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Transcranial Direct Current Stimulation (tDCS) in children with ADHD: A randomized, sham-controlled pilot study

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ABSTRACT

Background: ADHD is a common neurodevelopmental disorder with a pediatric prevalence of 5.2%.While medication treatment for ADHD is effective, it does not address all symptoms and a small but notable subgroup does not respond to medications. Adverse effects limit its use and some parents and participants resist use of medication. Thus, limitations of medication treatment for ADHD motivate searching for other therapeutic options. Transcranial Direct Current Stimulation (tDCS) has been suggested as a treatment for children with ADHD, with mixed results to date. Protocol variables employed, including combined use of cognitive training (CT) and scheduling of sessions, may explain diverse findings to date. The aim of this study was to examine safety, feasibility and efficacy of tDCS combined with CT provided three-times-per week for one-month to treat children with ADHD.

Methods: In a double blind, randomized, sham-controlled pilot study, 25 children with ADHD were randomized to receive 12 sessions of either anodal tDCS or sham-tDCS for 20 min combined with CT three-times-per-week for four weeks. The tDCS anode was over left dorsolateral prefrontal cortex (DLPFC) and cathode over vertex. Assessments were obtained prior to, after 6 sessions, 12 sessions and one-month after intervention.

Results: No significant post-intervention differences were found between those receiving tDCS or sham-tDCS. Both groups demonstrated significant improvement on questionnaire measures of ADHD and executive function with mixed results seen on computerized performance measures. Overall, adverse effects were mild with no significant difference between groups. However, three children, all from the tDCS group, experienced headaches with two requiring temporary cessation and one requiring removal from the study.

Conclusions: Anodal tDCS to the DLPFC using the above protocol in children with ADHD did not demonstrate additional treatment benefits beyond that of CT.

1. Introduction

ADHD is a common neurodevelopmental disorder with a pediatric prevalence of 5.2% (Thomas et al., 2015). It has negative implications over time with a meta-analysis that found that ADHD negatively impacts a child's or adolescent's health-related quality of life (Lee et al., 2016). Children with ADHD have impaired executive function (Gilbert et al., 2011) including working memory deficits that present as clinical symptoms (Kasper et al., 2012). Studies demonstrate that subjects with ADHD have decreased activity in frontal circuits, especially in the dorsolateral prefrontal cortex (Rubia et al., 2014).

Medication treatment for ADHD is effective for the majority of

Abbreviations: tDCS, Transcranial Direct Current Stimulation; ADHD, Attention Deficit Hyperactivity Disorder; DLPFC, Dorsolateral Prefrontal Cortex; CT, Cognitive Training; CPT, Computerized Performance Test; CBCL, Child Behavior Checklist; TMS, Transcranial Magnetic Stimulation; MRI, Magnetic Resonance Imaging.

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children, but twenty percent do not respond to treatment (Banaschewski et al., 2006). Furthermore, adverse effects limit use of medication (Sonuga-Barke et al., 2009), sometimes leading to medication stoppage (Gajria et al., 2014). Some parents resist medication treatment for their children with ADHD (Schatz et al., 2015). Many adolescents perceive medication treatment negatively (Bussing et al., 2012). Similarly, inappropriate use of stimulant medication is a concern (Clemow and Walker, 2014). Finally, there is limited evidence regarding long term efficacy (Cortese et al., 2015). Thus, the burden of ADHD to children and the limitations of medication treatment for this condition motivate searching for other therapeutic options.

Transcranial direct current stimulation (tDCS) (Woods et al., 2016), is a form of noninvasive brain stimulation. It has been found to be safe and well tolerated in children and adolescents (Buchanan et al., 2021; Palm et al., 2016). tDCS enables neuroplasticity (Stagg and Nitsche, 2011), allowing the brain to organize new connections between neurons, especially in response to learning or experience (Bernhardi et al., 2017). tDCS involves the application of very low electrical current via two electrodes placed on the scalp. The current flows from the anode to the cortex beneath the scalp and continues within the brain parenchyma to the area below the cathode (Stagg and Nitsche, 2011). Positive stimulation may enhance brain activity whereas negative stimulation reduces it. tDCS parameters include electrode location (montage), current intensity and number, schedule, and duration of stimulation sessions. Given that tDCS is subthreshold for inducing action potentials, improved therapeutic benefit may be realized by coupling tDCS with cognitive training (CT) (Allenby et al., 2018; Katz et al., 2017).

tDCS in pediatric ADHD has been examined using a variety of protocols with anodal tDCS to the Dorsolateral Prefrontal Cortex (DLPFC) being the most common montage examined. Studies to date have been mixed with earlier studies reporting clinical benefits (Salehinejad et al., 2020; Soff et al., 2017). However, recent studies (Berger et al., 2021; Westwood et al., 2021a), have found otherwise, necessitating further examination of this area.

Most multisession pediatric ADHD tDCS studies employed daily stimulation sessions lasting up to three weeks (Bandeira et al., 2016; Berger et al., 2021; Soff et al., 2017; Westwood et al., 2021a) with some finding short term effects. Three of the latter studies (Berger et al., 2021; Soff et al., 2017; Westwood et al., 2021a) included a follow-up assessment. For results to be clinically relevant, it is important to examine long term improvement and see if such an intervention would not require daily clinic sessions to achieve improvement in ADHD symptoms. One way of addressing such concerns is by assessing post treatment function one month after treatment completion.

2. Objective

The objective of this study was to explore safety, feasibility and efficacy when using three times a week over four weeks anodal tDCS to the DLPFC combined with CT of executive function to treat children with ADHD.

3. Methods

3.1. Study Design

Pre-registered double blind, sham-controlled pilot randomized controlled study. See Fig. 1.

3.2. Subjects

Twenty-eight children met study criteria and enrolled in the study. Parents of one child withdrew their child prior to beginning intervention, one was removed after developing headaches and one after testing positive for COVID-19. Thus, twenty-five children (18 boys, 7 girls), with mean age of 10.83 ± 1.79 years completed the intervention, and for whom data are presented. Of the 25 participants, four participants were ≥12 years of age including 3 of 13 in the tDCS group (ages 12.41, 15.95, and 13.33 years) and 1 of 12 in the sham-tDCS group (age 12.51 years). Of the 25 participants, in the tDCS group, seven had inattentive, two hyperactive and four had combined ADHD type. In the sham-tDCS group, seven had inattentive, one hyperactive and four had combined ADHD type. There were no significant differences between groups for gender (chi-square = .33, df = 1, p = .568), age (t = 0.82, df = 48, p = .413), child/adolescent ratio (those ≥12 years age) (chi-square = 1.0092, df = 1, p = .315) or ADHD type (chi-square = 0.294 df = 2, p = .863). See Fig. 2 for Consort form.

Inclusion criteria: Children and adolescents aged 8–16 years, seen at the Meuhedet North regional child developmental center with a diagnosis of ADHD as per DSM-V criteria (American Psychiatric Association, 2013). Diagnosis was made by a specialist in pediatric neurology and child development or a pediatrician with formal training in treating children with ADHD. The diagnostic procedure included 1) a semi-structured interview with the child and parents, 2) physical and

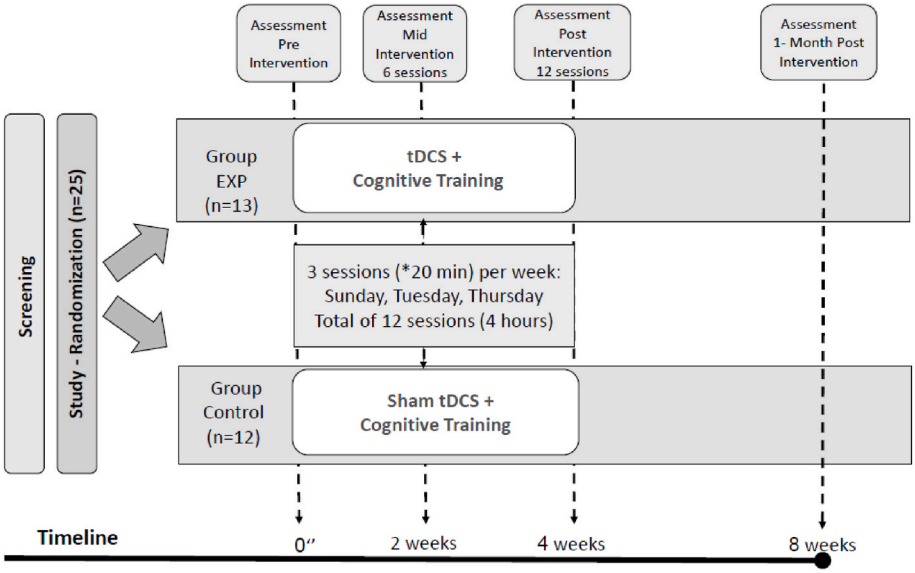

Fig. 1. Study design.

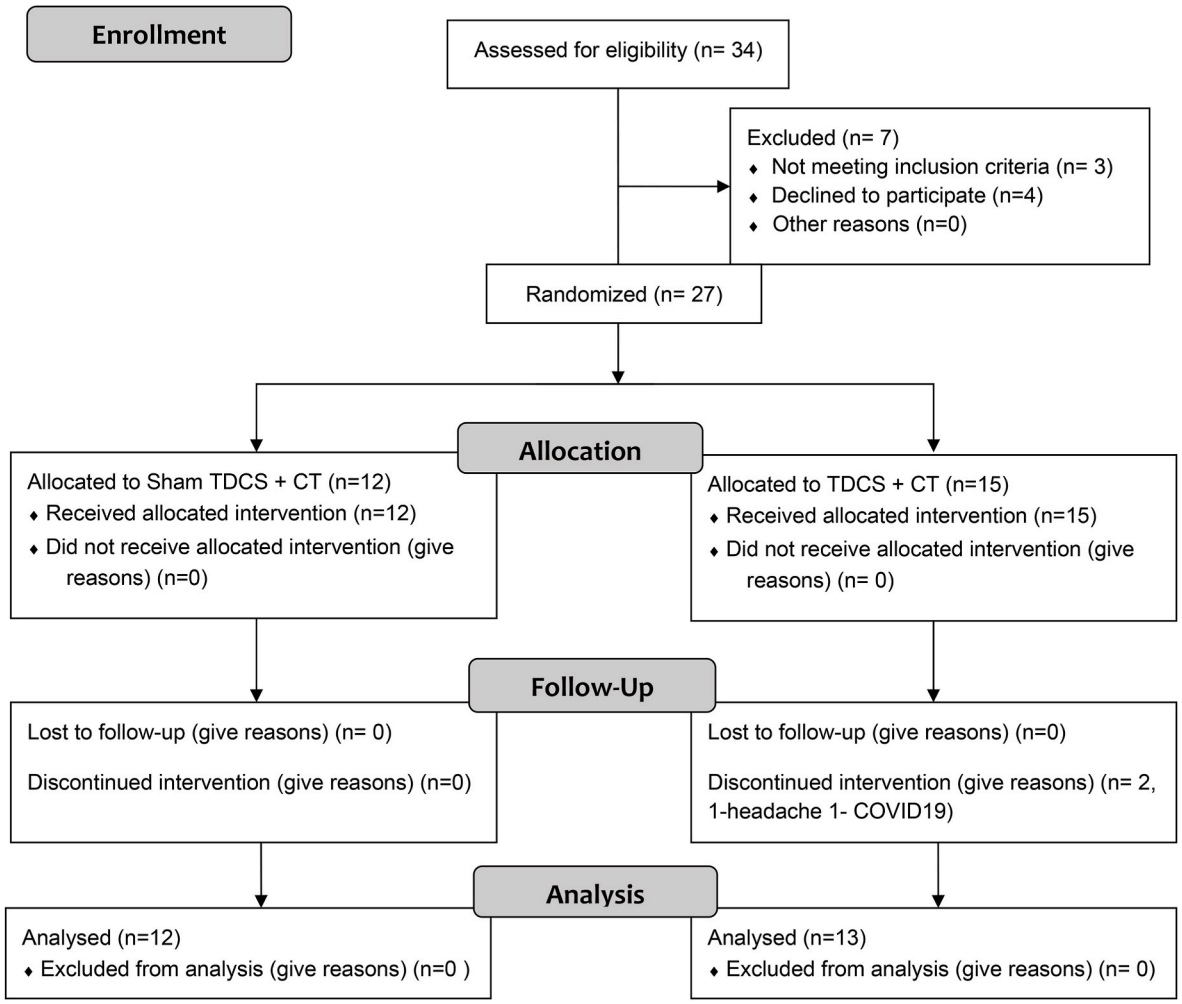

Fig. 2. CONSORT 2010 flow diagram.

neurological examination that confirmed that the clinical presentation was consistent with an ADHD diagnosis (e.g., no suggestion of regression, epilepsy); 3) a score of 2 or 3 on at least 6 of 9 of the inattention or hyperactive-impulsive items on the Vanderbilt ADHD Rating Scales – Parent and/or Teacher. Due to the COVID-19 pandemic, school was not consistently in session and teacher questionnaires were not readily available for many participants. Therefore, teacher questionnaires were used, when available, for inclusion criteria but were not included in the analyses. Additionally, participants scored >70 on the abbreviated version of the Stanford Binet-5 (Roid, 2003), had normal vision (with/without corrective lenses), no focal deficits on neurological examination, awake EEG with no epileptiform activity and were not on any medication for at least one month prior to and throughout the study period.

Exclusion criteria included history of seizure or presence of brain implant device, score above 70 on the anxiety/depression subtest of the CBCL (Achenbach, 1991), positive answer on any items 1–12 of the adapted TMS screening questionnaire (Rossi et al., 2011) including abnormality on brain MRI, if performed.

Other comorbid developmental conditions (e.g., learning disorder) were not formally assessed in this study. None of the participants had autism spectrum disorder.

3.3. Procedure

Pediatricians from the Meuhedet HMO that were local to where the study was being performed were contacted by the primary investigator and informed about the study. An information flyer was posted in the Meuhedet North Child Development Clinic, where parents of children with ADHD frequent the clinic. Finally, parents of children seen in the Meuhedet North Child Development ADHD clinic, where the study was being conducted, and who met diagnostic criteria were provided with information about the study. Parents accepting the referral were provided information about the study. After receiving written parental consent and participant assent, those meeting study entrance criteria were stratified for gender and age groups (8–12, 12–16). Matched participants were randomly divided into tDCS and sham-tDCS groups.

Within one week of performing initial assessment (see primary and secondary outcome measures), participants commenced intervention. Outcome measures were obtained two weeks (6 sessions), four weeks (12 sessions) and one month after intervention. Immediately prior to and immediately after each stimulation session, each participant was assessed by the attending physician for adverse effects, including completion of the Adverse Effects Questionnaire. If no problems were noted, then the child was discharged from the clinic for that day. If notable concerns were raised, the child was observed until symptoms resolved. The study was conducted from November 2018 till January 2021 at the Meuhedet North Child Development Center located in Haifa, Israel.

3.4. Intervention

The intervention consisted of tDCS or sham-tDCS combined with CT as follows: stimulation was performed using the Soterix Medical tDCS

device (soterixmedical.com) using two 5 × 5 electrodes infused with saline. The anode was placed on the scalp over the area of the DLPFC (F3 according to 10–20 system for EEG) and cathode was placed on the scalp over the area of the vertex, using a montage previously reported (Soff et al., 2017). Stimulation was administered three times per week, on non-consecutive days, for four weeks, for a total of 12 stimulation sessions. Stimulation lasted 20 min with current intensity of 1.0 milliamps which ramped up and down for the first and last 30 s of stimulation. Sham-tDCS was set up in the same way except that the current was shut off between the 30-s ramping periods at the beginning and end of each session, thus giving a sensation of tDCS. Using this approach, subjects theoretically have the same experience of itching and tingling during sham stimulation as they would during active stimulation. In active stimulation, sensations are transient because the subject accommodates to the current, whereas in sham stimulation, sensations fade because the current is tapered off (Kessler et al., 2012).

During the stimulation, children from both groups played with a video game, Cognifit (http://www.cognifit.com), that involves CT in the areas of auditory, visual, and cross-modal working memory. This program includes a baseline cognitive assessment that allows the training program to be individualized for each participant and that is further adjusted after each training session according to the participant's progress (Horowitz-Kraus, 2015).

The selection of the DLPFC as the stimulation site was based on two main reasons: 1) the demonstration that the left DLPFC has been found to be a site of under activation in those with ADHD in comparison to normal controls as well as those with other neurodevelopmental disorders (e.g. ASD) (Christakou et al., 2013; Hart et al., 2012) 2) the demonstration of safety reported in previous tDCS studies in children with ADHD that used the Left DLPFC as a stimulation site (Bandeira et al., 2016; Soff et al., 2017), a point of great importance given the dearth of clinical studies examining tDCS in children with ADHD.

3.5. Primary outcome measures

Adverse Effects Questionnaire – The questionnaire we used includes items that have been reported in previous tDCS treatment studies (Brunoni et al., 2011; Fertonani et al., 2010) and include headache, neck pain, scalp pain, tingling sensation, burning sensation, itching sensation, sleepiness, trouble concentrating, dizziness and nausea. Items are scored from 1 (no adverse effect) to 5 (severe). Based on the participant's response, the attending physician completed the questionnaire immediately prior to and after each of the sessions.

Vanderbilt ADHD Parent Rating Scale (VADPRS) (Wolraich et al., 2003) – This 55-item scale is composed of 18 (nine inattention, nine hyperactive/impulsive) DSM-IV ADHD items and items screening for oppositional defiant (eight), conduct (fourteen), and anxious/depressive behaviors (seven) scored using a 4-point scale (from 0 = 'never' to 3 = ''very often''). Academic, classroom, and interpersonal functioning (eight items) use a 5-point scale. The sum of items 1–9 yields an inattention score, the sum of items 10–18 yields a hyperactive/impulsive score and the sum of these together yields a total ADHD scale score. Higher scores indicate more severe symptomatology and behaviors. The VADPRS scales have good psychometric properties, and is widely used in pediatric practice (Bard et al., 2013; Wolraich et al., 2003). VADPRS data were missing for 3 subjects and thus they were excluded from this analysis.

3.6. Secondary outcome measures

Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge Cognition Ltd.) – is a computerized performance test (CPT) measuring neuropsychological skills with good psychometric characteristics (De Luca et al., 2003; Luciana, 2003) including the ability to identify changes in measures of attention in children with ADHD, including those occurring after medication intervention (Fried et al., 2012; Shang and Gau, 2012). The "attention" module administered includes measures of rapid visual information processing (RVPA-target sequences detection rate, RVPMDL-Median Response Latency, RVPPFA-probability of false alarm), response inhibition, (SSTSSRT) and spatial working memory (SWMBE).

Child Behavior Checklist (CBCL) (Achenbach, 1991) - This widely used instrument uses caregiver rating for assessing a child's overall behavioral profile. Areas measured include anxiety/depression, depression/seclusion, somatic complaints, social problems, thought problems, attention problems, rule violation, aggressive behavior and internalization and externalizing summary scores. We used the Hebrew version of the scale (Wild et al., 2012) and examined changes using T scores.

Behavior Rating Inventory of Executive Function (BRIEF-Parent) – This is a questionnaire assessing executive function in the child's environment (Gioia et al., 2000). It includes eight individual scales that assess inhibition, shifting, emotional control, initiation, working memory, planning/organization, environmental organization, and monitoring and three summary scales including regulation of behavior, metacognition and total score. It has also been used in evaluating children with ADHD (McCandless & O' Laughlin, 2007). We used the Hebrew version of the scale (Linder et al., 2010) and considered changes using T scores.

Resting state EEG and an additional CPT measure (*MOXO d-CPT - NeuroTech Solutions Ltd)* were obtained prior to and after intervention. Results will be provided in a separate publication.

3.7. Data analysis

Data were analyzed using a Multilevel Modeling (MLM) approach (Hox et al., 2017). In randomized controlled trials, MLM has superior statistical performance over traditional statistical methods such as repeated measures ANOVA when investigating the change effect across multiple time points or treatment effects over time. MLM can easily handle missing data from repeated measures using the maximum likelihood approach, has less stringent assumptions about the covariance matrix (e.g., sphericity), and provide more robust standard errors in small samples (Hox et al., 2017). The data analysis plan for this study required performing more than 50 statistical comparisons. A rigorous approach would require Bonferroni correction for multiple comparisons and thus require a $p < .001$ for a finding to be considered significant. However, given that this was a pilot study, we intentionally set a significance level of $p < .05$ for all statistical comparisons in order to identify possible beneficial effects.

The effect size was measured using the partial Eta squared ($\eta 2p$), which indicates the proportion of the variance in a dependent variable that is associated with the independent variable while the effects of other independent variables and interactions are partialled out. Values of 0.01 indicate a small effect size, values of 0.06 indicate a medium size effect, and values of 0.14 indicate a large effect size.

Since this was one of the first randomized intervention studies of its kind in children and with most tDCS studies at the time the study plan was submitted having samples size of <20 children, the study was set to be a pilot study with a focus on safety and feasibility of providing tDCS in a community clinic. Furthermore, a sensitivity analysis, calculated in GPower 3.1 (Faul et al., 2009), indicated that with $\alpha = 0.05$, and a power of .95, a sample size of $N = 25$ provides power to detect a 0.4 effect size using our 2 treatments (tDCS + CT vs. sham-tDCS + CT) × 4 measurement points mixed-subjects design. This effect size has been suggested for tDCS studies (Minarik et al., 2016). This translates into the ability of the present study to identify a response definition approximating a difference of 0.4 standard deviations between the two groups, which falls between a mild – moderate effect size (Cohen's $d = 0.3–0.5$). It should be noted that clinical effect sizes are usually significantly higher than statistical effect sizes (Bezeau and Graves, 2001). Thus, while the statistical analyses could identify an 0.4 effect size, neither the clinician nor parent would likely observe such a change clinically.

3.8. Ethics and consent

The study was approved by the Helsinki Committees of the Meuhedet Research Institute (Tel Aviv, Israel) and by the Israeli Ministry of Health. The study was prospectively registered at the Israeli Ministry of Health clinical trials website found at https://my.health.gov.il/CliniTrials/Pages/MOH_2018-07-24_002209.aspx). The Clinical Identifier is MOH_2018-07-24_002209. Parents of all participants gave written informed consent to have their child participate in the study and all participants gave their verbal assent to participate in the study.

4. Results

There were *no* significant effects ($p < .05$) for tDCS (group effects) on the primary outcome measures. On the secondary outcome measures, there were three significant effects for tDCS on the CBCL and BRIEF questionnaires, but none were seen on the CANTAB CPT measures. There were time effects, namely effects for CT, on some of the primary and secondary outcome measures. We now provide a detailed description for each of the measures.

4.1. Primary outcome measures

4.1.1. Adverse effects, feasibility & study blinding

Five adverse effects including tingling sensation, itching sensation, burning sensation, headache and scalp pain, were found to be statistically significant (in decreasing severity) when comparing pre/post scores over the 12 sessions. However, only one of these five, headache, was clinically significant. We considered an adverse effect to be clinically significant, as opposed to being just statistically significant, if the adverse effect affected the child's daily function at any given time during the study. Furthermore, no statistically significant differences were noted between the tDCS and sham-tDCS groups. (See Fig. 3 and Table 1).

Three children, all who received tDCS, developed notable headaches. In one child, the headaches necessitated stopping stimulation in session #1. This child had a prior history of mild headaches. After discussion with the parent, it was jointly decided to remove the child from the study. In two children, neither of whom had any prior history of headaches, parents contacted the primary investigator for evaluation of headaches noted at home between sessions seven and eight. Treatment intervention was suspended while clinical evaluation was performed, with physical, laboratory and ophthalmological examination being noncontributory. Headaches did not recur. Both children resumed intervention after a one-week hiatus. Headaches did not recur in these children for the remainder of the study nor were subsequent concerns noted one year post stimulation. One child, from the tDCS group, presented at the third session complaining of mild general weakness. Physical examination and blood testing were noncontributory. He resumed the intervention at the next scheduled date. Thus, 1/25 (4%) children did not complete the intervention due to adverse effects.

Regarding feasibility, 12 sessions were provided to each of the 25 subjects for a total of 300 sessions (25*12). 22 (7.3%) of the sessions were delayed due to either adverse effects noted above or due to the inability of participants to attend sessions due to personal reasons. Despite the missed sessions, 21/25 participants completed the 12 sessions within the planned 4 weeks, with four remaining participants completing all sessions within 5 weeks.

Group assignment blinding of parents: 12/25 (48%) of the parents correctly guessed their child's allocation status. Blinding was not assessed for experimenters.

4.2. VADPRS

The analysis revealed a main effect of *time* (CT) for improved scores on the inattention ($p < .001$), hyperactive-impulsive ($p = .024$), Total ADHD ($p < .001$), academic performance ($p = .007$) and ADHD performance ($p < .001$) measures. However, there were no *group* (tDCS) effects for any of these measures. There were no significant improvement effects for time nor group (tDCS) for oppositionality, conduct

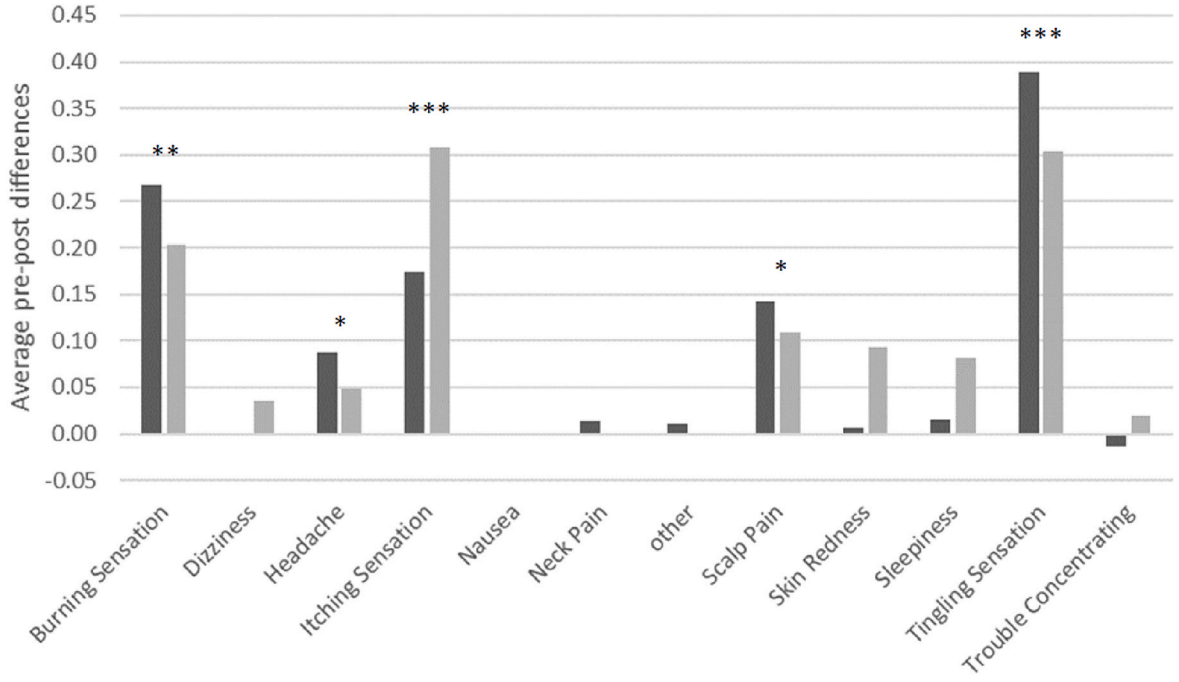

Fig. 3. Adverse Effects after receiving tDCS vs sham tDCS. Average pre-post differences over 12 sessions using a 1–5 scale.
*p < .05, **p < .01, ***p < .001.

Table 1
Adverse Effects. Means (SD) Scores at the pre and post intervention for tDCS & Sham-tDCS groups.

	TDCS		Sham		Time (df = 1,23)			Group (df = 1,23)			Time × Group (df = 1,23)		
	T1	T2	T1	T2	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2
Burning Sensation	1.00 (.00)	1.20 (.28)	1.00 (.00)	1.27 (.38)	12.61	**.002**	.35	.24	.627	.01	.24	.627	.01
Dizziness	1.01 (.02)	1.04 (.09)	1.00 (.00)	1.00 (.00)	2.88	.103	.11	2.52	.126	.11	2.88	.103	.11
Headache	1.06 (.11)	1.11 (.23)	1.04 (.07)	1.13 (.20)	4.87	**.038**	.17	.00	.956	.02	.40	.532	.02
Itching Sensation	1.01 (.02)	1.31 (.32)	1.00 (.00)	1.17 (.24)	17.12	**<.001**	.47	1.69	.207	.06	1.33	.261	.06
Nausea	1.01 (.02)	1.01 (.02)	1.01 (.03)	1.01 (.05)	.00	1.000	.00	.45	.511	.02	.00	1.000	.00
Neck Pain	1.00 (.00)	1.00 (.00)	1.00 (.00)	1.01 (.05)	1.09	.308	.05	1.09	.308	.05	1.09	.308	.05
Other	1.00 (.00)	1.00 (.00)	0 (.00)	1.01 (.04)	1.09	.308	.05	1.09	.308	.05	1.09	.308	.05
Scalp Pain	1.00 (.00)	1.11 (.21)	1.01 (.02)	1.15 (.37)	4.49	**.045**	.16	.16	.690	.01	.08	.781	.01
Skin Redness	1.00 (.00)	1.09 (.22)	1.00 (.00)	1.01 (.02)	2.49	.129	.10	1.84	.188	.07	1.84	.188	.07
Sleepiness	1.02 (.05)	1.10 (.21)	1.01 (.02)	1.02 (.08)	2.68	.115	.10	1.46	.239	.05	1.23	.280	.05
Tingling Sensation	1.00 (.00)	1.30 (.31)	1.01 (.02)	1.40 (.41)	22.62	**<.001**	.50	.45	.511	.01	.34	.568	.01
Trouble Concentrating	1.00 (.00)	1.02 (.05)	1.02 (.07)	1.01 (.02)	.07	.788	.01	.08	.780	.01	.84	.105	.11

problems, or anxious/depressive behaviors. (See Table 2).

Parents were verbally asked, using a yes/no format, to report if their child benefitted from the intervention. Parents of 8 of the 25 children reported improvement in their child's function after receiving the intervention, 4 of whom received tDCS and 4 of whom received sham-tDCS.

4.3. Secondary outcome measures

4.3.1. CANTAB

Significant improvement over *time* (CT) were noted on one of three measures of rapid visual processing (RVPMDL), on response inhibition (SSTSSRT) and spatial working memory (SWMBE). However, after removing outliers, only improvement on spatial working memory (SWMBE) remained significant. We found *no* effects for *group* (tDCS) for any of the variables. (See Table 3).

4.3.2. CBCL/BRIEF

On the CBCL, we found effects for *time* (CT) but not for *group* (tDCS) for anxiety/depression, thought problems, attention problems, rule violation, aggressive behavior and internalization. We noted effects for *group* for social problems. No *time* × *group* interaction effects were found (See Table 3). On the BRIEF we found significant improvement on effects for *time* for self-monitoring, working memory, inhibition, metacognition and overall score; for *group* for transitions; and for *time* × *group* for self-monitoring. Surroundings order was significant for all effects (*time, group, and time* × *group)* (See Table 3).

We examined for significant differences between the scores of the two groups at baseline using *t*-test for Equality of Means. Only 3 (6%) (CBCL- Anxiety Depression, Social Problems; BRIEF – Surrounding Disorder) of the 50 variables at baseline were significantly different between the two groups at the $p < .05$ level as follows: self monitoring (t-0.025, df = 22, p = .005), anxiety depression (t = −2.243, df = 23, p = .035), social problems (t = −2.512, t = 23, p = .019).

One of these variables, the surrounding order of the BRIEF, was the

Table 2
VADPRS Means (SD) Scores at the 4 assessment times for both tDCS & Sham-tDCS groups.

	TDCS				Sham				Time (df = 3,59)			Group (df = 1,22)			Time × Group (df = 3,59)		
	T1	T2	T3	T4	T1	T2	T3	T4	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2
Inattention	14.92 (5.77)	14.73 (5.78)	6.33 (6.23)	10.18 (5.46)	16.55 (3.72)	14.64 (4.11)	8.60 (4.79)	11.64 (4.06)	22.83	**<.001**	.60	.40	.535	.05	.19	.906	.01
Hyperactive/ impulsive	12.54 (7.14)	10.64 (7.76)	11.67 (7.33)	7.09 (7.65)	12.36 (6.38)	11.09 (6.19)	14.60 (4.77)	11.73 (5.41)	3.37	**.024**	.31	.88	.359	.03	1.21	.316	.07
Total ADHD	27.46 (10.90)	25.36 (12.42)	9.42 (8.14)	17.27 (11.51)	28.91 (8.89)	25.73 (8.93)	11.60 (5.82)	23.36 (8.56)	33.66	**<.001**	.69	.53	.475	.02	.65	.585	.04
Oppositional Defiant	3.69 (2.25)	3.27 (2.72)	2.36 (2.06)	1.73 (1.90)	2.82 (2.68)	1.91 (2.07)	2.30 (2.16)	2.36 (2.16)	2.42	.075	.11	.27	.606	.02	1.50	.223	.05
Conduct	.69 (.75)	.27 (.47)	.45 (.69)	.18 (.40)	.18 (.40)	.27 (.65)	.20 (.63)	.36 (.92)	.48	.697	.03	.60	.449	.03	1.63	.193	.05
Anxiety Depression	1.54 (2.07)	1.82 (1.99)	1.82 (2.52)	1.36 (2.20)	1.18 (1.25)	.45 (.69)	.90 (1.37)	.55 (.82)	.41	.746	.01	2.39	.136	.08	.58	.628	.02
Academic Performance	3.23 (2.42)	1.73 (1.35)	2.55 (2.70)	1.27 (1.49)	2.82 (1.72)	2.11 (1.36)	1.50 (1.60)	1.73 (1.68)	4.44	**.007**	.17	.17	.682	.02	.52	.671	.01
ADHD Performance	9.15 (4.72)	8.45 (5.35)	23.00 (13.16)	4.91 (4.95)	10.91 (3.70)	8.45 (3.98)	26.20 (9.20)	6.27 (4.96)	57.49	**<.001**	.78	.43	.516	.02	.48	.696	.01

p values < 0.05 are noted in **bold**.

Table 3
Secondary Outcome measures (CANTAB, CBCL & BRIEF) at the 4 assessment times for tDCS & Sham-tDCS groups.

	TDCS				Sham				Time			Group			Time × Group		
	T1	T2	T3	T4	T1	T2	T3	T4	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2
CANTAB																	
RVPA (+)	.92 (.07)	.89 (.09)	.88 (.07)	.92 (.04)	.92 (.05)	.92 (.05)	.88 (.08)	.88 (.08)	2.68	.053	.16	.00	.954	.01	1.28	.287	.07
RVPMDL (−)[a]	455.65 (93.23)	419.96 (94.60)	461.31 (86.31)	404.90 (74.98)	466.58 (152.26)	405.46 (64.73)	480.50 (282.41)	405.79 (76.03)	3.21	**.028**[b]	.14	.00	.963	.01	.15	.931	.01
RVPPFA (−)	.07 (.13)	.10 (.20)	.07 (.06)	.05 (.05)	.06 (.08)	.03 (.02)	.09 (.09)	.09 (.12)	.11	.957	.01	.03	.866	.01	1.51	.219	.12
SSTSSRT (−)	344.34 (71.41)	334.16 (99.92)	315.00 (91.02)	227.50 (249.22)	343.02 (60.16)	330.78 (72.78)	341.12 (58.81)	288.24 (96.01)	3.57	**.018**[b]	.10	.55	.466	.05	.53	.661	.04
SWMBE (−)	18.62 (7.26)	16.00 (8.50)	12.69 (7.25)	8.44 (7.67)	17.17 (7.58)	14.75 (8.65)	12.90 (8.99)	15.09 (8.97)	4.35	**.007**	.11	.52	.478	.01	.29	.832	.02
CBCL																	
Anxiety/depression	61.50 (7.14)	62.20 (9.31)	63.80 (9.67)	55.00 (5.29)	56.25 (5.90)	56.82 (6.06)	56.50 (7.62)	52.00 (3.66)	6.52	**.001**	.36	4.236	.052	.34	.376	.771	.07
Depression/seclusion	61.08 (8.46)	63.40 (9.07)	61.90 (11.05)	56.78 (6.96)	56.25 (6.51)	54.82 (5.56)	56.90 (7.67)	55.55 (5.61)	2.24	.093	.04	2.643	.118	.20	2.247	.093	.07
Somatic complaints	55.58 (7.18)	54.80 (4.98)	55.30 (4.11)	57.00 (4.97)	56.00 (7.53)	58.00 (7.31)	52.80 (5.25)	57.64 (6.25)	1.54	.215	.03	.079	.781	.01	1.487	.228	.06
Social problems	64.42 (7.28)	63.00 (10.01)	63.90 (9.87)	60.00 (11.24)	56.00 (4.84)	55.91 (5.26)	55.50 (5.34)	59.27 (6.29)	.07	.975		5.076	**.035**	.31	1.758	.166	.06
Thought problems	56.50 (6.50)	56.90 (7.42)	55.90 (6.94)	63.11 (9.97)	54.75 (5.17)	54.45 (4.50)	55.30 (7.06)	65.27 (7.20)	18.80	**<.001**	.57	.064	.803	.03	.454	.716	.04
Attention problems	65.58 (6.68)	66.50 (8.91)	63.10 (6.89)	53.89 (5.62)	64.75 (8.78)	67.27 (8.00)	64.70 (9.94)	53.00 (3.92)	29.52	**<.001**	.25	.001	.982	.01	.393	.759	.07
Rule violation	59.83 (6.83)	59.30 (7.83)	58.90 (8.27)	61.67 (8.77)	55.25 (4.52)	55.45 (5.41)	55.10 (4.86)	63.09 (7.62)	5.20	**.003**	.28	1.173	.291	.08	1.282	.289	.03
Aggressive behavior	65.67 (7.74)	64.30 (9.35)	63.70 (8.97)	57.67 (7.21)	61.42 (8.62)	59.73 (7.75)	59.50 (10.17)	59.27 (6.87)	4.07	**.011**	.25	.817	.376	.02	1.874	.144	.10
Internalization	61.23 (8.23)	61.09 (9.15)	55.91 (20.37)	53.40 (10.89)	55.64 (6.99)	58.73 (10.16)	52.50 (11.84)	53.18 (8.55)	3.33	**.026**	.22	.117	.736	.02	.849	.473	.09
Externalization	61.69 (11.60)	59.36 (14.19)	53.91 (22.31)	57.30 (10.10)	61.09 (6.63)	60.18 (12.89)	56.40 (11.95)	60.82 (8.49)	1.74	.169	.04	.446	.511	.05	.388	.762	.07
Overall score	63.69 (7.51	62.00 (10.29)	61.60 (9.71)	56.30 (12.30)	59.91 (5.34)	60.82 (12.11)	56.70 (10.34)	58.36 (9.10)	2.65	.057	.09	.129	.723	.13	.945	.425	.03
Self-monitoring	57.83 (13.13)	61.64 (12.63)	53.45 (13.01)	50.27 (11.69)	58.90 (6.62)	53.50 (9.63)	52.63 (11.55)	54.20 (12.87)	3.26	**.028**	.22	.221	.643	.01	2.779	.050	.17
Surroundings order	49.67 (8.18)	48.82 (8.49)	53.27 (8.37)	46.27 (8.74)	60.30 (8.67)	55.30 (8.46)	54.75 (8.89)	55.90 (9.21)	2.83	**.047**	.19	6.321	**.019**	.11	3.194	**.031**	.18
Planning/organizing	64.18 (11.00)	62.00 (10.24)	61.27 (9.92)	57.36 (13.76)	65.80 (5.61)	62.70 (10.11)	61.13 (11.63)	59.70 (10.14)	.08	.777	.02	.082	.777	.01	.074	.974	.01
Working memory	67.67 (12.89)	64.45 (6.88)	64.82 (8.86)	57.73 (9.77)	65.80 (6.05)	62.80 (6.80)	61.25 (6.73)	61.90 (8.67)	3.04	**.037**	.23	.000	.993	.01	.993	.403	.03
Initiative	63.75 (8.77)	60.82 (7.53)	57.27 (9.09)	54.18 (12.05)	61.20 (10.02)	57.20 (8.32)	57.63 (8.93)	60.10 (9.09)	2.59	.062	.12	.002	.969	.01	2.073	.115	.08
Emotional control	65.67 (17.38)	59.91 (13.68)	62.00 (16.16)	55.00 (16.19)	56.40 (13.53)	52.10 (10.56)	53.38 (16.56)	56.40 (13.57)	1.835	.152	.06	.729	.402	.05	1.167	.331	.07
Transitions	61.33 (14.22)	62.82 (8.64)	64.82 (10.77)	59.09 (14.46)	52.60 (7.93)	51.40 (10.38)	53.63 (11.61)	55.30 (11.35)	.23	.873	.03	4.664	**.041**	.27	.665	.577	.05
Inhibition	63.91 (13.78)	61.64 (12.41)	60.09 (12.71)	54.00 (13.54)	62.60 (14.52)	57.40 (11.26)	55.63 (14.18)	57.90 (11.47)	2.95	**.041**	.13	.010	.922	.01	.773	.514	.04
Regulation of behavior	65.00 (14.21)	63.27 (12.24)	64.09 (14.63)	56.55 (16.63)	61.10 (17.39)	54.40 (11.15)	54.38 (15.69)	58.20 (13.04)	1.09	.363	.07	.254	.620	.06	1.310	.281	.06

(*continued on next page*)

Table 3 (*continued*)

	TDCS				Sham				Time			Group			Time × Group		
	T1	T2	T3	T4	T1	T2	T3	T4	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2
Metacognition	64.62 (9.51)	61.82 (8.42)	60.27 (9.76)	54.55 (12.52)	65.50 (4.77)	60.60 (8.29)	59.75 (8.55)	59.80 (8.94)	5.68	**.002**	.27	.179	.676	.01	1.130	.345	.04
Overall score	65.75 (10.45)	63.18 (9.08)	62.36 (10.83)	55.64 (14.14)	65.50 (7.65)	58.60 (8.09)	61.25 (10.95)	59.90 (10.75)	3.92	**.013**	.21	.000	.993	.01	1.187	.323	.05

T1 = baseline, T2 = after 6 sessions, T3 = after 12 sessions, T4 = 1 month after intervention df for the following effects are: CANTAB: time 3,65, group 1,22, time × group 3,65; CBCL: time 3,59, group 1,23, time × group 3,59; BRIEF time 3,55, group 1,22, time × group 3,55.
p values < 0.05 are noted in **bold**.

[a] Interpretation – RVPMDL (−) indicates decreasing scores represent improvement. As seen from the data for this variable, both groups showed improvement over the course of the intervention but with no significant differences between the two groups. Thus time, but not group, was found to be significant.

[b] These variables were no longer significant after removing for outliers.

only variable in the study to have demonstrated a group x time interaction. Yet the interaction in the analyses using the MLM approach inherently controls for baseline differences, thus the differences at baseline (T1) should not affect the outcomes observed at the other three time points (T2,T3,T4).

Considering the essentially negative findings regarding TDCS using the MLM approach, we also ran the analyses using repeated measures ANOVA. We found only minimal differences between the MLM and ANOVARM approaches and indeed for the Adverse Effects the results were identical. (See Supplementary Tables 1 and 2).

5. Discussion

This study examined effects of tDCS vs. sham-tDCS combined with CT in children with ADHD using a protocol of 1.0 mA, anodal DLPFC/cathodal Vertex montage, and 12 sessions delivered over four weeks. Overall adverse effects reported were mild and resolved after the intervention with no significant differences found between the two groups. However, three children, all receiving active stimulation, reported notable headaches, resulting in removal from the study for one child and temporary suspension of intervention for two children. Feasibility in this study was acceptable. Parents and children accepted the randomized allocation nature of the study, The overwhelming majority completed all sessions in the intervention, with 84% completing the protocol in the planned four weeks. There were *no* significant effects for tDCS on any of the primary outcome measures. Three subscales reached significance on the secondary measures, yet none remained significant after Bonferroni correction. In contrast to the tDCS findings, there were significant effects for CT on both primary and secondary outcome measures. While the lack of a control group does raise the possibility of placebo effects explaining this observed improvement, the fact that an improvement was observed demonstrates that a potential tDCS effect was not obscured by floor effects. Regarding effect sizes, in most cases, findings that were significant showed medium-high effect sizes. Non-significant findings had small effect sizes.

Our findings regarding adverse effects is consistent with the tDCS literature in children (Zewdie et al., 2020). Similar to the pediatric tDCS ADHD literature (Breitling-Ziegler et al., 2021; Nejati et al., 2021), we found no significant differences regarding adverse effects between those receiving active tDCS and sham-tDCS. Nevertheless, we note with some concern the finding of three subjects, all from the tDCS group, who developed notable headaches leading to removal or temporary suspension from the study. This has been reported in a previous study (Berger et al., 2021). These cases, while small in number, raise the need for vigilance when providing tDCS treatment to children and do suggest that prior headache history be considered an exclusionary entrance criterion for future studies. Our findings regarding feasibility, are similar to those reported in other studies (Andrade et al., 2014). Furthermore, they expand on prior work by demonstrating that protocols using non-daily stimulation sessions with the described parameters that are provided over the course of a month are indeed feasible.

The tDCS intervention we employed is unique with respect to the number and schedule of sessions (12 sessions provided three times a week for one month). We chose to explore a longer protocol to assess for longer lasting effects. Furthermore, allowing three-times-weekly vs. daily session protocols has the practical advantage of being more feasible for parents, thus increasing availability of such treatments to families. Furthermore, we employed a comprehensive set of measures that theoretically could be impacted by an intervention, to increase the likelihood of identifying any changes seen after intervention.

Comparing tDCS studies is challenging due to the plethora of protocols with differences in current, montage, number, length and distribution of stimulation sessions and combination with CT. Three published reviews utilizing the same studies except one (Kashani Khatib et al., 2019) have reported on tDCS effects in pediatric ADHD. Two reviews (Brauer et al., 2021; Salehinejad et al., 2020) concluded that tDCS

has promise and one review found limited evidence for improvement (Westwood et al., 2021b). Subsequently, two pediatric ADHD tDCS intervention studies have been reported (Berger et al., 2021) (stimulation site: left DLPFC) and (Westwood et al., 2021a) (stimulation site: right inferior frontal cortex), with both reporting no clinical benefits in their respective cohorts.

Examination of individual studies are informative. To date, only five studies have reported five or more stimulation sessions (Bandeira et al., 2016; Berger et al., 2021; Kashani Khatib et al., 2019; Soff et al., 2017; Westwood et al., 2021a). Three studies reported improvement (Bandeira et al., 2016; Kashani Khatib et al., 2019; Soff et al., 2017), with those of the latter two reporting marked effect sizes. Yet, only one study (Soff et al., 2017) had a blinded treatment design with participants not on medication.

Specific comparison of our findings to those of Soff and colleagues (Soff et al., 2017) are warranted, as we adopted the montage they employed (Anode: DLPFC, Cathode VERTEX). That study was of high methodological rigor and reported marked benefit of tDCS treatment. Differences between the studies might explain the different results. The current study provided stimulation three times per week over four weeks, included children and adolescents, and had a CT component. Soff and colleagues provided tDCS for 5 days, included only adolescents, but without a CT component. Perhaps spreading out stimulation every other day, may not be sufficient to effect change. Suggesting otherwise is one study (Berger et al., 2021) that provided daily stimulation for two weeks but with no benefit of tDCS. Again, perhaps dosage exceeding five sessions provides a negative effect. Yet, in our study, outcome assessed after six sessions did not find benefit of tDCS. It is also possible that the benefit of adding CT may mask improvement seen with tDCS alone. Finally, age effects may possibly have played a role in the results as Soff et al. (2017), included only adolescents.

Comparing our findings to the two recent negative tDCS studies (Berger et al., 2021; Westwood et al., 2021a) are valuable, as they also used a combined tDCS + CT component, though the latter study stimulated the right inferior frontal cortex. Nevertheless, like our findings, neither of those studies found clinical benefit of tDCS treatment.

We inspected the individual data for clues suggesting tDCS benefits, given the possibility that positive effects for tDCS were masked given the individual variability seen in ADHD as well as in response to the intervention protocol (Breitling et al., 2020; Lipka et al., 2021). Nevertheless, we were unable to identify findings suggesting a latent benefit of tDCS. Overall, one-third of the parents of the participants reported on clinical improvement in their child, with equal numbers of parents from each group (tDCS vs. sham-tDCS) reporting on improvement, suggesting that tDCS was not the relevant factor.

Thus, the present pilot study findings of no beneficial clinical or cognitive effects for multi session pediatric tDCS using the above-described protocol adds to an emerging literature reporting on no benefits for pediatric tDCS (Berger et al., 2021; Westwood et al., 2022; Westwood et al., 2021a). Beyond the lack of significance for the primary outcome measures, effect sizes for these measures were also small, supporting our suggested conclusion of lack of benefits for this tDCS protocol. Nevertheless, we state again that being a pilot study, our sample size precluded subtype analyses (e.g., ADHD type) that could identify a subgroup of children who may benefit from tDCS.

A number of possible reasons for our lack of identifying differences between the two treatment arms exists despite tDCS being beneficial. Stimulation parameters including alternate day tDCS, intervention provided over 1 month and the wide range of ages of the participants may indeed explain our lack of findings. Furthermore, beyond its involvement in ADHD, the left DLPFC has been implicated in many higher brain functions including but not limited to language processing (Klaus and Schutter, 2018), perceptual decision making (Heekeren et al., 2006) and mood disorders (Caetano et al., 2005). Such multiple associations could affect the results of the present study and given that not all of the above factors were controlled for, indeed represent a limitation to the findings presented. Finally, the placebo effect and the Hawthorne effect may have influenced outcomes, though given that this was a double-blind study, with two types of intervention (tDCS + CT), we suggest that such effects while present should not unduly result in effects in a particular direction. However, fuller understanding of the Hawthorne effect will require more research (McCambridge et al., 2014).

As CT of executive function was part of the intervention, understanding it's contribution is warranted. Our findings suggest CT is beneficial. The beneficial findings seen on the CANTAB may be considered "near-transfer" effects vs. improvement on clinical executive function as measured by the BRIEF, ADHD symptoms as measured by the VADPRS and CBCL that may be considered "far-transfer effects. Previous work has suggested that executive function training has significant near-transfer effects but less far-transfer effects (Diamond and Ling, 2016; Kassai et al., 2019). Furthermore, the relationship between CPT results and ADHD symptoms based on parent rating scales are low to moderate (Forbes, 1998; Rielly et al., 1999) and that they probably assess different aspects of ADHD (Hall et al., 2016). Furthermore, traditional ADHD rating scales and the BRIEF have been found to assess different aspects of children with ADHD (Linder et al., 2010). The use of a comprehensive battery in this study provides an important contribution to this literature by allowing comparison of the various aspects of function noted above and suggest that comprehensive assessments are necessary when assessing for change after intervention in children with ADHD.

5.1. Limitations

We had eight subjects (5 tDCS, 3 sham-tDCS) who met entrance criteria at the time of inclusion but who on initial VADPRS were found to have scores not meeting clinical criteria (a score of less than 2 or 3 on the 6 attention or hyperactive-impulsive items) subtypes. This could have created a ceiling effect on possible improvement and thus limit the ability to identify a change. We therefore performed a repeat analysis on all measures, but with these subjects excluded. Our results remained unchanged, with no evidence suggesting benefits of stimulation. As noted earlier, this being a pilot study precluded analyses for ADHD type, severity and common comorbid conditions.

5.2. Future directions

Future studies would benefit by using more homogenous samples regarding age range and larger sample sizes. Additionally, given that recent studies have not identified positive benefit to tDCS (Berger et al., 2021; Westwood et al., 2021a, 2022), consideration should be given to revisiting and performing open label studies that systematically examine different tDCS stimulation parameters (e.g., intensity, duration, montage) to identify promising tDCS interventions protocols.

In conclusion, we found no benefit for the addition of tDCS beyond that seen with CT in pediatric tDCS. These results raise questions regarding tDCS for children with ADHD and call for rigorous attention to protocol parameters to advance the state of the tDCS intervention literature.

Authors' contributions

Mitchell Schertz conceptualized and designed the study, performed investigations, performed data interpretation, and drafted the initial manuscript.

Yael Karni-Visel performed methodology development, performed data interpretation, reviewed and revised the manuscript.

Jacob Genizi performed data acquisition, data interpretation, reviewed and revised the manuscript.

Hofit Manishevitch performed data acquisition, data curation, reviewed and revised the manuscript.

Menachem Lam performed data acquisition, reviewed and revised the manuscript.

Ashraf Akawi performed data acquisition, reviewed and revised the manuscript.

Michal Dudai performed project administration, performed data acquisition, reviewed and revised the manuscript.

André A Fenton performed methodology development, performed data interpretation, reviewed and revised the manuscript.

Marom Bikson performed methodology development, performed data interpretation, reviewed and revised the manuscript.

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Declarations

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All other authors have no declarations of interest.

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Appendix A. Supplementary data

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