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Anodal Contralesional tDCS Enhances CST Excitability Bilaterally in an Adolescent with Hemiparetic Cerebral Palsy: A Brief Report

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Abstract

Hemiparetic cerebral palsy (HCP), weakness on one side of the body typically caused by perinatal stroke, is characterized by lifelong motor impairments related to alterations in the corticospinal tract (CST). CST reorganization could be a useful biomarker to guide applications of neuromodulatory interventions, such as transcranial direct current stimulation (tDCS), to improve effectiveness of rehabilitation therapies. We evaluated an adolescent with HCP and CST reorganization who demonstrated persistent heightened CST excitability in both upper limbs following anodal contralesional tDCS. Results support further investigation of targeted tDCS as an adjuvant therapy to traditional neurorehabilitation for upper limb function.

Keywords

Brain Excitability, Hemiparesis, Motor Evoked Potential, Perinatal Stroke, Transcranial Direct Current Stimulation

Introduction

Cerebral palsy (CP) is the leading cause of physical disability in childhood and affects 2–3 children per 1000 born in the United States. Perinatal brain injury (i.e., stroke, brain bleed) is the most common cause of CP and may lead to lifelong motor function impairments that limit a child's ability to participate in daily activities.[1,2] Unilateral brain injury can lead to atypical reorganization during development of the corticospinal tract (CST), the primary motor pathway for voluntary skilled movement and the last motor system to develop in infants.[3] In typically developing children, contralateral projections within the CST strengthen while ipsilateral connections are pruned, resulting in a highly contralateral organization pattern (contralateral CST circuitry).[3,4] In some children with hemiparetic CP (HCP) due to unilateral perinatal stroke, typical CST organization is disrupted, and ipsilateral corticospinal projections from the contralesional hemisphere are strengthened during development while projections from the lesioned hemisphere are lost, resulting in bilateral upper extremity motor representations in the contralesional primary motor cortex (ipsilateral CST circuitry).[5] The CST reorganization following early brain injury has been suggested as an underlying basis of long-term motor impairments and may serve as a biomarker for response to therapies.[6,7]

Although current rehabilitation therapies can promote recovery, they are costly and yield modest improvements; therefore, more effective and accessible therapies for children with HCP are needed. Studies in adults with stroke show enhanced functional motor skill recovery when standard rehabilitation therapies are paired with transcranial direct current stimulation (tDCS).[8,9] In typically-developing children, tDCS of the motor cortex has been shown to improve motor learning;[10] however, therapeutic tDCS in children with HCP has yielded limited and heterogeneous results.[11–13]

Previous studies in pediatric populations have implemented protocols adapted from adult literature in which cathodal tDCS is applied to the contralesional motor cortex to reduce transcallosal inter-hemispheric inhibition (IHI).[9,14] However, this model may not be well-suited to children with HCP, who often have compromised interhemispheric connectivity and thus decreased IHI.[15,16] Furthermore, in children with predominately ipsilateral CST circuitry, unihemispheric cathodal contralesional tDCS may decrease excitability in both motor representations simultaneously, which may be detrimental for function.[17,18] Additionally, cathodal tDCS has variable effects on CST excitability that depend upon stimulation intensity.[19] Anodal tDCS, on the other hand, only elicits excitation and may therefore be a more reliable approach to facilitate motor learning in children with HCP to improve rehabilitation outcomes.[13,20]

In this brief report, we have investigated changes in CST excitability in a participant with hemiparesis and ipsilateral CST circuitry to illustrate using anodal tDCS of the contralesional hemisphere as a tailored model of stimulation in children with HCP. We hypothesized that anodal contralesional tDCS would increase CST excitability in the more- and less-affected upper limb in an adolescent with ipsilateral CST circuitry.

Materials and Methods

The participant was a 14-year-old male with a history of perinatal stroke who subsequently developed spastic hemiparesis affecting the right side. His Manual Ability Classification System (MACS) level was III ("handles objects with difficulty; needs help to prepare and/or modify activities"). The participant's structural MRI revealed cystic degeneration and significant volume loss of the left frontoparietal lobes and subcortical parenchyma, as well as dilation of the left lateral ventricle and midline shift to the left due to volume loss, consistent with an in-utero infarct of the left middle cerebral artery (Figure 1). He had no history of seizure, or of cardiac, pulmonary, GI, or renal impairment. Medications included 10mg Lisdexamfetamine Dimesylate (Vyvanse) taken once per day in the morning.

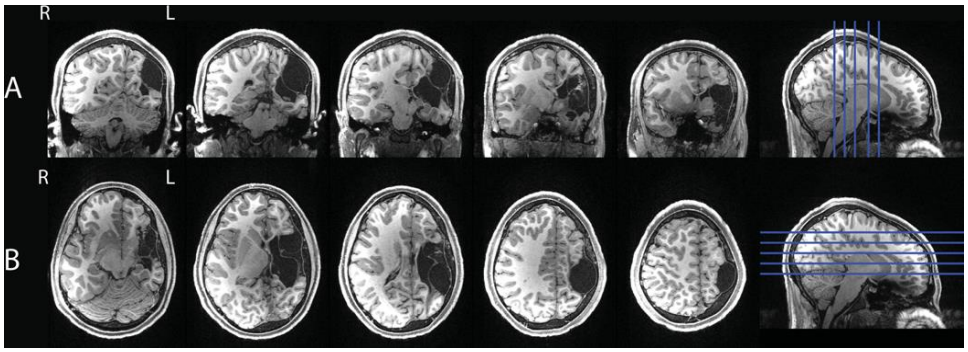

Figure 1. A) Coronal and B) Axial views of participant's T1-weighted MRI scan. Images are presented in radiological orientation (left side of the image displays the right hemisphere).

Study Design

The participant was enrolled in a double-blinded clinical trial (NCT03635775) in which he was randomized to receive anodal contralesional tDCS. The participant completed a one-hour MRI session which included a T1-weighted magnetization prepared rapid acquisition gradient echo (MP-RAGE) sequence (spatial resolution 1 mm isotropic) (Figure 1). One day later, the participant completed: 1) a

90-minute baseline single-pulse transcranial magnetic stimulation (spTMS) assessment, 2) a 20-minute intervention consisting of motor training and 1.5 mA tDCS, and 3) a 60-minute spTMS assessment with measurements taken every 15 minutes (Post0, Post15, Post30, Post45, and Post60). Safety assessments were completed at five timepoints throughout the study: at baseline, prior to tDCS, during tDCS, after tDCS, and at the end of the study. In each safety assessment, the participant was asked to identify any symptoms, and blood pressure and heart rate were monitored. We compared results in to a 13-year-old male participant with perinatal stroke and HCP (left middle cerebral artery ischemic injury, MACS level III) who completed the same protocol, but received sham tDCS.

Neurophysiologic Assessment Protocol

The participants' CST excitability and organization were assessed with spTMS based on our previously published protocols for HCP.[12] The T1-weighted image was used to generate head and tissue models that confirmed lesion location and guided stereotactic neuronavigation (Brainsight, Rogue Research, Montreal, Quebec, Canada) for spTMS, which was delivered using a 70-mm figure of eight coil held tangential to the scalp (Magstim 200^2, Magstim Corp, Whitland, UK). Electromyography (EMG) was recorded bilaterally using stainless steel surface electrodes placed superficially over hand (abductor pollicis brevis) and wrist (extensor digitorum) muscles, with a ground electrode placed proximal to the elbow joint. Resting motor threshold (RMT) was determined by stimulating the "hand knob" region of each primary motor cortex with spTMS while monitoring EMG responses in the contralateral hand muscle. SpTMS stimulation began at 50% of the maximum stimulator output (MSO). TMS stimulator intensity was then raised or lowered to determine the minimum intensity at which at least half of spTMS trials elicited an MEP greater than 50μV in the contralateral hand muscle, or until 84% MSO was reached; 84% MSO was the maximum allowable threshold to allow for suprathreshold testing at 1.2 times the RMT (1.2 × 84% = 100% MSO). This process was systematically repeated in areas 0.5–1.0 cm away from the hand knob region to determine if a lower RMT could be obtained. In both participants, no MEPs were elicited at or below 84% MSO in the left hemisphere; therefore, MEPs were considered absent in that hemisphere. Following RMT testing, 20 test trials of spTMS were completed at a stimulation intensity 1.2 times the RMT in the right hemisphere, while recording muscle activity in bilateral hand and wrist muscles.

tDCS Intervention

The intervention participant received tDCS to the right (contralesional) hemisphere for 20 minutes at an intensity of 1.5mA, previously been shown under similar study conditions to induce the greatest neurophysiologic effect within safe limits in pediatric populations.[22] tDCS was delivered using a Soterix 1×1 Limited Total Energy (LTE) device (Soterix Medical Inc. New York, NY) with 5×5cm electrodes enclosed in 5×7cm sponges moistened in saline solution. The anode was placed on the TMS-derived motor hotspot of the right hemisphere and the cathode was placed on the forehead contralateral to the anode. The sham participant had an identical montage, and sham stimulation was performed based on the sham settings (ramped onset/offset) of the device. During tDCS, the participant practiced tracing waveforms with TrackTest which consists of an electrogoniometer that allows a participant to control a cursor by flexing or extending the first digit.[21] Due to limited range of motion in the right (more affected) hand, motor practice was completed with the left (less-affected) hand. This motor task was implemented to provide concurrent motor training during tDCS, consistent with typical protocols

for rehabilitation clinical trials. Secondarily, this test was included as a component of the safety analysis to assess any potential decrements in hand function due to tDCS. Fine motor performance was assessed at baseline and one hour after tDCS using the TrackTest system.[21]

Results and Discussion

No major adverse events occurred during the TMS assessment or tDCS, nor were reported at one-day follow-up, and no decrements in hand function were observed during the intervention in either participant. Bilateral MEPs were observed in hand and wrist muscles of the intervention and the sham participant during TMS testing of the right motor hotspot (Intervention participant RMT = 68% MSO; Sham participant RMT = 42%). No MEPs were observed in either upper extremity during TMS testing of the left hemisphere. Following 1.5mA anodal tDCS in the right hemisphere, the intervention participant demonstrated increased excitability in both hands, as shown by a progressive increase in MEP amplitudes bilaterally until 30 minutes post-tDCS (pre-tDCS to Post 30 increase: left = 327%, right = 372%), followed by a decrease in amplitude. MEP amplitudes also increased in the left wrist immediately after tDCS (pre-tDCS to Post 0 increase: 285%), followed by a progressive return to baseline. No pulses elicited an MEP at the baseline assessment (pre-tDCS) in the right wrist for comparison to post-test amplitudes. MEP latencies in each muscle remained relatively stable in TMS assessments across all time points (left hand 21.38 +/− 1.00 ms, right hand 19.44 +/− 0.91 ms, left wrist 16.72 +/− 1.79 ms, right wrist 16.22 +/− 0.94 ms) and MEP morphology remained consistent across trials and between each side of the body (Figure 2, Supplemental Figure 1). In the sham tDCS participant, MEP amplitudes did not display a consistent pattern of change from pre-test to post-test. From pre-test to immediately after tDCS, MEP amplitudes decreased in most muscles (Supplemental Figure 2). Amplitudes at the Post 0 timepoint were 38% (left non-paretic hand), 27% (right paretic hand), 155% (left wrist), and 54% (right wrist) of baseline amplitudes. At the Post 30 timepoint, MEP amplitudes in muscle groups where MEPs were elicited also remained similar to those seen in the pre-test. Post-testing timepoints elicited fewer MEPs than pre-testing timepoints, with some eliciting no MEPs in right hand, right wrist, and/or left wrist muscles.

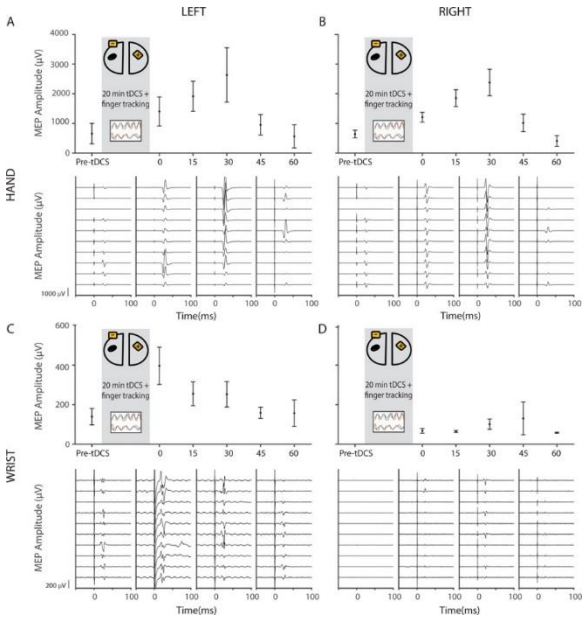

Figure 2. TMS assessment results displayed for intervention participant for A) Left Hand B) right Hand C) Left Wrist D) Right Wrist. Line graphs display MEP amplitudes (calculated from peak to peak, Mean +/− Standard Deviation) at each time point; Waterfall plots illustrate a subset of 10/20 trials (odd-numbered) at Pre-tDCS, Post 0, Post 30, and Post 60 assessments. The TMS pulse was delivered at time 0, with plots displaying EMG recordings from 50 msec before the TMS pulse to 100 msec after the TMS pulse. No MEPs were recorded at the baseline assessment (pre-tDCS) in the Right ED. Between Pre-tDCS and Post 0 assessments, the participant received 1.5 mA anodal tDCS to the right hemisphere while participating in the TrackTest fine motor activity. The diagram depicts an M1-SO montage wherein the left (lesioned) hemisphere displays the cathode placed on the forehead, and the right (non-lesioned) hemisphere displays the anode placed over the motor hotspot. Sample TrackTest traces are shown from the participant's pre-test trials, completed with his left hand.

Interpretation of neurophysiologic findings

The MEP data indicate a large increase in excitability of bilateral CST pathways following anodal tDCS, which lasted for 30 minutes following stimulation. The magnitude of increase (285–372%) and consistency of response latency and form suggest that the results are not spurious changes in excitability or related to outlier values and are consistent with the presumed excitatory effects of anodal tDCS. While practice with TrackTest may itself enhance motor learning and excitability, the results from a participant who received sham tDCS demonstrated that practice with TrackTest alone did not increase excitability. Importantly, this is one of the first studies, to our knowledge, to show that the excitability of ipsilateral CST pathways, particularly those innervating intrinsic hand muscles, can be modulated with unihemispheric anodal tDCS in children with HCP. The role of ipsilateral pathways for voluntary motor control is presumed to be minimal for individuals without brain injury. However, since consistent ipsilateral MEPs were observed in the right (more-affected) hand, this participant clearly showed CST reorganization that supports residual motor function.[23] Modulation of appropriate descending pathways with tDCS may help promote recovery.

Our results are similar to and build upon previous work in the adult stroke population. A study by McCambridge and colleagues used anodal tDCS to stimulate the contralesional hemisphere in adults with stroke and found a trend for increased excitability in the paretic (ipsilateral) biceps brachii.[24] Furthermore, a recent paper showed that anodal contralesional tDCS can modulate spinal motor networks for controlling arm movement in adults with stroke.[20] However, in adult stroke, other ipsilaterally descending pathways, like the reticulospinal tract, may support recovery after unihemispheric injury.[25] In this brief report, the findings and prior literature suggest that changes in excitability arose from CST pathways rather than another descending pathway. First, responses were recorded from intrinsic hand muscles necessary for fine motor control which are primarily innervated by descending fibers in the CST.[26] Second, closer inspection of individual MEP traces showed that ipsilateral and contralateral MEPs were similar in latency (19–21 ms) and morphology (Figure 2). Third, reticulospinal projections, for example, are linked to upper-limb synergies and these synergies are absent in children with hemiparesis with prenatal injuries.[27] Still, because we did not directly measure other pathways in this study, we cannot rule out their contributions to the MEPs.

Significance for neurorehabilitation and future directions

Predominantly ipsilateral CST projections are associated with poorer hand and arm function in children with HCP.[6] This brief report is the first to provide evidence that anodal contralesional tDCS increases excitability of bilateral CST projections in children with ipsilateral CST circuitry, supporting future

research of anodal contralesional tDCS as an adjuvant intervention to traditional rehabilitation to increase plasticity and motor learning. Previous clinical trials combining rehabilitation and tDCS have focused on contralesional cathodal tDCS montages for all participants; the results of these trials have been mixed.[12,13] Given a more advanced understanding of interhemispheric connectivity after perinatal stroke[15] combined with the present case study findings, contralesional cathodal tDCS is likely not an appropriate montage for children with ipsilateral CST projections and may explain the variable outcomes of prior clinical trials. More recent investigations aimed at tailoring therapies with and without non-invasive brain stimulation (NIBS) based on individual CST projection patterns offer a more precise approach for future neurorehabilitation trials.[18,28]

There are several limitations to the present case report. First, comprehensive motor performance data are not available. Inclusion of expanded clinical and functional measures would be useful in future research to understand the broader effects of tDCS.[29] Second, we can make conclusions about the short-term effects (up to 60 minutes) of a single session of tDCS on CST excitability, but understanding of long-term effects is unknown. Third, the intervention participant was taking a prescribed stimulant (Vyvanse) during the study, and the pharmaceutical effect of this drug on the neurophysiological results remains unknown. Lastly, while cessation of spTMS stimulation at 84% MSO during RMT assessment was necessary to provide consistent suprathreshold stimulation, we cannot confirm that stimulation at an intensity greater than 84% MSO would not have elicited contralateral MEPs from the lesioned hemisphere.

In conclusion, this case study reports on a child with HCP with ipsilateral CST circuitry who demonstrated increased CST excitability in bilateral upper extremity muscles following anodal 1.5 mA tDCS to the contralesional hemisphere. A matched participant who received sham tDCS did not demonstrate a comparable increase in excitability. As individualized, precision therapies become increasingly relevant in the treatment of HCP, the findings from this case study offer a framework for larger clinical trials of tDCS interventions that are tailored by individual patterns of CST development, towards optimizing cortical plasticity, motor learning, and rehabilitation outcomes.

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