Brain Stimulation 17 (2024) 633–635

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.journals.elsevier.com/brain-stimulation

Long-term outcome safety assessment after teleneuromodulation in children with cerebral palsy

ARTICLE INFO

Keywords
Cerebral palsy (CP)
Transcranial direct current stimulation (tDCS)
Teleneuromodulation
Long term follow-up
Pediatrics

Dear Editor

Transcranial direct current stimulation (tDCS) is a form of non-invasive brain stimulation (NIBS). When combined with rehabilitation therapies, tDCS shows promising outcomes at accelerating motor function improvement in children with cerebral palsy (CP) and is safe when administered by well-trained study staff and experienced research groups [1–5]. Consideration of safety in pediatric tDCS studies includes evaluation of serious adverse events (e.g. seizure) and stability of behaviors that might be influenced by a particular target (e.g. motor function following motor cortex stimulation). Zewdie and colleagues investigated over 2800 combined sessions in 500 children with no serious adverse events reported [6]. Despite robust evidence for tDCS safety and tolerability in the pediatric population, previous studies were performed in the laboratory setting and assessment immediately followed tDCS. Meanwhile, few have investigated long-term safety, and none have examined the safety of remotely monitored stimulation in pediatric participants [7]. With an increasing emphasis on rural access to neuromodulation and rehabilitation intervention studies, long-term safety and tolerability data from remotely monitored tDCS studies are needed to support the feasibility of future large-scale clinical trials. We previously demonstrated the feasibility [8] and short-term safety of remotely instructed tDCS [9] in children and young adults with CP. Here, we present a long-term follow-up investigation of safety after at-home tDCS from our pilot study which enrolled 10 participants with hemiparetic CP [9] (see Supplemental 1.1 for study design). Each participant received a total of 20 minutes of mock, 20 mins of sham, and 60 minutes of active tDCS stimulation. Across all participants, a total of 200 minutes of mock, 200 minutes of sham, and 600 minutes of active tDCS occurred. No serious adverse events occurred.

Caregiver/child 'dyads' from the pilot study were evaluated at 6-month and 12-month timepoints. This follow-up study was approved by the Institutional Review Board at the University of Wisconsin-Madison. Consent and assent forms were obtained from all dyads. Prior to each follow-up session, dyads received an emailed link to the videoconferencing platform and links to surveys regarding: tDCS tolerance (Supplemental 1.2a), Pediatric Cognition (Supplemental 1.2b), Gross Motor Function Classification System (GMFCS) levels (Supplemental 1.2c), current therapy involvement, and demographics. During the 6- and 12-month follow-up visits a Subject Report of Symptom (SRS) survey was completed to evaluate the occurrence of minor adverse events since the time of participation in the pilot study [9] (see Supplemental 1.3a). To evaluate stability in motor function, the Box and Blocks Test (BBT), a validated assessment tool to assess hand motor function, was performed as a safety measure [10]. The BBT was previously performed immediately before and after stimulation on days 2–5 (during the pilot study) and at the 6- and 12-month follow-up visits. Medical records were reviewed by the study medical monitor for any changes since the pilot study until the 6 and 12-month timeframes.

All 10 dyads from the pilot study approved medical record review follow-up and records were received. Eight of the 10 dyads completed the assessments at both the 6- and 12-month follow-up visits. Two dyads were unable to participate in the long-term follow-up visits due to time constraints.

One dyad initially self-reported GMFCS level I during the pilot study, then reported GMFCS level II during the follow-up visits. All other dyads reported GMFCS level I during baseline and follow-up visits. Participants' current therapies stayed the same or were reduced after participation in the pilot study.

All dyads reported symptoms from the SRS survey were deemed not related to stimulation by our medical monitor (see Supplemental 1.3b for additional symptom report analysis).

Wilcoxon signed-rank tests evaluated changes in the PCS and changes in BBT scores for the less-affected and more-affected hands. There was a significant improvement in BBT scores when compared to baseline which were stable between the 6 and 12-month follow-up visits (Table 1). No significant changes in the PCS were observed relative to baseline.

Based on the medical monitor review from the 6 and 12-month follow up timeframes, no participant experienced a seizure or other serious adverse event related to stimulation for participants who had records available. Two participants had new care needs for chronic issues and one had onset of a new minor health issue; however, all were deemed unrelated to the tDCS sessions by the medical monitor.

In the surveys conducted at the follow-up visits, high ratings in the tDCS tolerance surveys reflected a positive participant experience, highlighting the feasibility of remote tDCS interventions in this population. The stability of the PCS results from baseline to the 6- and 12-month follow-ups suggests that tDCS did not negatively impact

https://doi.org/10.1016/j.brs.2024.04.017
Received 15 April 2024; Accepted 29 April 2024
Available online 11 May 2024

Table 1
Baseline scores were taken prior to participation in the pilot study. "Mean Change" = baseline – follow-up. MA = More Affected Hand, LA = Less Affected Hand.

Measure	Baseline (n = 8)	6-month (n = 8)	12-month (n = 8)	Mean change (6 month - baseline)	Mean change (12 month - Baseline)	*p-value (6 month - baseline)	*p-value (12 month - Baseline)
Pediatric Cognition Survey	15.6 ± 6.6	16 ± 7.2	16.1 ± 8.1	0.375 ± 1.6	0.5 ± 3.4	p = 0.496	p = 0.891
Box and Blocks score (LI)	46 ± 5.3	52 ± 7	52.6 ± 5.8	6 ± 3.5	6.6 ± 5.5	p = 0.012	p = 0.012
Box and Blocks score (MI)	16.5 ± 11.9	21.3 ± 11.8	20.6 ± 12.1	4.8 ± 3	4.1 ± 4	p = 0.018	p = 0.042

cognitive function. Although one participant self-reported a change in GMFCS level from I to II, medical record review suggested that their mobility level remained similar over time, potentially falling between levels I and II. The consistency in therapy involvement and one participant's reported reduction in therapy needs suggest stability in overall therapeutic requirements post-tDCS intervention.

The findings from the SRS survey suggest that the remotely instructed tDCS intervention was well-tolerated and that any symptoms reported were not related to the stimulation. The increase in BBT scores at both the 6- and 12-month timepoints demonstrate there were no negative long-term consequences of tDCS on motor function. Conclusions on motor function improvement are not sufficient due to the small sample size and likely the result of learning and familiarity with the BBT.

The results of this follow-up study support the long-term safety of remotely instructed tDCS in children and young adults with CP. The combined findings from the medical monitor review and the SRS survey revealed no following up serious adverse events including seizures, and no reported symptoms related to tDCS. Moreover, consistent mobility levels as assessed by the GMFCS and the BBT underscore the safety of tDCS without adverse effects on motor skills. Together, these findings confirm the safety of remote tDCS interventions in the pediatric CP population, laying the groundwork for future expanded studies.

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Trial registration

https://clinicaltrials.gov/ct2/show/NCT05071586.

CRediT authorship contribution statement

Daniel H. Lench: Formal analysis, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Preston Christopher:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Marissa Gavioli:** Conceptualization, Writing – original draft, Writing – review & editing. **Gwendolyn Nytes:** Writing – original draft, Writing – review & editing. **Chrysanthy Ikonomidou:** Supervision, Writing – review & editing. **Melissa A. Villegas:** Formal analysis, Supervision, Writing – review & editing. **Bernadette T. Gillick:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that there are no known competing financial or personal interests that could have influenced the information reported in this paper.

Acknowledgements

We appreciate the dedication of the families, caregivers, and participants who participated in this study as well as the editorial efforts of Sally Jones. This work was supported by the National Institute of Health through the National Pediatric Rehabilitation Resource Center (Federal Award Number: 5P2CHD101912-02, Subaward Number: 412579-19126) and the University of Wisconsin Foundation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2024.04.017.

Abbreviations

tDCS	transcranial direct current stimulation
CP	Cerebral palsy
AE	Adverse event
NIBS	Non-invasive brain stimulation
PCS	Pediatric Cognition Survey
SRS	Subject Report of Symptom
HQ	Headquarters
FA	Family ambassador
BBT	Box and Blocks Test
GMFCS	Gross Motor Function Classification System

During the preparation of this work an author sparingly used ChatGPT to enhance readability of a few sentences. After using this tool/service, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

References

[1] Gillick B, Rich T, Nemanich S, Chen CY, Menk J, Mueller B, et al. Transcranial direct current stimulation and constraint-induced therapy in cerebral palsy: a randomized, blinded, sham-controlled clinical trial. Eur J Paediatr Neurol 2018;22(3):358–68.
[2] Rich TL, Nemanich S, Chen M, Friel K, Feyma T, Krach L, et al. Transcranial direct current stimulation (tDCS) paired with occupation-centered bimanual training in children with unilateral cerebral palsy: a preliminary study. Neural Plast 2018;2018:9610812.
[3] Saleem GT, Crasta JE, Slomine BS, Cantarero GL, Suskauer SJ. Transcranial direct current stimulation in pediatric motor disorders: a systematic review and meta-analysis. Arch Phys Med Rehabil 2019;100(4):724–38.
[4] Inguaggiato E, Bolognini N, Fiori S, Cioni G. Transcranial direct current stimulation (tDCS) in unilateral cerebral palsy: a pilot study of motor effect. Neural Plast 2019;2019:2184398.
[5] Grecco LA, Duarte NA, Zanon N, Galli M, Fregni F, Oliveira CS. Effect of a single session of transcranial direct-current stimulation on balance and spatiotemporal gait variables in children with cerebral palsy: a randomized sham-controlled study. Braz J Phys Ther 2014;18(5):419–27.
[6] Zewdie E, Ciechanski P, Kuo HC, Giuffre A, Kahl C, King R, et al. Safety and tolerability of transcranial magnetic and direct current stimulation in children: prospective single center evidence from 3.5 million stimulations. Brain Stimul 2020;13(3):565–75.
[7] Krishnan C, Santos L, Peterson MD, Ehinger M. Safety of noninvasive brain stimulation in children and adolescents. Brain Stimul 2015;8(1):76–87.
[8] Lench DH, Simpson E, Sutter EN, Gillick BT. Feasibility of remote transcranial direct current stimulation for pediatric cerebral palsy during the COVID-19 pandemic. Brain Stimul 2020 Nov-Dec;13(6):1803–4.
[9] Preston Christopher, Sutter Ellen N, Gavioli Marissa, Lench Daniel H, Nytes Gwendolyn, Mak Veronika, Simpson Emma A, Ikonomidou Chrysanthy,

Villegas Melissa A, Saiote Catarina, Gillick Bernadette T. Safety, tolerability and feasibility of remotely-instructed home-based transcranial direct current stimulation in children with cerebral palsy. Brain Stimul 2023;16(5):1325–7.
[10] Araneda R, Ebner-Karestinos D, Paradis J, Saussez G, Friel KM, Gordon AM, et al. Reliability and responsiveness of the jebsen-taylor test of hand function and the Box and block test for children with cerebral palsy. Dev Med Child Neurol 2019;61(10):1182–8.

Daniel H. Lench
Department of Neurology, Medical University of South Carolina, 208B Rutledge Ave, Charleston, SC, 29403, USA

Preston Christopher, Marissa Gavioli, Gwendolyn Nytes
Waisman Center, University of Wisconsin–Madison, 1500 Highland Ave, Madison, WI, 53705, USA

Chrysanthy Ikonomidou
Department of Neurology, University of Wisconsin-Madison, 1685 Highland Ave, Madison, WI, 53705, USA

Melissa A. Villegas, Bernadette T. Gillick*
Waisman Center, University of Wisconsin–Madison, 1500 Highland Ave, Madison, WI, 53705, USA
Department of Pediatrics, University of Wisconsin-Madison, 600 Highland Ave, Mail Code 4108, Madison, WI, 53792, USA

* Corresponding author.
E-mail address: bgillick@wisc.edu (B.T. Gillick).