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Multiday Transcranial Direct Current Stimulation Causes Clinically Insignificant Changes in Childhood Dystonia: A Pilot Study

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Abstract

Abnormal motor cortex activity is common in dystonia. Cathodal transcranial direct current stimulation may alter cortical activity by decreasing excitability while anodal stimulation may increase motor learning. Previous results showed that a single session of cathodal transcranial direct current stimulation can improve symptoms in childhood dystonia. Here we performed a 5-day, sham-controlled, double-blind, crossover study, where we measured tracking and muscle overflow in a myocontrol-based task. We applied cathodal and anodal transcranial direct current stimulation (2 mA, 9 minutes per day). For cathodal transcranial direct current stimulation (7 participants), 3 subjects showed improvements whereas 2 showed worsening in overflow or tracking error. The effect size was small (about 1% of maximum voluntary contraction) and not clinically meaningful. For anodal transcranial direct current stimulation (6 participants), none showed improvement, whereas 5 showed worsening. Thus, multiday cathodal transcranial direct current stimulation reduced symptoms in some children but not to a clinically meaningful extent, whereas anodal transcranial direct current stimulation worsened symptoms. Our results do not support transcranial direct current stimulation as clinically viable for treating childhood dystonia.

Keywords

dystonia, transcranial direct current stimulation, overflow, electromyogram, cerebral palsy

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Childhood dystonia is a debilitating movement disorder characterized by involuntary muscle contractions that lead to repetitive movements and/or abnormal postures.[1,2] Available treatment options for this disorder are limited in effectiveness,[3] and thus, there is a need for innovative interventions. Neuromodulation is emerging as a technique for treating dystonia.[3,4] Although deep brain stimulation can lead to dramatic improvements, especially in primary dystonia,[3,5,6] noninvasive methods avoid risks that accompany surgery and implantation.[3,5]

Several studies have shown that transcranial stimulation can improve motor symptoms[7,8] or reduce pain[9] associated with dystonia. In such studies, the stimulation delivered is based on the premise that dystonia results from reduced cortical inhibition[4,10-12] and that certain stimulation patterns can decrease excitability, increase inhibition, and improve control.[7,11,13,14] However, there is also evidence to suggest that cortical excitability might be mostly normal.[15] The mixed results may be due to the specific etiology of dystonia, and whether changes in excitability are a common feature in pediatric dystonia is unknown. Interestingly, in both healthy subjects and patients with movement disorders, other studies have shown that stimulation protocols that increase excitability of motor cortex[16] can also improve motor learning.[17-20] In the case of childhood dystonia, cathodal stimulation, which may modify inhibition to more normal levels but potentially slow learning, and anodal stimulation, which may decrease inhibition even further but

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Table 1. Patient Characteristics.

Patient no.	Age	Gender	Diagnosis	Barry-Albright Dystonia rating		Cathode location	Stimulation type
				Left arm	Right arm		
1	10	Male	Secondary dystonia; cerebral palsy	2	2	R M1	C, A
2	11	Female	Secondary dystonia; cerebral palsy	3	3	R M1	C, A
3	11	Male	Secondary dystonia; cerebral palsy	2	2	L M1	A
4	13	Male	Secondary dystonia; cerebral palsy	3	4	L M1	C
5	16	Male	Primary dystonia; early onset (*DYT1*)	0	2	L M1	C
6	17	Male	Secondary dystonia; cerebral palsy	3	4	L M1	A
7	19	Female	Secondary dystonia; cerebral palsy	1	1	R M1	C, A
8	20	Male	Secondary dystonia; vitamin E deficiency	1	1	L M1	C
9	21	Male	Secondary dystonia; brain injury at age 3	0	3	L M1	C, A

potentially enhance learning, may both have beneficial effects on symptoms.

In previous studies from our group,[13,14] we found that a single session of cathodal transcranial direct current stimulation, over motor cortex, which reduces excitability, can reduce motor overflow in childhood dystonia. However, the effects were small, there were no changes in functional clinical measures, and although there was a significant effect across the group, a few individual patients actually performed worse after cathodal transcranial direct current stimulation. These results suggest that for at least a subset of children, cathodal transcranial direct current stimulation can alleviate dystonic symptoms, while in others it may have no beneficial effects. Thus, it is possible that depending on the etiology of dystonia,[21] increasing excitability of motor cortex with anodal transcranial direct current stimulation may be more beneficial than cathodal transcranial direct current stimulation. However, another possibility is that anodal transcranial direct current stimulation will worsen symptoms by having a larger effect on increasing excitability and further reducing inhibition as compared to possible beneficial effects of learning. Such a result would suggest that, with regard to dystonia, transcranial direct current stimulation has a larger effect on unwanted excessive excitability than it does on modifying motor learning. Our hope is that the small effects measured in previous single-day studies will be amplified by repeated transcranial direct current stimulation sessions[17] and thus lead to clinically meaningful improvements.

To investigate these hypotheses, we conducted a controlled double-blinded multiday study of cathodal transcranial direct current stimulation and anodal transcranial direct current stimulation in children with primary and secondary dystonia. Patients attended 5 consecutive experimental visits (each approximately 24 hours apart) on 2 different weeks. They received either cathodal or anodal stimulation on each day of 1 week and they received sham stimulation each day during the other week. We quantified 2 outcome measures with an isometric electromyogram tracking task: (1) *tracking error*—accuracy of voluntary control using the first dorsal interosseus muscle and (2) *overflow*—excess muscle activity of hand muscles not involved in tracking.[22] The task involved isometric contraction of finger muscles to produce changes in electromyogram. Using customized electronics and signal processing, the electromyogram signals were used to move cursors up and down on a screen to match an automated target cursor. We also measured stimulation effects by examining videos of neurologic exams before and after each week and quantified clinically meaningful symptoms using the Barry Albright Dystonia Scale.

Methods

Patients

Nine individuals 10 to 21 years old (average age: 15.3 years $\pm$ 4.2 standard deviation) diagnosed with primary or secondary dystonia[23] affecting one or both hands participated in this study (Table 1). The patients were recruited from the Children's Hospital Los Angeles (CHLA) movement disorders clinic. The University of Southern California Institutional Review Board approved all experimental procedures. Parents gave informed written consent and, when possible, children gave written assent for study participation. The experiment was performed in accordance with the Declaration of Helsinki and all protected health information was obtained and stored according to the Health and Information Portability and Accountability Act. The study was registered with clinicaltrials.gov (NOC01460771).

Measurement Procedure

This study was composed of 2 experiments: experiment I—cathodal stimulation, and experiment II—anodal stimulation. For each experiment, participants attended 10 experimental sessions of approximately 1 to 1.5 hours each. Each session took place on a different day. The sessions were divided into weeks, with 5 consecutive sessions in each week, and at least 14 days between experimental weeks. For experiment I, patients received either real cathodal transcranial direct current stimulation or sham stimulation (sham) throughout a given week. For experiment II, patients received either real anodal transcranial direct current stimulation or sham throughout a given week (details on stimulation parameters below). Because of limited availability, only 4 patients participated in both experiments, whereas 3 patients participated in experiment I only (cathodal transcranial direct current stimulation) and 2 patients participated in experiment II only (anodal transcranial direct current stimulation). Thus, there were 7 patients in experiment I and 6 patients in experiment II. The order of

experimental weeks (ie, real or sham stimulation) was randomized and counterbalanced. At the start of the first day of each experiment week, patients were video recorded and later rated for dystonia severity using the Barry-Albright Dystonia Scale.[24] The patients were again recorded and rated at the end of the final day of each week.

To perform the electromyogram-tracking tasks (described below), patients were seated at a table in front of a computer monitor. As described in previous studies,[13,14,25] surface electromyogram electrodes (Delsys Inc, Boston, MA) were placed on the first dorsal interosseous and abductor digiti minimi of both hands. The electromyogram signals were sampled at 1 kHz (Power 1401, Cambridge Electronic Design Limited, Cambridge, UK) controlled by custom software. The electromyogram signals were filtered and amplified in hardware and filtered again in software. At the start of each experimental session, we measured the maximum voluntary contraction for the first dorsal interosseous and abductor digiti minimi muscles of both hands. (For more details on patient positioning, electromyogram filtering, and maximum voluntary contraction measurement, see Supplementary Material.)

Transcranial Direct Current Stimulation

A Magstim NeuroConn Direct Current Stimulator Plus Model 0021 (The Magstim Company Limited, Whitland, UK) with 4 × 7 cm saline-soaked electrodes was used for stimulation. Similar to previous studies,[13,14] one electrode (cathode for cathodal and anode for anodal transcranial direct current stimulation) was placed over the motor cortex at either the C3 (left hemisphere) or C4 (right hemisphere) location according to the 10-20 electroencephalography (EEG) placement system.[26] The other electrode was placed on the contralateral forehead. The hemisphere receiving stimulation was chosen as contralateral to (1) the hand most affected by dystonia or (2) if both hands were similarly affected, then contralateral to the patient's preferred hand.[13,14] For the stimulation condition, the current amplitude was 2 mA and duration was 9 minutes, with additional 30-second ramp up and ramp down phases at the beginning and end of stimulation. These parameters were similar in total charge delivered to those previously shown to be effective[13,14,27]; however, to accommodate limited patient availability, only a single stimulation epoch of 10 minutes was used, as compared to some previous studies that used 2 stimulation epochs separated by a 20-minute rest.[13,14] For the sham condition, the electrodes were placed on the patient's head for 10 minutes, but stimulation occurred only during the first 30 seconds. The patients, as well as the experimenters who performed data collection and analysis, were blinded to the stimulator condition. We reduced the stimulation amplitude to 1.5 mA for 2 participants because of skin discomfort. Discomfort occurred within moments of starting stimulation, and thus blinding was unaffected.

Electromyogram Tracking Tasks

All patients performed 2 electromyogram-tracking tasks, the "step task" and the "continuous task," before and after stimulation each day. For both tasks, the electromyogram from a single first dorsal interosseous muscle controlled the vertical position of a cursor on a display visible to the patient. Vertical cursor position was proportional to the electromyogram such that 0% maximum voluntary contraction was the bottom of the screen and 20% maximum voluntary contraction was the top of the screen. The cursor remained at the top of the screen for electromyogram values >20% maximum voluntary contraction and thus, feedback was effectively capped at 20% maximum voluntary contraction. Prior to experimental trials, patients practiced moving the cursor on the screen to ensure proper first dorsal interosseous activation.

Task 1 (step tracking). Patients performed 2 trials of the step task (described previously[13]) with each hand before and after stimulation. On each trial, the monitor displayed a target (horizontal line) that jumped vertically every 5 seconds between the bottom of the screen and the middle of the screen (10% maximum voluntary contraction). The position of a circular cursor was controlled by the patient's electromyogram (Figure 1A). Each trial lasted 55 seconds.

Task 2 (continuous tracking). Patients performed 2 trials of the continuous task (described previously[25]) with each hand before and after stimulation (Figure 1B). The target moved smoothly in the vertical direction in a randomly distorted smooth sinusoidal motion with an average period of 7 to 10 seconds. The mean target position was equivalent to approximately 10% maximum voluntary contraction. Each trial lasted 60 seconds. For both tasks, patients were instructed to relax all nontask muscles.

Analysis

As in previous studies,[13,14] we measured 2 aspects of task performance based on the normalized electromyogram: (1) tracking error and (2) overflow. Examples of the change in target location and normalized electromyogram (for all 4 different muscles) during step and continuous tasks are shown in Figure 1C and D. Tracking error was defined as the absolute difference between the target position and cursor position in units of normalized electromyogram (% maximum voluntary contraction). We truncated the electromyogram to 20% maximum voluntary contraction to match the range of electromyogram values displayed for the task muscle. Tracking error quantifies how well a patient can precisely control muscle activity. We defined overflow as the grand average across the normalized electromyogram of the 3 nontask muscles, each averaged across the entire trial (absence of nontask muscle activation resulted in 0 overflow). Overflow quantifies how well a patient can inhibit nontask muscles.

For analysis, we used the mean tracking error and overflow for each 5-second period. For the step task, there were a total of 22 periods and for the continuous task there were a total of 24 periods before and after stimulation. To test for changes due to 1 week of stimulation, we paired all mean values after stimulation on day 5 with the matching measurement before stimulation on day 1.

For both of the outcome measures, tracking error and overflow, we used a linear mixed-effects model to test for group effects of task hand (contralateral vs ipsilateral to stimulated motor cortex), stimulation type (real vs sham), and interaction between task hand and stimulation type across the entire patient group. Patients were considered as a random factor. We used the R software environment, with model lme(difference $\sim$ taskHand*stimType, random $= \sim 1|$patient), where "difference" represents the paired differences between prestimulation on day 1 and poststimulation on day 5. An analysis of variance was performed on the output of the lme model. We performed the same analysis for each individual patient.

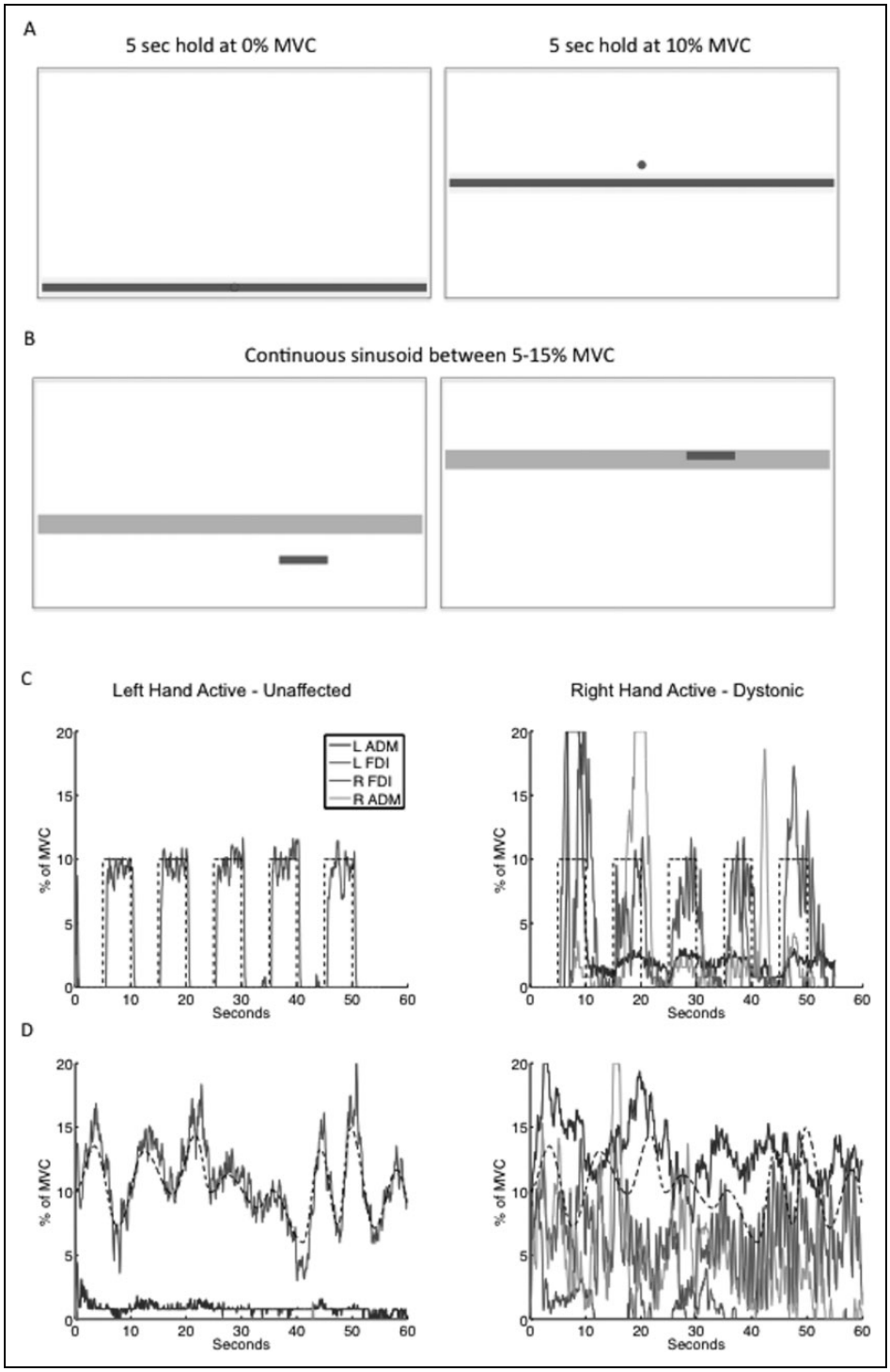

Figure 1. Overview of different electromyogram tasks and examples of muscle activation. (A) Step task. The horizontal bar was the target and jumped between the bottom of the screen (left) and middle of the screen (right). The position of a circular cursor was controlled by electromyogram activity of the FDI muscle. (B) Continuous task. The long horizontal bar was the target and moved smoothly in a randomly distorted sinusoidal motion between 5% and 15% MVC. Similar to the step task, the position of the short rectangular cursor was controlled by electromyogram of the FDI. For both tasks, the bottom of the screen corresponded to 0% MVC, the middle of the screen corresponded to 10% MVC, and the top of the screen corresponded to 20% MVC and above. Patients were instructed to track the moving target with the cursor to the best of their ability. (C, D) Examples of muscle activation during electromyogram tasks for a patient with right hemidystonia (Patient 9). (C) Tracking during step task. (D) Tracking during continuous task. Left panels show tracking with left FDI (unaffected), and right panels show tracking with right FDI (dystonic). There is clearly better performance with nonaffected hand as compared to the dystonic hand, in terms of lower tracking error (deviation of task muscle from target) and overflow (nonzero activity of nontask muscles). L, Left; R, Right; ADM, abductor digiti minimi; FDI, first dorsal interosseus; MVC, maximum voluntary contraction.

Results

Patient Comfort

Most patients reported some "tingling" at the start of both real and sham stimulation. For 2 patients who reported discomfort (1 and 4), we reduced the amplitude to 1.5 mA and restarted stimulation with no complaints. One patient reported mild headaches after stimulation, but they did not persist on following days. No other patients reported discomfort.

Cathodal Group Results

Seven patients participated in the cathodal study. The average differences in step task tracking error for each patient and grand average across the group are shown in Figure 2 (negative values indicate improvement). For this measure, there was no significant effect of task hand, stimulation type, or task hand–stimulation type interaction: $F(1, 612) < 7.45$ and $P > 0.39$. The average differences in step task overflow showed no significant effect of task hand, stimulation type, or task hand–stimulation type interaction for all effects: $F(1, 612) < 3.68$ and $P > 0.055$. In summary, across the group, cathodal stimulation did not significantly affect performance in the step task.

The average differences in continuous task tracking error are shown in Figure 3. For this measure, there was a significant effect of stimulation type, $F(1, 668) = 15.2$, $P < 0.001$. The mean difference in tracking error after 5 days of cathodal stimulation for the contralateral hand was –0.58% maximum voluntary contraction. There was no significant effect of task hand or task hand–stimulation type interaction for all effects, $F(1, 668) < 3.61$ and $P > 0.057$. The average differences in continuous task overflow are shown in Figure 4. There was a significant effect of task hand, $F(1, 668) = 18.4$ and $P < 0.001$, and task hand–stimulation type interaction, $F(1, 668) = 8.94$ and $P < 0.01$. The mean difference in overflow after 5 days of cathodal stimulation for the contralateral hand was +0.37% of maximum voluntary contraction. There was no significant effect of stimulation type, $F(1, 668) = 3.71$ and $P = 0.054$. In summary, across the group, cathodal stimulation led to an improvement in tracking error for the continuous task, but a worsening of overflow in the continuous task though both effects were small (less than 1% maximum voluntary contraction).

Anodal Group Results

Six patients participated in the anodal study. Again, for both the step and continuous tasks, we compared the tracking error and overflow from prestimulation on day 1 to poststimulation on day 5. The average differences in step task–tracking error for each patient and grand average across the group are shown in Figure 4. There was no significant effect of task hand or stimulation type, $F(1, 524) < .85$ and $P > 0.35$. There was a significant interaction effect of task hand and stimulation type interaction, $F(1, 524) = 8.5$ and $P < 0.01$. The mean difference in tracking error after 5 days of anodal stimulation for the contralateral hand was +0.47% maximum voluntary contraction. The average differences in step task overflow for each patient and grand average across the group are shown in Figure 4. For overflow in the step task, there was a significant effect of task hand, $F(1, 524) = 33.6$ and $P < 0.001$; stimulation type, $F(1, 524) = 34.9$ and $P < 0.001$; and task hand–stimulation type interaction, $F(1, 524) = 11.5$ and $P < 0.001$. The mean difference in overflow after 5 days of anodal stimulation for the contralateral hand was –0.53% of maximum voluntary contraction. In summary, across the group, anodal stimulation led to worsening in tracking error for the step task, but an improvement of overflow in the step task. Again, both effects were small (less than 1% maximum voluntary contraction).

The average differences in continuous task tracking error for each patient and grand average across the group are shown in Figure 5. There was a significant effect of task hand $F(1, 572) = 5.98$, $P < 0.05$, and task hand–stimulation type interaction $F(1, 572) = 6.93$, $P < 0.01$. The mean difference in tracking error after 5 days of anodal stimulation for the contralateral hand was +0.093% maximum voluntary contraction. There was no significant effect of stimulation type, $F(1, 572) = 0.001$ and $P > 0.97$. The average differences in continuous task overflow for each patient and grand average across the group are shown in Figure 5. For overflow in the continuous task, there was a significant effect of stimulation type, $F(1, 572) = 35.4$ and $P < 0.001$, and task hand–stimulation type interaction, $F(1, 572) = 4.90$ and $P < 0.05$. The mean difference in overflow after 5 days of anodal stimulation for the contralateral hand was +3.0% maximum voluntary contraction. There was no significant effect of task hand, $F(1, 572) = 0.013$ and $P > 0.90$. In summary, across the group, anodal stimulation led to a worsening of tracking error and overflow in the continuous task. The 3% maximum voluntary contraction increase in overflow was the largest group effect of stimulation observed in this study.

Cathodal Individual Results

In addition to investigating group effects, we ran statistical tests within data from individual subjects to determine if stimulation led to a significant improvement or worsening of tracking error or overflow for specific patients. After correcting for multiple comparisons, we determined if individuals showed a significant difference due to cathodal stimulation in any of the 4 performance metrics (ie, step task tracking error or overflow, continuous task tracking error or overflow) between poststimulation on day 5 and prestimulation on day 1. Based on the outcomes, we classified patients into 3 categories: "improved" (more metrics with significant improvement than significant worsening), "neutral" (equal number of metrics with significant improvement and significant worsening), or "worsened" (less metrics with significant improvement than significant worsening). With regard to cathodal stimulation, 3 patients improved (ie, patients 2, 8, and 9), 2 patients worsened (ie, patients 4 and 7), and 2 were neutral (ie, patients 1 and 5).

For those patients that improved with cathodal stimulation, we investigated their behavior further by looking at performance

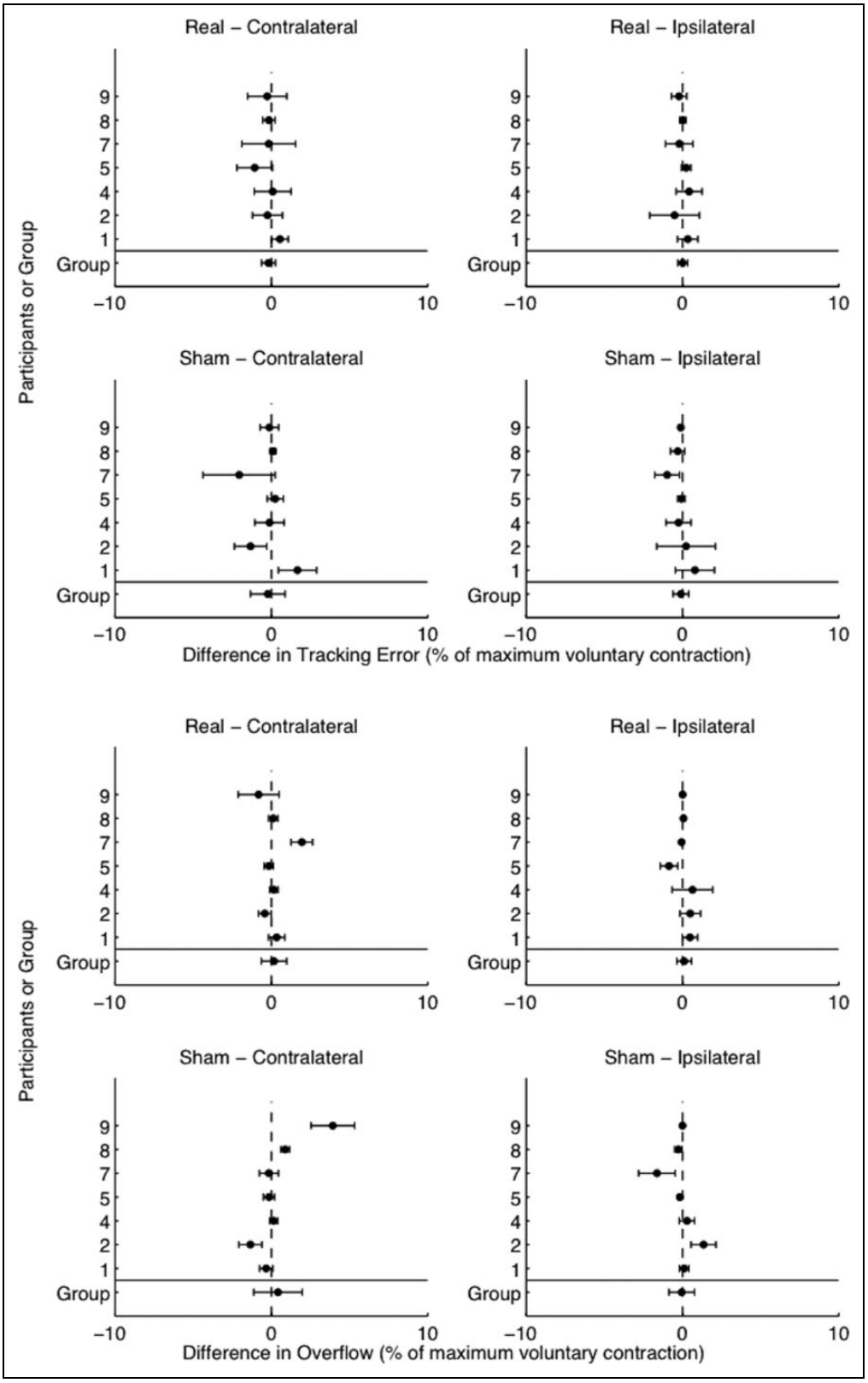

Figure 2. Experiment I cathodal stimulation *step task*. Mean differences from prestimulation on day 1 to poststimulation on day 5, in tracking error (top 4 panels) and overflow (bottom 4 panels) for individuals and group. Participants are arranged vertically with the group average at the bottom. Panels are organized by task hand (contralateral in left column, ipsilateral in right column) and stimulation type (real stimulation in first and third rows, sham stimulation in second and fourth rows). Negative values, left of the dashed line, indicate improvement, that is, lower overflow or tracking error after 5 days of stimulation. Circles represent means, and horizontal lines represent 95% confidence intervals.

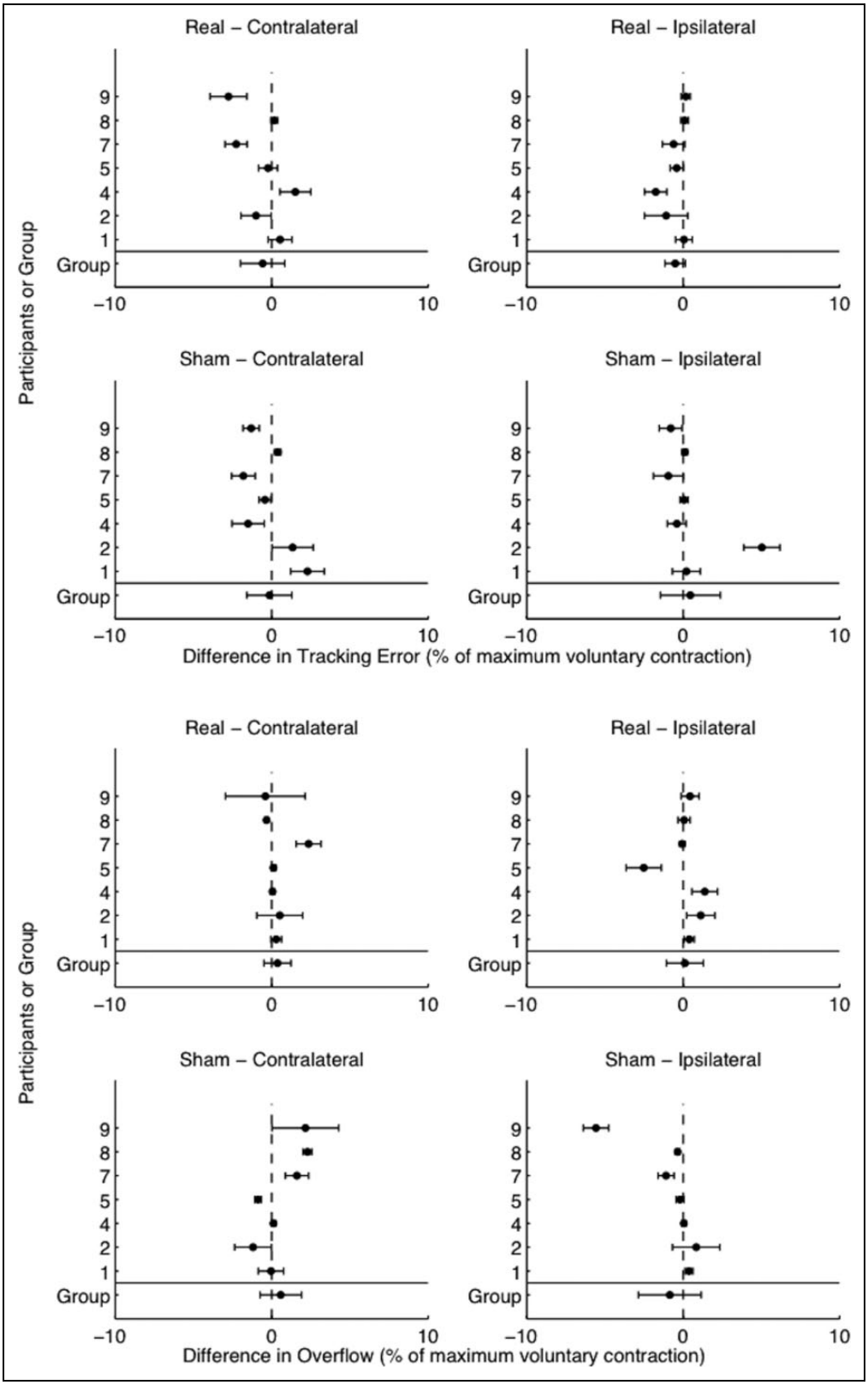

Figure 3. Experiment I cathodal stimulation *continuous task*. Mean differences from prestimulation on day 1 to poststimulation on day 5, in tracking error (top 4 panels) and overflow (bottom 4 panels) for individuals and group. Participants are arranged vertically, with the group average at the bottom. Panels are organized by task hand (contralateral in left column, ipsilateral in right column) and stimulation type (real stimulation in first and third rows, sham stimulation in second and fourth rows). Negative values, left of the dashed line, indicate improvement, that is, lower overflow or tracking error after 5 days of stimulation. Circles represent means, and horizontal lines represent 95% confidence intervals.

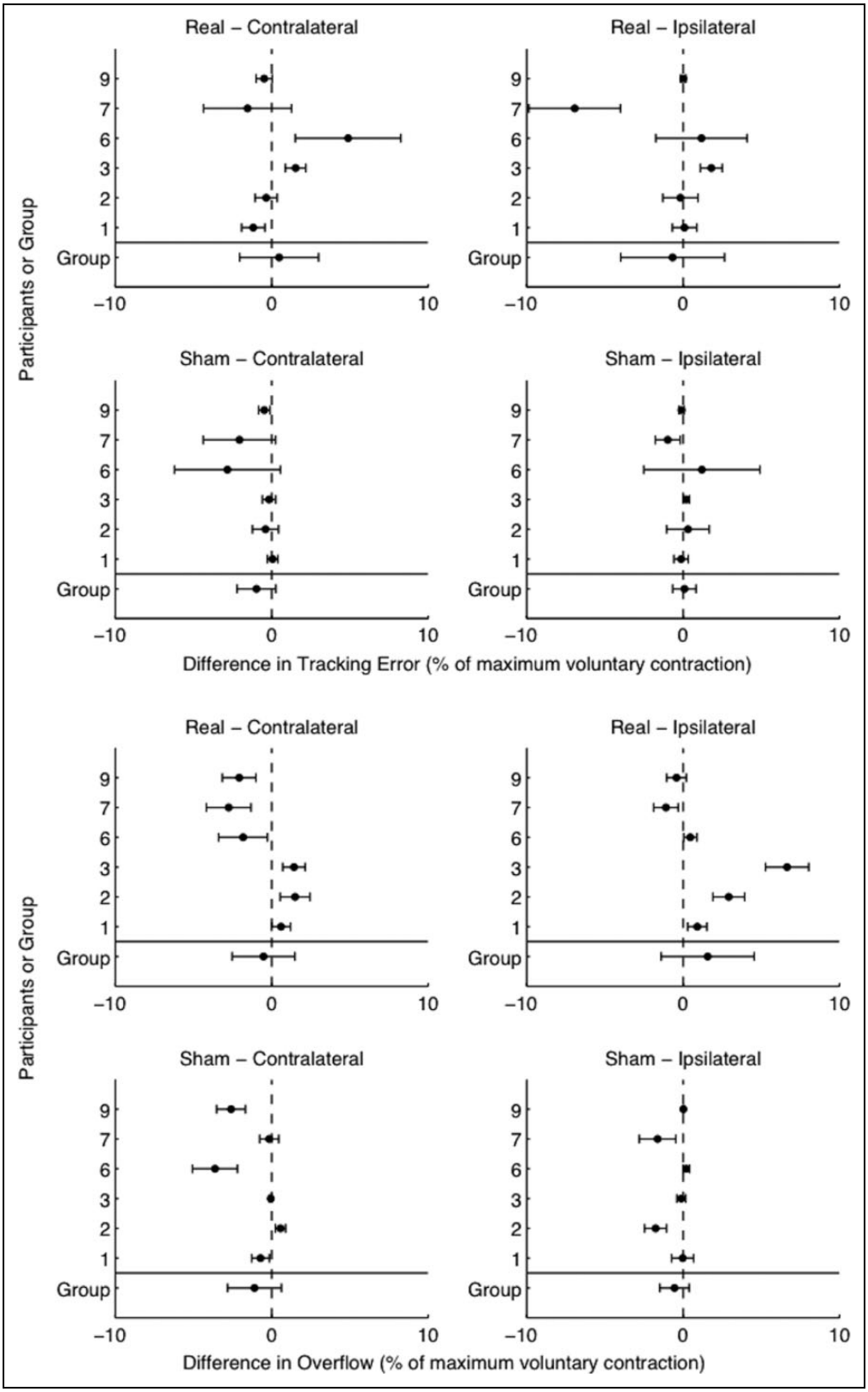

Figure 4. Experiment II anodal stimulation *step task*. Mean differences from prestimulation on day 1 to poststimulation on day 5, in tracking error (top 4 panels) and overflow (bottom 4 panels) for individuals and group. Participants are arranged vertically with the group average at the bottom. Panels are organized by task hand (contralateral in left column, ipsilateral in right column) and stimulation type (real stimulation in first and third rows, sham stimulation in second and fourth rows). Negative values, left of the dashed line, indicate improvement, that is, lower overflow or tracking error after 5 days of stimulation. Circles represent means, and horizontal lines represent 95% confidence intervals.

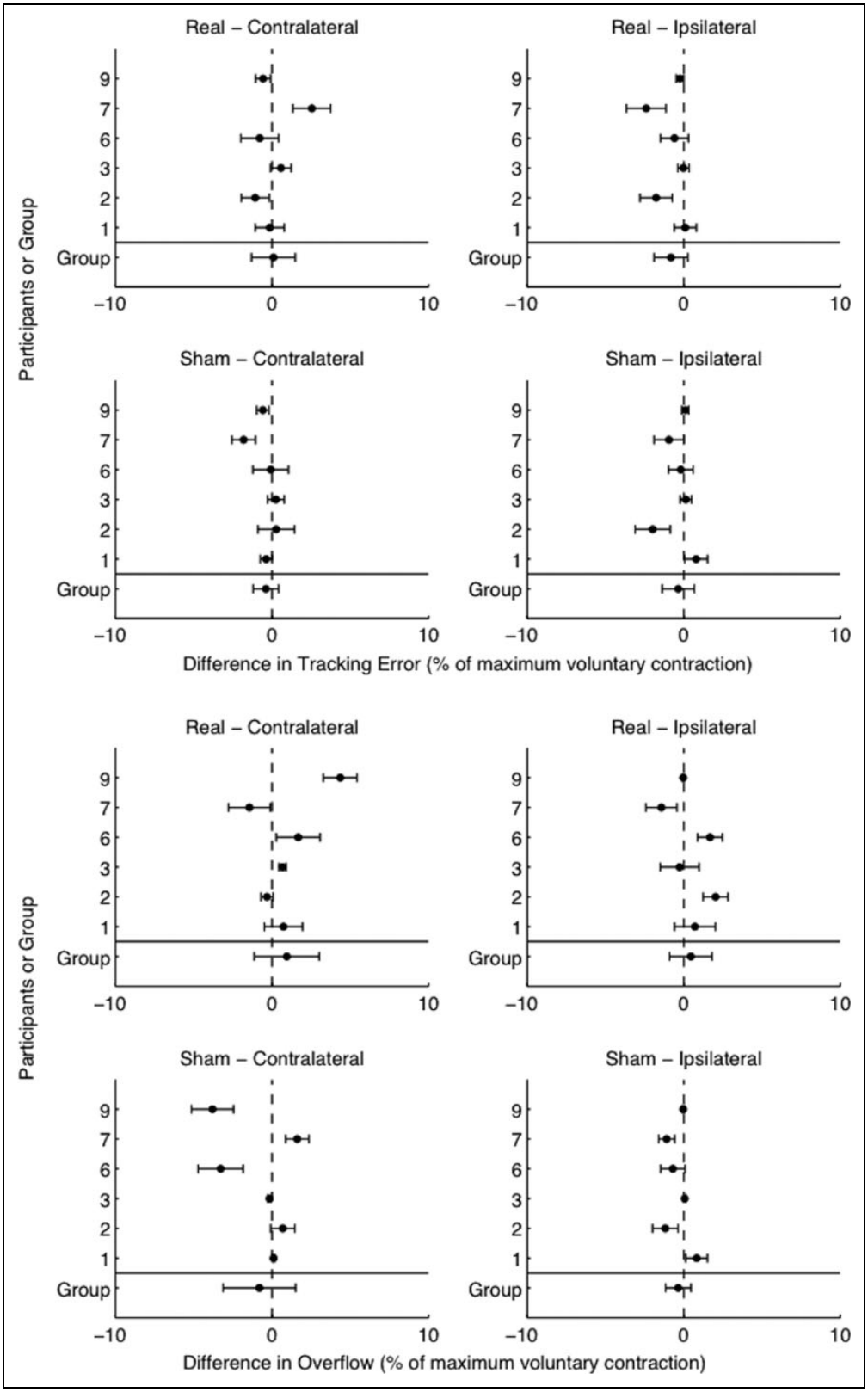

Figure 5. Experiment II anodal stimulation *continuous task*. Mean differences from prestimulation on day 1 to poststimulation on day 5, in tracking error (top 4 panels) and overflow (bottom 4 panels) for individuals and group. Participants are arranged vertically with the group average at the bottom. Panels are organized by task hand (contralateral in left column, ipsilateral in right column) and stimulation type (real stimulation in first and third rows, sham stimulation in second and fourth rows). Negative values, left of the dashed line, indicate improvement, that is, lower overflow or tracking error after 5 days of stimulation. Circles represent means, and horizontal lines represent 95% confidence intervals.

on a day-by-day basis (see Supplementary Material and Supplementary Figure 1). We found that these patients showed cumulative improvement over a span of 2 to 5 days. However, despite these cumulative effects, the overall change was only 1% to 2% maximum voluntary contraction for these patients. In addition, there were no changes to the Barry Albright Dystonia Scale from day 1 to day 5 for any of the patients tested. Lastly, we also reviewed their neurologic exam videos for subtle changes in dystonic symptoms beyond first dorsal interosseous and abductor digiti minimi control (see Supplementary Material and Supplementary Figure 2).

Anodal Individual Results

As with the cathodal condition, after correcting for multiple comparisons, we determined if individuals showed a significant difference due to anodal stimulation in any of the 4 performance measures. Based on the categories described above, no patients improved, 5 patients worsened (ie, patients 1, 2, 3, 6, and 9), and 1 was neutral (ie, patient 7). Although the differences were larger for anodal stimulation as compared to cathodal stimulation in terms of % maximum voluntary contraction, there were no clinically meaningful changes as measured by the Barry Albright Dystonia Scale.

Discussion

The results of this multiday, double-blind, sham-controlled study show that some children with dystonia show minor improvements in motor performance, while others worsen, when cathodal transcranial direct current stimulation is applied to the motor cortex. However, the changes were too small to be clinically relevant. These findings are similar to previous studies from our group for a single session of TDCS.[13,14] For those who benefited from cathodal transcranial direct current stimulation, the effect appeared to increase over the final 3 to 5 consecutive sessions. Interestingly, performance of almost all patients worsened with anodal transcranial direct current stimulation though, as with cathodal stimulation, the magnitude of effects were not clinically meaningful. Thus, this study agrees with previous findings that cathodal transcranial direct current stimulation can produce statistically significant yet minor benefits for some children with dystonia and also suggests that anodal transcranial direct current stimulation is not helpful and may make symptoms temporarily worse. The anodal results suggest that any potential benefits anodal transcranial direct current stimulation may have on increasing motor learning are probably overshadowed by exacerbation of overexcitability.

It is possible that the range of benefits due to cathodal transcranial direct current stimulation observed among the patient group could be due to the different etiologies of dystonia among our cohort. Our original intention was to identify a possible beneficial effect independent of etiology, but this does not seem to be the case. Importantly, because of limited availability, only 1 primary dystonia patient was included in this study, and for this patient there were no significant changes due to stimulation. However, it may be worthwhile to test more primary dystonia patients because transcranial direct current stimulation may disrupt abnormal oscillatory activity, which has been noted in neural recordings from these patients.[28,29] Future studies involving a larger population with a larger variety of etiologies may help to identify which patient characteristics predict beneficial outcomes. Although such studies may help in understanding the different physiology of various dystonias, those studies are unlikely to yield clinically meaningful benefits based on the results of this study.

Unlike the previous studies, which showed cathodal transcranial direct current stimulation improved overflow more than tracking error,[13,14] in this study we found that cathodal transcranial direct current stimulation could help either measure. Although there were no noticeable differences in the Barry-Albright Dystonia Scale, we identified subtle changes in arm or wrist control in at least 2 patients. As in previous studies,[13,14] the effect size was small. We cannot rule out the possibility that stimulation over longer spans (on the orders of months or years) may lead to larger effects, but given the small magnitude of effects seen over 5 days, we do not believe the time and resources needed to conduct this type of study are warranted.

One alteration between the present study and previous studies from our group,[13,14] is that the stimulation protocol was different. Although the total charge delivered was the same, in this study, the duration of stimulation was shortened and the amplitude of current was increased. This practical modification to the methods reduced the time burden of patients and their families, but it may have reduced the desired effect.

In contrast to deep brain stimulation, which can have profound benefits for childhood dystonia, especially in primary dystonia,[3,5,6] transcranial direct current stimulation over motor areas has only been shown to provide small[7] or isolated[30,31] changes or none at all.[32,33] There are many differences between the 2 methods, such as proximity to neural tissue and spatial selectivity of stimulation, and thus it is not surprising that outcomes differ. It has been suggested that dystonia results from pathologic oscillations in the pallidothalamocortical pathway and that deep brain stimulation normalizes such oscillations.[34] Perhaps transcranial alternating current stimulation, which can entrain neural oscillations,[4,35] will provide stronger effects than transcranial direct current stimulation. Another possibility to increase effectiveness is to combine cathodal transcranial direct current stimulation with pharmaceuticals that act on neurons in the basal ganglia, possibly amplifying effects on the pallidothalamocortical loop. Transcranial stimulation has obvious logistical advantages over deep brain stimulation: it does not require surgery and chronic implants, is far less expensive, and is easier to implement. It remains to be seen whether noninvasive neuromodulation in childhood dystonia can approach the clinical effects of invasive procedures.

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Author Contributions

NHB, MB, SJY, and TDS conceived and organized the study and designed the statistical analysis. NHB, MB, and SYJ executed the experiments. NHB and AAL executed the statistical analysis, which were reviewed by MB, SJY, and TDS. The first draft was written by NHB, which was reviewed by MB, SJY, AAL, and TDS.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental Material

The online [appendices/data supplements/etc] are available at http://jcn.sagepub.com/supplemental

Ethical Approval

The University of Southern California Institutional Review Board approved the study protocol (#UP-12-00490). All parents gave informed written consent for participation and authorization for use of protected health information. Children gave written assent when possible. The study was registered with clinicaltrials.gov (NCT01460771).

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