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Abstract

Purpose:

To determine the influence of combined transcranial direct current stimulation (tDCS) to the motor cortex (M1) and bimanual training on cardiovascular function in children with cerebral palsy (CP).

Methods:

Mean arterial pressure (MAP), heart rate (HR), and HR variability (HRV) were measured immediately before and after 20 minutes of cathodal tDCS to contralesional M1 and bimanual training on days 1, 6, and 10 of a 10-day trial in 8 participants (5 females, 7-19 years).

Results:

Baseline MAP and HR were similar across days (93 ± 10 mm Hg and 90 ± 10 bpm, $P > .05$). MAP was similar from baseline to postintervention across all 3 days. Systolic pressure, diastolic pressure, nor HR significantly changed. HRV was not influenced by the 10-day intervention.

Conclusions:

Combined cathodal tDCS to M1 and bimanual training does not influence autonomic and cardiovascular function in children with CP due to perinatal stroke.

Keywords:

autonomic dysfunction, blood pressure, cortical stimulation, heart rate, noninvasive brain stimulation, stroke

INTRODUCTION

Cerebral palsy (CP) due to perinatal stroke is the most common cause of physical disability in childhood.[1] In addition to physical challenges, children with CP have autonomic dysregulation, suggesting attenuated parasympathetic activity and exaggerated sympathetic activity at rest and abnormal responses to postural changes or orthostatic stress.[2] This impaired autonomic regulation can translate to impaired cardiorespiratory function.[3] Although mechanisms delineating autonomic dysregulation in CP are unclear, it is suggested that autonomic dysfunction in CP could be an effect of the brain insult or from inactivity, as people with brain damage demonstrate low tolerance to physical activity when compared with peers without brain damage.[4] Cardiovascular autonomic regulation is an important determinant of health, and the ability of the autonomic nervous system to adapt with therapy is important for long-term cardiovascular outcomes.

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique used to influence depolarization or hyperpolarization of the neuronal membrane to alter neuronal excitability, resulting in instantaneous “online” and long-lasting “offline” modifications of brain activity.[5–7] The exact mechanism of tDCS is unclear, but the cathodal tDCS appears to be mediated, in part, by a reduction in the excitation of the glutamatergic system[5,8] by causing a hyperpolarization and thus inhibition. The neurotransmitter release (acetylcholine) is what is thought to promote brain-derived neurotrophic factor–dependent synaptic plasticity. The safety, feasibility, and efficacy of tDCS on motor function in children with CP have previously been reported.[9,10]

The primary motor cortex (M1) is a common target for neuromodulation to improve motor function in populations with neurological impairment. It is well-established that autonomic function is related to motor function.[11–13] Imaging studies have reported an interaction between autonomic function and cerebral activation of the motor system.[13] The influence of tDCS on the autonomic nervous system function, however,[14] is less clear and has not been studied in children with CP.[14] Specifically, previous literature has yet to demonstrate a clear depiction of how tDCS to M1 may influence autonomic function.[15–17] This is likely due to the heterogeneity between studies. For example, heart rate (HR), heart rate variability (HRV), and blood pressure (BP) are common outcome variables, but the influence of tDCS on these measures varies considerably depending on whether the (1) population was healthy or unhealthy, (2) M1, the dorsolateral prefrontal cortex (DLPFC), or temporal lobe was stimulated, and (3) the anode or cathode was the active electrode. Anodal tDCS causes alterations in HRV toward sympathetic dominance,[18–20] but not always.[15–17] The majority of these studies, except da Silva et al,[18] were conducted in healthy individuals. Clancy et al[20] demonstrated an increase in muscle sympathetic nerve activity, a gold standard assessment for sympathetic activity with anodal tDCS to M1. Based on some of this work,[18–20] it is plausible that cathodal tDCS, often used to suppress cortical excitability,[21] could improve autonomic function by inhibiting sympathetic activity and restoring parasympathetic activity, in children with CP due to perinatal stroke. Further, bimanual training in the upper extremity in children with CP improves walking endurance and significantly improves HR and HRV.[3] The rehabilitative pairing with tDCS may mitigate maladaptive autonomic regulation and promote improved regulation of BP in people with stroke. Thus, we explored whether cathodal tDCS to M1 paired with bimanual training would influence autonomic function in children with CP, due to perinatal stroke. We hypothesized that HR and BP would be reduced and HRV would increase after a 10-day treatment of combined tDCS and bimanual training.

METHODS

General Overview

Participants with congenital hemiparesis, secondary to perinatal stroke, underwent combined tDCS and bimanual training for 5 consecutive days, with 2 days off and with a second period of 5 consecutive days.[9] Blood pressure, HR, and HRV were assessed during days 1, 6, and 10 of this 10-day intervention. Resting HR and BP were monitored immediately before and after the intervention.

Participants

A total of 8 participants (5 female, age range 7-19 years) attended a 10-day protocol as part of a clinical trial (NCT02250092) that investigated effects of tDCS paired with occupation-centered bimanual training in children with CP.[9] Participants were recruited locally from pediatric hospitals via mailings and nationally through web postings (eg, the Children's Hemiplegia and Stroke Association Web site: http://chasa/org/). Participants were eligible for inclusion if they were between the ages of 7 and 21 years, and demonstrated congenital unilateral CP secondary to perinatal stroke as confirmed by MRI or CT radiologic report.[9] Participants were excluded if they had a history of seizures within the last 2 years, implantation of medical devices contraindicated for tDCS testing, or other coexisting neurological conditions (eg, other brain or spinal cord injury). The study was approved by the University of Minnesota's Institutional Review Board and Clinical Translational Science Institute, and the procedures were performed in accordance with the Declaration of Helsinki. Prior to study

enrollment, participants 18 years and older provided written informed consent and those younger than 18 years provided written informed assent along with consent from their legal guardian/caregiver.

Transcranial Direct Current Stimulation and Bimanual Training Protocol (Intervention)

The protocol consisted of 10 weekday sessions of tDCS and bimanual training in a group setting at the same time every day, as described previously.[9] Twenty minutes of 1.5-mA cathodal tDCS was applied to M1 of the nonlesioned hemisphere (Soterix 1 × 1 Limited Total Energy [LTE], New York) while participants engaged in seated, low-intensity bimanual activities (eg, board and card games). Medical grade electrode sponges (5 × 7 cm) housing a 25-cm^2 rubber electrode were used to deliver stimulation, with the cathode placed on the primary motor cortex of the nonlesioned hemisphere and the anode placed on the contralateral forehead. The stimulation intensity of 1.5 mA was chosen based on previous work that showed this magnitude of stimulation can enhance motor learning,[22] and based on available safety and tolerability data.[23–25] Following stimulation, participants continued to engage in goal-directed bimanual activities for 100 minutes per day.

Assessment of Cardiovascular and Autonomic Function

Autonomic function via HRV and cardiovascular responses (HR and BP) were measured pre- and post-intervention on days 1, 6, and 10. Five minutes of continuous data was recorded immediately pre- and post-intervention in a quiet and private room adjacent to the room where the intervention occurred. Because of the simultaneous bimanual training and tDCS, autonomic function was not recorded in real time during the intervention. Heart rate was measured continuously via a 3-lead electrocardiogram (ECG) (ADInstruments, Colorado Springs, Colorado). Alcohol wipes were used to clean the skin surface prior to electrode placement. Three electrodes were placed on the chest; 1 on the right clavicular fossa, 1 on the left clavicular fossa, and 1 below the anterior thoracic cage on the left side of the chest cavity, superior to the anterior iliac crest. Heart rate was continuously sampled at a rate of 1 kHz for 5 minutes prior to and 5 minutes after tDCS and bimanual therapy. Beat-to-beat BP was measured continuously with a noninvasive BP monitoring system (Human NIBP, ADinstruments, Colorado Springs, Colorado) with a cuff that measured BP from the annular or middle finger of the hand. Beat-to-beat BP was recorded and analyzed at a sampling rate of 200 Hz. Heart rate variability measurements in both the time and frequency domains were calculated from the 3-lead ECG (LabChart v8, ADInstruments, Colorado Springs, Colorado).

Data Analysis

For resting/baseline and postintervention HR and BP average data, the last minutes of the 5 minutes of data were averaged. The last minute of the 5-minute data was used to ensure stable data. For short-term HRV analysis, the entire 5-minute period[26] was analyzed to obtain time-domain characteristics (standard deviation of R-R intervals [SDRR] and root mean square of successive differences in R-R intervals [RMSSD]) and frequency-domain HRV characteristics (total power and absolute high-frequency [HF] power, absolute low-frequency [LF] power, and LF/HF power ratio).[26] For both, time and frequency analysis, the interbeat interval (between successive R waves of the QRS complex) was measured. The time-domain variables quantify the variance of time from 1 R-wave to the successive R-wave. The SDRR and RMSSD are 2 key variance measures for short-term HRV assessment. A power spectral analysis allows for separating out different frequency components of the heart rhythm, which may provide additional information on autonomic function. Two frequency components: HF (0.15-0.4

Hz) power, which can be dependent on respiration, but is usually indicative of parasympathetic dominance and LF (0.04-0.15 Hz) power, which is more controversial but likely incorporates baroreflex activity.[26–28] We calculated LF/HF ratio and total power, which is the sum of all frequency bands. The total power is associated with greater overall fluctuation of HR and is considered to be overall HRV. Total power also includes very low frequency (VLF, 0.0033), but the interpretation and mechanism of this frequency band is unclear and thus not reported here.

Statistical Analysis

Normality of data was assessed via Shapiro-Wilk tests. All data were normally distributed and therefore parametric tests were used. Cardiovascular responses to the intervention were assessed via 2-way—baseline to postintervention (time effect) and day of testing (days 1, 6, and 10, day effect)—repeated-measures (RM) analysis of variance (ANOVA) tests. A Bonferroni correction was used to adjust the *P*-value cutoff for multiple comparisons. Statistical significance was considered if $P < .05$. Because of the small sample size, male and female data were pooled for analyses. A post hoc power calculation was performed to determine statistical power for main outcome variables (see the Supplemental Digital Content, available at: https://links.lww.com/PPT/A306). All analyses were performed using SPSS version 25 (IBM, Armonk, New York).

RESULTS

Participants

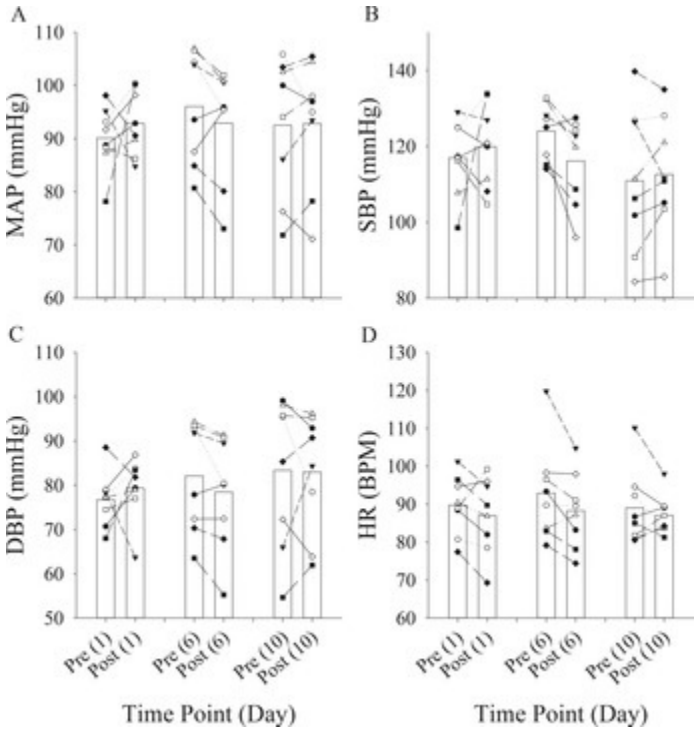
Participants were 13 ± 4 years old. Six of 8 participants had a right hemisphere perinatal infarct (4 female) while 2 participants had a left hemisphere perinatal infarct (1 female). Participants denied having cardiovascular disorders or anxiety. Based on a formal study questionnaire,[29] no anxiety was reported prior to or following tDCS. No serious adverse events occurred during this study, and minor adverse events from tDCS have previously been reported with “unusual feelings on the skin of the head” being the most common.[9] Two participants were taking medication, specifically 1 was taking an oral contraceptive (desogestrel 0.15 mg/ethinyl estradiol 0.03 mg) and 1 was using a daily eye drop for allergies (tobramycin).

Cardiovascular and Autonomic Response to Transcranial Direct Current Stimulation

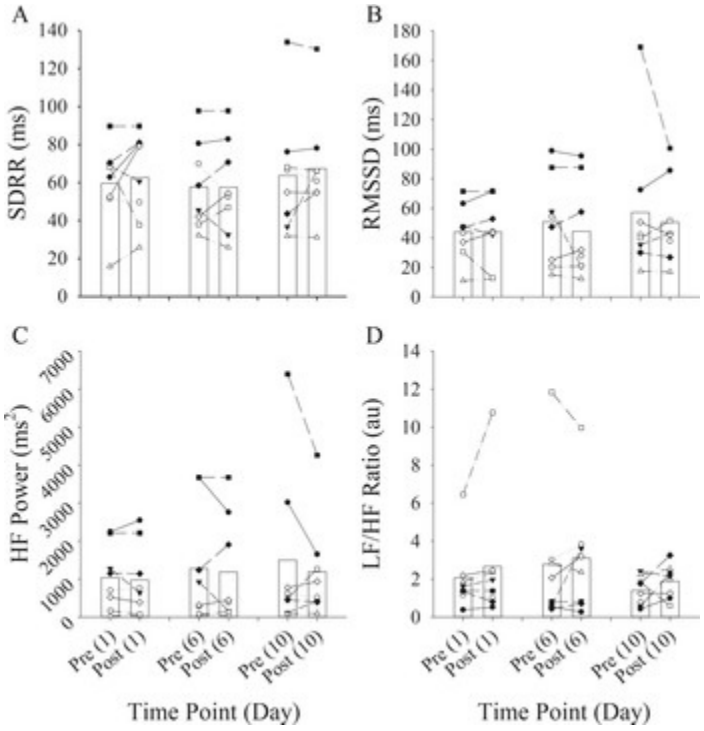
Baseline mean arterial pressure (MAP) and HR were not different across days (average for all 3 days: MAP: day 1: 90 ± 6; day 6: 96 ± 11; day 10: 93 ± 12 mmHg, day effect, $P = .20$, RM-ANOVA, HR: day 1: 90 ± 8; day 6: 93 ± 13; day 10: 89 ± 10 bpm, day effect, $P = .47$; RM-ANOVA). Absolute changes from baseline to postintervention were similar for MAP (day 1: Δ + 3 ± 10; day 6: Δ − 3 ± 6; day 10: Δ 0 ± 6 mm Hg, time effect, $P = .37$, RM-ANOVA), systolic blood pressure (SBP) (day 1: Δ + 3 ± 15; day 6: Δ −8 ± 7; day 10: Δ + 2 ± 8 mm Hg, time effect, $P = .12$, RM-ANOVA) and diastolic blood pressure (DBP) (day 1: Δ + 3 ± 9; day 6: Δ − 4 ± 5; day 10: Δ 0 ± 11 mm Hg, time effect, $P = .46$, RM-ANOVA). Similarly, the absolute change in HR was similar from baseline to postintervention (day 1: Δ − 3 ± 6; day 6: Δ −5 ± 6; day 10: Δ − 2 ± 6 bpm, time effect, $P = .58$, RM-ANOVA).

Mean arterial pressure (time × day interaction, $P = .99$, RM-ANOVA, Figure 1A), SBP, (time × day interaction, $P = .64$, RM-ANOVA, Figure 1B), and DBP (time × day interaction, $P = .74$, RM-ANOVA, Figure 1C) were similar from baseline to postintervention across all 3 days of testing. There was, however, a nonsignificant trend for the baseline to postintervention change in HR to decrease

across the 3 days of testing (time × day interaction, *P* = .08, RM-ANOVA, Figure 1D). Further, there were no differences in the time-domain HRV characteristics post-intervention in SDRR (time effect, *P* = .46, RM-ANOVA, Figure 2A) and RMSSD (time effect, *P* = .24, RM-ANOVA, Figure 2B) or in the frequency-domain HRV characteristics HF power (time effect, *P* = .29, RM-ANOVA, Figure 2C) and total power (day 1: Δ − 2 ± 1671 au; day 6: Δ170 ± 1763 au; day 10: Δ1645 ± 3125 au, time effect, *P* = .20, RM-ANOVA). It is important to note that there is an outlier within the data, as can be shown in Figure 2, with the individual in 2A-2C being the same individual. When this outlier is removed, the statistical *P* value remains nonsignificant. There was no change in LF power from baseline to postintervention (day 1: Δ − 198 ± 411 au; day 6: Δ165 ± 669 au; day 10: Δ1067 ± 2165 au, time effect, *P* = .23, RM-ANOVA) across days (time × day interaction, *P* = .19, RM-ANOVA). LF/HF ratio increased from baseline to postintervention (time effect, *P* = .002, RM-ANOVA, Figure 2D). However, there was no difference in LF/HF ratio between days (day 1 vs day 6: −0.6 ± 1.1 au, *P* = .59, day 1 vs day 10: 0.7 ± 2.8 au, *P* = 1.00, and day 6 vs day 10: −1.3 ± 3.6, *P* = 1.00, RM-ANOVA with Bonferroni correction, Figure 2D). As of note, there is an outlier in LF/HF ratio on day 1 with a large increase in the ratio. When eliminating this outlier, the *P* value of the time effect is still significant at *P* = .006 (RM-ANOVA).



Cardiovascular measures of mean arterial pressure (MAP, 1A), systolic blood pressure (SBP, 1B), diastolic blood pressure (DBP, 1C), and heart rate (HR, 1D) during the last minute of rest prior to tDCS (baseline) and during the last minute of each 5-minute measure following tDCS (post-tDCS). tDCS indicates transcranial direct current stimulation.



Heart rate variability characteristics including time-domain measures of standard deviation of R-R interval (SDRR, 2A) and root mean square of successive R-R interval differences (RMSSD, 2B) as well as frequency-domain measures including high-frequency domain power (HF power, 2C) and low-frequency/high-frequency power (LF/HF power, 2D) during the last minute of rest prior to tDCS (baseline) and during the last minute of a recovery period following tDCS (post-tDCS). tDCS indicates transcranial direct current stimulation.

As this was a pilot study, a post hoc power analysis, using an α value of 0.05 was calculated to determine the power for each outcome measure. For MAP, there was 6% power with an effect size (η^2) of 0.001 to detect a difference between pre- and post-tDCS. For SBP, there was 53% power with η^2 of 0.052 to detect a difference between pre- and post-tDCS. For DBP, there was 18% power with η^2 of 0.015 to detect a difference between pre- and post-tDCS. In final, for HR, there was 100% power with η^2 of 0.944 to detect a difference between pre- and post-tDCS.

DISCUSSION

This is the first study to explore the autonomic and cardiovascular effects of a combined intervention of tDCS and bimanual therapy in children and adolescents with CP due to perinatal stroke. The intervention consisted of cathodal tDCS to M1 and bimanual training in a daily 20-minute therapy over the course of 10 days with autonomic and cardiovascular function measured pre- and post-intervention on days 1, 6, and 10. Contrary to our hypothesis, in this small sample size, the combined intervention did not have acute (daily) or longer-term (post 10 days) effects on cardiovascular or autonomic function in children/adolescents with CP after perinatal stroke.

tDCS and Autonomic Function

Although the precise pathways are not completely understood, historical studies using exercise or electrical stimulation of the motor system, as modalities to understand the interaction of the autonomic and motor systems, demonstrate a possible connection from the motor cortex to the hypothalamus, among other important brain regions, and subsequently to the pons and medulla of the brainstem.[12,30–34] The pons and medulla are where the cardiovascular regulatory centers are located[12,35,36] and, when activated via neuromodulation, can alter sympathovagal balance[37,38] and therefore autonomic function. However, the neuromodulatory effect of tDCS on autonomic function is less clear. This is likely due to the electrode montage and/or the cortical structures targeted. Literature suggests that, when using anodal tDCS, there is a predominant shift to increased sympathetic tone.[14] Cathodal stimulation was used on the basis that it would reduce interhemispheric inhibition in the motor system, and thereby would also potentially inhibit sympathetic activity through hypothalamic and pontine pathways,[39] subsequently decreasing BP and HR. Based on this previous work, an increase in HRV, particularly HF power, which is indicative of parasympathetic tone and a decrease in LF power, more controversial,[27] but is indicative of mixed sympathetic tone and baroreflex function,[27] and a decrease in BP and HR was expected. In contrast, we did not observe significant changes in BP or HR and the largest change in BP observed pre- to post-intervention was a change in systolic pressure on day 6 with an 8-mm Hg decrease. Importantly, there was a variable response in MAP from day to day, wherein some individuals *increased* from pre- to postintervention and some individuals *decreased* from pre- to postintervention (Figure 1A). These responses were not always similar from days 1 through 10.

Autonomic function, indicated by HRV, was not altered with tDCS for the majority of the HRV measures in this study. The LF/HF ratio did increase from baseline to postintervention, although this is difficult to interpret as LF power likely incorporates more than just sympathetic activity and can be a poor indicator of autonomic function.[27] Further, we did observe a trend suggesting a decrease in HR from pre- to postintervention. The lack of significance is likely due to the small sample size, as the responses were fairly consistent across individuals and study days. This decrease in HR, however, is consistent with the hypothesis of cathodal tDCS suppressing cortical/hypothalamic pathways and potentially decreasing sympathetic activity. Alternatively, the decrease in HR could also be due to increasing familiarity and acclimatization with the 10-day protocol. As LF power is not an accurate measure of sympathetic activity, we are not able to confirm the effects of tDCS on sympathetic activity in this study. What is fairly clear is that cathodal tDCS does not appear to influence HF power and thus parasympathetic activity in children with CP, as HF power is a reliable noninvasive measure of parasympathetic nervous system activity.[27]

Literature suggests that anodal tDCS may have a greater influence on autonomic or cardiovascular function, when stimulating M1.[15,16] For example, Binkofski et al[16] demonstrated a decrease in BP and cortisol with 90 minutes of anodal stimulation to M1.[16] Vernieri et al[15] similarly demonstrated that, in a healthy population, anodal tDCS to M1 increased LF power and cathodal stimulation decreased HF power.[15] In contrast, Nguyen et al.[40] demonstrated that anodal tDCS of M1 corresponding to the lower limb did not acutely affect BP or HR in adults who were healthy and/or post-stroke. Further, anodal tDCS to M1 did not decrease BP or HR when individuals were exposed to a cold pressor test to induce pain.[41] Collectively, the effects of tDCS on autonomic function when stimulating M1 are not consistent

across studies, and therefore it is challenging to ascertain the influence that tDCS to M1 may have on autonomic function.

It is likely that other regions of the brain may be modulated to a greater degree with tDCS. As such, the DLPFC is known to modulate brain regions involved in the regulation of the autonomic nervous system activity.[42] Recently, Nikolin et al (2017) demonstrated an increase in HF power with anodal tDCS to the DLPFC in healthy adults, which is consistent with other work in this field.[14,43] Although both M1 and the DLPFC appear to be able to influence autonomic function in some capacity, there are other factors that should be considered in optimizing the therapeutic effects of tDCS, such as the montage of electrodes, the parameters and duration for stimulation, whether tDCS works best as an adjunct therapy or in isolation, and the population that is being targeted.

Bimanual training is a type of upper limb rehabilitation designed to activate the more affected (eg, weaker) and less affected (eg, stronger) limbs during daily living skills and goal-directed training.[44] Further, the use of bimanual training of the upper extremities in a previous study, in the absence of tDCS, improved not only endurance of walking and function, but also HRV in children with CP.[3] The aforementioned study is important because it is further evidence of how altering motor function can impact autonomic function. In addition, it is suggested in other clinical populations that tDCS is most effective when combined with a behavioral task.[45] Thus, we would likely expect that the combined tDCS and bimanual training would have a positive effect on autonomic function, but we did not observe this in our cohort.

Limitations

Conclusions of this study are limited by the sample size, heterogeneity in lesion location and size, measurements of autonomic and cardiovascular function pre-/post-intervention versus during intervention and a lack of a control group. Future studies and optimizing the study design construct based on sample size and power should be integrated. The neurophysiologic effects of tDCS have been shown to last up to an hour after treatment.[46,47] Therefore, if cathodal tDCS to M1 were to have a significant influence on the cardiovascular system, we would have been able to observe the effects 5 minutes after the treatment. Still, the electric field induced by tDCS is likely altered in children, and especially in the presence of brain pathology such as a cortical lesion.[48] This variability may have produced a net reduction in the effect of tDCS to modulate cardiovascular and autonomic function. Further, as this study was an open-label exploratory investigation, without a control group, we are not able to determine whether baseline cardiovascular or autonomic function is truly altered in our cohort.

CONCLUSIONS

This study is the first to demonstrate that, in a small sample of children with perinatal stroke, combined cathodal tDCS to M1 and bimanual training does not influence cardiovascular or autonomic function. Further, in performing a post hoc power analysis, we demonstrate that larger numbers of participants would be necessary to make a definitive conclusion on the effects of cathodal tDCS and bimanual training on autonomic function in children with CP. Future studies should address both cathodal and anodal tDCS to various cortical structures, such as DLPFC, and measure autonomic function both during and after treatment to determine the influence of tDCS therapy on the autonomic and cardiovascular system in children/adolescents with CP due to perinatal stroke.

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