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Neuromodulation for Children With Hemiparesis and Perinatal Stroke
A Randomized Clinical Trial

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IMPORTANCE Current upper-extremity therapies provide inconsistent outcomes for children with unilateral cerebral palsy. Noninvasive brain stimulation, specifically transcranial direct current stimulation, may enhance motor gains when combined with therapy.

OBJECTIVE To determine whether the addition of neurostimulation to upper-extremity therapy enhances motor function in children with perinatal stroke and unilateral cerebral palsy.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, randomized, sham-controlled phase 3 trial was conducted from July 2017 through March 2023. Investigators, treating therapists, outcome assessors, parents, and participants were blinded to intervention allocation. The study took place at 3 tertiary care Canadian pediatric rehabilitation hospitals. From a population-based sample of children 6 to 18 years old with perinatal stroke and disabling unilateral cerebral palsy, 196 children were approached and 107 were excluded.

INTERVENTION Participants were randomly assigned in permuted blocks of 2 (1:1) to receive daily sham or cathodal stimulation to the contralesional motor cortex during 10 days of high-dose, child-centered intensive upper-extremity therapy.

MAIN OUTCOMES AND MEASURES The primary end points were changes from baseline to 6 months posttherapy in affected hand function and attainment of child-identified functional goals assessed by the Assisting Hand Assessment and Canadian Occupational Performance Measure. Safety was assessed, including any decrease in the function of either hand. Analysis was intention to treat.

RESULTS Eighty-nine children were enrolled with 45 randomized to sham (62% male, 38% female; mean [SD] age, 10.7 [2.8] years) and 44 to stimulation (52% male, 48% female; mean [SD] age, 10.7 [2.1] years). Eighty-three participants had complete outcome data (42 sham, 41 stimulation). High proportions of children in both groups demonstrated significant functional gains sustained at 6 months ($P < .001$) with large effect size (Cohen $d > 1$). There were no differences between groups for mean (SD) change in hand function (5.2 [5.3] vs 4.6 [5.7]; $P = .63$) or goal attainment (3.0 [2.0] vs 3.6 [2.3]; $P = .25$). Procedures were safe and well tolerated with no serious adverse events.

CONCLUSIONS AND RELEVANCE In this study, results showed that patient-centered intensive motor learning programs could produce marked and sustained improvements in upper-extremity function in children with perinatal stroke and unilateral cerebral palsy. The addition of 1 milliampere contralesional motor cortex transcranial direct current stimulation did not improve outcomes compared with sham stimulation.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03216837

Visual Abstract

Supplemental content

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Perinatal stroke causes lifelong disability for millions of children and their families. Unilateral cerebral palsy (UCP) is usually caused by perinatal stroke, limiting activities and life participation. Physical disability is the largest determinant of quality of life for children with UCP.[1]

Effective interventions for children with UCP remain elusive. Improvements in affected hand function are observed following 60 or more hours of intensive constraint-induced movement therapy or bimanual therapy, but effect sizes are modest and not all children achieve clinically significant gains.[2,3] Accordingly, there is a compelling need to enhance these rehabilitation approaches. Importantly, marked progress in preclinical and human brain mapping of motor system development following perinatal stroke has informed models that identify the contralesional motor cortex as a key node in the network that controls affected limb function and is a target for neuromodulation.[4,5]

Noninvasive brain stimulation can enhance motor learning in typically developing children.[6,7] Adult stroke hemiparesis trials[8] and early pediatric trials[9-11] suggest the same potential in children with UCP. Transcranial direct current stimulation (tDCS) is a painless, inexpensive, safe, and portable option for noninvasive neuromodulation. It is considered very unlikely that neurostimulation alone will produce functional gains in the injured motor system. Rather, the induction of endogenous motor learning plasticity through personalized, goal-directed upper-extremity therapies is likely a required substrate on which neurostimulation might act to increase the effectiveness of natural, physiological processes. Accordingly, most modern neuromodulation trials pair stimulation with the large doses of such intensive therapies required to induce such plasticity. While the number of established neuromodulation therapies has increased, the same evidence base has also highlighted the complexity and marked interindividual variability that must be considered in less studied populations, such as children with perinatal stroke. The limited tDCS trials in patients with UCP have been underpowered or underdosed in terms of therapy, but phase 2 trials have confirmed safety and feasibility with preliminary evidence of efficacy.[11] We conducted a clinical trial to determine if motor cortex tDCS could improve upper-extremity rehabilitation outcomes for children with perinatal stroke and UCP.

Key Points

Question Does transcranial direct current stimulation improve upper-extremity therapy outcomes for children with perinatal stroke and unilateral cerebral palsy?

Findings In this randomized clinical trial that included 89 children, improvements in function and goal achievement were observed with large effect sizes but these were not enhanced by the addition of transcranial direct current stimulation.

Meaning In this study, intensive upper-extremity therapy could produce sustained, clinically relevant functional benefits for children with perinatal stroke and unilateral cerebral palsy, and transcranial direct current stimulation did not appear to enhance therapy outcomes.

Methods

Trial Design

We conducted a multicenter, randomized, double-blind, sham-controlled trial at 3 Canadian hospitals. Local ethics committees approved the protocol at the University of Calgary (Calgary), University of Alberta (Edmonton), and Holland Bloorview Kids Rehabilitation Hospital (Toronto). Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines were followed. Written informed consent/assent was obtained from participants and guardians. An independent, centralized data safety and monitoring board monitored trial safety, data integrity, and interval analysis. Nonparticipant patient partners with lived experience were engaged in trial design and results interpretation.

The trial was registered on ClinicalTrials.gov prior to randomization of the first participant (NCT03216837). Randomization was centralized and performed electronically. Participants were randomly assigned (1:1) to receive sham or active tDCS using permuted blocks of 2 to ensure even distribution within sites. Investigators, treating therapists, outcome assessors, parents, and participants were blinded to intervention allocation.

Participants

Eligible participants were aged 6 to 18 years with magnetic resonance imaging (MRI)–confirmed unilateral perinatal ischemic stroke, specifically neonatal arterial ischemic stroke, arterial presumed perinatal ischemic stroke, or periventricular venous infarction. Participants were required to have UCP with child/parent perceived limitations in function but minimal affected arm function (ie, able to lift a light object against gravity). Exclusion criteria included severe intellectual disability, unstable epilepsy, and neurostimulation, botulinum toxin, orthopedic surgery, or constraint therapy in the last 6 months. Criteria are detailed in eTable 1 in Supplement 1.

Intervention

Motor Learning Therapy

Participants completed a child-centered, goal-directed, intensive motor learning therapy camp over 10 consecutive weekdays. Therapy was led at each site by an experienced occupational therapist. Daily therapy duration was 7.5 hours in a peer-supported environment (total 75 hours), with concentrated therapy to target high therapy dose.[12] Participants wore a cast on their unaffected arm 24 hours per day during the first 5 days of constraint-induced movement therapy, followed by removal of the cast and bimanual therapy for the last 5 days. Constraint-induced movement therapy and bimanual approaches have comparable benefits for children with UCP.[13] An emerging concept is to combine the 2 in series, first to focus exclusively on the attainment of personalized, goal-specific target movements in the affected hand (constraint-induced movement therapy, week 1) followed by integration of emerging unimanual skills into bimanual activities of daily living (bimanual, week 2). A complete description of the therapy camp protocol is available (eAppendix in Supplement 1).

Transcranial Direct Current Stimulation

This trial assessed cathodal tDCS over the contralesional primary motor cortex. At baseline, the hotspot for the unaffected first dorsal interosseous muscle was identified using single-pulse transcranial magnetic stimulation (Magstim) and coregistered to each participant's MRI (Brainsight2 Neuronavigation, Rogue). Two saline-soaked 25-cm^2 electrodes (Soterix Medical Inc) were placed on the scalp with the cathode over the mapped contralesional hotspot and the reference electrode over the contralateral orbit. The current-controlled model stimulator (Soterix Medical) automatically ramped up current intensity to 1.0 milliampere over 30 seconds. Current was maintained for 20 minutes (active tDCS) or automatically ramped down after 30 seconds (sham), following validated blinding procedures.[11] tDCS or sham procedures were completed each day during the first 30 minutes of daily 1-to-1 therapy sessions with therapy health care professionals.

Data Collection

Demographic information was collected at baseline from the medical records and MRI review. Motor outcomes were measured at baseline, 1 week, 2 months, and 6 months postintervention (eFigure 1 in Supplement 1). Assessments were completed by a blinded, nontreating occupational therapist. The coprimary end points were changes from baseline to 6 months postintervention in the objective Assisting Hand Assessment (AHA) and subjective Canadian Occupational Performance Measure (COPM). Performance scores with 6 months were chosen for the clinical relevance of long-term effects. The AHA was used to assess affected hand function during a bimanual play session, resulting in a Rasch-scaled score of 0 to 100 logit units where a higher score indicated better function. Using the COPM, participants scored their performance on self-identified functional goals on a 0 to 10 scale where a higher score indicated better perceived performance. Both measures have strong psychometric properties and thresholds for clinically significant change (5 logit units for AHA; 2 points for COPM) in children with UCP.[14,15]

Secondary outcomes were: (1) hand function and impairment (COPM satisfaction score, Actigraphic Movement Asymmetry Index, bilateral mirror movement scores and directionality factor, Children's Hand-Use Experience Questionnaire, Jebsen Taylor Test of Hand Function, Box and Block Test [BBT]); (2) quality of life, participation, and social outcomes (Child and Adolescent Social Support Scale, Loneliness and Social Dissatisfaction Questionnaire, Pediatric Quality of Life Inventory Cerebral Palsy Module, Child and Adolescent Scale of Participation, Alberta Perinatal Stroke Program parental outcome measure; (3) treatment expectations (Stanford Expectations of Treatment Scale [SETS]); and (4) an anonymous trial exit evaluation. The Pediatric Stroke Outcome Measure further characterized participants at baseline. The primary safety outcome was the BBT score for the unaffected hand to monitor decline in function on both group and individual levels. Additional safety outcomes included CNS Vital Signs and the tDCS Safety and Tolerability scale (TST). A complete description of all outcomes is provided in the eAppendix in Supplement 1.

Sample Size

Our sample size calculation was anchored on the objective, coprimary outcome of the AHA. Engagement with patient/family advisors and expert clinicians estimated a clinically significant difference of doubling the chances of a significant change in AHA (more than 5 points at 6 months). This was validated as reasonable based on 3 earlier-phase trials using contralesional inhibitory neuromodulation in the same population (references). This evidence-based dichotomization of 35% vs 70% yielded group sizes of 37 participants per group (90% power; 2.5% type 1 error rate).

Data from the same trials yielded pooled effect sizes (approximately 1.4) and SDs (approximately 1.85) for change in AHA estimated 39 participants per group (90% power). We harmonized these similar estimates to conservatively target 40 participants per group. Following this calculation, we returned to the COPM (and all secondary outcomes) to confirm this sample would provide even higher power (eg, 94% for change in both COPM scores).

Statistical Analysis

Analyses included all randomized participants (intention-to-treat) with a subsequent per-protocol analysis. Given the sample size (less than 100), missing data were handled by complete case analysis. Participants were described with respect to age, sex, stroke type, stroke side, study site, and baseline outcome measures using the appropriate descriptive statistics, namely means, SDs, medians, and IQRs for continuous variables, and frequency with proportions for discrete variables. For the coprimary end points, the difference in logit AHA score and COPM performance score at baseline and 6 months postintervention were compared between groups using either *t* test (normal distribution) or Wilcoxon rank sum test (nonparametric). Effect size was calculated by Cohen *d*. A χ^2 test was used to compare proportions of clinically significant increases in AHA and COPM scores. The *P* value was adjusted to .03 using Bonferroni correction for the coprimary outcomes.

AHA and COPM performance scores at the 4 time points were compared using repeated measures mixed models to account for potential missing data. The interaction between group and time point was assessed. Study site was considered as a random effect. For secondary outcomes, the difference in score at baseline and 6 months was compared between groups and over time. Additional analyses included dividing participants into early responders (1-week change of 5 or more logit AHA score) and nonresponders, and assessing interactions between group, sex, age, stroke type, stroke side, baseline AHA and COPM performance, mirror movement directionality factor, SETS positive score, and affected hand BBT. To test interactions, continuous scores were divided at the median value. Lastly, the potential effect of corticospinal tract (CST) configuration to the affected hand was explored by dividing participants within each group into ipsilateral (directionality factor more than 1.61) and nonipsilateral (directionality factor less than 1.61) CST configuration.[16] Statistical analyses were performed using Stata version 18 (Stata Corp) and SAS version 9.4 (SAS Institute).

Table 1. Baseline Demographics and Function

Characteristic	Group, No. (%)	
	Sham	tDCS
Age, mean (SD) [range], y	10.7 (2.8) [6.1-18.9]	10.7 (2.1) [7.3-16.8]
Sex		
Male	28 (62.2)	23 (52.3)
Female	16 (37.8)	22 (47.7)
Stroke type		
NAIS	6 (13.3)	5 (11.6)
APPIS	17 (37.8)	18 (40.9)
PVI	22 (48.9)	21 (49.4)
Side left	30 (66.7)	29 (65.9)
Ipsilateral CST	9 (20.9)	14 (32.6)
Baseline function, mean (SD)		
AHA logit	54.51 (13.75)	55.65 (12.29)
COPM performance	3.42 (1.66)	3.09 (1.54)
COPM satisfaction	3.76 (1.95)	3.65 (1.51)
AMAI awake	0.69 (0.11)	0.69 (0.15)
BBT affected hand	22.27 (11.80)	22.07 (9.84)
PSOM total	1.52 (1.18)	2.01 (1.75)
PSOM nonmotor delays, No./total No.	9/36 (25)	11/31 (35.5)
JTTHF	337.50 (320.50)	316.54 (275.46)
CHEQ		
Hand use	49.57 (14.01)	47.51 (11.24)
Time required	56.09 (14.17)	54.39 (12.61)
Feeling	64.22 (15.48)	61.51 (16.16)
CASSS		
Total importance	132.84 (2477)	136.81 (23.32)
Total support	276.98 (45.46)	269 (53.55)
LSDQ	13.98 (4.87)	18.81 (8.80)
PedsQL-CP child assessment		
Daily activities	77.29 (12.97)	71.15 (13.89)
School activities	70.69 (20.89)	60.17 (22.54)
Movement and balance	74.0 (19.27)	67.47 (20.51)
Pain and hurt	75.56 (18.88)	74.71 (20.82)
Fatigue	69.58 (23.21)	67.15 (21.99)
Eating activities	81.56 (11.22)	77.56 (13.73)
Speech and communication	86.11 (21.15)	81.83 (21.17)
CASP	87.76 (9.41)	82.89 (10.23)
POM	37.2 (15.98)	39.77 (16.23)
Mirror movements affected hand	2.00 (1.31)	2.34 (1.44)
Mirror movement directionality factor	0.99 (0.91)	1.1 (0.80)
SETS		
Positive	4.43 (1.12)	4.45 (1.32)
Negative	2.48 (1.61)	2.58 (1.71)
CNS Vital Signs		
Visual memory	87.7 (18.3)	85.3 (21.4)
Reaction time	91.1 (20.8)	78.3 (20.9)
Simple attention	78.1 (35.6)	73.3 (43.6)
Unaffected hand function		
BBT	50.2 (9.49)	47.07 (9.64)
JTTHF	62.49 (108.20)	37.51 (8.15)
Mirror movements	1.36 (1.10)	1.44 (1.17)

Abbreviations: AHA, Assisting Hand Assessment; AMAI, Actigraphic Movement Asymmetry Index; APPIS, arterial presumed perinatal stroke; BBT, Box and Block Test; CASP, CNS Vital Signs, child and adolescent scale of participation; CASSS, Child and Adolescent Social Support Scale; CHEQ, Children's Hand-Use Experience Questionnaire; CNS Vital Signs, Child and Adolescent Scale of Participation; COPM, Canadian Occupational Performance Measure; CST, corticospinal tract; JTTHF, Jebsen Taylor Test of Hand Function; LSDQ, Loneliness and Social Dissatisfaction Questionnaire; NAIS, neonatal arterial ischemic stroke; PedsQL-CP, Pediatric Quality of Life Inventory Cerebral Palsy Module; PVI, periventricular venous infarction; PSOM, Pediatric Stroke Outcome Measure; POM, Alberta Perinatal Stroke Project parental outcome measure; SETS, Stanford Expectations of Treatment Scale.

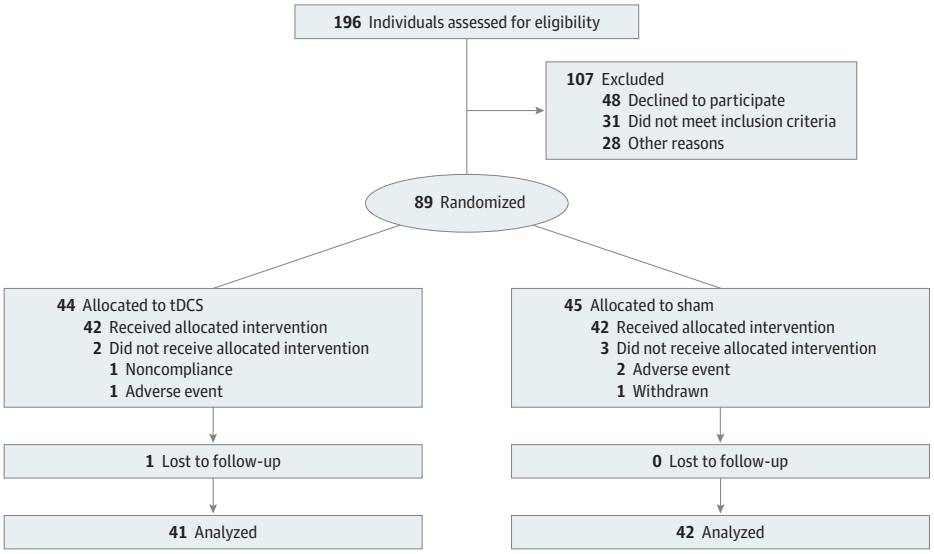
Results

From July 21, 2017 through July 12, 2022 (with no camps in 2020 through 2021 due to the pandemic), a total of 89 participants were enrolled and randomized at the 3 sites (46.5% Calgary, 28.4% Edmonton, 25.0% Toronto). Forty-four participants were assigned to the tDCS group and 45 participants were assigned to the sham group. The treatment groups were well balanced with respect to baseline characteristics (**Table 1**). The median age of both groups was 10.7 years with comparable sex proportions. Stroke types were equally divided into arterial and venous. Baseline function, as measured by the primary outcomes, was consistent with moderate hemiparesis. See **Figure 1** for trial flow.

There were 83 participants with complete primary outcome data (42 sham, 41 tDCS). The mean (SD) baseline logit AHA score was 54.5 (13.8) for the sham group and 55.7 (12.3) for the tDCS group. AHA scores were significantly higher than baseline at 1-week (4.6; 95% CI, 3.1-6.0; $P < .001$), 2-month (5.0; 95% CI, 3.5-6.4; $P < .001$), and 6-month (5.2; 95% CI, 3.8-6.7; $P < .001$) postintervention time points, with no differences between groups or interaction between group and time (**Figure 2**). Change in AHA from baseline to 6 months across all participants demonstrated a large effect size ($d = 0.90$). The mean change at 6 months postintervention was 5.2 (SD, 5.3) for the sham group and 4.6 (SD, 5.7) for the tDCS group ($P = .63$). The proportion achieving sustained, clinically significant, increases of more than 5 points was 20 of 41 (48.8%) for sham and 20 of 40 (50.0%) for tDCS ($P = .90$). There was no effect of study site on AHA score change.

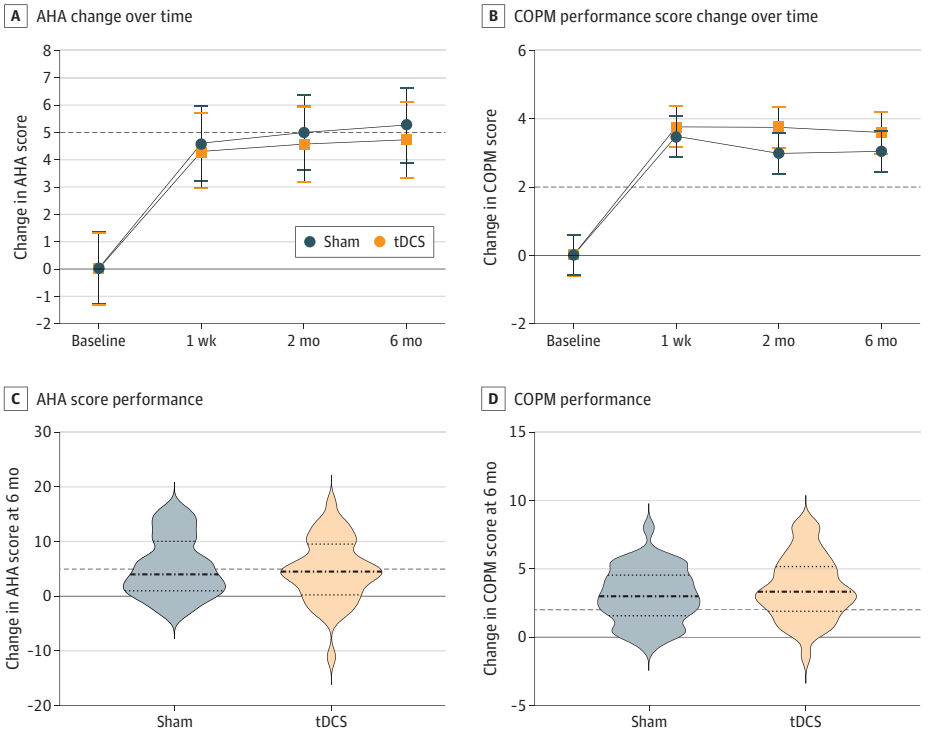
The mean (SD) baseline COPM performance score was 3.4 (1.7) and 3.1 (1.5) for the sham and tDCS groups. Change in both COPM scores from baseline to 6 months across all participants demonstrated large effect sizes (performance $d = 1.53$; satisfaction $d = 1.38$). The mean (SD) change at 6 months postintervention was 3.0 (2.0) for the sham group and 3.6 (2.3) for the tDCS group ($P = .25$). There were 29 of 41 (70.7%) and 31 of 40 participants (75.6%) with clinically significant increases of 2 or more points in each group ($P = .60$). Scores were higher than baseline at 1-week (3.5; 95% CI, 2.9-4.0; $P < .001$),

Figure 1. Eligibility, Randomization, and Assessment of the Participants



tDCS indicates transcranial direct current stimulation.

Figure 2. Assisting Hand Assessment (AHA) and Canadian Occupational Performance Measure (COPM) Performance Scores Demonstrated Sustained Increases Across Time Points



Linear prediction (with site as a random effect) of AHA change over time (A) and COPM performance score change over time (B). Violin plots demonstrating 6-month change from baseline in AHA score (C) and COPM performance (D). Dash-dot line indicates median, small dots indicate IQRs, dotted-background line indicates clinically significant improvement, solid line indicates baseline, error bars indicate 95% CIs. tDCS indicates transcranial direct current stimulation.

2-month (3.0; 95% CI, 2.4-3.5; $P < .001$), and 6-month (3.0; 95% CI, 2.5-3.6; $P < .001$) postintervention time points, with no differences between groups or interaction between group and time (Figure 2). There was no effect of study site on COPM performance score change.

Secondary outcomes are summarized in **Table 2**. No secondary outcomes differed significantly between the groups. Additional measures demonstrated improvements at 6 months postintervention compared with baseline, including the Children's Hand-Use Experience Questionnaire (hand use, time required, and feeling scores), Pediatric Quality of Life Inventory Cerebral Palsy Module (daily activities, movement/balance, school activities), Loneliness and Social Dissatisfaction Questionnaire, and parental outcome measure (**Table 3**).

Table 2. Changes From Baseline at 6 Months by Treatment Group

Characteristic	Group, Mean (SD)		*P* value (*t* test)	No.
	Sham	tDCS		
AHA logit	5.2 (5.3)	4.6 (5.7)	.63	81
COPM performance	3.0 (2.0)	3.6 (2.3)	.25	83
COPM satisfaction	3.5 (2.52)	3.47 (2.56)	.95	83
AMAI	−0.03 (0.10)	−0.05 (0.19)	.63	57
BBT affected	3.81 (4.15)	3.71 (4.76)	.92	82
JTTHF	−77.39 (129.91)	−130.11 (148.38)	.09	82
CHEQ				
Hand use	6.25 (10.58)	9.39 (10.78)	.19	81
Time required	3.68 (10.64)	6.61 (12.32)	.26	81
Feeling	3.85 (15.75)	4.73 (15.03)	.79	81
CASSS				
Total importance	−14.98 (46.21)	−5.40 (32.55)	.27	88
Total support	−1.97 (39.26)	10.83 (47.93)	.19	82
LSDQ	−1.51 (5.45)	−4.61 (9.72)	.08	82
PedsQL-CP				
Daily activities	7.64 (11.2)	9.07 (11.64)	.58	81
School activities	3.96 (21.73)	12.71 (18.32)	.05	81
Movement and balance	7.32 (18.64)	11.63 (17.07)	.28	81
Pain and hurt	2.59 (18.69)	6.88 (18.39)	.30	81
Fatigue	5.64 (16.29)	3.91 (19.80)	.67	81
Eating activities	2.80 (16.43)	6.84 (12.29)	.22	81
Speech and communication	10.52 (15.05)	9.53 (15.21)	.77	81
CASP	0.74 (7.50)	2.34 (9.34)	.40	79
POM	−1.88 (9.21)	−3.22 (12.53)	.59	82
Mirror movements	0.13 (1.05)	0 (1.15)	.60	81
Safety				
CNS Vital Signs (no change/better/worse)				
Visual memory	27/7/3	30/1/2	.31	70
Reaction time	21/10/5	10/18/4	.06	68
Simple attention	32/0/0	28/1/2	.41	63
Unaffected hand function				
BBT	7.65 (6.6)	7.32 (7.64)	.84	81
JTTHF	7.09 (142.54)	−0.63 (20.11)	.73	82
Mirror movements	0.11 (0.78)	0.09 (0.95)	.94	81

Abbreviations: AHA, Assisting Hand Assessment; AMAI, Actigraphic Movement Asymmetry Index; BBT, Box and Block Test; CASP, CNS Vital Signs, Child and Adolescent Scale of Participation; COPM, Canadian Occupational Performance Measure; CHEQ, Children's Hand-Use Experience Questionnaire; CASSS, Child and Adolescent Social Support Scale; JTTHF, Jebsen Taylor Test of Hand Function; LSDQ, Loneliness and Social Dissatisfaction Questionnaire; PedsQL-CP, Pediatric Quality of Life Inventory Cerebral Palsy Module; POM, Alberta Perinatal Stroke Project parental outcome measure; SETS, Stanford Expectations of Treatment Scale.

The interaction between group (tDCS, sham) and age, baseline AHA score, baseline COPM performance score, directionality factor of mirror movements, SETS positive score, stroke side, and stroke type did not reveal any consistent relationships. Exploratory analysis found that 38 of 83 participants (46.0%) were early responders (ie, with 1 week minus baseline change of 5 or more logit AHA score) and the remainder were nonresponders. However, AHA scores of the nonresponders tended to increase more over time (eFigure 2 in Supplement 1). The only variable associated with early response was a lower AHA baseline score (nonresponders: median, 60; IQR, 48-70; early responders: median, 52; IQR, 43-57; odds ratio [OR], 0.95; 95% CI, 0.91-0.98); eTable 6 in Supplement 1). The proportion of early responders who achieved an AHA difference of 5 or more at 6 months was 28 of 37 (76%), compared with 12 of 44 (27%) achieved by those participants without an early response (OR, 8.3; 95% CI 2.8-25.7).

Possible associations emerged between sex and group. The female sham group (n = 16) experienced ongoing improvement in their AHA score, which was not seen in males (n = 25; coefficient for 6 months difference 5.8; 95% CI, 2.2-9.5). There was no effect of group for male or female early responders. However, in the nonresponder male group, tDCS was associated with an increase in 6-month AHA score compared with sham (coefficient, 4.1; 95% CI, 0.84-7.4), but not for female nonresponders.

Safety

Two adverse events occurred unrelated to the study intervention: (1) chipped tooth, no study action; (2) hand fracture, withdrawn. The primary safety outcome of BBT score for the unaffected hand was assessed in 40 participants in the sham group and 41 in the tDCS group. The mean (SD) difference from baseline to 6 months postintervention was 7.65 (6.6) in the sham and 7.3 (7.6) in the tDCS (*P* = .84; eFigure 3 in Supplement 1). No adverse change was observed in the secondary neuropsychological safety outcomes from CNS Vital Signs (Table 3). For the other secondary safety outcome of Safety and Tolerability scale, the most reported sensations during tDCS were mild unpleasant tingling (21.0% in tDCS group and 28.9% in

Table 3. Baseline and 6-Month Scores, All Participants

Characteristic	Mean (SD)		*P* value (paired *t* test)	Effect size (Cohen *d*)
	Baseline	6 mo		
AHA logit	54.91 (13.22)	59.84 (13.69)	<.001	0.90
COPM performance	3.27 (1.58)	6.56 (1.95)	<.001	1.53
COPM satisfaction	3.70 (1.73)	7.18 (2.12)	<.001	1.38
AMAI awake	0.68 (0.14)	0.65 (0.14)	.08	0.24
BBT affected	21.93 (10.91)	25.70 (12.15)	<.001	0.85
JTTHF	11.87 (9.44)	11.64 (20.86)	.84	0.74
CHEQ				
Hand use	48.75 (13.09)	56.59 (13.59)	<.001	0.73
Time required	55.54 (13.44)	60.70 (14.12)	.001	0.45
Feeling	63.31 (16.04)	67.61 (15.04)	.01	0.28
CASSS				
Total importance	134.78 (24.02)	124.49 (42.29)	.02	0.26
Total support	274.89 (48.68)	279.32 (50.43)	.37	0.1
LSDQ	16.14 (7.45)	13.09 (6.15)	.001	0.38
PedsQL-CP				
Daily activities	74.23 (15.68)	82.58 (14.51)	<.001	0.73
School activities	65.82 (21.38)	74.1 (18.8)	.001	0.41
Movement and balance	71.42 (19.4)	80.86 (18.39)	<.001	0.53
Pain and hurt	74.92 (20.02)	79.63 (20.56)	.03	0.25
Fatigue	69.29 (22.84)	74.07 (22.32)	.02	0.27
Eating activities	80.56 (11.99)	85.36 (14.37)	.004	0.33
Speech and communication	84.34 (21.33)	90.59 (14.26)	<.001	0.67
CASP	85.44 (10.28)	86.99 (11.62)	.11	0.18
POM	38.80 (15.59)	36.26 (16.48)	.04	0.23
Mirror movements	2.18 (1.39)	2.24 (1.41)	.59	0.06
Unaffected hand function				
BBT, mean (SD)	48.64 (9.62)	56.12 (9.89)	<.001	1.1
JTTHF	3.61 (0.84)	3.82 (4.09)	.64	0.03
Mirror movements	1.39 (1.13)	1.49 (1.20)	.31	0.11

Abbreviations: AHA, Assisting Hand Assessment; AMAI, Actigraphic Movement Asymmetry Index; BBT, Box and Block Test; CASSS, Child and Adolescent Social Support Scale; CASP, CNS Vital Signs, Child and Adolescent Scale of Participation; COPM, Canadian Occupational Performance Measure; CHEQ, Children's Hand-Use Experience Questionnaire; JTTHF, Jebsen Taylor Test of Hand Function; LSDQ, Loneliness and Social Dissatisfaction Questionnaire; PedsQL-CP, Pediatric Quality of Life Inventory Cerebral Palsy Module; POM, Alberta Perinatal Stroke Project parental outcome measure; SETS, Stanford Expectations of Treatment Scale.

sham group) and mild itching (33.9% in tDCS group and 35.2% in sham group), detailed in the eAppendix in Supplement 1. On average, children ranked their enjoyment of tDCS as similar to a long car ride and better than going to the dentist. Anonymous trial exit evaluations were positive with a mean score of 3.9 of 5.0 (range, 2.6-4.9) and 73% recommending the program to another family.

Discussion

We found that personalized, goal-directed, peer-supported, intensive manual therapy can produce marked and lasting functional gains in most children with UCP and perinatal stroke. Adding cathodal tDCS over the intact motor cortex did not measurably enhance these benefits.

The effect sizes of our therapeutic intervention were larger than most manual therapy trials in this population.[2,17] This included both objective measures of manual function and subjective measures of participant goal achievement. These combined effects align with the emphasis placed on the interconnection of functioning, participation, and the rights of children with disabilities espoused by global authorities.[18,19] Explanations for the large gains observed may include the high therapy dose in a full-day camp-based model with 24-hour casting in week 1, customized therapies based on individual goals, therapy intensity targets, a peer-supported environment, or other psychosocial factors.[12]

Significant gains were also observed across nonmotor outcomes. These included sustained improvements in metrics of quality of life, specifically related to school, fatigue, and activities of daily living, and reduced loneliness. Insight for possible explanations for these observations was gleaned from our patient partners, whose interpretation suggested possible benefits of the program regarding participant autonomy, independence, personalized goal setting, and enhanced peer relationships. These observations complement the primary findings of the trial, suggesting that focus on engagement and personalized goals may be more effective than approaches aimed at specific impairments or technologies. However, the motivations and rights of families to try emerging technologies, and possible added benefits of such (eg, increased therapy dosing, placebo effects), must also be considered.

Participant gains were independent of the treatment group, refuting our primary hypothesis that contralesional tDCS would enhance gains in motor function. Our rationale specifically avoided the basic assumptions made in early adult motor stimulation studies that have since been disproven, such as cathodal tDCS being simply inhibitory in its effects.[20] Previous studies have demonstrated the efficacy of tDCS in

enhancing motor learning in adults,[21,22] typically developing children,[6,23] and possibly children with UCP.[11] However, despite a much larger volume of adult stroke clinical trials, the role of tDCS in motor rehabilitation remains undefined.[8] Why tDCS was ineffective here is unknown, with many possible considerations. Our targeting of the contralesional motor cortex was informed by robust evidence of its importance in clinical motor function in participants with UCP but the same studies also highlight the marked complexity of this neurophysiology and its heterogeneity across individuals.[4,5,24] Specific differences in the effects of tDCS in the developing brain are only beginning to be defined.[20,25,26] Deeper explorations to understand these differences, including advanced neuroimaging and brain mapping, are underway.

Our exploratory analyses probing for interactions between treatment group and predictors of response were not fruitful. The lack of relationship with CST configuration[16] supports observations that this metric may not be predictive of therapy response in patients with UCP,[9,27,28] nor influence the effects of contralesional cathodal tDCS. Corticospinal tract laterality likely exists as a continuous spectrum in children with early unilateral brain injury. Detailed mapping of ipsilateral status has weak associations with degree of disability but does not strongly predict response to therapies.[9,27,28] Accordingly, mirror movement scores were considered a reasonable, clinically relevant proxy for this spectrum while ongoing secondary, detailed brain-mapping studies in this trial population will yield more specific exploration of this important issue. Results may reflect the larger complexities of motor system developmental neurophysiology following early unilateral brain injury[4] and the need to consider alternative neuromodulation strategies.

Response predictor analyses focused on clinically available baseline outcomes, including age and function, with the aim of informing clinical decisions for personalized therapy. Only a lower baseline AHA score was associated with early responders, supporting indications that children with poorer motor function may benefit most from intensive therapy.[29] The trends in AHA score changes following 1-week postintervention appear promising, with children in the nonresponder group continuing to realize improvements postintervention. Additional analyses revealed potential interactions between sex and group that were underpowered but may warrant consideration in future trials.

Our results increase the level of confidence that tDCS is safe in children. The high power of our sample combined with both motor and nonmotor measures increases the level of evidence for safety. This is consistent with the largest published experience (more than 4 million stimulations in more than 400 children),[30] though published populations are heterogeneous and none used the neuropsychological measures we report here. Safety outcomes did not decline; in fact improvements were observed due to possible practice effects or cross-education between hemispheres described in other tDCS studies. We also demonstrated that tDCS can be consistently applied across sites in complex rehabilitation programs to children with disabilities with favorable tolerability. We conclude that tDCS remains a feasible neuromodulatory strategy that should be considered minimal risk in school-aged children.

Limitations

Limitations include possible variability in therapy and neuromodulation methods across sites, though we found no effect of site. The risk of expectation bias by the therapists measuring outcomes was mitigated by blinding them to previous assessment scores. The same blinding was not possible for participants and families who may have been biased on follow-up subjective measures. Brain stimulation targeting was personalized but is also complex, introducing possible heterogeneity in addition to known differences in age, brain structure, stroke type, and other factors that may have impacted efficacy.

Conclusions

In conclusion, personalized, intensive manual therapy programs can produce marked and sustained improvements in upper-extremity function in children with perinatal stroke and hemiparesis. Daily contralesional cathodal tDCS is feasible, well tolerated, and safe, but does not appear to enhance the benefits of intensive manual therapy.

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