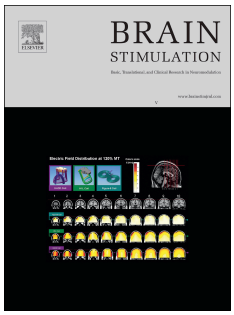

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A randomized controlled trial of transcranial direct-current stimulation and cognitive training in children with fetal alcohol spectrum disorder

Elias Boroda[1], Alyssa Krueger[1], Priya Bansal[2], Mariah J. Schumacher[1], Abhrajeet V. Roy[1], Christopher J. Boys[1], Kelvin O. Lim[1], & Jeffrey R. Wozniak[1]

[1]University of Minnesota, Twin Cities; [2]University of Maryland

Abbreviated Title: TDCS in Children with FASD

Correspondence:

Jeffrey R. Wozniak, Ph.D.

Department of Psychiatry

University of Minnesota

F282/2A West

2450 Riverside Ave.

Minneapolis, MN 55454

612-273-9741

612-273-9779 (FAX)

E-mail: jwozniak@umn.edu

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Abstract

Background: This study was a randomized double-blind sham-controlled trial examining the effects of transcranial direct current stimulation (tDCS) augmented cognitive training (CT) in children with Fetal Alcohol Spectrum Disorders (FASD). Prenatal alcohol exposure has profound detrimental effects on brain development and individuals with FASD commonly present with deficits in executive functions including attention and working memory. The most commonly studied treatment for executive deficits is CT, which involves repeated drilling of exercises targeting the impaired functions. As currently implemented, CT requires many hours and the observed effect sizes are moderate. Neuromodulation via tDCS can enhance brain plasticity and prior studies demonstrate that combining tDCS with CT improves efficacy and functional outcomes. TDCS-augmented CT has not yet been tested in FASD, a condition in which there are known abnormalities in neuroplasticity and few interventions.

Methods: This study examined the feasibility and efficacy of this approach in 44 children with FASD. Participants were randomized to receive five sessions of CT with either active or sham tDCS targeting the dorsolateral prefrontal cortex, a region of the brain that is heavily involved in executive functioning.

Results: The intervention was feasible and well-tolerated in children with FASD. The tDCS group showed nominally significant improvement in attention on a continuous performance test compared to sham (p=.043). Group differences were observed at the third, fourth and fifth treatment sessions. There was no effect of tDCS on working memory (p=.911). Further, we found no group differences on a trail making task (p=.659) or on the verbal fluency test (p=.826). In the active tDCS group, a significant correlation was observed between improvement in attention scores and decrease in parent-reported attention deficits (p=.010).

Conclusions: These results demonstrate that tDCS-augmented CT is well tolerated in children with FASD and potentially offers benefits over and above CT alone.

Introduction

Prenatal alcohol exposure (PAE) has profound detrimental effects on brain development and has permanent consequences for cognition, learning, and behavior [1, 2]. Individuals with Fetal Alcohol Spectrum Disorders (FASD) commonly have a range of neurocognitive impairments that directly lead to practical problems with learning, attention, working memory, and decision making, among other areas of functioning [3]. Recent data indicate that 2-5% of the U.S. population has FASD [4] yet, despite the profound public health burden, there have been very few treatment studies in this population [5]. The current study was a randomized, double-blinded, sham-controlled trial of transcranial direct current stimulation (tDCS) augmented cognitive training (CT) in children and adolescents with FASD.

Pre-clinical studies demonstrate that neuronal plasticity is broadly affected by PAE [6, 7]. Given the fundamental role of plasticity in healthy brain development and function, disrupted plasticity could be a primary contributor to the cognitive deficits associated with FASD [8]. In animal models, PAE persistently disrupts glutamatergic neurotransmission, leading to impaired long-term potentiation [9, 10] and contributes to behavioral and cognitive deficits [11-13]. Many of these deficits have been reported in humans with FASD as well [14]. For example, Hamilton et al. [15] utilized a virtual Morris water maze - a task requiring hippocampal plasticity [12, 16], to demonstrate that individuals with FASD show the same deficits in place learning as those seen in animal models of PAE.

Deficits in plasticity are thought to underlie many of the behavioral and neuropsychological impairments seen in FASD [8, 17], including impairments in executive functioning (planning, goal-directed behavior, working memory, alternating attention and response inhibition [8, 14, 18]. Executive functions are dependent on cortico-striatal pathways, including projections from basal ganglia and thalamic nuclei to the prefrontal cortex [19] and these networks are known to be susceptible to PAE [20, 21]. Individuals with FASD perform poorly on executive tasks involving attentional control and working memory [22, 23]. Human neuroimaging demonstrates impaired prefrontal connectivity in FASD, specifically within the dorsolateral prefrontal cortex (DLPFC), which correlates with decreased executive functioning [24]. Impaired day-to-day executive functioning in FASD [25] contributes to poor social functioning and other behavioral problems [26].

Cognitive training (CT), which involves repeated practice of the targeted ability, improves cognitive skills (such as working memory), but with modest effect sizes and considerable participant effort [27, 28]. A significant limitation of traditional CT is the narrow scope of improvement and lack of transfer to “untrained” cognitive domains and to daily functioning [29].

Kerns et al. [27] tested 16 hours of computer-based attention training in ten children with FASD ages 6-15 years over 9 weeks. Significant improvement was noted in several attention measures (Cohen’s d=0.1-0.77) and there were trend-level improvements in working memory. In a study of both autism spectrum disorder and FASD [28], a game designed to target attention and working memory was used in 6-11 year-old children with 12 hours of training over a 12-week period. Significant improvements were noted in attention (d=0.17-0.87) and working memory (d=0.37-0.72).

In the current study, we sought to augment CT with tDCS, which is an effective modulator of brain plasticity [30-32]. TDCS is a non-invasive method of delivering low intensity electrical current to the brain. Studies in animal models show that tDCS boosts synaptic plasticity, leading to improvements in learning and memory [31]. In humans, tDCS has been shown to boost plasticity in an activity-dependent manner [30, 32] and can enhance a wide range of cognitive and motor functions [33-36].

The activity-selective nature of tDCS makes it an especially attractive candidate to pair with CT [32, 37, 38]. It has been demonstrated that augmenting CT with concurrent tDCS boosts outcomes and improves transfer to non-trained tasks [39-41]. For example, in patients with major depressive disorder, prefrontal tDCS (anode placed over F3, cathode over F4) combined with cognitive control therapy led to improved clinical outcomes and improved attentional functioning compared to sham (39). Further, adding DLPFC tDCS (anode over F3, cathode over Fp2) to CT was tested in schizophrenia, resulting in improved effects sizes above CT alone (Cohen's d = 1.21 vs .61) and enhanced transfer [39, 41]. It is important to note that some heterogeneity of effects does exist in the tDCS literature, with several studies reporting little or no beneficial effects of tDCS on cognitive performance or motor learning [42, 43]. Nevertheless, the promising findings across a number of clinical studies warrant further investigation.

To our knowledge, this is the first randomized controlled trial testing the effects of CT augmented with tDCS in children and adolescents with FASD. The primary aims of this study were to characterize the feasibility and tolerability of tDCS and CT in children with FASD and to the evaluate efficacy of this approach as a potential future intervention for neurocognitive deficits.

Methods

Participants

Participants were recruited from the University of Minnesota's FASD Clinic and Adoption Medicine Clinic. Inclusion criteria required a documented history of heavy PAE (self-report, social service record, medical records, or adoption records). Heavy PAE was considered >13 drinks/week or >4 drinks per occasion at least once per week during pregnancy or when such exposure was suspected in a child with a full-FAS diagnosis based on dysmorphology. In some cases, detailed history about exposure amounts was unattainable and decisions about inclusion were made on available evidence. For example, heavy PAE was inferred if the mother was known to have had alcoholism and had contact with the police or social services during the pregnancy. At baseline, all participants were characterized according to modified Institute of Medicine (IOM) criteria [44].

All participants underwent an informed consent process and all procedures were approved by a University institutional review board. Participants (ages 9 to 16 years) with FASD (N=44) were randomized in a 1:1 ratio from a pre-prepared randomization table to either active or sham tDCS. There were no significant group differences (active vs. sham) on any demographic or clinical characteristic (**Table 1**).

Study Design

This was a randomized, double blind, sham-controlled clinical trial. All research team members, participants, and family members were blind to tDCS assignment.

Visit 1 was comprised of a baseline assessment including standardized cognitive tests and parent/guardian questionnaires. Visits 1-5 (approximately weekly) included 46 minutes of CT

and two 13 minute blocks of tDCS which were administered during the CT. The CT undertaken during visit 1 was completed after the baseline measures were collected. Visit 6, approximately one week after visit 5, included cognitive testing but no CT or tDCS.

Cognitive Training and tDCS

CT utilized five tasks from BrainHQ (Posit Science): two working memory, two attention/cognitive control, and one processing speed task. Participants were seated at a computer while wearing the tDCS cap (Starstim, Neuroelectrics). A research team member observed and assisted with each treatment visit. Each task was completed four times during a single day's treatment. The tasks employed an adaptive difficulty algorithm that adjusted difficulty based on participant performance during the previous session.

Anodal tDCS was targeted to the left DLPFC using a bipolar montage with the anode placed at F3 and the cathode placed over the supraorbital bone at Fp2 (according to the 10-20 electrode placement system) [45] (**Fig. 1**). This is a common montage in studies targeting left DLPFC for enhancing cognitive function [41]. TDCS leads were connected to 25cm^2 saline-soaked sponges on the scalp. Stimulation was initiated 30 seconds prior to the start of CT and lasted for 13 minutes. After 13 minutes, the tDCS device turned off and remained off for 20 minutes. CT continued during this time. After the 20-minute tDCS break, the device re-engaged for another 13-minute stimulation period while the CT continued. The 13-20-13 procedure was employed to account for the "metaplastic effects" of tDCS (33), by which constant long duration (20+ min) stimulation periods my lead to an undesirable engagement of hemostatic brain mechanisms that can limit plasticity enhancement. Multiple, spaced stimulation periods have been shown to facilitate tDCS-based interventions [30, 46].

Active stimulation was delivered at a 2mA intensity for each of the two stimulation periods. In the sham condition, the device ramped up to 2mA over the course of 30 seconds but then ramped down to 0mA over 30 seconds and remained at 0mA. This method facilitates blinding by mimicking the sensations which are commonly associated with active tDCS.

Prior to the start and also at the end of each treatment session, a tDCS side-effect questionnaire was completed by the participant [47].

Cognitive & Behavioral Assessments

Two computerized cognitive tests (Posit Science) were used to measure learning and near transfer of cognitive gains. These tests were administered a total of 5 times: first at baseline, prior to the initial treatment session, and then again at the end of each subsequent treatment session. The tests examined the domains drilled during CT but within an alternate context. On a visuospatial working memory test adopted from Störmer and colleagues [48], participants tracked and recalled locations of an increasing number of objects amidst distractors. The outcome measure was the average number of objects recalled over the task. On a computerized continuous performance test (CPT) assessing sustained attention, participants pressed a button in response to a frequent visual cue and inhibited button-pressing in response to a rare non-target cue.

Far-transfer of training to cognitive domains that were not directly trained was assessed using non-computerized tasks from the Delis-Kaplan Executive Function System (DKEFS): trail making test (TMT) and verbal fluency test (VFT) [49]. These two tasks were administered at baseline, prior to the first treatment session, and then again after the end of the last treatment session. The TMT requires the participant to quickly draw lines to connect numbers and letters in

sequence. The TMT is a measure of attention and set-shifting [50]. For the VFT, participants were asked to produce as many words as possible within a specific semantic category, or to produce words starting with a specific letter. VFTs require multiple executive functions (e.g. working memory, inhibition, and flexibility) [51].

The Behavior Assessment System for Children – 3nd Edition (BASC-3) [52], a standardized parent-report questionnaire, was completed by a parent or guardian at visit 1 and at visit 6. Analyses were limited a priori to four BASC-3 scales: Internalizing Problems, Externalizing Problems, Attention Problems, and Hyperactivity. Internalizing Problems characterizes inwardly directed distress (anxiety, depression) while Externalizing Problems comprises aggression, or other overt behavioral problems. Attention Problems is a scale measuring concentration difficulties. Hyperactivity is a scale reflecting a tendency for over-activity, carelessness, and impulsive behavior.

Data Analysis

Assessment Tasks & BASC-3 Analysis

For the working memory task, the average number of objects recalled was the outcome measure. For the CPT, performance was indexed via standard deviation of the response time, a commonly-used measure of consistency of engagement and sustained attention [53] and the primary output from Brain HQ's CPT. For each task, four baseline-adjusted scores were derived by subtracting each participant's baseline score from scores at each subsequent treatment session. These delta scores (**Δ**-score) were used in the final analyses. Hierarchical Linear Modeling (HLM) tested for effects of treatment and time, as well as their interaction on task performance.

The TMT and VFT yield standardized scores (mean = 10; SD = 3). Baseline-adjusted **Δ**-scores were derived for each participant. A general linear model (GLM) tested for group differences (active vs. sham) in **Δ**-score.

The BASC-3 yields t-scores (mean = 50, SD = 10) with higher scores indicating greater impairment. Statistical models for BASC-3 data were identical to those used with the DKEFS data.

TDCS-related Side-effects

At the start and end of each treatment session, participants were asked to report the presence and severity of 17 different side-effects potentially related to tDCS. Two-tailed chi-square tests assessed for group differences (active vs. sham) in potential tDCS side-effects.

Results

Feasibility and Tolerability

Forty-four participants were recruited; 20 were randomized to active treatment and 24 were randomized to sham (**Fig. 1**). One individual in the active group terminated because of tDCS intolerance. Five individuals in the sham group terminated early: one for tDCS intolerance, two for time commitment, and two without explanation. All six visits were completed by 19 active and 19 sham group participants. These 38 participants were included in all analyses.

No significant differences (active vs. sham) were found for tDCS related side-effects ($p>.05$ for all comparisons; **Table 2**) suggesting that tDCS was well tolerated.

Near-Transfer: Visuospatial Working Memory & Continuous Performance Test

Baseline working memory performance and CPT performance were tested for group differences and no active vs. sham differences were found (p>.05); nevertheless we analyzed **Δ**-scores to account for any baseline variability. For working memory, a significant effect of time was observed ($F_{1/144}$=2.46, p=.047), with both groups showing improvement over the visits, but no significant effect for active vs. sham tDCS ($F_{1/39}$=.017, p=.911) was seen, nor was there an interaction effect ($F_{1/144}$=4.41, p=.612) (**Fig. 2**). For the CPT, a significant effect of tDCS ($F_{1/39}$=4.31, p=.043) was seen, with the active group performing better over time compared to sham (**Fig. 3**). There was not a significant overall effect of time ($F_{1/144}$=1.36, p=.247) nor an interaction ($F_{1/144}$=1.46, p=.221). Post-hoc contrast analyses revealed significant active vs. sham differences at visit 3 (p=.033), visit 4 (p=.043), and visit 5 (p=.046). It is worth noting here that, because **Δ**-scores were analyzed as opposed to performance at individual timepoints, the main effect of group is the relevant finding from this analysis because it reflects the magnitude of the difference in performance as opposed to the interaction term which merely reflects the pattern of performance over the timepoints.

To calculate between group effect sizes (Cohen's d), the **Δ**-scores were collapsed across visits 2, 3, 4, and 5 for each participant to derive a single overall **Δ**-score. For working memory, the effect size was not meaningful (*d* = 0.05) but, for the CPT, the effect size was large (*d* = 0.64).

Far-Transfer: Trail Making and Verbal Fluency Tasks

No group differences (active vs. sham) were seen for baseline performance on far-transfer tasks (p>.05; **Table 3**). **Δ**-scores were used for analysis. For VFT performance, no

significant effects of tDCS were seen for either letter VF ($F_{1/36}$=.067, p=.797), or category VF ($F_{1/36}$=.049, p=.826).

No treatment effect was seen for TMT performance for number sequencing ($F_{1/36}$=.064, p=.801), letter sequencing ($F_{1/36}$=2.75, p=.107), nor combined letter and number sequencing ($F_{1/36}$=.197, p=.659).

BASC-3 Parent/Guardian Questionnaires

No significant differences were observed between groups (p>.05 for all comparisons) on any of the four BASC-3 measures (**Table 4**).

Associations Between CPT Performance with Attention Problems & Hyperactivity

Associations between CPT performance change (Visit 5 minus baseline) and two measures of change from the BASC-3 (Attention Problems and Hyperactivity) were analyzed using two HLMs testing for the main effects of treatment and CPT performance, as well as their interaction. For Attention Problems, we observed a significant interaction between treatment and CPT performance change ($F_{1/31}$=7.47, p=.010), meaning that the correlation between CPT change scores and the Attention Problems change scores differed between the two groups (active vs. sham). In the active tDCS group, there was a significant positive correlation (r^2=.354, p=.009; **Fig. 4**), whereas in the sham tDCS group, a weaker and non-significant correlation was found (r^2=.027, p=.530; **Fig. 5**). There were no significant interactions with the Hyperactivity change score.

Discussion

To our knowledge, this study represents the first effort to evaluate the feasibility, tolerability, and efficacy of a tDCS-augmented CT regimen in children with FASD. The study demonstrates that tDCS is well-tolerated in children and adolescents with FASD and the preliminary findings suggest that tDCS may contribute to an enhancement of cognitive training within specific domains, especially attentional control.

There are limited data on the use of tDCS in children and adolescents in general [54], and no studies have been published in FASD. In the current study, tDCS over multiple sessions was well-tolerated in this population, with no serious adverse events. Of the 44 children and adolescents enrolled, only two found the tDCS / CT procedure to be aversive (one of whom was in the sham group) (**Fig. 1**). Furthermore, there was no measurable differences in the total number of tDCS side-effects reported between groups (t=-.813, p=.438). Therefore, these data suggest that tDCS may be a viable treatment option for children with FASD, despite initial concerns that their tactile hypersensitivity could interfere with tolerating the tDCS cap and the sensations of electrical stimulation [55]. It is also noteworthy that the study employed stimulation parameters similar to those used in adult studies, demonstrating that it is not necessary to lower stimulation intensity and duration for tDCS to be tolerated in children with FASD. This contrasts with the suggestion that reduced tDCS intensity is needed with children [54]. Certainly, given the smaller head size and thinner skull of a child, there may very well be differences in current flow between adults and children that are yet to be elucidated in the literature. Also, differences in current flow may be even more likely in children with FASD as a result of smaller head circumference in this population. Modeling studies are needed to more accurately characterize these differences.

Cognitive training is one of the few interventions that have been tested for cognitive dysfunction in FASD [27, 28]. In general, these studies have reported moderate effect sizes as a result of considerable participant training. Adding tDCS to CT is worth exploring as a potentially effective method of catalyzing cognitive gains and maximizing efficiency of the training. The mechanism for tDCS is thought to be based in its ability to enhance neural plasticity, leading to improved learning [56, 57]. This aspect of tDCS may be especially relevant for application in FASD because plasticity abnormalities have been demonstrated in both animal models of FASD and in humans with this disorder [8].

We found a significant effect for tDCS on sustained attention, with the active-tDCS group showing improved performance over the course of repeated sessions compared to the sham group (**Fig. 3**). The analyses revealed that measurable active-sham differences emerged at the third treatment visit, suggesting that the effects of CT and tDCS may be additive with repetition. Past CT studies in FASD have also reported improvement on attention measures [27, 28] after 12-16 hours of training. Although comparing findings across these studies is difficult due to design differences, the fact that attentional differences were emergent after just three sessions of combined CT and tDCS is promising. Still, it is important to note that the main effect of treatment was only marginally significant and would likely not remain significant after correction for multiple-comparisons. However, given that this was a first of its kind pilot study in FASD, these results are promising and warrant further investigation.

The intervention effect measured here is clinically relevant because deficits in attention are common in children with FASD, with extremely high rates of comorbid attention deficit hyperactivity disorder (ADHD) being reported in this population [58]. Availability of even modestly effective interventions could improve long-term outcomes. Although the current study

did not demonstrate a measurable direct behavioral effect of the intervention, the data did reveal a tDCS-group dependent correlation between CPT improvement and improvement in attention problems as reported on the BASC-3 parent/guardian questionnaire (**Fig. 4 & 5**).

In addition to attentional deficit, working memory impairment is a core feature of FASD [59]. The data did not show a significant effect of tDCS on the working memory task (**Fig. 2**). Working memory enhancement with tDCS has been extensively explored but, findings are inconsistent across studies with a general trend toward a small to moderate net benefit [60]. A lack of a measurable tDCS effect on working memory in the current study may be due to the design of the CT regimen. Only two of the five training tasks were focused on working memory, with the other training tasks primarily focusing on attention and processing speed. TDCS effects are thought to occur relative to concurrent endogenous patterns of brain activity, with only task-specific circuits and related functions being facilitated [32, 37, 61]. Because the training sessions incorporated several cognitive domains in close succession, together with the generally enhancing effect of tDCS, some dispersion of efficacy may have occurred relative to other studies that focused on a single cognitive domain. The attention effect seen on the CPT may be related to the fact that attention was emphasized in several tasks and the fact that sustained attention was naturally engaged throughout the duration of the cognitive training. The circuits that sub-serve sustained attention processes were likely active concurrent with tDCS for a longer period and were, perhaps, preferentially affected by stimulation. Ultimately, with follow-up studies, targeting a widely dispersed set of cognitive functions may not be the most efficient way to pair CT with the plasticity-enhancing effects of tDCS. Some studies have demonstrated, for example, that there may be an advantage to activating a single network when pairing training with tDCS [62].

Finally, it is worth noting that the current study did not demonstrate an effect of tDCS on far-transfer measures (no significant group differences on either the VFT or the TMT). Achieving far-transfer to untrained tasks and cognitive domains is ultimately the goal of cognitive training interventions, but few studies have reported such transfer despite many hours of training [63, 64]. There is some evidence that tDCS may be able to enhance far-transfer, leading to improvements on untrained tasks [41, 65]. In the current study, the small "dose" of cognitive training (fewer sessions and a wider time span) compared with past studies [54, 66] may have limited the opportunities to achieve far transfer. Future studies may benefit from a higher density of training, more specific training focus, and a longer duration of training in order to achieve maximum cognitive benefit.

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Conflict of Interest Declaration

The authors have no conflicts of interest to declare.

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N(%) or mean (SD)	Sham (*n*=19)	Active (*n*=19)	Statistical Test
Age	12.79 (2.10)	12.05 (1.90)	$t(36)=1.13$, $p=.264$
Gender			
Male	10 (52.6%)	12 (63.2%)	$x^2(1)=.432$ $p=.511$
Female	9 (47.4%)	7 (36.8%)	
Racial Categories			
White	11 (57.9%)	9 (47.4%)	$x^2(5)=.395$ $p=.557$
Black or African American	2 (10.5%)	2 (10.5%)	
American Indian/Alaska Native	3 (15.8%)	1 (5.26%)	
Asian	1 (5.26%)	0 (0%)	
More than One Race	2 (10.5%)	6 (31.6%)	
Other	0 (0%)	1 (5.26%)	
Ethnicity			
Hispanic	0 (0%)	1 (5.26%)	$x^2(1)=.027$ $p=.311$
Not Hispanic or Latino	19 (100%)	18 (94.7%)	
Alcohol Exposure			
Alcohol Confirmed	19 (100%)	16 (84.2%)	$x^2(1)=3.25$ $p=.071$
Alcohol Suspected	0 (0%)	3 (15.8%)	
Other Drug Exposure			
None	3 (15.8%)	6 (31.6%)	$x^2(1)=1.31$ $p=.519$
Drug Exposure Suspected	5 (26.2%)	4 (21.1%)	
Drug Exposure Confirmed	11(57.9%)	9 (47.4%)	
Dysmorphic Facial Features			
Lip (score 4 or 5)	8 (42.11%)	6 (31.6%)	$x^2(1)=.452$ $p=.501$
Philtrum (score 4 or 5)	11 (57.9%)	10 (52.6%)	$x^2(1)=.106$ $p=.744$
Palpebral Fissure *($\leq 10^{th}$ percentile)* [a]	7 (36.8%)	6 (31.6%)	$x^2(1)=.117$ $p=.732$
$\geq$ 2 Facial Features Present	11 (57.9%)	7 (36.8%)	$x^2(1)=1.68$ $p=.194$
Growth Deficiency ($\leq 10^{th}$ percentile)			
Height	3 (15.8%)	3 (15.8%)	$x^2(1)=.001$ $p=1.00$
Weight	0 (0.00%)	1 (5.29%)	$x^2(1)=1.02$ $p=.311$
Deficient Brain Growth ($\leq 10^{th}$ percentile) [a]			
Occipital-Frontal Circumference (OFC)	3 (15.8%)	2 (10.5%)	$x^2(1)=.230$ $p=.631$
IOM Diagnostic Category			
Fetal Alcohol Syndrome	1 (5.29%)	2 (10.5%)	$x^2(5)=2.80$ $p=.247$
Partial Fetal Alcohol Syndrome	10 (52.6%)	5 (26.3%)	
Alcohol-related neurodevelopmental disorder	8 (42.1%)	12 (63.2%)	

Table 1: Participant demographic and clinical characteristics. For diagnostic categorization the Institute for Medicine criteria was used.

Symptom	Sham (n=24)	Active (n=20)	χ2 Value (df=1)	Asymptotic Significance (2-sided)
Headache	4	5	.466	.495
Unusual feelings on the skin of your head	7	8	.570	.450
Neck Pain	0	2	2.51	.113
Tingling	6	6	.138	.711
Itchiness	10	8	.013	.911
Sleepiness	12	12	.440	.507
Difficulty paying attention	5	7	1.10	.293
Unusual feelings, attitudes, or emotions	2	2	.037	.848
Tooth pain	0	1	1.23	.268
Change in hearing	0	1	1.23	.268
Nausea/Sick to Stomach	0	2	2.51	.113
Unusual twitches or movements in muscles	1	0	.853	.356
Dizziness	0	1	1.23	.268
Anxious/Worried/Nervous	1	2	.584	.445
Forgetful	3	3	.058	.810
Difficulty with your balance	2	1	.191	.662
Change in movement in your stronger hand	0	1	1.23	.268

Table 2: Potential TDCS related side-effects with number of participants reporting each side-effect across the two groups is reported.

VERBAL FLUENCY (LETTER)	BASELINE (MEAN ± SD)	FOLLOW-UP	Δ-SCORE	$F_{1/36}$	P-VALUE	COHEN'S *D*
ACTIVE TDCS	7.32 ± 2.69	7.21 ± 2.05	-0.105 ± 2.05	0.008	0.796	0.084
SHAM TDCS	5.42 ± 2.08	5.47 ± 1.68	0.051 ± 1.68			
VERBAL FLUENCY (CATEGORY)						
ACTIVE TDCS	9.21 ± 3.88	5.53 ± 4.53	-3.68 ± 3.93	0.049	0.826	0.072
SHAM TDCS	7.42 ± 3.81	4.00 ± 3.18	-3.42 ± 3.37			
TRAIL MAKING (NUMBERS)						
ACTIVE TDCS	9.53 ± 3.19	10.6 ± 1.86	1.11 ± 3.20	0.064	0.801	0.082
SHAM TDCS	7.79 ± 3.46	9.16 ± 3.27	1.37 ± 3.20			
TRAIL MAKING (LETTERS)						
ACTIVE TDCS	8.05 ± 3.85	9.11 ± 3.75	1.05 ± 3.29	2.75	0.102	0.534
SHAM TDCS	5.58 ± 3.89	8.63 ± 3.67	-2.95 ± 3.73			
TRAIL MAKING (COMBINED)						
ACTIVE TDCS	9.37 ± 4.90	8.21 ± 5.14	-1.16 ± 6.24	0.197	0.659	0.144
SHAM TDCS	10.0 ± 5.26	7.95 ± 4.96	-2.05 ± 6.18			

Table 3: Summary metrics and analysis for the Verbal Fluency and the Trail Making Tasks. Mean and standard deviation scores are shown the for baseline and follow-up visits. Baseline adjusted Δ-scores were calculated on a per participant basis, positive Δ-scores indicate improved performance. An ANOVA was conducted on the Δ-scores to identify differences across groups. Cohen's *D* was computed using the Δ-scores to estimate effect sizes.

EXTERNALIZING PROBLEMS	BASELINE (MEAN ± SD)	FOLLOW-UP	Δ-SCORE	$F_{1/35}$**	P-VALUE	COHEN'S *D*
ACTIVE TDCS	72.1 ± 17.2	68.1 ± 11.8	-4.00 ± 12.7	2.78	0.101	0.222
SHAM TDCS	73.3 ± 15.2	71.7 ± 13.7	-1.67 ± 7.29			
INTERNALIZING PROBLEMS						
ACTIVE TDCS	58.0 ± 12.8	56.1 ± 10.1	-1.89 ± 5.79	2.50	0.122	0.521
SHAM TDCS	60.6 ± 12.9	61.4 ± 12.4	0.833 ± 4.59			
ATTENTION PROBLEMS						
ACTIVE TDCS	66.9 ± 6.93	65.4 ± 8.60	-1.53 ± 6.26	0.717	0.401	0.278
SHAM TDCS	67.4 ± 7.83	67.6 ± 6.92	0.167 ± 5.88			
HYPERACTIVITY						
ACTIVE TDCS	73.2 ± 13.3	69.7 ± 11.7	-3.47 ± 9.65	0.010	0.912	0.034
SHAM TDCS	73.8 ± 11.7	70.0 ± 11.2	-3.78 ± 8.37			

Table 4: Summary metrics and analysis of BASC-3 questionnaire data. Mean and standard deviation scores are shown the for baseline and follow-up visits. Baseline adjusted Δ-scores were calculated on a per participant basis; negative Δ-scores indicate reduced impairment. An ANOVA was conducted on the Δ-scores to identify differences across groups. Cohen's D was computed using the Δ-scores to estimate effect size. ** 1 individual in the sham group did not complete the follow up DKEFS testing. Sample sizes are as follows (active, *n=19*; sham, *n=18*).

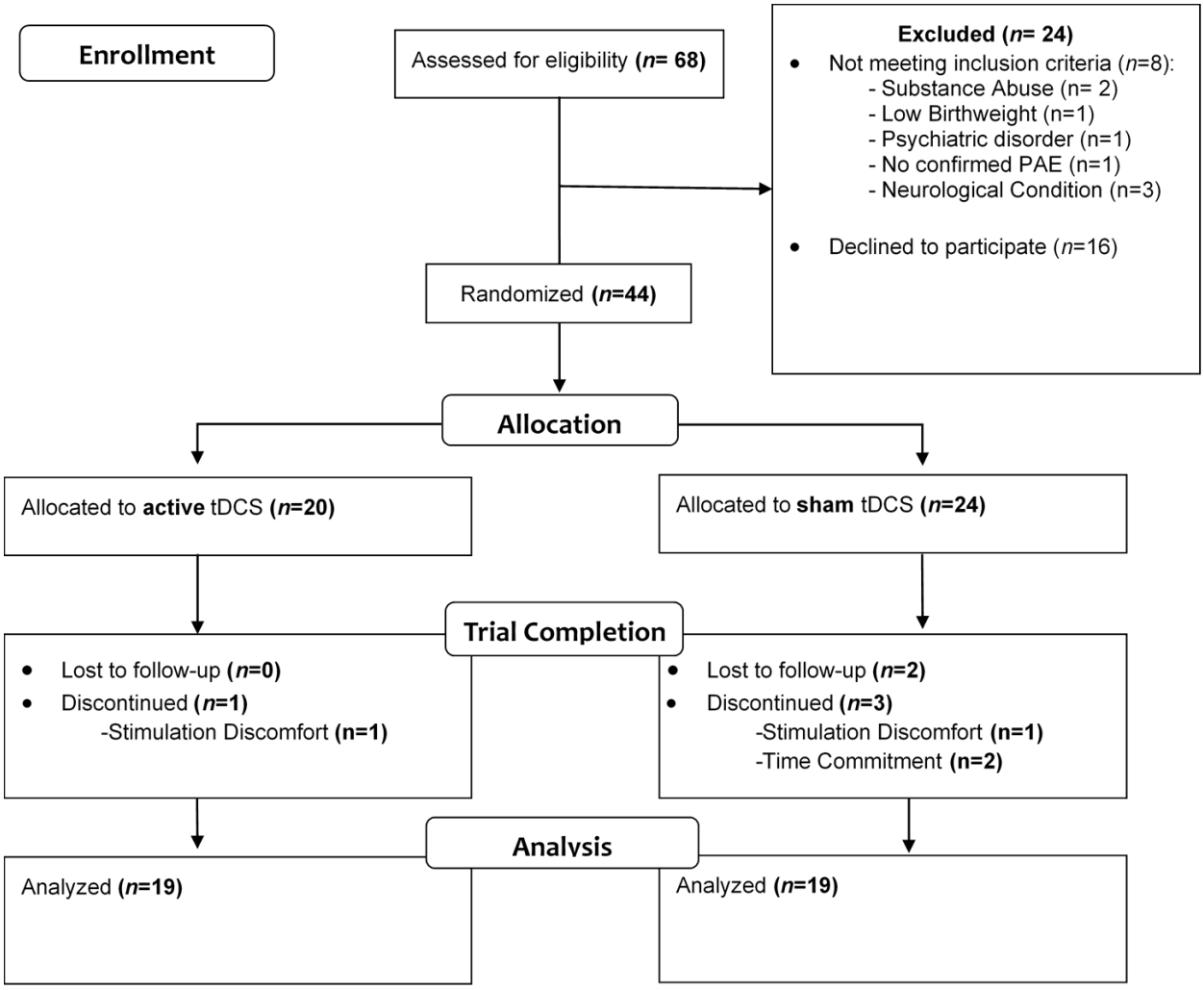
Figure 1: Consort diagram of trial.

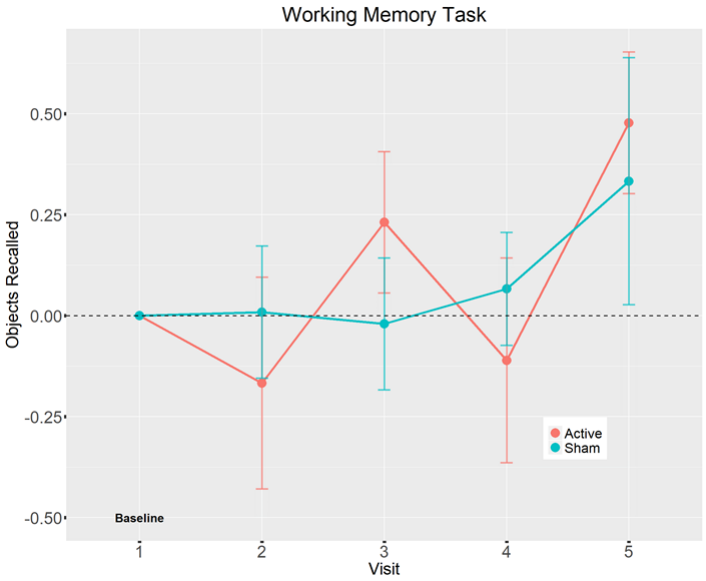
Figure 2: Visuospatial working memory task. The y axis represents the baseline adjusted average number of objects recalled at each visit. Error bars represent standard error of the mean. Both groups showed improvement across time, there was no tDCS effect on performance.

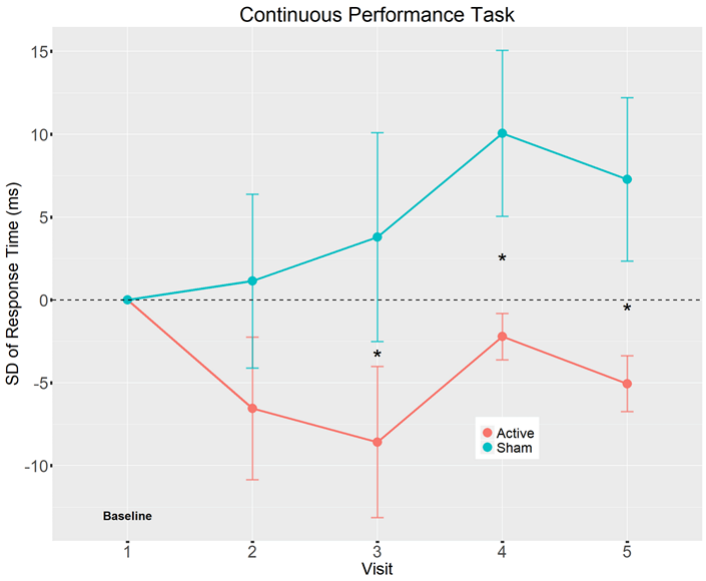
Figure 3: Continuous performance task (CPT): The primary metric of performance is the standard deviation (SD) of response time, with lower SD indicative of improved performance. The y-axis represents baseline adjusted average SD of response time. There was a significant effect of tDCS on performance at visits 3, 4 and 5 (ANOVA contrasts).

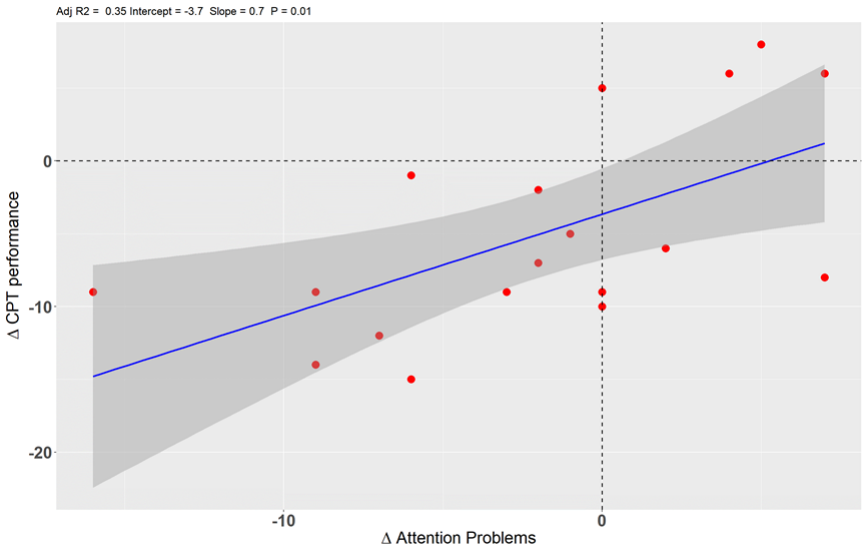
Figure 4: Correlating change in CPT with change in the Attention Problems metric in the **Active** tDCS Group. We correlated average change in CPT performance with change in the attention problems metric from the BASC. When analyzing the active tDCS group we obtained significant positive correlation.

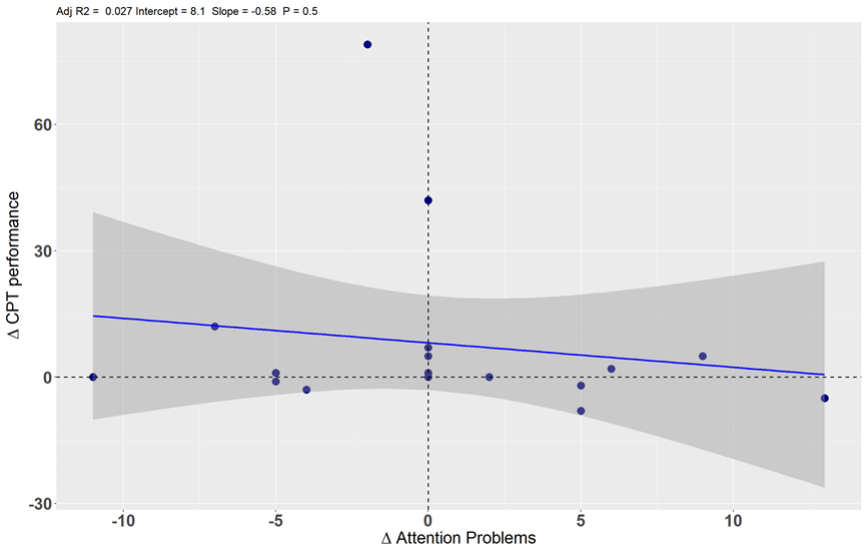
Figure 5: Correlating change in CPT with change in the Attention Problems metric in the **Sham** tDCS Group. We correlated average change in CPT performance with change in the attention problems metric from the BASC. No significant correlation was detected in the group receiving sham tDCS.


Enrollment
Assessed for eligibility (n= 68)
Excluded (n= 24)
Not meeting inclusion criteria (n=8):
- Substance Abuse (n= 2)
- Low Birthweight (n=1)
- Psychiatric disorder (n=1)
- No confirmed PAE (n=1)
- Neurological Condition (n=3)
Declined to participate (n=16)
Randomized (n=44)
Allocation
Allocated to active tDCS (n=20)
Allocated to sham tDCS (n=24)
Trial Completion
Lost to follow-up (n=0)
Discontinued (n=1)
-Stimulation Discomfort (n=1)
Lost to follow-up (n=2)
Discontinued (n=3)
-Stimulation Discomfort (n=1)
-Time Commitment (n=2)
Analysis
Analyzed (n=19)
Analyzed (n=19)









Highlights

- First randomized controlled trial utilizing tDCS-augmented cognitive training in children with FASD
- TDCS led to improved outcomes compared to cognitive training alone, specifically in attention
- TDCS was well tolerated in children with FASD

AUTHOR CONFLICT OF INTEREST DECLERATION

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email from (jwozniak@umn.edu)

Author Signatures:

Elias Boroda	Alyssa Krueger	Priya Bansal	Mariah J. Schumacher
12/17/2019	12/17/2019	12/17/2019	12/18/2019
Kelvin O. Lim	Christopher J. Boys	Abhrajeet V. Roy	Jeffrey R. Wozniak
12/18/2019	12/19/2019	12/19/2019	12/19/2019

Elias Boroda: conceptualization; methodology; software; formal analysis; investigation; data curation; writing – original draft, review, and editing; visualization

Alyssa Krueger: investigation; data curation; writing – original draft, review, and editing; project administration

Priya Bansal: investigation; data curation; writing – review and editing; project administration

Mariah J. Schumacher: investigation; data curation; writing – review and editing; project administration

Abhrajeet V. Roy: conceptualization; methodology; investigation; writing – review and editing

Christopher J. Boys: resources; writing - review and editing

Kelvin O. Lim: conceptualization; methodology; resources; writing - review and editing; funding acquisition

Jeffrey R. Wozniak: conceptualization; methodology; resources; writing – original draft, review, and editing; supervision; project administration; funding acquisition