



Research Paper

The Effect of a Single Session of Transcranial Direct Current Stimulation on Attention in Pediatric Acquired Brain Injury: Characterizing Interindividual Structural and Functional Network Response Variability

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ABSTRACT

Background: Approximately one in four children who sustain an acquired brain injury (ABI) have attention difficulties impacting education, employment, and community participation. These difficulties arise from dysfunction in attention-related brain networks, incentivizing the use of transcranial direct current stimulation (tDCS). We investigated whether a single tDCS session improved attention following childhood ABI and whether baseline structural connectivity (sc), functional connectivity (fc), attention, and/or simulated electric fields (E-fields) explained variability in response.

Methods: In a randomized, single-blind, within-subject, sham-controlled trial, 15 children with ABI (mean 12.7 years) and 15 healthy controls (HCs) received three single tDCS sessions (1 mA dorsolateral prefrontal cortex [dlPFC], 1 mA inferior frontal gyrus [IFG], sham; 20 min) during gamified attention training. We examined postintervention changes in attention according to flanker and stop signal reaction time (RT). We used multimodal analyses (high-density electroencephalography [HD-EEG], diffusion tensor imaging, magnetic resonance imaging) to investigate interindividual variability in tDCS response, according to associations between RT change and baseline fc, sc, attention, and E-fields. **Results:** Although no effect of active versus sham tDCS was found overall, participants with lower theta or higher gamma default mode network connectivity and poorer attention at baseline showed greater response to tDCS. Higher E-fields were associated with greater response. No serious adverse effects occurred.

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Data statement: The data that support the findings of this study are available on request from the corresponding author, A.S. The data are not publicly available due to the sensitive nature of clinical data.

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Conclusions: A single tDCS session targeting dlPFC or IFG did not improve attention following pediatric ABI. We demonstrated how HD-EEG source-based connectivity may be used to personalize tDCS. Future research should explore whether personalization and/or repeated tDCS sessions can improve attention following pediatric ABI.

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Introduction

Acquired brain injury (ABI), defined as any injury occurring to the brain since birth, is a leading cause of death and lifelong disability in children.^{1,2} ABI can have lifelong neurological, psychological, and cognitive sequelae, which impair learning and development in childhood and adolescence, affecting later educational attainment, career opportunities, and community participation.³ One of the most commonly reported cognitive problems following ABI is attention deficit, and in particular, inhibitory control,^{4–6} where up to 20% of children are diagnosed with attention-deficit/hyperactivity disorder (ADHD) after traumatic brain injury (TBI)⁷ and up to 46% following childhood stroke.⁸ As a component of attention, inhibitory control relates to the ability to engage in an appropriate attentional focus while suppressing a more dominant, but less appropriate, focus.⁹ Disruptions to prefrontal attention networks such as the executive control network (ECN) and salience network (SN) are thought to underpin attention deficits following ABI.^{10,11}

Although stimulant medications are the mainstay treatments for attention problems, patient compliance is often poor due to side effects, concerns about misuse,¹² and stigmatization.¹³ Therefore, nonpharmacologic methods to improve attention following ABI are attractive alternatives. Transcranial direct current stimulation (tDCS) has been demonstrated to improve attention in adult ABI¹⁴ by transiently modulating cortical activity in regions with abnormal activity.^{15–18} Two main tDCS targets have been previously studied: the left dorsolateral prefrontal cortex (ldlPFC), an important hub of the ECN^{19–21} and a postulated key player in executive dysfunction following ABI,^{22,23} and the right inferior frontal gyrus (rIFG), a key hub in the SN^{14,21,24–32} that is thought to underpin problems with impulsivity and inhibition in children.^{33–36} However, as key developmental changes occur in these networks during adolescence, the optimal target for tDCS in a childhood ABI population is unknown.

Interindividual variability in tDCS response is a challenge.³⁷ This is especially true following ABI due to the heterogeneous nature of injury and the resultant brain network changes. Brain connectivity changes have been traditionally measured using magnetic resonance imaging (MRI)^{23,38,39} but more recently with high-density electroencephalography (HD-EEG),^{40–42} which has the advantage of being more child friendly, cost effective, and portable, facilitating use at the point of care.^{43–45} Furthermore, injury-related differences in tDCS-induced cortical electric field (E-field) can occur due to secondary gliosis, leukomalacia, and/or cortical atrophy, leading to differences in response.^{46–48} This has been seen in adults with ABI where greater SN structural integrity was associated with a greater response to tDCS,²⁴ indicating the importance of accounting for brain connectivity when assessing tDCS effects.

In this study, we investigated the use of tDCS targeting the dlPFC or IFG during gamified training to improve attentional inhibition in children with ABI. To address the challenge of interindividual variability in tDCS response, we also investigated the association of structural connectivity (sc), functional connectivity (fc), baseline attention, and simulated cortical E-fields with tDCS

response. We hypothesized that tDCS would be feasible and tolerable and that active tDCS (targeting dlPFC or IFG) would result in greater attention improvements compared with sham tDCS. Finally, we hypothesized that tDCS-related attention improvement would be the greatest in those with greater sc and fc in attention networks, greater baseline attention, and higher simulated E-field in the prefrontal regions.

Methods

Our study investigated whether a single session of 1-mA tDCS during attention training significantly improved attention when applied over the bilateral dlPFC or bilateral IFG in children and adolescents in the chronic stage of ABI and similar healthy controls (HCs). This preregistered, randomized, sham-controlled trial was conducted at the University of Queensland Child Health Research Centre (Brisbane, Australia) between November 2021 and December 2022 (OSF registration: osf.io/b43nh). Fifteen participants with ABI between ages seven and 18 years (inclusive) and 15 HCs participated in the study. Three single sessions of tDCS were given (ldlPFC anode/right dlPFC cathode, rIFG anode/left IFG cathode, or sham), separated by > 48 hours (Fig 1). Baseline assessments included HD-EEG, MRI (optional), and clinical/neurocognitive assessments. Change in flanker reaction time (RT) or stop signal reaction time (SSRT) was used to measure changes in attention following tDCS.^{49–51} Any short-acting ADHD medication was temporarily discontinued 48 hours before the study. The study was conducted in accordance with Good Clinical Practice, and ethical approval was provided by the University of Queensland and Queensland Children's Hospital (HREC/21/QCHQ/73034). All participants gave written assent, and a parent/guardian gave written consent for participation in the study.

Inclusion and exclusion criteria

Participants were eligible if they were aged between seven and 18 years (inclusive), and participants with ABI were >3 months post-injury (mild TBI) or >1 year post injury (moderate-severe TBI). ABI was defined as any injury to the brain occurring after birth.¹ Exclusion criteria included contraindications to tDCS, hypoxic-ischemic encephalopathy, significant past medical or psychiatric history before injury, recent or planned change in neuroactive drugs, pre-existing neurological disorders including moderate to severe learning difficulties, or presence of a condition that in the opinion of the investigator would compromise the safety of the patient or quality of the data. See [Supplementary Methods](#) for definition of ABI and more details about these exclusion criteria.

Sample size, randomization, and blinding

Based on previous work in adult ABI,¹⁴ a sample size of 13 participants per group would allow detection of a moderate effect (Cohen $d = 0.69$) using EEG changes. To compare group differences in flanker RT or SSRT, a Bayesian stopping rule was set at $BF_{10} > 3$. Maximum group sample size was set at $n = 15$. The session order

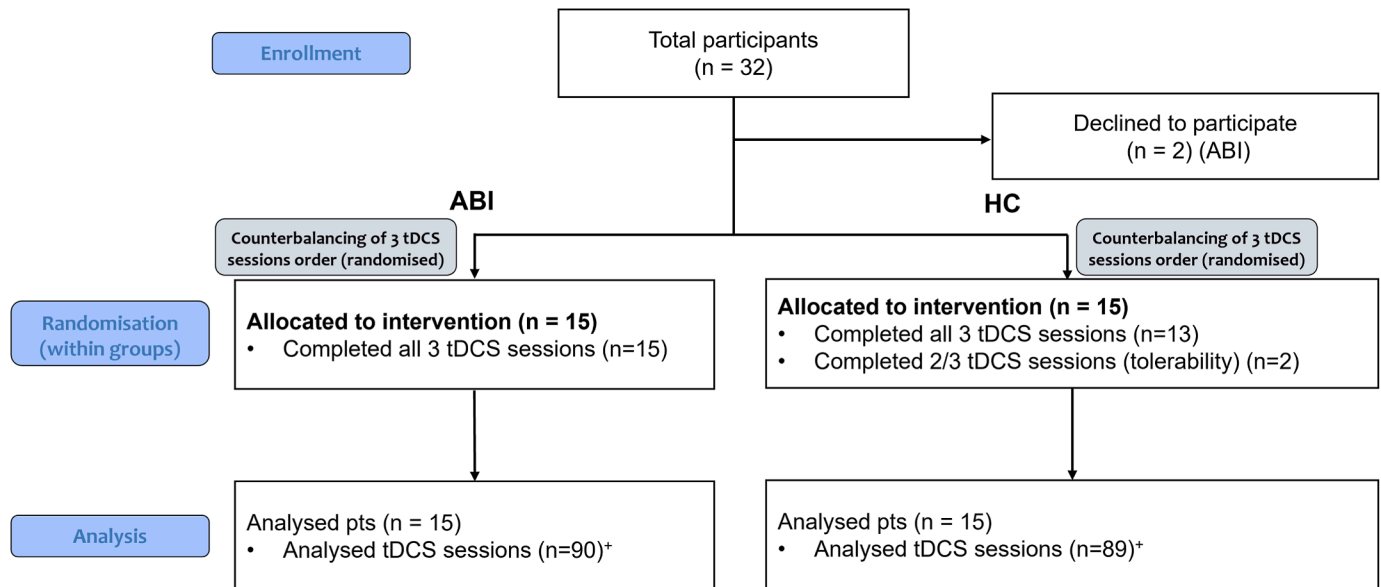


FIGURE 1. CONSORT flow diagram. CONSORT, Consolidated Standards of Reporting Trials; tDCS, transcranial direct current stimulation *Of a total of 90 tDCS sessions.

was counterbalanced using computer-generated block randomization sequences (block size 6). Participants and families only were blinded to the intervention.

Outcome measures

The primary outcome was change in flanker⁵² RT using the NIH toolbox (iPad).⁵³ This three-minute task consists of 24 congruent and incongruent trials. The flanker task has strong validity and test-retest reliability in pediatric TBI populations.⁵⁴ Change in RT was also assessed using a gamified Stop Signal Task (the “Fairy Game”⁵⁵) consisting of 200 trials (148 Go and 52 Stop trials) across two six-minute blocks with a 15-second break. This game has demonstrated validity compared with the traditional stop signal task,⁵⁶ has been used in children with ADHD,⁵⁶ and is sensitive to change with dlPFC tDCS⁵⁷ (see [Supplementary Methods](#) for further details). Safety and tolerability were assessed immediately following each session using the Sensations/Adverse Effects Questionnaire ([Supplementary Figure 1](#)).

Intervention

Each participant received three single sessions of tDCS (two active, one sham) separated >48 hours using a counterbalanced, within-subjects design. Using the 10-20 EEG system,¹⁸ the anodal stimulation site was F3 (ldlPFC) or F8 (rlFG). The cathode was placed contralaterally on F4 (right dlPFC) or F7 (left IFG), respectively. The ldlPFC was chosen as a target for executive control of attention^{19,21} and rlFG as a target for inhibitory control.^{30,36} For the sham condition, participants were equally randomized to a sham ldlPFC or sham rlFG montage. Active stimulation was delivered for 20 minutes at 1 mA using 25 cm² saline-soaked sponge electrodes (NeuroConn DC Stimulator Mobile, Ilmenau, Germany), with a calculated current density of 0.04 mA/cm² per electrode. Ramp-up and ramp-down time was 30 seconds. Sham stimulation involved 30 seconds of ramp-up followed by an immediate 30-second ramp-down.⁵⁸ During stimulation, participants completed gamified attention training (16 minutes, Go/No-Go task: “Wormy Fruit,” and continuous performance task: “SnappyApp”; see [Supplementary Methods](#)).⁵⁹

Baseline assessments

Cognitive function was assessed using a computerized neuropsychologic assessment (CNS Vital Signs), which has demonstrated validity in this population.⁶⁰ The Behavior Rating Inventory for Executive Functioning (BRIEF2 Parent Report, Second Edition) was used to assess executive functioning and the likelihood of ADHD.

Structural and anatomical MRI

MRI acquisition

Structural MRI was acquired using a 3T Siemens Prisma scanner with a 64-channel head coil at the Herston Imaging Research Facility (HIRF; Brisbane, Australia). MRI was used to assess anatomy (T1, T2) and sc (diffusion tensor imaging) and to perform E-field modeling in the participants with ABI.

Electric field modeling

Individual head models (n = 12) were created for participants with ABI from T1 and T2 scans (n = 9) or T1 scans only (n = 3) using the headreco segmentation and meshing pipeline (Copenhagen, Denmark)^{61,62} in MATLAB (R2021a, Massachusetts: The MathWorks, Inc). Following segmentation, head models were converted to SimNIBS 4.0.0 where E-field models were created for each montage.⁶³ The ldlPFC/right dlPFC montage was modeled according to F3-anode/F4-cathode (10-20 EEG), and the rlFG/left IFG montage was modeled according to F8-anode/F7-cathode (electrode size: 5 × 5cm; 4 mm thickness). Electrode y-axis pointed toward FC3 and FC4 for F3 and F4 electrodes, respectively. Current intensity was 1 mA/−1 mA for anode and cathode, and default conductivity was utilized.

Mean E-field magnitude (E_{norm}, V/m) was calculated in a 10-mm spherical radius region of interest (ROI) with a gray matter mask centered at the cortical projection underneath the anodal and cathodal electrodes at the following Montreal Neurological Institute (MNI) locations: F3 (−35.5, 49.4, 32.4), F4 (40.2, 47.6, 32.1), F7 (−54.8, 33.9, −3.5), and F8 (56.6, 30.8, −4.1).^{63–65} Sham E-field was calculated by dividing the calculated E-field for each participant by 20 due to the linear relationship between active and sham tDCS. The E-field distribution map was visualized using gmsh.⁶⁶

Tractography

Details about diffusion tensor imaging preprocessing and model fitting are given in the [Supplementary Methods](#). Tracts of interest underlying the SN and default mode network (DMN) were used to examine associations between sc and RT change following tDCS²⁴ including the frontal aslant tract (FAT)^{67–69} and the cingulum bundle⁷⁰ ([Supplementary Figure 2](#)). Mean fixel density and fractional anisotropy were extracted from all tracts of interest for subsequent correlation with tDCS response.

Functional connectivity

HD-EEG acquisition

HD-EEG was used to assess fc at baseline using a 128-channel cap (Geodesic EGI Hydrocel GSN 130), during five minutes of resting eyes open (EO) while watching “Inscapes”⁷¹ and five minutes of resting eyes closed (EC), sampled at 250 Hz using Net Station (Version 5.4.2, Philips Electrical Geodesics, Eugene, OR, USA). Impedance was kept below 100 k Ω .

Source-based connectivity model

The HD-EEG preprocessing pipeline is outlined in [Fig 2](#) and [Supplementary Methods](#). The Brainstorm toolbox (Version February 2023)⁷² was used for source-based connectivity analysis. Where available, T1 MRI scans were used for subject anatomy (n = 12 participants with ABI). Alternatively, National Institutes of

Health Pediatric Data Repository age-specific asymmetric T1 templates were used (n = 15 HCs and n = 3 participants with ABI).⁷³ CAT12⁷⁴ was used for T1 segmentation, and EEG channel files were registered onto MRI-based head models. Boundary element model⁷⁵ surfaces were generated using default Brainstorm settings to define conductor models in forward model computation. Diagonal noise covariance was computed (default identity matrix), and head models were created (15,002 vertices, adjoint formulation). Forward model source reconstruction was conducted using dynamical statistical parametric mapping⁷⁶ with single kernel.

Functional connectivity

To analyze connectivity, the cortex was parcellated according to the Desikan-Killiany Atlas,⁷⁷ and the source-reconstructed time series was computed across 68 cortical regions. Orthogonalized envelope correlation was used to measure brain connectivity across frequency bands (Hilbert time-frequency transformation; delta = 1–3.99 Hz, theta = 4–7.99 Hz, alpha = 8–12.99 Hz, beta = 13–30 Hz, gamma = 30.01–40 Hz, and broadband = 1–40 Hz; static time resolution; sliding window length = 1500 ms with 50% overlap).⁷⁸ Significant group differences in subnetwork connectivity were identified using network-based statistics.⁷⁹ ROI-based analyses were also conducted within the DMN, SN, and ECN (see [Supplementary Methods](#)).

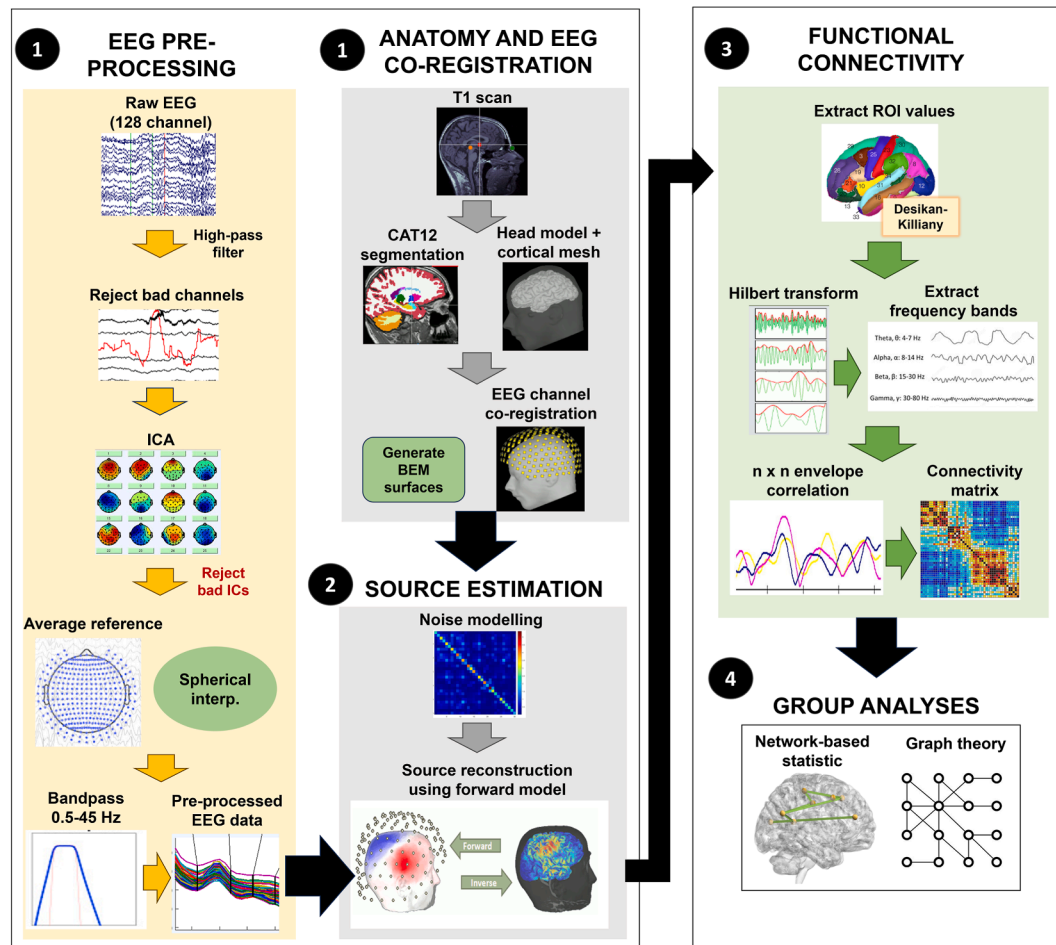


FIGURE 2. HD-EEG preprocessing and functional connectivity analysis pipeline. HD-EEG, high-density electroencephalography; ICA, independent components analysis; IC, independent components; CAT, computational anatomy toolbox; BEM, boundary element method; ROI, region of interest.

Statistical analysis

Statistical analysis and visualization were performed using MATLAB Version 9.12 (R2022a, The MathWorks Inc, Natick, MA, USA), RStudio (Version 2023.9.1.494, PBC, Boston, MA, USA), Just Another Statistics Program (JASP; Version 0.16.2.0 for Windows), GraphPad Prism Version 9.0.0 (GraphPad Software, Boston, MA, USA), and Statistical Package for the Social Sciences (SPSS; IBM, Armonk, NY, USA). Flanker trials were excluded if RT < 100 ms or the response was incorrect.⁸⁰ SSRT was calculated using the Verbruggen method.⁸¹ Trials were excluded if the accuracy rate was <80%, if RT on unsuccessful Stop trials was longer than RT on Go trials (race model violation), or if probability of responding on a stop signal was <0.25 or >0.75.^{82,83} Non-normal RT data were not transformed as per Lo and Andrews, 2015.⁸⁴ Posthoc analysis of outliers was conducted using the extreme studentized deviate (Grubbs) test.⁸⁵

The primary outcome (post-tDCS flanker RT) was assessed in each group (ABI, HC) using a series of linear mixed models, controlling for pre-tDCS flanker RT and intervention arm (dIPFC, IFG, sham) as fixed effects and participant ID as a random effect. A between-group model was also performed with a fixed effect of group. Posthoc session order was added as a fixed effect. A random intercept model was used with sham condition as the reference category. Details of the statistical models are given in [Supplementary Equations 1 and 2](#). As a secondary outcome, change in SSRT across interventions was compared using repeated-measures analysis of variance in each group separately with time as a repeated factor and a between factor of intervention. Finally, group differences were assessed by adding group as a between-subjects factor.

To test for significant differences in baseline fc between groups, we performed groupwise contrasts including with age as a covariate. Network-based statistics tests were conducted with 5000 permutations at $P = 0.05$. Comparisons were made across delta, theta, alpha, beta, gamma, and broadband frequencies in EC and EO conditions at a t statistic threshold of 3.1 or 3.8 (expected medium effect size between 0.5 and 0.6). For network ROIs (ECN, SN, DMN), independent two-sample t tests were conducted (two-tailed, $P < 0.05$) to investigate differences in connectivity in each ROI between groups. Correlation analysis was used to examine the association between baseline attention performance and baseline fc. Similarly, we also examined associations between baseline attention performance and baseline sc (FA, FD).

Potential factors affecting tDCS response

In a series of exploratory analyses, we examined the effect of ABI-related anatomic variation on outcome. Correlations were used to examine the association between RT change following dIPFC or IFG tDCS and baseline fc ($n = 15$ ABI, $n = 15$ HC), sc ($n = 10$ ABI), attention ($n = 15$ ABI, $n = 15$ HC), and magnitude of simulated anodal E-field ($n = 12$ ABI). The association between E-field and microstructural injury (FA, FD) was also examined. As a posthoc analysis, we assessed the effect of age on the factors listed above. Multiple comparison correction was not performed due to the exploratory nature of the analyses.⁸⁶

Results

Participants

Demographic and clinical details of participants are reported in [Table](#). Mild TBI was the commonest cause of injury (TBI $n = 13$, stroke $n = 1$, meningitis $n = 1$). Baseline cognitive function did not significantly differ between groups. Behavioral attention was

significantly poorer in the ABI group (see [Table](#)). Baseline flanker RT was not significantly different between groups ($t = -0.83$, $P = 0.41$; see [Supplementary Table 1](#) for values across tDCS arms). As expected, baseline flanker RT correlated with age in both the ABI ($r = -0.86$, $P < 0.001$) and HC groups ($r = -0.72$, $P = 0.002$), where older participants had faster RT.

RT change following intervention

One session (HC) was incomplete (less than half of the session completed) and excluded. A total of 89 sessions (of 90) were included in the analysis. There was no effect of intervention on postintervention flanker RT in either group (ABI: $F = 0.40$, $P = 0.67$; HC: $F = 0.55$, $P = 0.58$; [Fig 3](#), [Supplementary Tables 2–4](#)). Less RT change was seen in participants with ABI with faster baseline RT ($F = 25.11$, $df = 1064.3$, $P < 0.001$; [Supplementary Table 3](#)). Post-intervention flanker RT did not significantly differ between groups (ABI versus HC) across interventions, after controlling for baseline flanker RT ($F = 0.66$, $P = 0.42$). There was no significant effect of tDCS condition on SSRT ([Supplementary Table 5](#), [Supplementary Figure 3](#)). Slower baseline flanker RT was correlated with greater flanker RT change (i.e., better RT) in the dIPFC tDCS condition only. Baseline flanker RT was not associated with flanker RT change in the IFG or sham tDCS conditions ([Supplementary Figure 5](#)).

Baseline connectivity and attention

Significant between-group differences were identified in several subnetworks across spectral bands (delta, theta, alpha, beta, gamma, broadband) and are demonstrated in [Fig 4](#). In the EO condition, participants with ABI showed significantly increased delta connectivity in an insula-centric subnetwork connecting to parietal DMN nodes and another subnetwork involving the superior frontal, inferior frontal, transverse temporal, posterior cingulate, and fusiform regions ($t = 3.1$, Network 1: $p_{FWE} = 0.013$, Network 2: $p_{FWE} = 0.012$; [Fig 4A, B](#)). In participants with ABI only, this was associated with higher (i.e., slower) baseline flanker RT (Spearman $\rho = 0.60$, $P = 0.02$; [Fig 4C](#)). Participants with ABI also had increased theta connectivity in the EO condition in a frontoparietal subnetwork compared with HCs ($t = 3.1$, $p_{FWE} = 0.016$; [Fig 4D, E](#)). In the EC condition, participants with ABI had significantly decreased alpha connectivity in a subnetwork of nodes across frontoparietal DMN regions (age corrected, $t = 3.8$, $p_{FWE} = 0.003$; [Fig 4F, G](#)) and significantly increased gamma in another frontoparietal DMN-like subnetwork (age corrected, $t = 3.1$, $p_{FWE} = 0.009$; [Fig 4H, I](#)) compared with HCs. Significant nodes in each network are listed in [Supplementary Table 6](#). There were no significant group differences in ROI connectivity (ECN, DMN, or SN) or power spectra in delta, theta, alpha, beta, gamma, or broadband and no associations between connectivity and baseline SSRT. Greater sc (increased FA of the right FAT) was associated with faster baseline flanker RT in participants with ABI (see [Supplementary Figure 4](#)).

Factors affecting tDCS response in children with ABI

Functional connectivity

Both with and without a consistent outlier that was finally removed from analysis, greater (faster) flanker RT change following IFG tDCS was associated with lower theta (slow wave) fc in DMN (ROI analysis) and greater (faster) SSRT change following dIPFC tDCS was associated with higher gamma fc in DMN ([Fig 5](#)). There were no other significant associations, and ROI fc was not associated with age.

TABLE.
Baseline Demographic, Neurocognitive, Behavioral, and Quality-of-Life Measures

Measure	HC	ABI	Test Statistic	P Value
Age (y), mean (S.D., 95% CI)	11.41 (2.87, 9.82-13.00)	12.68 (3.33, 10.84-14.53)	$t = -1.12$	0.27
Sex, n males (%)	9 (60.00)	11 (73.3)	$\chi^2 = 0.60$	0.70
Handedness, n right (%)	12 (80.00)	14 (93.33)	$\chi^2 = 1.15$	0.27
Time postinjury (y), mean (S.D., range)	NA	3.81 (2.74, range 1-9 y)	NA	NA
Injury severity			NA	NA
Mild	NA	10		
Moderate	NA	2		
Severe	NA	3		
CNSVS NCI, mean (95% CI)	96.73 (91.22, 102.25)	91.00 (83.38, 98.63)	$t = 1.31$	0.20
CNSVS RT, mean (95% CI)	94.80 (83.62, 105.98)	93.47 (86.27, 100.66)	$t = 0.22$	0.83
CNSVS Simple Attention, mean (95% CI)	83.00 (68.50, 97.50)	64.33 (40.13, 88.54)	$t = 1.42$	0.17
CNSVS Complex Attention, mean (95% CI)	94.27 (88.65, 99.88)	77.73 (59.98, 95.48)	$t = 1.91$	0.07
BRIEF2 BRI, mean (95% CI)	47.47 (44.19, 50.74)	64.93 (57.52, 72.34)	$t = -4.62$	<0.001
BRIEF2 Inhibit, mean (95% CI)	48.13 (44.20, 52.07)	62.93 (55.53, 70.34)	$t = -3.79$	0.001
BRIEF2 Shift, mean (95% CI)	47.80 (43.63, 51.97)	73.00 (64.92, 81.08)	$t = -5.95$	<0.001

Abbreviations:
ABI = Acquired brain injury
BRI = Behaviour Regulation Index
BRIEF2 = Behavior Rating Inventory for Executive Functioning
CI = Confidence interval
CNSVS = CNS Vital Signs
HC = Healthy control
NA = Not applicable
NCI = Neurocognitive Index
RT = Reaction time
Significant at $P < 0.05$ are indicated in bold.

E-field and structural connectivity

Mean normalized E-field in the anodal target regions were 0.211 (S.D., 0.05) V/m in the dlPFC, 0.209 (S.D., 0.07) V/m in the rIFG, and 0.011 (S.D., 0.01) V/m in the sham condition (Fig 6). E-field was not correlated with age in either the dlPFC ($r = -0.56$, $P = 0.06$) or IFG ($r = 0.13$, $P = 0.69$) conditions.

Participants with higher E-field at the dlPFC showed faster flanker RT following the dlPFC tDCS intervention ($\rho = -0.60$, $P = 0.04$; Supplementary Figure 6). No other significant associations were found between E-field and flanker RT change following the IFG tDCS or sham conditions or between E-field and SSRT change.

Baseline sc (FA or FD) was not associated with flanker RT or SSRT change in any ROI across interventions. Right-hemisphere FA and FD in both the FAT and cingulum bundle were positively associated with age. E-fields were not associated with sc.

Tolerability and blinding

Most participant sessions ($n = 88$) were tolerated well, and only minor adverse effects were reported. No differences in tolerability were seen between groups (Fig 7). Two HC participants (eight and nine years old) were unable to tolerate one session each (IFG and sham) due to itching and discomfort. Both participants, however, successfully completed the remaining tDCS sessions. The most common sensation was mild itching and did not differ between groups ($\chi^2 = 1.4$, $P = 0.75$). Reports of mild pain during tDCS did not differ between groups (ABI, 4%; HC, 7%; $t = 2.04$, $P = 0.49$). One participant with ABI retrospectively reported the pain as strong, yet the participant was not distressed during the session and wished to complete the session (Fig 7C). Blinding was successful as the majority of participants incorrectly guessed that they received sham, and there were no significant

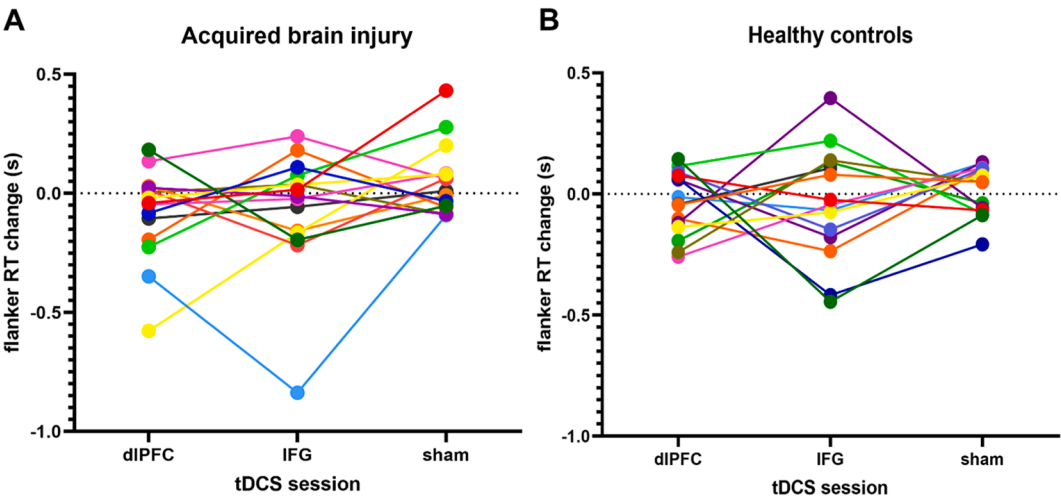


FIGURE 3. Mean flanker RT change across tDCS arm (dlPFC, IFG, sham) in ABI and HC groups. Colors represent within-subject data. RT, reaction time; tDCS, transcranial direct current stimulation; dlPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; ABI, acquired brain injury; HC, healthy control.

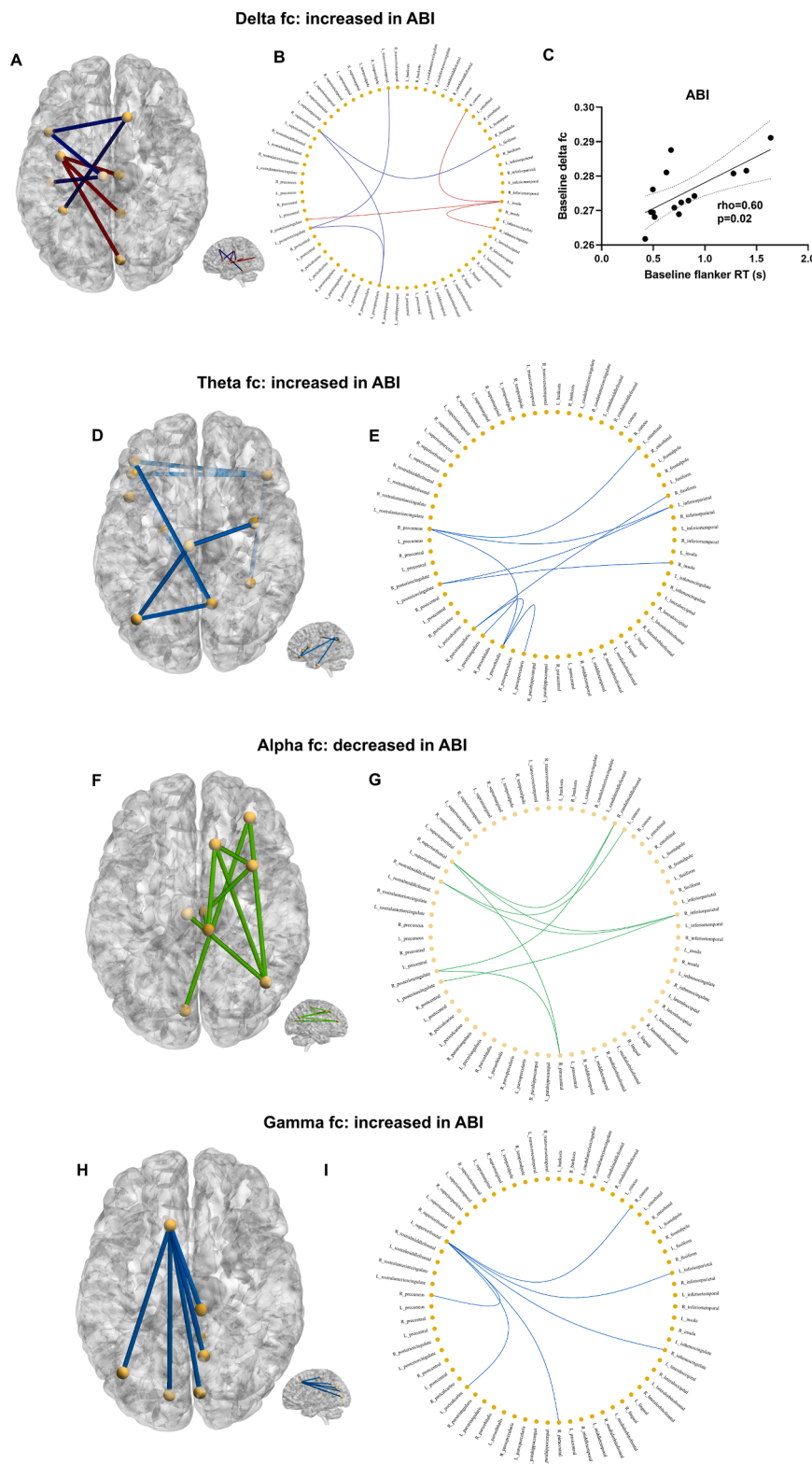


FIGURE 4. NBS subnetworks showing significant differences in connectivity in participants with ABI compared with HCs at baseline and associations with baseline flanker RT. Increased resting EO delta connectivity in participants with ABI displayed as (A) nodes and edges on brain template or (B) in a circular graph. (C) Increased delta connectivity associated with slower flanker RT at baseline in participants with ABI. Increased resting EO theta connectivity in participants with ABI displayed as (D) nodes and edges on brain template or (E) in a circular graph. Decreased resting EC alpha connectivity in participants with ABI displayed as (F) nodes and edges on brain template or (G) in a circular graph. Increased resting EC gamma connectivity in participants with ABI displayed as (H) nodes and edges on brain template or (I) in a circular graph. No significant associations between connectivity and attention in theta, alpha, beta, gamma, or broadband subnetworks. NBS t tests used to determine significant subnetworks. All networks corrected for age. $t = 3.1$ in delta, theta, and gamma, and $t = 3.8$ in alpha network. Edge colors represent separate significant subnetworks. Displayed using BrainNet Viewer and NeuroMarvl. NBS, network-based statistics; RT, reaction time; ABI, acquired brain injury; HC, healthy controls; EO, eyes open; EC, eyes closed.

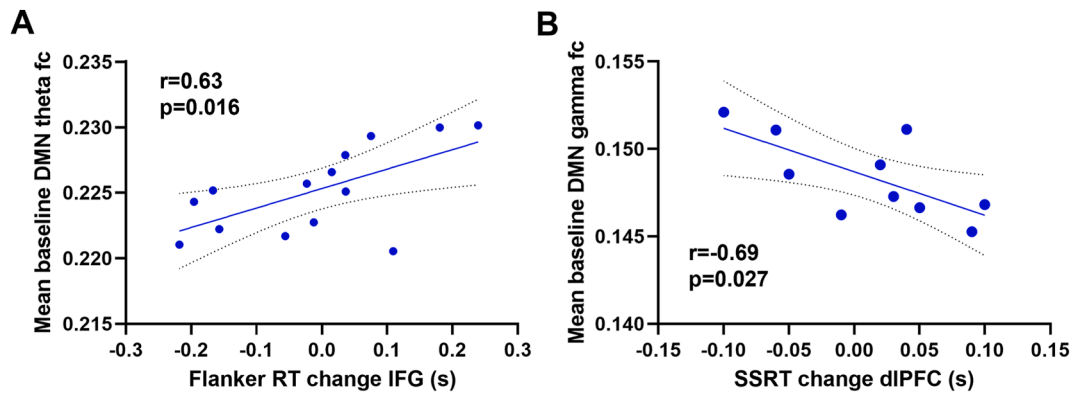


FIGURE 5. Significant correlations between mean baseline functional connectivity using HD-EEG (resting EC) and mean RT change following tDCS in participants with ABI after excluding persistent outlying participant. (A) Lower baseline theta DMN connectivity was associated with faster flanker RT following IFG tDCS. (B) Higher baseline gamma DMN connectivity was associated with faster SSRT following dIPFC tDCS. Pearson correlations and 95% confidence intervals displayed. tDCS, transcranial direct current stimulation; RT, reaction time; SSRT, stop signal reaction time; DMN, default mode network; dIPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; ABI, acquired brain injury; EC, eyes closed; HD-EEG, high-density electroencephalography.

differences in correct sham guess between groups ($\chi^2 = 0.59$, $P = 0.70$) (Fig 7D).

Discussion

Attention problems following childhood ABI cause lifelong disruptions in functioning and quality of life.^{1–3} Pharmacological therapies are effective but are associated with significant side effects.^{12,13} In this study, we investigated the efficacy and feasibility of tDCS during attention training as a potential alternative to treat attention problems in children with acquired brain injury. We evaluated two common stimulation sites for attention (dIPFC and IFG, as hubs for the ECN and SN, respectively) given the potential for differences in attention network organization across childhood development to influence tDCS response.⁸⁷ We also addressed the challenge of interindividual variability in response in this heterogeneous population through a multimodal analysis investigating whether fc, sc, baseline attention, or simulated E-fields were associated with response to the tDCS intervention. Overall, we found that 1 mA was tolerable in children with ABI. A single session of tDCS during gamified attention training did not

significantly improve attention measured using flanker or SSRTs when compared with sham tDCS, in either participants with ABI or HC participants. However, we found several sources of interindividual variability that may have affected tDCS response.

Although children with ABI in our study had attention-related disruptions in functional brain connectivity, there was no effect of a single tDCS session on attention when delivered to the dIPFC or IFG. The lack of a robust effect of a single tDCS session has been reported previously, albeit in other populations.^{26,88–98} Our small sample size may well have influenced our ability to demonstrate any effect.⁹⁹ More recently, the utility of multiple tDCS sessions to facilitate the neuroplastic changes required for a robust response to tDCS has been reported in healthy populations, in adults with ABI, and in children and adults with ADHD.^{14,25,100–104} When applied repeatedly (i.e., over the course of a day or several days), the effects of tDCS are cumulative.^{103,104} Our null results could also have reflected suboptimal brain targeting in a childhood population as attention networks shift from a rostral to caudal distribution, mirroring the shift from dependence on lower-level sensory areas to complex association areas.^{87,105–107} It is also important to consider that variability in tDCS response may have occurred due

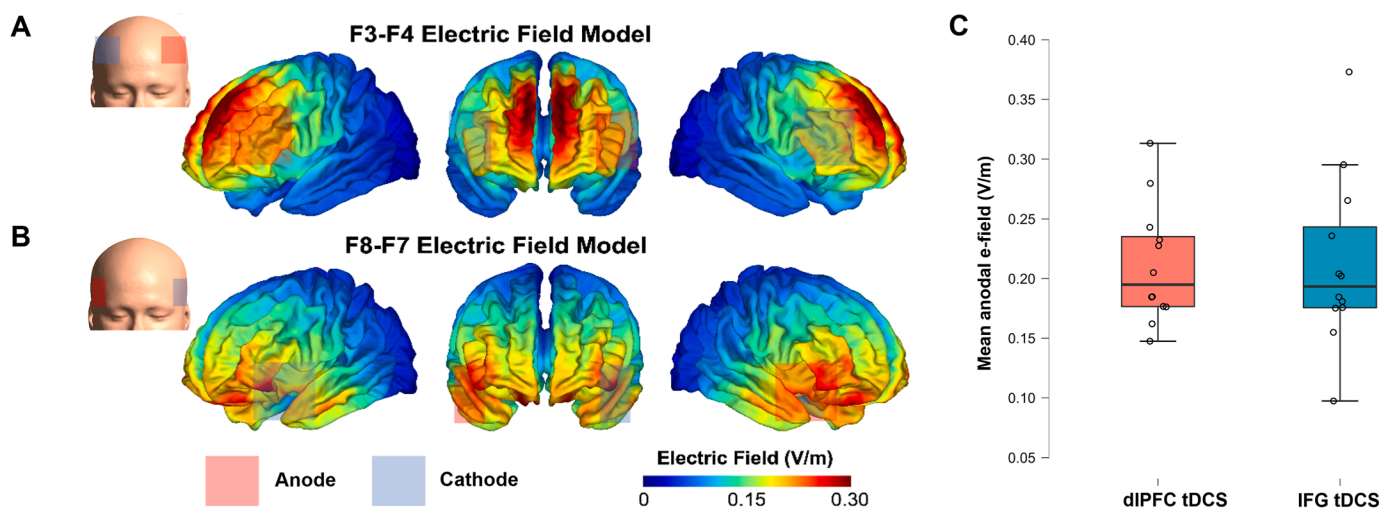


FIGURE 6. Mean normalized electric field across participants with ABI in active tDCS sessions. (A) Visual representation of tDCS montage in dIPFC (F3/F4) and (B) IFG arms (F8/F7). (C) Mean normalized electric field across participants in dIPFC and IFG tDCS ($n = 12$). dIPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; tDCS, transcranial direct current stimulation; E-field, electric field; RT, reaction time; ABI, acquired brain injury.

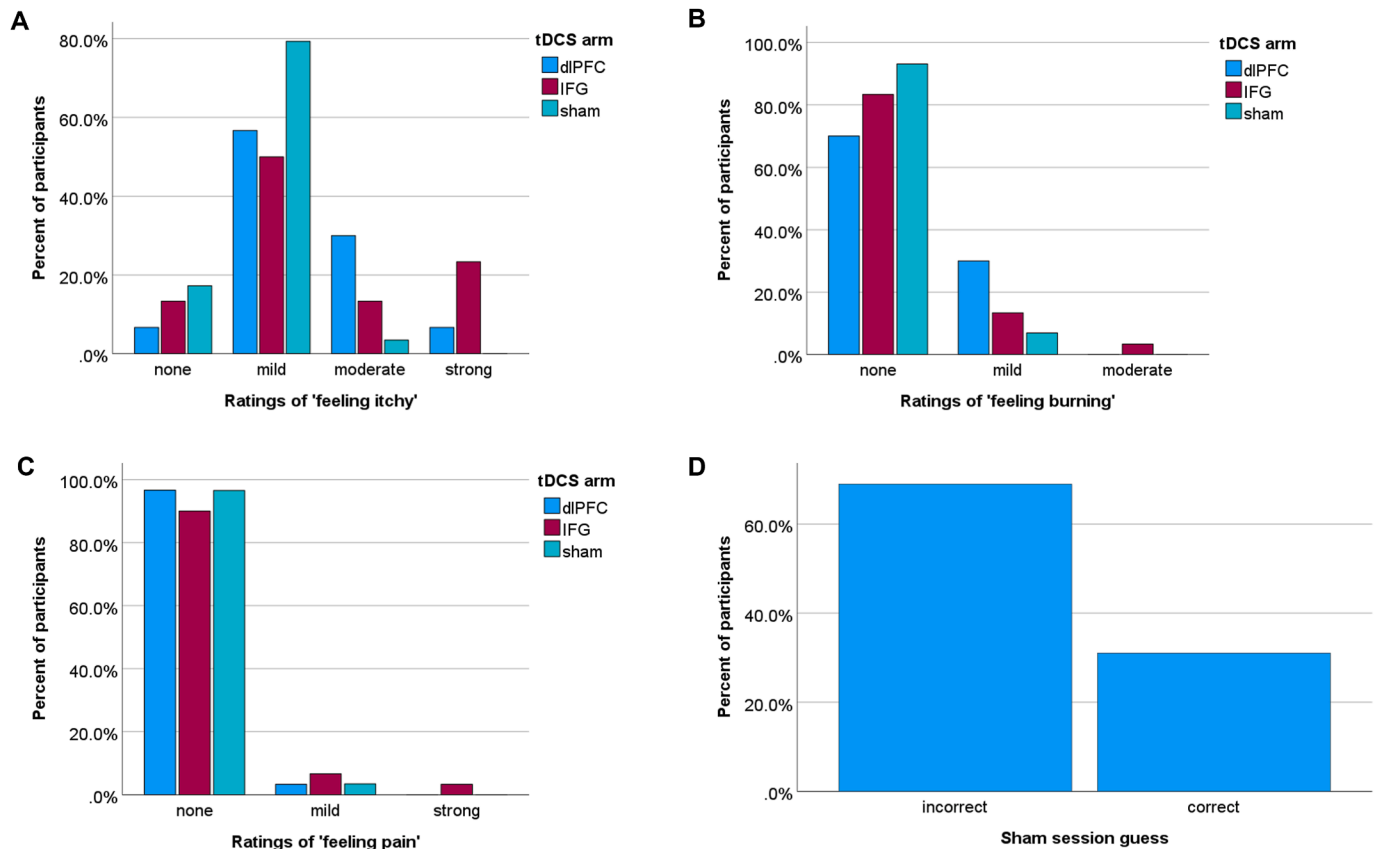


FIGURE 7. Percentage of patients reporting severities of (A) “itchy,” (B) “burning,” and (C) “pain: sensations (ABI and HC) following each tDCS session. Sensation severity ratings did not differ across tDCS arms or between study groups. (D) Percentage of participants who correctly or incorrectly guessed that they received sham stimulation in the sham tDCS session. tDCS, transcranial direct current stimulation; dIPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; ABI, acquired brain injury; HC, healthy control.

to interindividual variability arising from injury, ongoing development, or other comorbid diagnoses.³⁷ In the future, measurement of EEG following the intervention should be included to provide greater insight into neurophysiological changes.

A unique element of our study was the use of HD-EEG to measure source-derived fc at baseline, which provided a simple child-friendly measure of brain connectivity.^{44,45,108} We found that children with ABI had poorer attention before the intervention, which correlated strongly with evidence of frontoparietal network dysfunction (increased slow wave connectivity). This finding, at least in part, supports our use of prefrontal tDCS to modulate attention.^{41,109–113} We also found evidence of DMN hyperactivity in children with ABI before the intervention, including decreases in frontoparietal alpha connectivity and increases in gamma connectivity in a DMN-like network. This result is similar to that of previous functional MRI research that has found DMN hyperactivity following pediatric ABI to be a hallmark of injury-related executive dysfunction.^{23,42,114–122} Our hypothesis that increased functional network connectivity following ABI would relate to greater tDCS response was supported, as participants with greater gamma (fast wave) connectivity and lower theta (slow wave) connectivity in the DMN showed greater improvements in RT following tDCS. Although an understanding of frequency-dependent connectivity changes following ABI is limited, this suggests that DMN connectivity may explain some of the interindividual variability in tDCS response. However, as this association was derived from fc measured from predefined ROIs in patients only, it is not clear whether this relationship is purely due to injury factors, as we did not find differences in ROI connectivity

in this network between participants with ABI and HC participants. Therefore, it seems likely that abnormal DMN activity may influence response to tDCS in children with ABI^{11,23,122,123}; however, future research is needed to confirm this finding.

Interestingly, those participants with ABI with poorer attention at baseline had the greatest improvement in attention following dIPFC tDCS. This finding is in keeping with previous literature and may potentially explain the lack of overt response to tDCS in our sample as most had RTs within the normal range. Participants with faster RT before the intervention demonstrated less change following the intervention, perhaps because they had less “room to improve” compared with those with a slower RT.^{124–127} This phenomenon has been reported in a tDCS trial in adults with TBI,¹⁴ as well as in healthy adults in both the cognitive^{128–130} and motor domains.¹²⁷ We suggest that future research should consider baseline attention as a potential mediator of tDCS response, as participants with attention deficit may benefit most greatly from tDCS intervention.²³

Heterogeneity in the severity and extent of brain tissue injury affects tDCS current flow and magnitude, leading to variability in tDCS response.^{46,131,132} We hypothesized that our participants would have variable cortical E-fields, despite receiving the same “scalp intensity” of tDCS, and that this could contribute to interindividual differences in tDCS response. Supporting our hypothesis, we found a moderate E-field “cortical dose”-response relationship where higher dIPFC E-field was associated with greater RT improvement following the dIPFC tDCS condition. This relationship was not seen in the IFG condition despite similar mean E-fields. Although inhibitory control has been modulated

using SN-targeted tDCS (i.e., IFG tDCS) in healthy populations,^{133,134} in an ABI population, tDCS targeting the ECN (i.e., dlPFC tDCS) may be more effective in improving attention as it may address a more “top-down” control of attention, in line with the executive dysfunction hypothesis in ABI.²³ We suggest that this dose-response relationship may go some way to explain the null results of tDCS across our study population, where participants on the lower end of the dose-response (i.e., those with the lowest E-fields) may not have received a high-enough cortical dose of tDCS to result in cognitive changes.^{135,136} This should be considered in the context that higher intensities of tDCS do not necessarily produce linearly greater effects, suggesting that a blanket approach of increased dose is not correct, and instead may require some personalization.¹³⁷ Further research using large sample sizes is needed to determine the optimal tDCS dose for attention improvement in populations with underlying anatomic/fc differences.

We also explored the relationship between sc, E-field variability, and response to tDCS. E-field variability in brain injury populations may be caused by differences in tissue conductivity following the injury and resultant changes in structural integrity.^{46,131,132,138} In our small sample, consisting of children with relatively mild injuries (and therefore less structural damage¹³⁹), we failed to demonstrate an association between structural integrity and E-field or RT change in children with ABI, unlike a previous tDCS study in adults with moderate to severe ABI.²⁴ Indeed, our E-field modeling methods may have been insensitive to the subtlety of microstructural changes seen in mild TBI.^{139,140} In the future, E-field analyses incorporating diffusion tensor imaging data could increase the sensitivity of computational models.

In keeping with the previous literature using tDCS in children,^{141–144} our results indicated that most children with ABI were able to tolerate tDCS delivered at 1 mA and that tDCS was feasible in this population. The most commonly reported side effect in our population was tingling.¹⁴¹ Although some children verbally reported uncomfortable itchy sensations during the tDCS session, particularly near the beginning of stimulation, they were not distressed and wished to continue the session and most retrospectively reported “mild” sensations following completion of sessions. If higher stimulation intensities in children are warranted, future research should consider employing a short tolerability test¹⁴⁵ and practices to habituate participants to tDCS sensations.

Our study has several limitations. The small sample size decreases the power of the study and robustness of any conclusions. Furthermore, our stimulation montage was bilateral, meaning that both sides of the prefrontal cortex were stimulated. This montage was used to maximize current flow, because higher peak cortical E-fields are found when electrode distance is closer (i.e., in bilateral stimulation), compared with larger distances (i.e., extracranial electrodes),⁶⁵ but may have decreased specificity of effects. The timing of tDCS sessions varied due to school commitments, which may have affected fatigue levels, RTs, and apparent tDCS response in after-school sessions.¹⁴⁶ We were unable to determine the flanker congruency effect due to the limited number of flanker trials presented (NIH Toolbox),^{53,147} and future studies should ensure a greater number of flanker trials. Given the findings of this study, future research should also evaluate whether higher dosages, personalized E-field dosing, or repeated tDCS sessions have a greater effect on attention following ABI using larger sample sizes.

Conclusions

Children with ABI tolerated 1-mA tDCS during attention training tasks well, but we failed to find any robust cognitive effect of a single session of tDCS over the dlPFC or IFG on attention in

children with or without brain injury. Greater tDCS response correlated with several baseline measurements, including lower theta and higher gamma-band fc in the default mode network, lower baseline attention performance, and higher strength of cortical E-fields. We demonstrated how HD-EEG source-based connectivity may be used to personalize tDCS. Further research using larger sample sizes and tDCS personalization, particularly HD-EEG-derived connectivity, may allow for more robust characterization of potential responders to tDCS in children with ABI.

CRedit authorship contribution statement

Athena Stein: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Visualization, Writing – original draft. **Kevin A. Caulfield:** Formal analysis, Methodology, Visualization, Writing – original draft. **Mervyn Singh:** Formal analysis, Methodology, Visualization, Writing – original draft. **Justin Riddle:** Formal analysis, Software, Writing – review & editing. **Maximilian A. Friehs:** Methodology, Software, Writing – review & editing. **Michael P. Craven:** Methodology, Software, Writing – review & editing. **Madeleine J. Groom:** Software, Writing – review & editing. **Kartik K. Iyer:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Software, Writing – review & editing. **Karen M. Barlow:** Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.pediatrneurol.2025.06.005>.

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