connectivity.

Assessment of recruitment and adherence

Since this is a pilot study, and to our knowledge we are the first tDCS study to deliberately target and assess participants with impairments in both upper and lower limbs, we wished to determine the rate of recruitment that could be anticipated for future studies. We have reported the number of participants consented relative to the number who contacted the research team or for whom contact information was provided to researchers by the NHS teams. To address adherence, the number of sessions attended is reported, and any reasons for non-attendance or study withdrawal described if known.

Sample size

It was difficult to accurately estimate the expected effect size given limited reporting from prior studies and wide variety in effect sizes where these could be estimated. The median estimate from a selection of relevant previous studies [23,25,26], was approximately $d = 0.5$. The intended sample size of 24 completed participants (1:1 treatment to control ratio) was chosen (calculated using G*Power v3.1) to be adequate to detect an effect if this estimate is correct (alpha 0.05, power 0.8) or to give a better indication of the potential effect size if not, and to evaluate ease of recruitment and delivery of the intervention. Allowing for approximately 20% attrition we intended to recruit up to 30 participants.

Randomisation and blinding

Following baseline assessment, participants were randomly allocated to group (active or sham tDCS; 1:1 randomisation ratio) by an investigator not involved in participant recruitment or outcome assessment (MKF). Randomisation included minimisation of baseline variables age, JTT time and TUG time using an online minimisation randomisation programme (rando.la). The participants, researchers

recruiting participants and delivering the intervention, and outcome assessors were blinded to group allocation. This was done by using the function of the tDCS unit called "double-blinded mode" whereby a unique code for each participant (provided by MKF to the researcher) was entered into the tDCS stimulator to deliver active or sham stimulation. This is a standard process for ensuring allocation concealment in tDCS studies.

Statistical methods

Analyses of non-MRI data were conducted using Jamovi v2.3.28. MRI data were analysed using the FMRIB Software Library (FSL). Where appropriate we used Linear Mixed Effects Models (LMMs), with fixed factors (group, time) and random factor of participant. The LMM is capable of dealing with missing data by utilising maximum likelihood estimation to account for uncertainty in missing values without requiring imputation. For all LMMs, we checked whether addition of covariates age, sex or baseline GMFCS/MACS improved the model fit (reduced AIC, BIC, log likelihood and increased R-squared) and if so, they were included as a covariate in the model. Significance was set at $p < 0.05$ and Bonferroni corrections were applied to all post-hoc t-tests to correct for multiple comparisons. When LMMs were not appropriate, we used complete case analyses with Mann Whitney U tests instead.

Motor function

Data for the primary outcome measures (JTT and TUG) were analysed using intention-to-treat (ITT) principles. As the assessment at 1-week post-intervention was our primary timepoint of interest, the LMM tested for between-group differences specifically at this timepoint with fixed factors of group (active, sham) and time (baseline, 1-week) and participant as a random factor. TUG data were log-transformed to compensate for violations of the normality assumption. To estimate potential effect sizes, we report partial eta-squared (η^2). To better explore the time course of changes, we also conducted LMMs with all timepoints included.

Secondary measures

Gait data (speed, step time, and cadence) were log transformed to compensate for violations of the normality assumption and analysed using LMMs.

The difference between groups for MAS (summed across joints), FMS, and FAQ were analysed for each timepoint separately using Mann Whitney U tests. Data were analysed as complete cases (no imputation for missing data).

The Woods and Teuber scores were analysed using LMMs, with most-affected side (left/right) included as a covariate. Analyses were conducted separately for mirror movements during active movement of the more-affected or the less-affected hand.

For the CHEQ the total score of the units were analysed using a LMM with MACS score as covariate. The GOAL scores were analysed (for parent and child completed assessments separately) using LMMs.

Brain structure and function

To identify potential candidate predictors of functional impairment at baseline, as well as response to the intervention, measures of diffusivity, resting state connectivity, and grey matter volume at baseline were correlated with the baseline JTT and TUG or the percentage change in JTT and TUG between baseline and 1-week post-intervention, using Spearman correlations.

Adverse effects

Any adverse effects identified were recorded as related/unrelated. We used chi-square tests to determine whether the frequency of experiencing an adverse event differed between groups. Expected adverse effects included tingling or itching under the electrodes, scalp redness, or a mild headache. There were no expected or reported serious adverse effects in the present study.

Results

Recruitment and adherence

Participant flow is shown in Figure 1. Recruitment was open between March 2021 and October 2023. Due to restrictions in the UK from the COVID-19 pandemic, the first participant was not enrolled in the study until October 2021. Of the 98 potential participants identified, 28% ($n = 27$) were consented within the available timeframe. This was slightly less than our initially planned recruitment of 30, with recruitment stopped due to the end of the funding period. The main reason for non-participation was due to a loss of contact following initial provision of the participant information sheet and/or failure to complete the required screening procedures (38%) followed by ineligibility (17%), and 15% declined to participate. The most common reason to decline was due to the time commitment required.

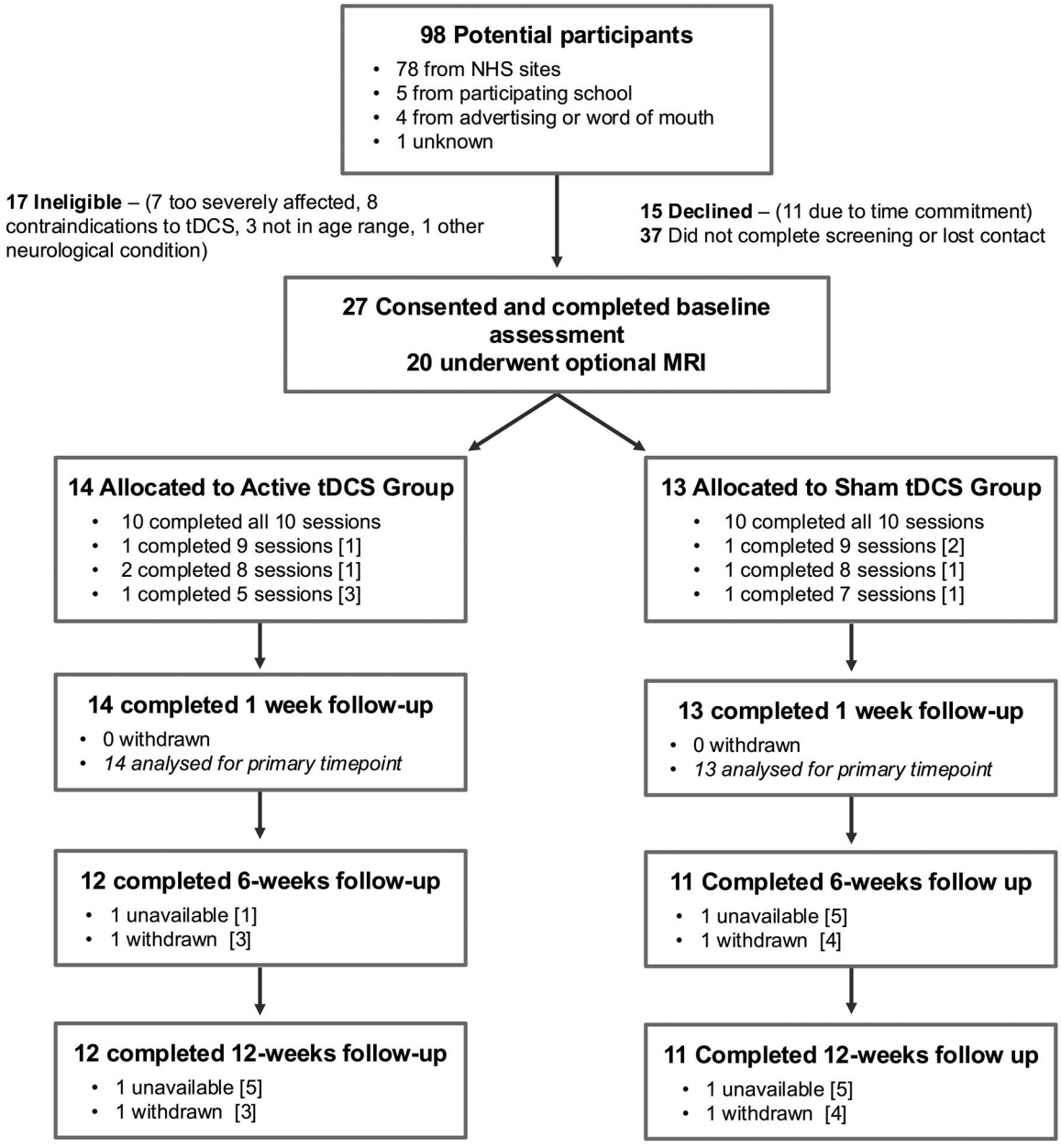

Figure 1. CONSORT diagram. All consented participants were included in analysis of the primary outcomes (Jebsen Taylor Test and Timed Up and Go, $n = 14$ active, $n = 13$ sham) using linear mixed model analyses. Reasons for non-attendance were [1] scheduling difficulties & staff availability [2], injury (not related to study) [3], declined to continue [4], left the UK [5], participant on holiday.

All consented participants completed the baseline assessment and were randomised ($n = 14$ to the active stimulation group, $n = 13$ to the control group). Adherence to the study protocol was good, with 74% of participants completing all 10 intervention sessions, and 100% completing the primary endpoint (1 week follow-up). The study was stopped in May 2024 when the last consented participant completed the final follow-up assessment.

Baseline data

Baseline demographic and clinical characteristics are shown in Table 1. The mean age was 12.7 years (range 10–16 years) and 10 were female.

Primary outcome: Motor function

For the upper limb primary outcome (JTT $n = 14$ active, $n = 13$ sham), there was an effect of time (LMM with baseline and 1-week follow-up, $p < 0.05$, $\eta^2 = 0.18$) but no group by time interaction ($p > 0.05$, $\eta^2 = 0.05$). The secondary analysis including all timepoints revealed a significant effect of time ($p < 0.05$, $\eta^2 = 0.19$) but no interaction between group and time ($p > 0.05$, $\eta^2 = 0.03$; Figure 2A). Bonferroni corrected post-hoc comparisons showed an improvement in performance at 12-weeks compared to baseline only ($t = 3.856$, $p = 0.002$, Cohen's $d = 1.5$). For LMM statistics see Table 2.

For the lower limb primary outcome (TUG_{log} $n = 14$ active, $n = 13$ sham) there was no effect of time (LMM with baseline and 1 week follow-up; $p > 0.05$, $\eta^2 = 0.03$) nor group by time interaction ($p > 0.05$, $\eta^2 = 0.06$). This was also the case when all timepoints were included (effect of time; $p > 0.05$, $\eta^2 = 0.05$; group by time interaction; $p > 0.05$, $\eta^2 = 0.06$; Figure 2B). For LMM statistics see Table 2.

Secondary outcomes

Instrumented 10 m walk (supplementary figure S1)

The were no effects of time (LMM; $p > 0.05$), nor group by time interactions ($p > 0.05$) for variables speed, cadence, or step time. See supplementary results for statistics.

Table 1. Participant characteristics.

	Active	Sham
N	14	13
Age: mean (SD) years	13 (1.6)	12 (1.9)
Sex (F:M)	4:10	6:7
Motor cortex stimulated (R:L)	11:3	7:6
Laterality (unilateral:bilateral)	8:6	1:12
Limbs affected		
Hemiplegia (n)	8	1
Diplegia (n)	2	5
Triplegia (n)	2	3
Quadriplegia (n)	2	3
Unknown (n)	0	1
Predominant Motor Type		
Spastic (n)	8	10
Dyskinetic dystonia (n)	2	1
Dyskinetic choreoathetosis (n)	0	1
Unknown (n)	4	1
Prior seizure history (n)	2	2
Taking seizure medication (n)	1	1
GMFCS: median (range)	2 (1–3)	2 (2–3)
GMFCS I (n)	6	5
GMFCS II (n)	6	5
GMFCS III (n)	2	3
MACS: median (range)	2 (1–3)	2 (1–3)
MACS I (n)	4	0
MACS II (n)	8	9
MACS III (n)	2	4
JTT, seconds: mean (SD)	99 (102)	117 (170)
TUG, seconds: mean (SD)	10 (2)	25 (31)

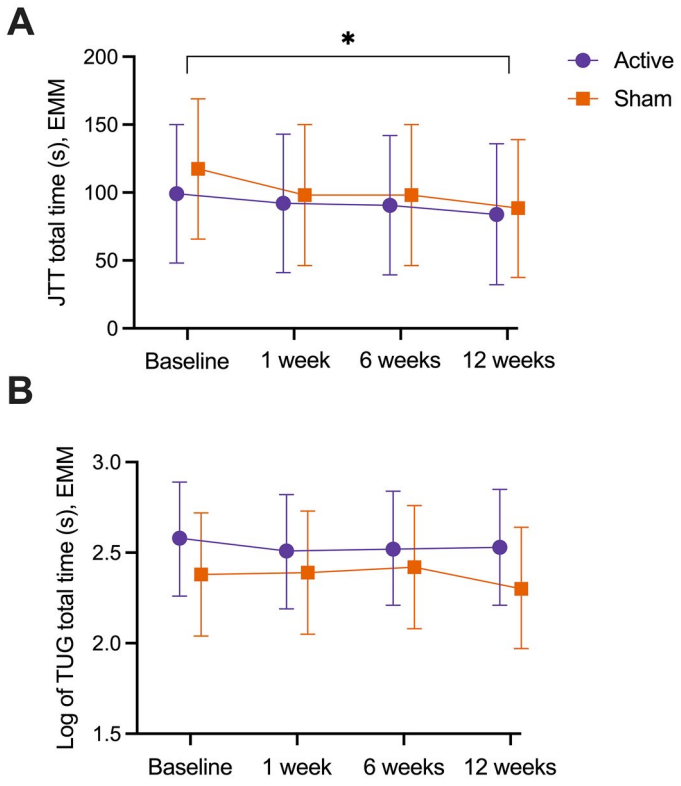

Figure 2. Estimated marginal means (EMM) and 95% confidence interval for Jebsen Taylor test (A) and log of Timed Up and Go (B). The active tDCS group is shown with purple circles and the sham group shown with orange squares. There was a significant effect of time for JTT, with faster performance at the 12-week follow-up compared to baseline (corrected $p = 0.002$).

Table 2. Linear mixed model statistics for evaluation of primary upper and lower limb motor outcome (Jebsen Taylor test and Timed Up and Go).

	Primary timepoint (1-week follow-up)		All timepoints	
	effect of time	*group by time interaction*	*effect of time*	*group by time interaction*
Jebsen Taylor Test^	$F(1,25) = 5.5$, $p = 0.027$	$F(1,25) = 1.189$, $p = 0.286$	$F(3,66.8) = 5.260$, $p = 0.003$	$F(3,66.6) = 0.643$, $p = 0.590$
Timed Up and Go_{log}#	$F(1,25) = 0.894$, $p = 0.353$	$F(1,25) = 1.605$, $p = 0.217$	$F(3,63.1) = 1.148$, $p = 0.337$	$F(3,62.9) = 1.313$, $p = 0.278$

^with MACS score as covariate. #with GMFCS as covariate.

Modified Ashworth Scale (supplementary figure S2)

The were no differences between groups at any follow-up timepoint (Mann Whitney U test; all $p > 0.05$). The results were the same when only the most-affected side (i.e., the side contralateral to the stimulation; 6 muscles) was included (all $p > 0.05$). See supplementary results for statistics.

Functional Mobility Scale and Functional Assessment Questionnaire

For the FMS, there were no differences between groups for any of the distances or timepoints, with median values of 0 for all measures (Mann Whitney U tests; all $p > 0.05$). Similarly for the FAQ, there was no difference between groups for any of the follow up timepoints (Mann Whitney U tests; all $p > 0.05$). See supplementary results for statistics.

Woods and Teuber (supplementary figure S3)

There was no effect of time (LMM, with most-affected side as covariate; $p > 0.05$) nor interaction between group and time ($p > 0.05$) for mirror movements during active movement of the more or less-affected hands. See supplementary results for statistics.

CHEQ (supplementary figure S4)

For the total score of the units there was an effect of time (LMM with MACS score as covariate; $p < 0.001$) but no group by time interaction ($p > 0.05$). Bonferroni corrected post-hoc tests showed an increase in total score from baseline at all follow-up timepoints and between 1 and 12-week follow-up ($p < 0.04$). Results of individual components and statistics are shown in the supplementary results.

GOAL

The child completed GOAL questionnaire revealed a significant main effect of time (LMM with MACS score as covariate; $p < 0.001$), but no group by time interaction ($p > 0.05$). Bonferroni corrected post-hoc tests showed a significant increase from baseline at all follow-up timepoints (all $p < 0.017$), with no further differences between timepoints. For the parent completed assessment there was also a main effect of time (LMM; $p < 0.001$) and a group by time interaction ($p = 0.043$). Post-hoc tests (Bonferroni corrected) found an improvement between baseline and all other time points in the sham group (all $p < 0.015$) but not the active group (all $p > 0.99$).

Brain structure and function

Diffusion tensor imaging (DTI)

Corticospinal tracts (CST) were identified in 18 participants, which respected the underlying structural variation and were anatomically plausible. Data suggest that CST integrity (higher CST volume and fractional anisotropy, and lower mean diffusivity) were associated with better hand function at baseline ($|r| > 0.3$). However, these associations were not statistically significant (supplementary figure S5). Diffusion metrics did not significantly relate to TUG at baseline, nor to individual's response to the intervention (percent change in JTT and TUG between baseline and 1-week follow-up; supplementary figures S5/S6).

Voxel-based morphometry (VBM)

There was a significant negative relationship between JTT time (most affected hand) at baseline and a cluster of voxels in the right caudate nucleus (Figure 3). This suggests that better hand function correlated with increased grey matter volume in the caudate nucleus (corrected p-values <0.05). There were no significant relationships between grey matter volume and TUG time nor response to the intervention (change in JTT or TUG at 1-week follow-up).

Resting state connectivity

From the group level analysis, 3 main networks were selected for further analysis: the sensorimotor network was the main network of interest, with the visual and default mode networks used as comparative controls (see supplementary materials for full details). There was a significant negative relationship between JTT time (most affected hand) and sensorimotor network strength only ($r = -0.503$, $p = 0.042$), suggesting that better hand function at baseline related to stronger resting state sensorimotor network strength (Figure 3B). There were no further significant relationships in the data (all $p > 0.06$, see supplementary figure S8/S9).

Experience and side effects

Most participants found the sessions to be appropriate and felt that the study helped them (Table 3). When asked to compare the brain stimulation to common activities, 50% of the active group and 42% of the sham group found the stimulation comparable to the "pleasantness" of a long car ride, with no clear differences in ratings between groups (Table 3). There was no difference between groups for the proportions rating each of the common adverse effects (Table 4) and no other adverse effects identified.

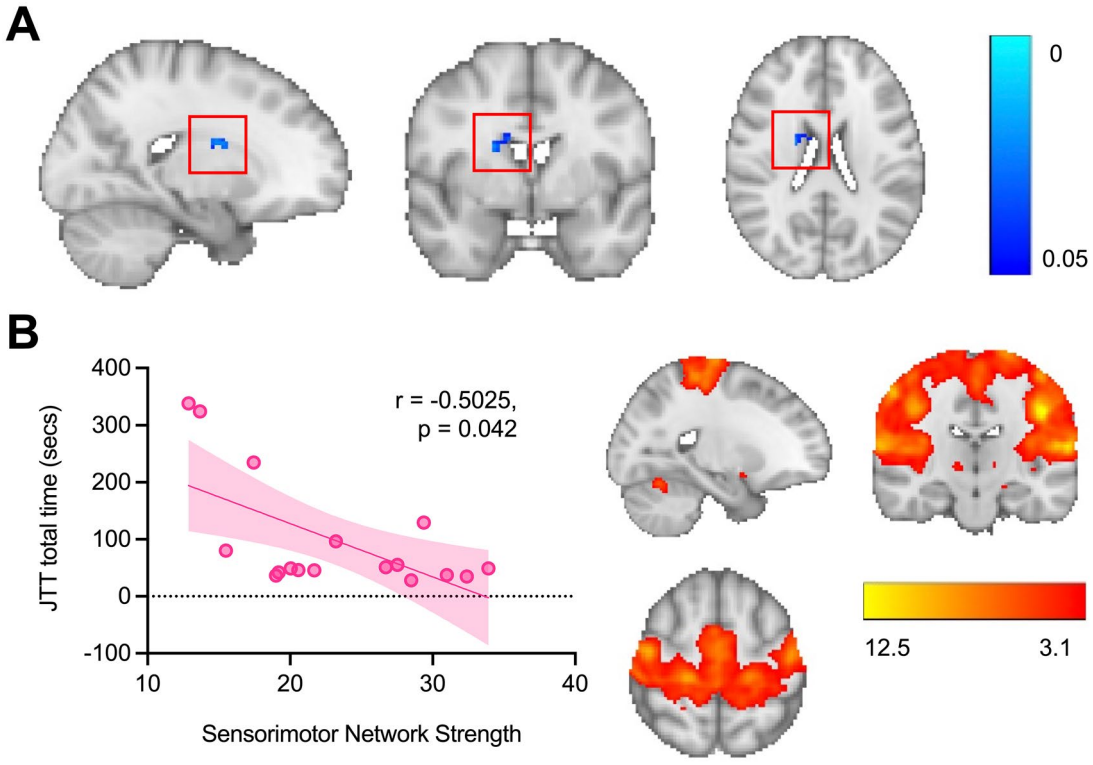

Figure 3. A: Voxel-based morphometry analysis showed a significant relationship between volume in a region of the right caudate nucleus and better times in the JTT nucleus (corrected p-values following 5000 permutations and Threshold-Free Cluster Enhancement (TFCE)). B: (left) Scatter plot (with regression line and 95% CI overlaid) indicating strength of sensorimotor resting state networks vs baseline JTT total time (most affected hand). Lower times in JTT represent better hand function. A Spearman correlation revealed that there was a significant negative relationship between JTT time (secs) and sensorimotor network strength, r = -0.503 (95% CI [−0.798, - 0.0133]), $p = 0.042$. (right) A visual representation of the sensorimotor network identified from group level independent component analysis.

Table 3. Participant evaluation.

	Active	Sham
Did you think the 90-minute sessions were…		
Too long	3 (21%)	1 (9%)
Too short	1 (7%)	0 (0%)
Just right	10 (71%)	10 (91%)
Did you think 10 sessions of exercises were…		
Too many	0 (0%)	3 (27%)
Too few	1 (7%)	2 (18%)
The right amount	13 (93%)	6 (55%)
How did you find the activities and exercises?		
Too easy	4 (31%)	2 (20%)
Too difficult	0 (0%)	2 (20%)
It was alright	9 (69%)	6 (60%)
Do you think the study helped you?		
Yes	13 (93%)	10 (91%)
No	1 (7%)	1 (9%)
It helped me with moving my arm(s)	12 (86%)	10 (91%)
It helped me with moving my leg(s) and/or walking	13 (93%)	10 (91%)
It helped me with my balance	4 (29%)	5 (45%)
It helped me make friends	2 (14%)	1 (9%)
I think the brain stimulation was as pleasant as:		
A birthday party	0 (0%)	0 (0%)
Playing a game	2 (14%)	2 (17%)
Watching television	1 (7%)	1 (8%)
Long car ride	7 (50%)	5 (42%)
Going to the dentist	1 (7%)	1 (8%)
Throwing up	1 (7%)	0 (0%)
Getting an injection	2 (14%)	3 (25%)

Table 4. Frequency of adverse effect reporting.

	Participant report			Parent report		
	Active	Sham		Active	Sham	
Headache	3 (21%)	2 (18%)	χ^2=0.7, p=0.4	1 (8%)	0 (0%)	χ^2=0.9, p=0.3
Itchiness	7 (50%)	9 (82%)	χ^2=1.3, p=0.3	3 (23%)	1 (9%)	χ^2=0.8, p=0.4
Feeling dizzy	0 (0%)	3 (27%)	χ^2=2.8, p=0.1	0 (0%)	0 (0%)	–
Tingling	3 (21%)	5 (45%)	χ^2=1.6, p=0.2	3 (23%)	0 (0%)	χ^2=2.9, p=0.1
Neck pain	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–
Feeling tired	3 (21%)	7 (64%)	χ^2=2.9, p=0.1	4 (31%)	3 (27%)	χ^2=0.08, p=0.8

Discussion

This pilot study demonstrates good adherence to an intervention comprising 10 sessions of tDCS during motor training for the upper and lower limbs. We included a diverse group of children with CP, with 74% completing all intervention sessions, and 100% completing the primary outcome assessment. However, there were no clear changes in either upper or lower limb functional performance, with small effect sizes observed. Brain imaging revealed subtle associations between baseline hand function and brain structure/function, yet no relationships to intervention response.

We found that, whilst difficult, it was possible to recruit to a combined upper and lower limb intervention trial through a variety of sources, with adherence comparable to similar studies [26,27,49]. Reports from participants and their parents suggest that stimulation was tolerable, with the most common adverse effects including tingling, itchiness, and feeling tired. These symptoms are common across tDCS interventions [50–53]. A potential limitation of this study is that we relied on parent/guardian report on potential contraindications to tDCS, rather than a thorough medical history review. Of the sample included, four reported previous seizures more than two years prior to the study, and two were on seizure medications at the time of the study. Whilst this could theoretically have safety implications, tDCS is considered safe in children, including with neurological conditions [18], and we were reassured that no serious adverse events occurred with this pragmatic and proportionate risk-based approach.

Despite good adherence, we found no effect of stimulation on motor function. This is counter to some similar previous studies showing that tDCS can improve upper or lower limb function [20,24–27,54]. Our results do, however, mirror findings from a smaller pool of studies with varied study designs and stimulation protocols, with no or mixed effects of tDCS [53,55–57]. There are several reasons why stimulation may have been ineffective. Firstly, to maximise generalisability, we did not restrict the study to a specific CP subtype. This approach resulted in a relatively heterogeneous sample (see Table 1). The varied clinical presentations is also likely to be associated with differences in underlying brain anatomy [58–60], potentially influencing the resulting electrical current flow [61]. Improved precision when localising the motor cortex, for example, using single-pulse transcranial magnetic stimulation (TMS), may have allowed for a more personalised electrode placement. However, the use of TMS adds additional burden, limiting future clinical translation opportunities. Moreover, positive effects of tDCS have previously been found without using TMS [21,27].

Besides electrode positioning, there are also other elements of the stimulation protocol which could explain the null result. There is growing evidence that tDCS preferentially modulates neural circuits that are activated by task performance [62,63]. Although stimulation was applied during the first 20 min of the motor training, participants carried out a variety of different motor tasks that were not necessarily directly related to the main outcome measures. This protocol was chosen to optimise engagement, but may have led to non-specific excitability modulations in multiple cortical circuits that confound the overall effect [64]. This is especially pertinent given recent evidence suggesting the timing of tDCS interventions may influence effectiveness [65,66]. That said, our tDCS protocol, along with the intervention schedule, intensity, and duration, is comparable to other studies reporting positive effects [20,67]. This suggests that the null result is unlikely to be solely attributable to the tDCS application itself.

Finally, there is consensus within the brain stimulation field that more judicious decisions need to be made when estimating sample sizes [68]. We used reported effect sizes from previous relevant literature, but despite recruiting more than 24 participants, the final number of participants included was still low. Post-hoc power analysis from the primary outcome (change in JTT and TUG at 1-week) suggests group

sizes of ~150 participants would be required. Notwithstanding, our final sample is reflective of other trials, where an effect was found [20]. Studies with larger sample sizes and more precise protocols are required in order to untangle how tDCS may be used in this population.

Given the prevalence and permanence of CP, robust biomarkers of underlying motor system integrity across disease sub-types are needed to better understand individual symptom variability, as well as predict responses to therapeutic interventions. Grey matter injury is thought to occur in ~20% of children with CP, with the location of the lesion likely influencing the resulting motor pathology [69]. Voxel-based morphometry has emerged as a valuable tool for detecting structural brain differences in CP. We found a significant relationship between grey matter volume in an area of the right caudate nucleus and greater hand function (JTT). Along with the putamen, the caudate nucleus forms part of the striatum - a main component of the basal ganglia [70]. Generally speaking, the caudate nucleus has been flexibly linked with a number of sensorimotor functions and receives inputs from cortical sites involved in motor control [71,72]. Prior research in CP has found that lesions to the basal ganglia (including the caudate) are associated with impaired hand function [73] and are more commonly observed in non-spastic/mixed motor CP sub-types [74].

We also identified a relationship at baseline between sensorimotor resting state connectivity and hand function. Resting state connectivity can be particularly useful for exploring dysfunction in CP, as it provides insights beyond task-based measures by minimising the influence of differences arising from functional impairments. Prior research has reported both increases [75,76] and decreases [77] in sensorimotor resting-state connectivity in individuals with CP compared to controls. While fewer studies have explored the relationship between connectivity and motor performance, our findings align with prior work highlighting similar associations [78,79]. However, despite previous reports [80], we did not observe significant associations between diffusion metrics and baseline function, nor relationships between any imaging measure and intervention response. The variability in grey and white matter injuries across different CP subtypes in our study sample is potentially a contributing factor to these inconsistent findings. As a pilot study, this neuroimaging analysis is constrained by its small and heterogeneous sample size and should therefore be interpreted with relative caution.

In summary, this pragmatic pilot study demonstrates good adherence to a trial involving 10 sessions of tDCS combined with upper and lower limb motor training, with multiple follow-up assessments, in young people with CP. Notwithstanding, with this small sample we found no evidence that a non-specific application of tDCS improves upper or lower limb function at any time-point post intervention. Finally, neuroimaging revealed subtle relationships between sensorimotor structure/function and hand function at baseline only. Further research is needed to determine if tDCS can be used as an adjunct therapy in CP and also to understand whether MRI measures can translate clinically to useful biomarkers.

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Data availability statement

Data are available upon reasonable request to HD.

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