Transcranial Direct-Current Stimulation Can Enhance Motor Learning in Children

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Abstract

This study aims to determine the effects of transcranial direct-current stimulation (tDCS) on motor learning in healthy school-aged children. Safety, tolerability, and translation of effects to untrained tasks were also explored. We recruited 24 right-handed children for a randomized, sham-controlled, double-blinded trial to receive: right primary motor cortex (M1) 1 mA anodal (1A-tDCS), left M1 1 mA cathodal (1C-tDCS), left M1 2 mA cathodal tDCS (2C-tDCS), or sham tDCS over 3 consecutive days of motor task practice. Participants trained their left hand to perform the Purdue Pegboard Test (PPT) during tDCS application. Right hand and bimanual PPT, the Jebsen–Taylor Test (JTT), and the Serial Reaction Time Task (SRTT) were tested at baseline and post-training. All measures were retested 6 weeks later. Active tDCS montages enhanced motor learning compared with sham (all \( P < 0.002 \)). Effects were sustained at 6 weeks. Effect sizes were large and comparable across montages: contralateral 1A-tDCS (Cohen’s \( d = 2.58 \)) and ipsilateral 1C-tDCS (3.44) and 2C-tDCS (2.76). Performance in the untrained hand PPT, bilateral JTT, and SRTT often improved with tDCS. tDCS was well-tolerated and safe with no adverse events. These first principles will advance the pairing of tDCS with therapy to enhance rehabilitation for disabled children such as those with cerebral palsy.

Key words: motor cortex, motor learning, noninvasive brain stimulation, pediatrics, tDCS

Introduction

Transcranial direct-current stimulation (tDCS) is a form of non-invasive brain stimulation with potential for therapeutic neuro-modulation. Adult studies have demonstrated the ability of tDCS to alter cortical excitability (Nitsche and Paulus 2000) and the corresponding behavioral effects such as the enhancement of motor learning (Reis and Fritsch 2011). Application of “excitatory” anodal tDCS to the contralateral motor cortex enhances motor learning across single or multiple day training sessions (Reis et al. 2009; Prichard et al. 2014). Cathodal (“inhibitory”) tDCS applied to the motor cortex ipsilateral to the trained hand may also enhance learning, presumably by influencing interhemispheric motor network connectivity (Vines et al. 2006). Whether these primary principles of tDCS modulation of motor learning apply in the developing brains of children is unknown.

With relatively simple application and low cost, tDCS has permeated into many clinical fields, including stroke rehabilitation. Application of tDCS in post-stroke hemiparesis uses reorganization models to define cortical targets for modulation such as imbalanced motor cortex interhemispheric inhibition (IHI; Fregni and Pascual-Leone 2007; Kirton 2013), a marker of poor motor outcome (Murase et al. 2004). Application of perilesional motor cortex anodal or contralesional cathodal tDCS has been shown to improve motor function in chronic stroke patients (Fregni et al. 2005; Zimerman et al. 2012). Such clinical applications are desperately needed in the developing brain. Despite evidence of efficacy and safety in adults, tDCS experience in children has been limited. Cerebral palsy (CP) is the leading cause of lifelong neurological disability (Oskoui et al. 2013). Accordingly, much of the pediatric tDCS experience to date has focused on CP...
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populations. Recent trials suggest favorable tolerability and possible efficacy in gait training (Collange Grecco et al. 2015) and spasticity (Auvichayapat et al. 2013) in children with CP. Perinatal stroke causes most hemiparetic CP (Kirton and Devere 2013), and emerging models have defined therapeutic targets within the motor cortex that might be modulated to facilitate motor function (Kirton 2013). Two recent controlled trials have shown that repetitive transcranial magnetic stimulation can enhance motor learning therapy in hemiparetic children with perinatal stroke (Gillick, Kirton, et al. 2014; Kirton et al. 2015).

Excitement from these early results is tempered by acknowledgement that the primary principles of tDCS effects on motor learning in the developing brain have not been defined. The preclinical, neuroimaging, pharmacological, and neurophysiological studies beginning to elucidate the mechanisms of brain stimulation (Dayan et al. 2013) have not been completed in children. Current modeling studies of tDCS suggest that electric fields may be 2-fold stronger in children compared with adults (Kessler et al. 2013). Exceptions to the accepted “rules” of tDCS such as often described dichotomy of increased or decreased excitability with anodal and cathodal montages, respectively, are increasingly described in adults (Batsikadze et al. 2013; Monte-Silva et al. 2013) but unstudied in children. Neurophysiological studies suggest 1 mA cathodal currents in children may mimic adult anodal effects (Moliadze et al. 2015). Noninvasive brain stimulation approaches are further complicated by a large number of variables (including dose, duration, location, and type) resulting in innumerable permutations. These and other issues must be considered before the widespread application of tDCS to children with CP (Gillick, Krach, et al. 2014).

For all these reasons, it is essential that the first principles of tDCS effects on motor learning in children be carefully defined to efficiently, safely, and effectively advance applications in both experimental research and clinical therapeutics. We conducted a double-blinded, randomized, controlled application of 4 commonly described tDCS montages to determine safety, tolerability, and effects on motor learning in typically developing school-aged children.

Materials and Methods

Participants

Subjects were recruited through our population-based Healthy Infants and Children Clinical Research Program. Inclusion criteria were 1) typical neurodevelopment, 2) healthy (the absence of major medical condition), and 3) right handed (as considered by self and parent; the Edinburgh Handedness Inventory was applied at enrollment to ensure a laterality index >0). Those with any neuropsychological or developmental diagnoses or taking neuropsychiatric medications were excluded. All participants were screened and required to meet published safety criteria for noninvasive brain stimulation (Keel et al. 2001). Methods were approved by the Research Ethics Board of the University of Calgary. All participants gave written consent and, when applicable, assent.

Study Design

Participants were randomly assigned to one of 4 tDCS conditions by selecting an envelope with treatment group on Day 1. Treatment groups were 1) sham, 2) right (contralateral) hemisphere 1 mA anodal (1A-tDCS), 3) left (ipsilateral) hemisphere 1 mA cathodal (1C-tDCS), or 4) left hemisphere 2 mA cathodal tDCS (2C-tDCS). Each participant underwent the same testing, training, and stimulation procedures over 3 consecutive days (Fig. 1A).

Transcranial Direct-Current Stimulation

Direct current was delivered according to generally accepted practices in adults using a DC Stimulator (Neuroconn GmbH; Ilmenau, Germany). Two 25 cm² saline-soaked sponge electrodes were applied to the scalp and held in place by a commercially available light plastic “headband” system (Soterix Medical Inc., New York, USA). The active electrode was placed over the respective primary motor cortex while the reference electrode was placed over the contralateral hemisphere. Primary motor cortex location was determined using single-pulse transcranial magnetic stimulation (Magstim 200²; The Magstim Company Ltd; Whittington, UK) to localize the “hot spot” of the first dorsal interosseous muscle according to the standard criteria. If the hot spot could not be localized due to high resting motor thresholds in young children, the international 10–20 electroencephalography electrode system was used to localize the M1 (C3 and C4). In anodal and sham tDCS conditions, the anode was centred over the right M1 with the cathode over the contralateral supraorbital area (Fig. 1B). For cathodal tDCS conditions, the cathode was centred over the left M1 with the anode over the contralateral supraorbital area. These electrode montages target the trained (left) hand using contralateral anodal or ipsilateral cathodal M1 stimulation approaches as described in adult tDCS motor learning studies (Vines et al. 2006; Reis et al. 2009; Reis and Fritsch 2011).

With active stimulation conditions, the current was ramped up to the desired level (1 or 2 mA) over 45 s, held for 20 min, and then ramped down to 0 mA over 45 s. Sham conditions performed the same ramping of the current to 1 mA over 45 s but held it only for 60 s after which it was ramped down to 0 mA over 45 s. This procedure produces the same transient scalp sensations for all subjects and has been validated as an effective sham technique where subjects naïve to tDCS cannot predict their treatment group assignment (Ambrus et al. 2012). Resulting current densities were calculated and ranged from 0.04 to 0.08 mA/cm². Resistance was kept below 40 kΩ throughout the stimulation.

Motor Learning Measures

The primary outcome was the Purdue Pegboard Test (PPT). This validated and reliable measure of hand dexterity is described in detail elsewhere (Tiffin and Asher 1948). In summary, the test consists of 4 subtests: 1) left hand peg placement [PPTL], 2) right hand peg placement [PPTR], 3) bimanual peg placement [PPTLR], and 4) bimanual assembly [PPTA]. The PPTL, PPTR, and PPTLR are simple tasks in which participants have 30 s to place pegs into simple tasks in which participants have 30 s to place pegs into a pegboard using their left, right, or both hands, respectively. The total number of pegs (or pairs of pegs for the PPTLR) is scored. The PPTL, (nondominant hand) was used to monitor motor learning to increase task difficulty, producing a steeper learning curve, ensuring a skill “ceiling” was not reached. The PPTLR served as both a safety outcome (i.e., no decrease in function) and a measure of possible “spill-over” effects of training of the left hand. The PPTA, is a bimanual assembly task where participants build structures by placing a peg, washer, pin, and washer. The score corresponds to the number of pieces placed. Each subtest was repeated 3 times, and an average score was calculated. A composite sum of scores (PPT3) was also calculated for average PPTL + PPTR + PPTLR.

PPTL learning curves were generated by comparing the score difference at each training point to Day 1 baseline score. Skill decay was quantified by comparing the 6-week RT score to the post-training (Day 3) score. Online and offline learning effects were explored. Online (within-day training) effects were determined by comparing Day 1 baseline to Day 1 post-training performance, Day 2 baseline to Day 2 post-training performance,
etc. Offline (consolidation) effects were quantified by comparing Day 2 baseline with Day 1 post-training performance, and Day 3 baseline with Day 2 post-training performance. Day 1, 2, and 3 online effects were combined to generate a score change, and likewise Day 2-1 and Day 3-2 changes were combined. To quantify total learning within a day, we used a “sum total learning” analysis, where each training point on Day 1 is compared with Day 1 baseline performance; each training point on Day 2 is compared with Day 2 baseline performance, etc. This method of quantification accommodates both physical and mental fatigue associated with repetitive performance of a task.

Secondary motor outcomes were the Jebsen–Taylor Test of Hand Function (JTT) and the Serial Reaction Time Task (SRTT). The JTT is a unimanual test that examines performance in activities of daily living and is described in detail elsewhere (Jebsen et al. 1969). A score for each hand is obtained by recording the time to complete each JTT task, then taking the sum. Each subtest was performed with the trained left hand first (JTTL), followed by the right hand (JTTR). The writing and simulated feeding subtests were not included due to poor reproducibility in children (Elizabeth Reedman et al. 2015). The SRTT is commonly used to assess implicit motor learning (Honda et al. 1998). Participants are seated in front of a computer monitor and keyboard. Participants naturally place their left hand "A-S-D-F" (with the fifth digit on "A" and second digit on "F") and are presented with an on-screen target (green box), indicating which key should be pressed; target locations follow key location, where a target on the far left requires the key "A" to be pressed, a middle-left side target requires the key “S” to be pressed, and so on.

Eight blocks were performed, where each block was composed of 96 keystrokes. A 250 ms delay separated each keystroke from appearance of the subsequent target. Blocks 1 and 6 contained a real-time randomly generated string of targets, whereas the remaining blocks contained a repeating 12-character sequence. Repeating sequence patterns were S-F-A-D-F-A-S-D-S-A-F-D, D-S-F-A-S-F-D-A-S, and F-D-S-A-S-F-D-A-F-S for baseline, post-training, and RT, respectively. Reaction time and accuracy were recorded. Keystrokes quicker than 200 ms or slower than 1000 ms were excluded, as they do not represent a reaction-based response. Our SRTT was custom built using PsychoPy software (Peirce 2007).

Performance of motor outcomes was video recorded for offline analysis. Scoring was completed by multiple raters including those blinded to treatment allocation and not present during performance of the original measures. Quality assurance measures for accurate scoring were performed on the first 10 subjects. The primary outcome was recored from video by both the initial rater (>2 weeks later) and a blinded second rater. The participant’s head and body, excluding the hands, were cropped out for retroactive video scoring, ensuring the rater could not infer the stimulation type. The stimulation condition was not revealed to the participants until after they completed all sessions.

Training Protocol

On Day 1, participants performed all motor tests (above) to assess baseline skill (Fig. 1A). Participants first performed all subtests of
the PPT, followed by the JTT and SRTT. A rest break of 15 min then occurred.

Twenty minutes of tDCS was subsequently applied, during which the participant trained their left, nondominant, hand using the PPT (PPTL). Three trials were performed 5, 10, and 15 min into the stimulation period. After the stimulation period concluded, the PPTL was performed again. On Day 2, participants performed the PPTL to determine baseline ability for that day. As in Day 1, 20 min of tDCS was applied again, during which the PPTL was trained at 5-min intervals. Day 3, the final training day, followed the same protocol as in Day 2. After the final training block, participants took a 75 min break. All subtests of the PPT were then performed, followed by the JTT and the SRTT. Subjects returned to the same location 6 weeks later and performed the PPT, JTT, and SRTT again to examine retention of skill (RT).

Safety and Tolerability Questionnaire

Participants completed a modified pediatric brain stimulation safety and tolerability questionnaire (Garvey et al. 2001) immediately following tDCS on Days 1, 2, and 3. The duration and severity of symptoms were reported. Symptoms screened included: headaches, burning, itching, neck pain, unpleasant tingling, nausea, light-headedness, and any other self-reported symptoms. Participants also ranked the tolerability of the tDCS session compared with 7 common childhood experiences.

Statistical Analysis

Statistical analysis was performed using SigmaPlot 12.5 (Systat Software Inc.; San Jose, USA). Group demographics and baseline motor scores were compared using a 1-way ANOVA. A $\chi^2$ test examined gender distribution between groups. Paired t-tests described differences between baseline left- and right-hand motor scores. A 2-way repeated-measures (RM) ANOVA was performed for factors TRAINING BLOCK and STIMULATION GROUP to evaluate our primary outcome, change in PPTL score. Effect sizes were reported as a Cohen’s $d$. Skill decay between the final training block versus RT and online versus offline effects were quantified using paired t-tests. Daily sum learning curves were compared using a 2-way RM ANOVA for factors STIMULATION GROUP and DAY. Paired t-tests were used to assess change in PPT score compared with baseline. One-way RM ANOVA assessed changes in JTT within stimulation groups, and 2-way RM ANOVA assessed between group changes. SRTT curves were compared using a 2-way RM ANOVA for factors BLOCK and TIME POINT. Tolerability scores of $1 \text{mA}$ versus $2 \text{mA}$ versus sham tDCS were compared using a 1-way ANOVA. Holm–Sidak post-hoc analyses, which correct for multiple comparisons, were employed to identify differences between groups for ANOVAs. With the exception of tolerability, our analysis plan compared active stimulation conditions with sham tDCS, rather than focusing on differences between active stimulation conditions, which did not have a consistent stimulation target (contralateral vs. ipsilateral M1). Statistical significance was evident when $P < 0.05$.

Sample size calculations suggested that 5 subjects per stimulation group would be 95% powered to detect a 2-fold greater improvement in PPTL at the end of training, with a type-1 error of 0.05. Our power calculations were based on a pilot study completed in young adults receiving right M1 1A-tDCS or sham tDCS over 3 consecutive days of PPTL training. Pilot testing was completed prior to this study.

Results

Population Characteristics

Twenty-four children were recruited and completed all stages with no drop-outs and all outcomes collected. Subject demographics and baseline motor function across treatment groups are shown in Table 1. Age, gender, self-reported laterality index, and baseline PPT, JTT, and SRTT scores did not differ between intervention groups (all $P > 0.31$). For all groups, PPTL scores were higher than PPTL scores (all $P < 0.03$; group $P < 0.001$). There were no differences in JTT versus JTTL stimulation group scores (all $P > 0.20$).

Motor Learning

Motor learning curves by treatment group are shown in Figure 2. All participants displayed motor learning over the training days, regardless of stimulation condition [$F_{14} = 28.78$, $P < 0.001$]. Significant differences were seen between stimulation groups [$F_{4} = 11.36$, $P < 0.001$]. Participants receiving active tDCS conditions displayed greater improvements in PPTL scores compared with those receiving sham tDCS. Those receiving 2C-tDCS displayed the largest improvements in PPTL scores compared with sham ($P < 0.001$); by Day 3, the 2C-tDCS group improved their score 2.5-fold more than sham (4.5 ± 1.1 vs 1.8 ± 0.7 pegs). 1C-tDCS ($P < 0.001$) and 1A-tDCS groups ($P = 0.002$) demonstrated similar gains in PPTL scores compared with the sham tDCS group.

Table 1 Participant information

<table>
<thead>
<tr>
<th>Stimulation Group</th>
<th>Age (years)</th>
<th>Laterality index</th>
<th>Gender, F:M</th>
<th>Baseline PPT scores</th>
<th>Baseline JTT scores</th>
<th>Baseline reaction time (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Left hand</td>
<td>Right hand</td>
<td>Left versus right</td>
</tr>
<tr>
<td>Sham</td>
<td>13.4 (±4.0)</td>
<td>74.1 (±12.8)</td>
<td>3:3</td>
<td>14.4 (±1.8)</td>
<td>15.9 (±2.3)</td>
<td>$P = 0.01$</td>
</tr>
<tr>
<td>1A-tDCS</td>
<td>13.2 (±3.1)</td>
<td>65.8 (±27.3)</td>
<td>3:3</td>
<td>13.4 (±1.5)</td>
<td>14.8 (±2.3)</td>
<td>$P = 0.03$</td>
</tr>
<tr>
<td>1C-tDCS</td>
<td>14.4 (±4.1)</td>
<td>83.3 (±13.3)</td>
<td>1:5</td>
<td>13.8 (±2.7)</td>
<td>15.5 (±2.7)</td>
<td>$P = 0.01$</td>
</tr>
<tr>
<td>2C-tDCS</td>
<td>15.1 (±1.7)</td>
<td>80.0 (±12.7)</td>
<td>3:3</td>
<td>13.7 (±1.1)</td>
<td>16.0 (±1.5)</td>
<td>$P = 0.01$</td>
</tr>
<tr>
<td>Mean</td>
<td>14.0 (±3.2)</td>
<td>75.8 (±17.0)</td>
<td>10:14</td>
<td>13.8 (±1.8)</td>
<td>15.6 (±2.1)</td>
<td>$P = 0.001$</td>
</tr>
<tr>
<td>Between group</td>
<td>$P = 0.72$</td>
<td>$P = 0.36$</td>
<td>$P = 0.56$</td>
<td>$P = 0.82$</td>
<td>$P = 0.80$</td>
<td>—</td>
</tr>
</tbody>
</table>

Note: Demographics and baseline Purdue Pegboard Test (PPT) scores, Jebsen–Taylor Test of Hand Function (JTT) scores, and reaction time. Data are given as group mean (± standard deviation).
There were no significant differences between active stimulation groups (all $P > 0.67$). Effect sizes were large for all active tDCS groups at the end of the 3rd day of training: 1A-tDCS (Cohen’s $d = 2.58$), 1C-tDCS (3.44), and 2C-tDCS (2.76). Improvements in rate of learning were evident early in actively stimulated groups. For example, participants receiving 2C-tDCS displayed improve rate of learning were evident early in actively stimulated groups. $P = 0.032$, $P < 0.01$, and $P = 0.003$). Participants in the active stimulation groups did not have significantly smaller online gains than those receiving sham tDCS ($P = 0.215$). In addition to large online improvements, participants in the 1A-tDCS and 1C-tDCS group also have significantly lower offline learning compared with online motor learning ($P = 0.012$, respectively). The 2C-tDCS group showed no significant difference between online and offline effects ($P = 0.156$). Offline effects appeared modest and did not differ between treatment groups.

Participants in the sham and 1A-tDCS condition showed no difference in sum total learning between days (Fig. 4A; $P = 0.190$), suggesting a constant change in skill. Both 1C- and 2C-tDCS conditions were associated with large tDCS improvements with significantly higher learning in Day 1 compared with Days 2 and 3 (all $P < 0.015$). No significant differences were seen between Days 2 and 3 sum total learning, suggesting constant training effects between the 2 days. Sum total learning was quantified by combined sum daily learning from each day (Fig. 4B). Participants in the 1A-tDCS ($P = 0.003$) and 1C-tDCS groups ($P = 0.016$) showed significant higher sum learning compared with sham.

**Untrained PPT Tasks**

Effects of treatment group on the untrained and bilateral hand functions are summarized in Figure 5. At both the end of training (Day 3) and RT, all groups showed no difference in PPTL versus PPTLR scores (all $P > 0.44$) in contrast to the laterality observed at baseline. However, PPTLR scores did improve across the active treatment groups (all $P < 0.025$). PPTL training alone did not improve Day 3 PPTLR scores in controls (Fig. 5B; $P = 0.63$). Increases in PPTLR scores correlated with PPTL improvements ($r = 0.518$, $P = 0.009$). Participants in the active stimulation groups did not demonstrate any decay in PPTLR scores at 6 weeks.

Post-training PPTLR (bimanual) scores correlated with change in PPTL ($r = 0.466$, $P = 0.022$). PPTL training alone did not improve PPTLR scores in controls (Fig. 5C; $P = 0.419$). 1A-tDCS ($P = 0.013$) and 2C-tDCS ($P = 0.031$) improved PPTLR scores with trending improvements in the 1C-tDCS group ($P = 0.063$). Participants showed no evidence of skill decay by 6 weeks. The 1C-tDCS group had significantly improved PPTLR scores at 6 weeks ($P = 0.021$). All participants improved their PPTL score with training, regardless of stimulation (Fig. 5D; all $P < 0.01$). Active stimulation groups had larger improvements compared with controls: 1A-tDCS ($P = 0.003$), 1C-tDCS ($P = 0.026$), and 2C-tDCS ($P = 0.026$). There was no skill decay at 6 weeks. All participants showed improvements in PPTLR scores (Fig. 5E; all $P < 0.027$) with no differences between stimulation groups. There was no skill decay at 6 weeks, and the 2C-tDCS showed significant improvement.

**JTT**

Training effects on JTT performance are summarized in Figure 6. While sham conditions produced modest changes in JTTL score at post-training ($P = 0.039$), significance was lost by 6 weeks RT.
Both 1C and 2C-tDCS groups displayed improvements in JTT\textsubscript{T} score (both \(P < 0.043\)) that were stable or continued to improve at RT. The 1A-tDCS group displayed the largest improvements in JTT\textsubscript{T} following training (\(P = 0.002\)) and at RT (\(P < 0.001\)). Effects in the untrained hand were also observed, as JTT\textsubscript{T} scores improved with PPT\textsubscript{T} training in the 1A- and 1C-tDCS groups (all \(P < 0.003\)) but not sham (\(P = 0.286\)) or 2 mA cathodal tDCS (\(P = 0.116\)).

There was no evidence of skill decay at 6 weeks. Between-group analysis revealed a significant reduction in JTT\textsubscript{T} and JTT\textsubscript{X} scores of the 1A-tDCS group compared with sham tDCS controls, both at post-training and at 6-week retention testing (all \(P < 0.028\)). Although 1C- and 2C-tDCS groups displayed within-group reductions in bimanual JTT scores, there were no significant differences between the sham condition (all \(P > 0.268\)).

SRTT

Baseline reaction time showed a strong negative correlation with age (\(r = -0.845\); \(P < 0.000001\)). To correct for age effects, reaction time of each block was standardized to Block 1 reaction time, eliminating the correlation (\(r = 0.289\); \(P = 0.170\)). Grouped baseline SRTT followed a standard pattern, where a 15% decrease in reaction time was seen by Block 5 (Fig. 7A). The introduction of a random sequence (Block 6) slowed reaction time, such that it was not significantly different from Block 1. Reaction time decreased with reintroduction of the sequence (Block 7).

Training alone (sham) did not shift SRTT curves towards decreased reaction time [Fig. 7B; \(t_{(2)} = 2.06; P = 0.128\)]. However, by 6 weeks, there was a significant decrease in reaction time [\(t_{(2)} = 4.02; P = 0.007\)]. Similarly, participants receiving 1A-tDCS showed downwards shifts in SRTT curves that were significant at 6 weeks (\(t = 4.31; P = 0.008\)) and almost significant at Day 3 post-training [\(t_{(2)} = 2.70; P = 0.090\)]. Significant SRTT shifts between all test intervals were seen with 1C-tDCS. Steady decreases in reaction time were seen between baseline and post-training [\(t_{(2)} = 2.78; P = 0.039\)], with further decreases between post-training and RT [\(t_{(2)} = 2.54; P = 0.030\)], resulting in large differences between baseline and RT [\(t_{(2)} = 5.31; P = 0.001\)]. Similarly, 2C-tDCS was associated with significant downward shifts in SRTT curves between baseline and post-training [\(t_{(2)} = 2.95; P = 0.029\)], with continued decrease at 6 weeks [\(t_{(2)} = 2.41; P = 0.037\)]. No changes were seen in error rates between stimulation groups or time points.

Inter-Rater Assessment Correlation

Motor outcome scores were highly correlated between raters (PPT, \(r = 0.99\); JTT, \(r = 0.98\)), and mean scores were not different between raters.

Safety and Tolerability

A total of 72 tDCS sessions were performed without complications. There were no serious adverse events. The most commonly reported sensation was itching under the site of the anode (44%). The proportion did not differ between treatment groups. Younger children (< 11 years) were more likely to rank the intensity of sensation as moderate or severe, rather than mild (33 vs 14%). Additional sensations included: mild burning (7%) or unpleasant tingling (6%) under the site of the electrode. Headache was reported in 1 session of sham tDCS. In all sham tDCS sessions, any sensations faded within 5 min of stimulation. Sensations reported with active tDCS persisted for the duration of the stimulation in 40% of anodal and 77% of cathodal tDCS sessions, with no difference between stimulation intensities. Regardless of sensation, participants were unable to correctly predict whether they received sham, 1 mA or 2 mA stimulation (39% accuracy). Overall the tolerability ranking of tDCS was 3.9 (±1.0) on an 8-point scale, comparable to watching TV (2.9 ± 1.6) or a long car ride (4.9 ± 1.4). There were no significant differences between the tolerability of sham, 1 mA or 2 mA tDCS (\(P = 0.19\)).

Discussion

We demonstrate the ability of tDCS to enhance motor learning in children. While all montages produced lasting effects with large effect sizes, distinct patterns of skill acquisition were observed. Extension of effects to untrained tasks including the opposite hand, bimanual tasks, and different elements of learning suggests broad effects on motor learning systems. Our evidence of efficacy combined with favorable safety and tolerability should...
facilitate the advance of tDCS research and clinical applications in the developing brain.

Enhanced motor learning with tDCS is well described in adults. Single sessions appear to produce improvements in motor skill (Boggio et al. 2006; Vines et al. 2008) but may be less applicable to rehabilitation interventions that typically involve multiple days of training. Studies examining tDCS effects over multiple days of training have demonstrated robust effects of the same tDCS conditions employed here (Reis et al. 2009; Schambra et al. 2011; Frichard et al. 2014). Training alone (sham tDCS) resulted in clear learning but with a slower rate of early learning and suggestion of a ceiling effect whereby further improvements were limited. tDCS appeared to change both these early and late elements of the learning curve, facilitating increased skill acquisition. Sum daily learning suggested that tDCS shifts learning curves including larger gains early in training. Similar findings are described in adult motor learning studies (Reis et al. 2009; Frichard et al. 2014).

Stimulating the trained hemisphere with anodal tDCS or the untrained hemisphere with cathodal tDCS both enhanced learning with sustained improvements in skill. Adult evidence suggests that while motor learning occurs mainly online, anodal tDCS may enhance learning via offline consolidation effects (Reis et al. 2009). In contrast, we found that tDCS-associated skill improvements were primarily through online effects. Interestingly, 2 mA cathodal tDCS produced the greatest improvements

Figure 5. Change in Purdue Pegboard Test (PPT) scores at post-training (white bars) and 6-week retention test (RT), compared with baseline for sham (white triangles), 1A-tDCS (light gray circles), 1C-tDCS (light gray squares), and 2C-tDCS (dark gray squares) groups. Each point represents the mean change in score from baseline, based on 3 repetitions of the subtest. Subscripts L, R, LR, S, and A refer to the PPT subtests left hand (A), right hand (B), both left and right hands (C), sum of scores (D), and assembly (E), respectively. Active stimulation groups demonstrate immediate improvements in untrained unimanual and bimanual tasks. No differences were seen in complex bimanual tasks. There was no evidence of skill decay at RT. Data show group mean (± standard error). *P < 0.05, **P < 0.01, ***P < 0.001.

Figure 6. Change in left- and right-hand Jebsen–Taylor Test of Hand Function (JTTL, JTTR) scores at post-training (white squares) and RT (white triangles) from baseline (white circles) for sham (white bars), 1A-tDCS (lightest gray bars), 1C-tDCS (gray bars), and 2C-tDCS (dark gray bars). Active stimulation groups, but not sham, display improved performance at post-training, with no evidence of skill decay at RT. Data show group mean (± standard error). *P < 0.05, **P < 0.01.
in motor skill; however, online effects were relatively attenuated compared with offline effects, suggesting stronger cathodal currents may affect different elements of motor learning. Whether these differences in the timing of learning are attributed to differences in the tasks employed by each study, stage of brain development, or additional factors remains to be determined.

Motor skill enhancement was not restricted to the trained task or the trained hand. Active stimulation groups increased their right-hand PPT scores, whereas training alone (sham) did not. Both cathodal conditions (left hemisphere) improved right-hand scores compared with sham. Adult studies suggest that cathodal approaches improved untrained JTT and SRTT scores to a similar degree (Hummel et al. 2009). These findings suggest over- and ipsilateral cathodal approaches improved untrained JTT and SRTT scores to a similar degree (Hummel et al. 2009). Our choice of motor tasks was strategic but constrained by the practical nature of the trial, particularly in young children where maintaining attention and participation was essential. Adult studies have shown that anodal tDCS improves JTT and SRTT performance (Nitsche et al. 2003; Hummel et al. 2009; Stagg, Bachtiar, et al. 2011; Convento et al. 2014), while some suggest cathodal tDCS may actually worsen performance (Stagg, Bachtiar, et al. 2011; Convento et al. 2014). We found that both anodal and ipsilateral cathodal approaches improved untrained JTT and SRTT scores to a similar degree (Hummel et al. 2009). These findings suggest over-all motor function improvements, rather than proficiency limited to a trained task. PPT training alone did not improve JTT or SRTT scores, suggesting stimulation-specific effects on broader motor network components. That effects were unchanged at 6 weeks despite no additional training suggests the possibility that tDCS is facilitating lasting alterations in synaptic function.

Anodal tDCS likely modulates cortical excitability to a state of increased excitation (Nitsche and Paulus 2001). This polarized state increases neuronal firing rates (Bindman et al. 1964) and promotes spontaneous and strengthened neuronal activity between stimulated and distal locations (Bindman et al. 1962). This long-term potentiation (LTP)-like modulation parallels motor learning processes and suggests that tDCS paired with training may improve synaptic efficacy with lasting changes in cortical networks (Fritsch et al. 2010). Recent evidence has further described the role of GABA in motor learning (Stagg, Jayaram et al. 2011). The GABAergic system modulates LTP-like plasticity in M1 where reductions in GABA are necessary for LTP to occur (Hess et al. 1996). Magnetic resonance spectroscopy studies have demonstrated that the degree of M1 GABA reduction during anodal tDCS correlates with the degree of motor learning (Stagg, Jayaram et al. 2011). Therefore, it is conceivable that our anodal tDCS results involve changes in contralateral M1 GABA, a hypothesis that might now be tested in children. Mechanisms of cathodal tDCS are less investigated and even adult behavioral...
studies remain mixed in their results (Nitsche et al. 2003; Stagg, Bachtai et al. 2011). Here we demonstrate, for the first time, enhancement of motor learning with ipsilateral cathodal tDCS. Bi-hemispheric tDCS (anode contralateral and cathode ipsilateral) may improve motor skill in adults with corresponding changes in IHI (Williams et al. 2010) but is unstudied in children. Elucidating the mechanisms of such effects with neuropharmacological, neuroimaging (e.g., structural and functional connectivity, spectroscopy), and neurophysiological (e.g., TMS, EEG) studies is a promising direction for future research.

The safety of tDCS has been established in adults, with >20 000 sessions performed, but data are limited in paediatric populations. The safety of tDCS is limited to currently applied tDCS protocols in a controlled research and clinical setting, and does not encompass increasing do-it-yourself tDCS protocols. A recent review assessed the safety of tDCS and transcranial alternating current stimulation in children and adolescents based on 16 studies (Krishnan et al. 2015). Since then, an additional 10 studies have been published. Overall, tDCS appears to be well tolerated with only mild tingling and itching reported in 11.5 and 5.8%, respectively. These rates appear lower than in adults (Kessler et al. 2012), although this may be attributed to incomplete safety reporting in children where it was rarely a primary outcome. We propose employing safety and tolerability questionnaires after each session to advance pediatric safety profiles. Our safety measures revealed that itching was most common with rates comparable to adult reports (Kessler et al. 2012). Whereas children and adolescents are typically grouped, we analyzed these populations separately, finding that children were more likely to describe itching as moderate to severe. To accommodate sensation severity in children, adjusting saline concentration may be necessary and does improve tolerability (Dundas et al. 2007). Although described as lasting only 1–2 min in adults, we found that sensations with active tDCS often lasted the duration of the stimulation. Lasting sensations were more likely to be reported with cathodal tDCS, likely related to the position of the active electrode over the supraorbital region (Ambrus et al. 2012). Sham stimulation sensations faded quickly. Despite differences in sensation duration, participants were unable to distinguish sham from active tDCS, suggesting participant blinding is achievable in tDCS but perhaps only in naïve subjects.

In conclusion, tDCS of either motor cortex can enhance motor learning with sustained and diverse effects on motor performance and favorable tolerability in school-aged children. tDCS promises to be an increasingly important tool in the study and treatment of neurological disorders in children.

Supplementary Material
Supplementary material can be found at http://www.cercor.oxfordjournals.org/online.

Funding
This work was supported by The Heart and Stroke Foundation of Canada and The Alberta Children’s Hospital Foundation. Funding for P.C. was provided by Alberta Innovates - Health Solutions.

Notes
We acknowledge Dr Katie Chaput (Alberta Children’s Hospital Research Institute, University of Calgary) for her support in developing and optimizing our statistical analysis. Conflict of interest: None declared.

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