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REVIEW

Transcranial Direct Current Stimulation in ADHD: A Systematic Review of Efficacy, Safety, and Protocol-induced Electrical Field Modeling Results

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Abstract Transcranial direct current stimulation (tDCS) is a promising method for altering cortical excitability with clinical implications. It has been increasingly used in neurodevelopmental disorders, especially attention-deficit hyperactivity disorder (ADHD), but its efficacy (based on effect size calculations), safety, and stimulation parameters have not been systematically examined. In this systematic review, we aimed to (1) explore the effectiveness of tDCS on the clinical symptoms and neuropsychological deficits of ADHD patients, (2) evaluate the safety of tDCS application, especially in children with ADHD, (3) model the electrical field intensity in the target regions based on the commonly-applied and effective *versus* less-effective protocols, and (4) discuss and propose advanced tDCS parameters. Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses approach, a literature search identified 14 empirical experiments investigating tDCS effects in ADHD. Partial improving effects of tDCS on cognitive deficits (response inhibition, working memory, attention, and cognitive flexibility) or clinical symptoms (e.g., impulsivity and inattention) are reported in 10 studies. No serious adverse effects are reported in 747 sessions of tDCS. The left and right dorsolateral prefrontal cortex are the regions most often targeted, and anodal tDCS the protocol most often applied. An intensity of 2 mA induced stronger electrical fields than 1 mA in adults with ADHD and was associated with significant behavioral changes. In ADHD children, however, the electrical field induced by 1 mA, which is likely larger than the electrical

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field induced by 1 mA in adults due to the smaller head size of children, was sufficient to result in significant behavioral change. Overall, tDCS seems to be a promising method for improving ADHD deficits. However, the clinical utility of tDCS in ADHD cannot yet be concluded and requires further systematic investigation in larger sample sizes. Cortical regions involved in ADHD pathophysiology, stimulation parameters (e.g. intensity, duration, polarity, and electrode size), and types of symptom/deficit are potential determinants of tDCS efficacy in ADHD. Developmental aspects of tDCS in childhood ADHD should be considered as well.

Keywords Transcranial direct current stimulation · Attention-deficit hyperactivity disorder · Dorsolateral prefrontal cortex · Executive function · Systematic review · Brain modeling · Non-invasive brain stimulation · Pediatric

Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most commonly-diagnosed neurodevelopmental disorders. It is characterized by the symptoms of inattention, hyperactivity, impulsivity [1], and various cognitive dysfunctions [2, 3]. A precise description of the neuropathology underlying ADHD is difficult due to its neuropsychological heterogeneity [4] and the substantial overlap between children with ADHD and typically developing children [5]. However, based on neuroimaging and neuropsychological findings, distinct brain regions and networks have been identified to account for the hallmark symptoms [6, 7] and subtypes [8] of ADHD.

Poor inhibitory control resulting from deficient executive resources (i.e., the inhibition-based model) and impulse control deficits that lead to hyperactivity (i.e., the motivational dysfunction model) are influential theories of ADHD pathophysiology. According to the first model, the decisive factor in ADHD pathophysiology is impaired executive functions [9, 10], which are associated with hypoactivation of the dorsolateral prefrontal cortex (dlPFC) [11, 12] and hyperactivation of some subcortical regions [13]. Some executive functions play more critical roles in the ADHD symptoms and deficits, including cognitive flexibility, inhibitory control, and working memory [14, 15]. In the "motivational dysfunction theory" [16, 17], hyperarousal to environmental stimuli leads to an inability of the executive functioning system to control the respective stimuli [18, 19]. This theory attributes these symptoms to the medial frontal cortex, orbital and ventromedial prefrontal areas [7], and subcortical regions such as the caudate nucleus, amygdala, nucleus accumbens, and thalamus [20].

Such large-scale brain abnormalities in ADHD pathophysiology have encouraged researchers to look for novel treatment options that target the symptoms by modulating, altering, and remediating deficient brain functions. Recent studies highlight the relevance of non-invasive brain stimulation for modulating cortical excitability [21]. Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that uses a weak electrical current and can modulate cortical excitability [22]. Anodal stimulation increases cortical excitability, while cathodal stimulation usually decreases it [23] although an excitatory-enhancing effect on motor cortical excitability [24] and on non-motor areas [25] has recently been reported. TDCS has been shown to improve impaired components of executive functions not only in ADHD [7, 26] but also in other disorders accompanied by impaired executive functions such as depression [27], obsessive-compulsive disorder [28], anxiety disorders [29], and drug addiction [30], as well as in healthy populations [31–34], depending on the stimulation parameters. The safety of tDCS in adults [35] and children has been documented in previous studies [36] and confirmed by recent large dataset [37] although more evidence is needed for its safe application in pediatric populations.

Application of tDCS in pediatrics, especially children with neurodevelopmental deficits, has gained attention in recent years and has been suggested to be a promising tool for their rehabilitation and/or treatment [38, 39]. In ADHD with a typical onset of symptoms in childhood, early interventions that may modify the atypical neural circuits and networks involved in its pathophysiology might be promising. Several studies have shown the efficacy of tDCS for improving cognitive and behavioral functioning in both children and adults with ADHD, such as inhibitory control [40–43], visual attention [44], declarative and working memory [40, 44–46], and clinical symptoms [47, 48].

Most of the studies so far have investigated the effects of tDCS on neuropsychological symptoms (i.e., response inhibition and working memory) [26] and others were limited to behavioral and clinical symptoms [48, 49]. Furthermore, knowledge of the tDCS efficacy and safety in the clinical pediatric population, including ADHD, is still relatively limited and warrants further investigation [39, 50, 51]. Recently, several reviews have discussed non-invasive brain stimulation in neurodevelopmental disorders including ADHD [52–54]. These reviews however are not specifically dedicated to tDCS or ADHD. Furthermore, they do not provide an objective and comprehensive picture of tDCS efficacy in improving both the clinical symptoms and cognitive deficits with respect to effect size. Moreover, systematic investigation of tDCS safety, computational modeling of the electrical current

flow in the head that is associated with neurophysiological modulation [55], and a detailed discussion of potential stimulation parameters are still missing.

Here, we used the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) method to systematically review the studies that investigated the effects of tDCS on the clinical symptoms and cognitive-behavioral impairments in both childhood and adult ADHD in order to (1) evaluate the efficacy of this technique in improving the clinical symptoms and neuropsychological deficits, (2) calculate the effect sizes and the magnitude of changes in outcome variables, (3) investigate the safety aspects of tDCS in clinical pediatric populations, (4) model the electrical fields induced by the commonly-used tDCS protocols in ADHD, and (5) discuss and propose advanced tDCS parameters and montages for ADHD treatment.

Methods

Data for this systematic review were collected in accordance with the PRISMA checklist [56]. Our checklist can be found in the supplementary information.

Eligibility Criteria

Only peer-reviewed published studies were included in our analysis. The inclusion criteria were (1) randomized placebo (sham)-controlled or baseline-controlled design and open-label studies with sham or baseline control, (2) published in English, (3) targeting the clinical symptoms and/or cognitive deficits of ADHD, (4) no comorbidity with other developmental disorders/disabilities (e.g. autism, learning disabilities, conduct disorder, or oppositional defiant disorder) in childhood ADHD and psychiatric disorders in adult ADHD, and (5) published as empirical and not review or methods articles. Having a history of or under stimulant medication was allowed as long as the regimen was stable. In Munz *et al.* [41] ($n = 14$) and Breitling *et al.* [42] ($n = 21$), 3 patients had comorbid conduct disorders. No studies were excluded based on the participants' age, and both adult and childhood ADHD were included. In addition, a clinical diagnosis of ADHD based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV/V) confirmed by a psychiatrist, and/or meeting accepted cut-off values on validated ADHD symptom rating scales were required (see supplementary information for details of rating scales).

Information Sources

The primary sources of information for identifying studies were the PubMed and Scopus databases. We also used other widely-used search engines, such as Google Scholar, and reference lists from the identified articles.

Search Strategy and Study Selection

A comprehensive literature search was conducted by two independent data extractors [the first (MAS) and fourth (AM) authors] with the final search updated on January 30, 2020. The search terms were: attention-deficit hyperactivity disorder, ADHD, attention disorders, transcranial direct current stimulation, tDCS, transcranial electrical stimulation, and tES. Furthermore, a manual search of the reference sections of the retrieved studies and review articles was carried out. The final search identified a total of 241 articles, which were reduced to 31 after removing duplicates. The titles and abstracts of the remaining records were screened for eligibility, which led to the exclusion of 15 for either being animal model studies or with an inappropriate scope. Afterwards, the full text of each publication was assessed and eligible studies according to the inclusion criteria were selected. In this step, 2 more articles were excluded since the main text was not written in English. In sum, 17 ($15 + 2$) articles were excluded for not meeting the inclusion criteria after the abstract and full-text screening. Thus 14 articles remained for full-text assessment and data extraction (Fig. 1).

Outcome Variables

Major clinical symptoms (inattention, hyperactivity, and impulsivity) and executive dysfunctions were the main outcome measures. Clinical symptoms were measured by DSM-IV/V diagnostics and/or the scores on ADHD self-reports and other-report scales [i.e., Adult ADHD Self-Report Scale (ASRS), Conner's Adult ADHD Rating Scale–Self Report, Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale, Swanson, Nolan and Pelham Rating Scale–IV (SNAP-IV), German Adaptive Diagnostic Checklist for ADHD (FBB-ADHD), and Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime (K-SADS-PL)], or performance in behavioral tests like the QbTest [57], or Conners Continous Performance Test [58]. Neuropsychological and cognitive deficits included response inhibition, working memory, interference control, attention, and cognitive flexibility. Response inhibition and interference control were measured with Go/No-Go, Stroop, Flanker, and Neuropsychological Development Assessment (NEPSY II). For working memory, the following tasks were included: (1) N-back, (2) Digit Span, and (3) Corsi block-tapping test. [59]. Cognitive flexibility was measured by the Wisconsin Card Sorting Test [60]. Details of the

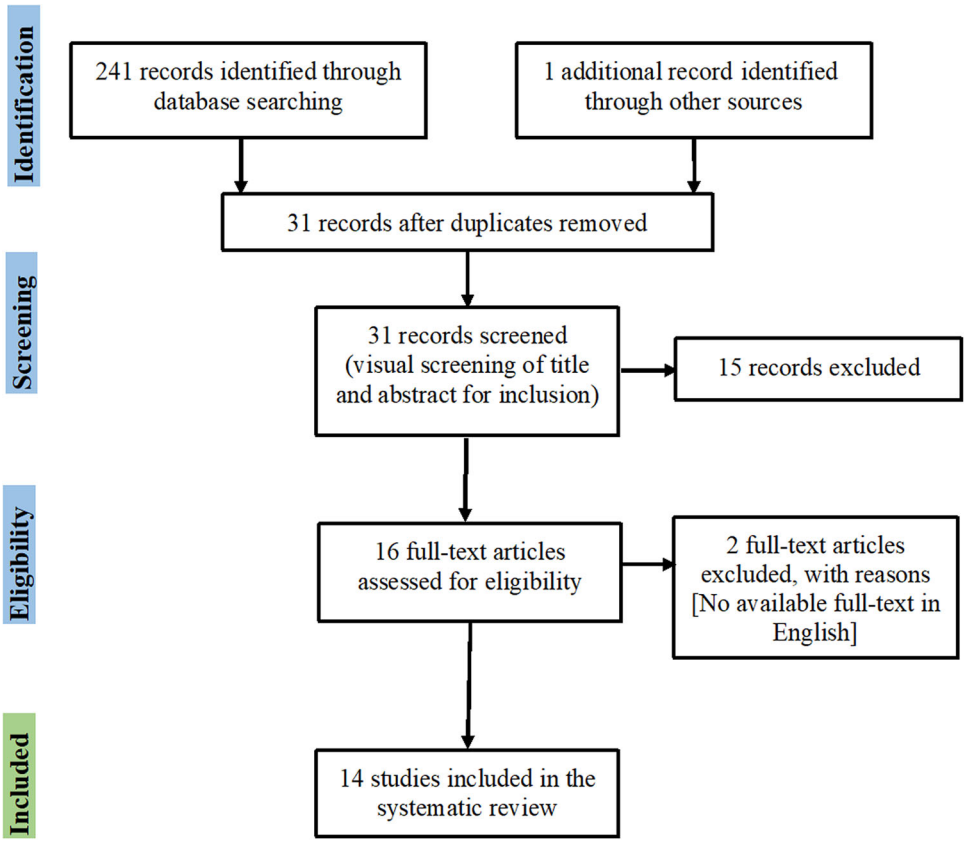

Fig. 1 PRISMA flow diagram of included studies investigating the effects of transcranial direct current stimulation in ADHD.

outcome measures examined in each task are presented in the supplementary materials.

Risk of Bias

Risk of bias assessment was performed using the Cochrane Collaboration's tool [61]. For each study, the authors judged the risk of selection, performance, detection, attrition, reporting, and other biases. Risk of bias was categorized as low, high, or uncertain. The evaluation of each study is displayed in Fig. 2.

Results

Inter-rater reliability for the inclusion and exclusion of studies was high (Cohen's k = 0.84). In total, 14 separate studies published between 2014 and the end of January 2020 were included [40–49, 62–64]. Details of the studies are summarized in Table 1 and Fig. 3.

Risk of Bias

Risk of bias as judged by the authors is represented in Fig. 2. Generally, the risk of bias was very low with no indication of selection, performance, or attrition bias. In Jacoby *et al.* [63] the sources of other biases include no formal diagnosis for 3 participants in the ADHD group, recruitment of 3 participants from the student community, and no randomization/counterbalancing of the task in each session. In Breitling *et al.* [64], the sources of other biases are different experimental procedures in the control and ADHD groups, and reduction of stimulation intensity to 50% in 3 out of 14 participants due to low tolerability of the standard current intensity. Three studies used a single-blind design [42, 62, 63] yielding a potential detection bias as the experimenter was not blind to the tDCS condition. A blinding efficacy check was not explicitly reported in 6 studies [44–46, 62–64], hence these were categorized as uncertain for selection bias. No other biases were found.

Clinical Efficacy

Three of the included studies specifically investigated the effects of tDCS on the clinical symptoms of ADHD [47–49]. The results of these studies show that anodal tDCS can improve impulsivity and inattention and suggest that tDCS over the dlPFC might be suitable as a potential therapeutic approach in ADHD. While anodal left dlPFC tDCS was applied in two studies [47, 49], anodal right dlPFC tDCS was used in the Cachoeira *et al.* study. In the Allenby *et al.* study, the stimulation protocol was selected

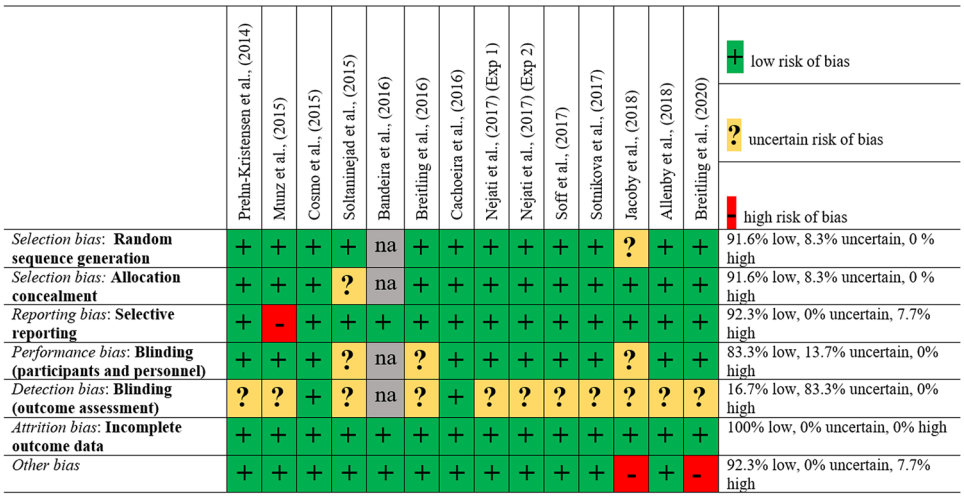

Fig. 2 Bias assessment of included studies using the Cochrane risk of bias tool (na, not applicable).

based on cognitive control and attention networks, which are more closely related to left dlPFC activation [65, 66] and task-based functional patterns in ADHD [7]. Similarly, in the Soff *et al.* study, the montage was selected based on the targeted cognitive deficit, which was working memory that strongly depends on left dlPFC activation. In the Cachoeira *et al.* study, no specific cognitive deficit was targeted. Based on the right hemisphere dysfunction in the frontal network, including the dlPFC, in ADHD [67], they applied anodal right dlPFC tDCS with the reference electrode over the left dlPFC and symptoms were monitored using self-report scales rather than behavioral tasks. Details of these studies are displayed in Table 1 and Fig. 3.

Neuropsychological and Cognitive Effects

The remaining studies [40–46, 62–64] mainly investigated the effects of tDCS on specific neuropsychological and cognitive deficits in ADHD (e.g., working memory, inhibitory control, attention, executive functions) (study details are summarized in Table 1). Briefly, the results show that dlPFC tDCS – specifically over the left dlPFC – improved the response inhibition, attention, working memory, and cognitive flexibility in ADHD patients. To be more specific, anodal left dlPFC tDCS, but not cathodal stimulation, improved working memory in ADHD [46]. Anodal right IFG (r-IFG) stimulation did not improve working memory [64]. With regard to inhibitory control, anodal left or right dlPFC tDCS [41, 45, 46], compared to bilateral dlPFC tDCS[43, 46] and anodal r-IFG tDCS [42], had a larger impact on response inhibition in ADHD. For those executive function domains that involve motivational and emotional processing [e.g. the Wisconsin Card Sorting Task (WCST)], tDCS over both prefrontal and frontopolar areas was more effective than dlPFC-only tDCS [46]. In other words, only when both the dlPFC and orbitofrontal cortex (OFC) were stimulated, did performance in the WCST improve [46].

Size of Effects

We calculated the effect sizes (Cohen's *d*) of the outcome measures reported in the included studies (Table 2). Due to the heterogeneity of outcome measures, calculation of cumulative overall effect size (meta-analysis) is not accurate and informative. Therefore, we separately analyzed the effects of tDCS for each clinical symptom and neuropsychological deficit. A recently published meta-analysis on the effects of tDCS on response inhibition and working memory in ADHD showed a significant tDCS effect (especially anodal dlPFC tDCS) on response inhibition with a small effect size, but no significant effect on working memory, except for performance speed, with a medium effect size [26]. In the present study, we calculated Cohen's *d* not only for clinical symptoms, but also for other cognitive/neuropsychological measures reported in the tDCS studies, including selective attention and cognitive control (Table 2). For cognitive control, the results show that the acquired effect sizes strongly depend on the stimulation protocol. With regard to tDCS effects on ADHD clinical symptoms, a large effect size for the inattention subscale was revealed [47, 48] and a medium effect size for hyperactivity/impulsivity [47, 49]. However, a definite conclusion with respect to the clinical efficacy of tDCS based on the results of these three studies is not possible.

Adverse Effects

Of 14 studies included in the present review, 10 were conducted in patients with childhood ADHD. Of 747 sessions of tDCS applied in 278 ADHD patients, 449

Table 1 Characteristics of included studies investigating the effects of tDCS in ADHD.

Reference	Study type (Blinding)	*n* (mean age ± SD); gender (m/f)	ADHD type (inattentive/ hyperactive/ combined)	Medication intake (*n*)	Task (measure)	Expected outcome	Current intensity; duration	Repetition rate	Polarity/electrode size	Control	Results
Prehn-Kristensen *et al.* [45]	RCT (double blind)	ADHD children *n* = 12 (12 ± 1.4, 10–14 years)/ Healthy control *n* = 12; 24/0	4/0/8	Off stimulants 48 h (*n* = 12)	Declarative memory	Change in score in the retrieval phase	So-tDCS (0–250 μA, 0.75 Hz); 5 × 5 min	Single session	Anodal F3- cathodal M1 & anodal F4 - cathodal M2/ 0.503 cm^2 (Ag/ AgCl sintered skin electrodes)	Sham	Enhanced memory consolidation and retrieval following active tDCS vs sham tDCS
Munz *et al.* [41]	RCT (double blind) successful blinding	*n* = 14 (12.3 ± 1.39, 10–14 years); 14/0	6/0/8	Off stimulants 48 h (*n* = 10)	Go/No-Go (response inhibition), motor memory task	Change in the RT and accuracy of tasks	So-tDCS (0–250 μA, 0.75 Hz); 5 × 5 min	Single session	Anodal F3- cathodal M1 & anodal F4 – cathodal M2/ 0.503 cm^2 (Ag/ AgCl sintered skin electrodes)	Sham	Significantly improved RT after active stimulation vs sham in Go/No-Go and motor memory tasks but no significant improvement in the correct responses.
Cosmo *et al.* [43]	RCT (double blind) successful blinding	*n* = 60 (32.25 ± 10.96,18–-65 years); 35/25	13/3/44	On stimulants (*n* = 11)	Go/No-Go (response inhibition)	Change in the Go/No-Go task performance	1 mA; 20 min	Single session	Anodal F3-cathodal F4/5 × 7 cm	Sham	No significant differences in inhibitory control between active tDCS vs sham tDCS
Soltaninejad *et al.* [62]	RCT (single-blind)	*n* = 20 (16.40 ± 1.09, 15–17 years); 20/0	NR	Off medication	Go/No-Go and Stroop (response inhibition, attention, interference inhibition)	Change in Go/ No-Go & Stroop tasks performance	1.5 mA; 15 min	Single session	(1) anodal F3 - cathodal Fp2 (2) cathodal F3, anodal Fp2 /5 × 7 cm	Sham	Anodal left dlPFC tDCS vs sham, did not improve response inhibition in the Go-No/Go task. Cathodal left dlPFC Tdcs vs sham, improved inhibition accuracy in the Go-No/Go task. Noprotocols improved selective attention
Bandeira *et al.* [44]	Open-label study	*n* = 9 (11.11 ± 2.08, 6–16 years); 8/1	NR	Off medication 1 week before	TAVIS 3, Corsi Cube test, NEPSY II & Digit Span (selective attention, WM, response inhibition) ADHD symptoms via SNAP-IV	Changes in selective attention, WM, IC tasks, and SNAP-IV	2 mA; 30 min	Five sessions	Anodal F3 cathodal Fp2/5 × 7 cm	Baseline Control	Significantly reduced omission errors in selective attention task, shorter RT and reduced errors in the switching but not inhibition phase. Clinical symptoms slightly improved according to the parent's response in the SNAP-IV

Table 1 continued

Reference	Study type (Blinding)	*n* (mean age ± SD); gender (m/f)	ADHD type (inattentive/ hyperactive/ combined)	Medication intake (*n*)	Task (measure)	Expected outcome	Current intensity; duration	Repetition rate	Polarity/electrode size	Control	Results
Breitling *et al.* [42]	RCT (single blind) unsuccessful blinding	ADHD children *n* = 21 (14.33)/ Healthy control *n* = 21 (14.24); 21/0	5/0/6	Off stimulants 24 h (*n* = 11)	Flanker task (interference control, response inhibition) (online)	Changes in the Flanker task	1 mA; 20 min	Three sessions	Anodal-cathodal-shamF8, reference electrode over left mastoid/5 × 7 cm	Sham	No significantly improved interference control in ADHD patients. Only anodal tDCS, if applied in the first session, significantly diminished commission errors in ADHD group *vs* healthy controls (learning effect).
Cachoeira et al. [48]	RCT (double blind) successful blinding	*n* = 17 (32.37 ± 4.91, 18–45 years); 8/9	7/0/10	Off stimulants	ASRS (ADHD symptoms) & SDS	Change in the ASRS and SDS scores	2 mA; 20 min	Five sessions	Anodal F4- cathodal F3/5 × 7 cm	Sham	Bilateral dlPFC tDCS (anodal right) improved symptoms in adult ADHD. This improvement persisted after the end of the stimulation
Nejati *et al.* [46] (Exp 1)	RCT (double-blind)	*n* = 15 (10 ± 2.3, 8–15 years); 15/0	6/0/9	Off stimulants	Go/No-Go (response inhibition)/1-back (WM)/ Stroop (interference control)/WCST (cognitive flexibility)	Change in the Go/No-Go, 1-back, Stroop & WSCT tasks performance	1 mA; 15 min	Two sessions	Anodal F3- cathodal F4/5 × 5 cm	Sham	Bilateral dlPFC tDCS (anodal left) improved executive control function (WM, interference control) but not prepotent response inhibition and cognitive flexibility
Nejati *et al.* [46] (Exp 2)	RCT (double-blind)	*n* = 10 (9 ± 1.8, 7–12 years); 5/5	5/5	Off stimulants	Go/No-Go (response inhibition)/1-back (WM)/ WCST (cognitive flexibility)	Change in the Go/No-Go, 1-back, & WSCT tasks performance	1 mA; 15 min	Three sessions	(1) Anodal F3-cathodal Fp2 (2) cathodal F3-anodal Fp2/ 5 × 5 cm	Sham	Anodal left dlPFC tDCS improved WM accuracy and RT. Cathodal left dlPFC tDCS improved response inhibition. Both anodal and cathodal left dlPFC tDCS improved cognitive flexibility.

Table 1 continued

Reference	Study type (Blinding)	*n* (mean age ± SD); gender (m/f)	ADHD type (inattentive/ hyperactive/ combined)	Medication intake (*n*)	Task (measure)	Expected outcome	Current intensity; duration	Repetition rate	Polarity/electrode size	Control	Results
Soff *et al.* [47]	RCT (double-blind) successful blinding	*n* = 15 (14.20 ± 1.2, 12–16 years); 12/3	patients were combined or hyperactive type	Off stimulants 96 h (*n* = 5)	FBB-ADHD &QbTest	Change in the inattention, hyperactive and impulsivity scales	1 mA; 20 min	Five sessions	Anodal F3, cathodal Cz/5 × 7 cm	Sham	Anodal tDCS significantly reduced symptoms of inattention (measured by FBB-ADHD), and hyperactivity/inattention(measured by the Qbtest) in adolescents with ADHD compared to sham stimulation
Sotnikova *et al.* [40]	RCT (double-blind) successful blinding	*n* = 13 (14.33 ± 1.32, 12–16 years); 11/2	patients were combined or hyperactive type	Off stimulants 96 h (*n* = 5)	Q-b Test (WM)	Changes in the Qb test scales	1 mA; 20 min	Two sessions	Anodal F3, cathodal Cz/5 × 7 cm	Sham	Moderate effect of tDCS. Anodal tDCS led to significantly less increased RT and RT variability but also more errors. Increased neuronal activation and connectivity in the left dlPFC and other remote brain regions
Jacoby *et al.* [63]	RCT (single-blind)	ADHD group *n* = 21/ Healthy control *n* = 16 (23.03 ± 2.54, 19–29 years); 23/12	NR	On stimulants	MOXO-CPT (Attention, hyperactivity)	Changes in the CPT performance	1.8 mA; 20 min	Two sessions	Double anodal bilateral tDCS (anodal *1* F3, anodal *2* F4, cathodal cerebellar cortex)	Sham	tDCS did not improve attention, timing, and impulsivity. The only measure which was improved by tDCS was hyperactivity
Allenby *et al.* [49]	RCT (double-blind) unsuccessful blinding	*n* = 37 (18–65); 26/11	21/0/16	On stimulants (*n* = 17)	CPT, SST	Change in the CPT false error and SST accuracy and RT	2 mA; 20 min	Three sessions	Anodal F3-cathodal Fp2/5 × 5	Sham	Anodal left dlPFC tDCS improved impulsivity symptoms in ADHD compared to sham tDCS

Table 1 continued

Reference	Study type (Blinding)	*n* (mean age ± SD); gender (m/f)	ADHD type (inattentive/ hyperactive/ combined)	Medication intake (*n*)	Task (measure)	Expected outcome	Current intensity; duration	Repetition rate	Polarity/electrode size	Control	Results
Breitling *et al.* [64]	RCT (double-blind)	ADHD children $n = 14$ (13.3 ± 1.9)/ Healthy control $n = 15$ (13.3 ± 1.8); 25/4	4/0/10	Off stimulants 24 h ($n = 5$)	2-back (WM) (online) and right after tDCS during EEG/K-SADS-PL (symptoms)	Change in 2-back task performance	1 mA (conventional) 0.5 mA (4 × 1 montage); 20 min	Three sessions	(1) Anodal F8, cathodal Fp1/5 × 7 cm; (2) 1 cm diameter electrodes in 4 × 1 montage (HD-tDCS)	Sham	No effect of conventional or HD-tDCS on WM performance. Numerically higher rate of responders for 4 × 1 (50%) than conventional (35%) tDCS. Higher N200 and P300 amplitudes after both protocols

[a]tDCS, transcranial direct current stimulation; So-tDCS, Slow-oscillating tDCS; ADHD, attention-deficit hyperactivity disorder; RCT, randomized control study; SD, standard deviation; RT, response time; m, male; f, female; F3, left dorsolateral prefrontal cortex (dlPFC); F4, right dlPFC; F8, right inferior frontal gyrus (rIFG); M1, A1 in 10-20- EEG system (left mastoid); M2, A2 in 10-20 EEG system (right mastoid); IFG, inferior frontal gyrus; Fp1, left supraorbital area; Fp2, right supraorbital area; NR, not reported; TAVIS 3, computerized test of visual attention; WM, working memory; ASRS, Adult ADHD Self-Report Scale Symptom Checklist 3; SDS, Sheehan Disability Scale; CPT, Conners Continuous Performance Task; SST, Stop Signal Task; FBB-ADHD, German adaptive ADHD Diagnostic Checklist; QbTest, Quantified Behavior Test; SNAP-IV, Swanson, Nolan, and Pelham–IV; K-SADS, Schedule for affective disorders and schizophrenia for school-age children; WSCT, Wisconsin Card Sorting Test.

sessions of tDCS were conducted in 143 ADHD children and none of them reported serious adverse effects during or after tDCS. No adverse effects were reported by the participants during or after tDCS in the Prehn-Kristensen *et al.* [45] and Munz *et al.* [41] studies. Soltaninejad *et al.* [62] used a side-effect survey after tDCS to assess potential side-effects and reported there were none. In the Bandeira *et al.* study [44], the authors reported that adverse effects were mostly mild; however, they reported a feeling of ''shock'' during tDCS in some patients. Breitling *et al.* [42] reported no adverse effect beyond skin sensations (tingling and itching) during active and sham stimulation, with trend-wise stronger sensations during cathodal stimulation. In their recent report [64], medium- intensity tDCS-related sensations were reported for itching, pain, fatigue, low headache, and phosphenes. In both experiments of Nejati *et al.* [46] no severe adverse effects were reported, but mild tingling and itching under the surface of the electrodes were mentioned. Similarly, adolescent participants in the Soff *et al.* study [47] tolerated the stimulation without any problem, except for one case of headache after anodal tDCS, and mild tingling and itching under the electrodes. Last, in the Sotnikova *et al.* study [40], no signs of fatigue, burning, pain, or other uncomfortable sensations during stimulation were reported. Only one participant felt nervous or overexcited during stimulation and another reported headache.

In four studies conducted in adult patients with ADHD, no major adverse effects of tDCS were reported. Cosmo *et al.* [43] assessed the safety and potential side-effects *via* open questions based on the tDCS adverse events questionnaire [68] and reported none. In the Cachoeira *et al.* study [48] only one participant experienced an acute mood change, sadness, hypobulia, and tension 5 h after stimulation. No more side-effects were reported. All participants in the Jacoby *et al.* study [63] tolerated tDCS well and no adverse effects were reported. Finally, Allenby *et al.* [49] reported that the average side-effects experienced during tDCS were generally mild, rated below 3 out of 10. Tingling (Mean = 1.9), burning sensation (Mean = 2.8), and difficulty concentrating (Mean = 2) were the most prominent experiences.

Electrical Current Flow in the Head

Neurophysiological modulations induced by tDCS are associated with electrical field strength [55]. The flow of electrical current in the head depends on stimulation intensity, electrode size, angle, and the developmental stage of the participant (child or adult). Modeling current flow in the head can mathematically indicate how much cortical/subcortical regions are affected by the current and allow evaluation of the protocol-induced modulation of

activity in targeted regions. In 12 studies, the anodal electrode was placed over the left dlPFC, and in these studies, bilateral dlPFC tDCS and anodal left dlPFC – cathodal right supraorbital tDCS were the most used protocols (Table 1) in both adults and children. We modeled the current flow induced by these two commonly-used protocols at current intensities of 1 mA and 2 mA for both adults and children with ADHD (Fig. 4). We also modeled the r-IFG protocol [42], which found null effect of r-IFG stimulation on executive control in ADHD (Fig. 4D). Cosmo *et al.* [43] and Cachoeira *et al.* [48] used bilateral dlPFC tDCS with 35 cm^2 electrodes and 1 mA and 2 mA, respectively, in adult ADHD patients (Fig. 4A). While Cosmo *et al.* found no significantly superior effect of active tDCS compared to sham tDCS, Cachoeira *et al.* reported improved ADHD symptoms. This difference could be due to the repetition rate of stimulation in the latter study; however, modeling of the current flow induced by these two protocols shows that the current flow induced in cortical regions by 1 mA is approximately half (0.4 V/m) of that by 2 mA (0.8 V/m) in adults (Fig. 4). We also modeled bilateral dlPFC tDCS with 25 cm^2 electrodes and 2 mA to compare the current flow induced by smaller electrode size (Fig. 4Ag).

The current flow induced by 2 mA anodal left dlPFC – cathodal right supraorbital tDCS through 25 cm^2 electrodes in the adult population reported in the Allenby *et al.* study [49] found a significant reduction of impulsivity scores induced by tDCS (Fig. 4B). The same protocol (anodal F3–cathodal Fp2, 25 cm^2 electrodes) with 1 mA and 2 mA was used for ADHD children in studies by Nejati *et al.* [46] (2^{nd} experiment) and Bandiera *et al.* [44], respectively (Fig. 4C). The first important point to note here is the resulting electrical field in children compared to adults. 1 mA (anodal F3–cathodal Fp2) induces a field strength of 0.6 V/m in the brain of children (Fig. 4Ce), which has been shown to be sufficient to modulate target regions, while the same intensity (anodal F3–cathodal F4) in adults induces a field strength of 0.4 V/m (Fig. 4Af) which was insufficient to alter performance in the studies. Second, it is important to take into account that the resultant electrical field is determined not only by current strength, but by the combination of electrode size, stimulation intensity, and distance between electrodes. In the Bandiera *et al.* study, the current intensity was 2 mA, which results in an induced electrical field of $\sim$ 0.7 V/m, while in the study of Nejati *et al.*, 1 mA induces an electrical field of 0.6 V/m in the target region. A major reason for this lower than expected difference between resultant electrical fields is that in the Bandiera *et al.* study, the distance between electrode edges was smaller than that in the study by Nejati *et al.*, due to the larger electrode size used in the former study, and the relatively close positions of the targeted areas in the heads of children, which increases the shunting of current between the electrodes through the skin. This shows the importance of electrode size and the distance between electrodes for the effects of tDCS; this is especially relevant in children, where the distance to target regions is smaller than in adults due to the smaller head size. The electrical field induced by the anodal r-IFG tDCS protocol at 1 mA is shown in Fig. 4D (last row) [42]. No significant tDCS-specific effect on ADHD symptoms was reported. As our modeling suggests, the electrical field induced by this electrode arrangement does not properly target the r-IFG (the area under the electrode), which could be one reason for the reported null effects. We discuss the impact of stimulation parameters on tDCS efficacy in more detail in the next section.

Discussion

The results of this systematic review show that tDCS at least partially improves the symptoms of ADHD, especially the cognitive deficits. All of the included studies, except for three experiments, reported significant improving effects of tDCS on some of the target variables (Table 1). However, tDCS efficacy and importantly its clinical utility in ADHD cannot be concluded yet and warrant further investigation with optimized designs. One source of variability in the findings was the heterogeneous stimulation parameters that may not be well-suited for all ADHD subtypes. In what follows we discuss how these parameters could yield larger effects, and the clinical and methodological implications for future studies. Given that the majority of studies were conducted on childhood ADHD, we discuss the developmental aspects of tDCS separately.

Stimulation Parameters

Stimulation Site

Three cortical regions were targeted by tDCS in the studies included in this review: the dlPFC [40, 41, 43–49, 62, 63], the OFC (supraorbital cortex) [44, 46, 49, 62], and the r-IFG[42, 64]. In 13 experiments, the dlPFC was the primary target of stimulation, while the r-IFG was stimulated in only two experiments. For stimulation over the dlPFC, both left and right dlPFCs were targeted in different studies, but left dlPFC tDCS was applied more frequently (Table 1).

The rationale for targeting the dlPFC, r-IFG, or OFC was based on the involvement of these regions in ADHD

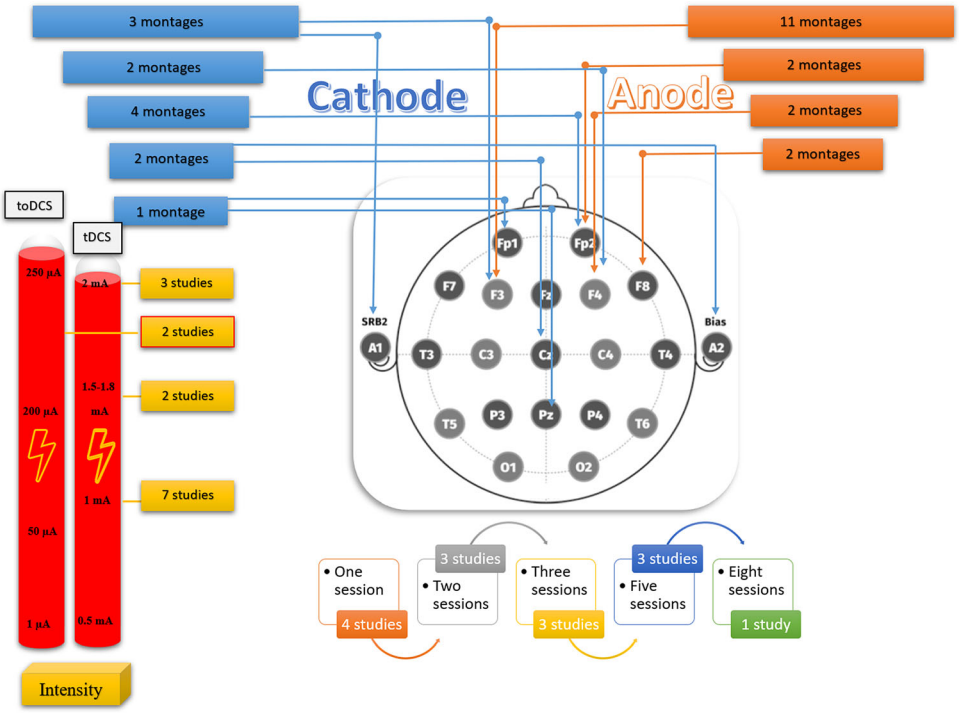

Fig. 3 Stimulation parameters of included studies investigating the effects of tDCS in ADHD (tDCS, transcranial direct current stimulation; toDCS, transcranial slow-oscillating direct current stimulation; Fp1, left supraorbital area; Fp2, right supraorbital area; F3, left dorsolateral prefrontal cortex; F4, right dorsolateral prefrontal cortex; F8, right inferior frontal gyrus; A1, left mastoid; A2, right mastoid; Cz, vertex; Pz, cerebellar cortex).

symptoms and pathophysiology. Recent meta-analyses of neuroimaging studies in ADHD showed bilateral hypoactivity of the dlPFC [73], reduced activity of the right inferior and dorsolateral PFC [67], and reduced left and medial frontal cortex activation [74] during the response inhibition, working memory, and attention tasks. For some dlPFC-related deficits, such as in working memory, an association between the stimulation site (i.e., left dlPFC) and deficit-specificity was established. In other deficits such as response inhibition, both the left and right dlPFC are involved and tDCS effects differ depending on the type of task applied and the outcome measure (i.e., commission *versus* omission error, reaction time). Nevertheless, the right dlPFC, which seems to be more relevant to ADHD with impaired inhibitory control, has not yet been studied enough. A recent repetitive transcranial magnetic stimulation study showed involvement of the right prefrontal cortex in alleviating symptoms of adult ADHD [75]. The importance of right dlPFC is partly due to its connections with the r-IFG.

The r-IFG has reduced activity in individuals with poor inhibitory control [76, 77] and is therefore regarded as a potential region of interest in ADHD pathophysiology [78, 79]. Only two studies in the database targeted the r-IFG with anodal tDCS and reported no significant improving effect on interference control [42] and working memory [64]. As our modeling results suggest (Fig. 4D), the electrode arrangement in the first Breitling *et al.* study [42] was likely suboptimal, and did not target the r-IFG sufficiently. According to the modeling results, placing the reference electrode on a more superior region rather than the mastoid could increase the electrical field in the r-IFG. Moreover, since this region is anatomically deeper than the dlPFC, it might be necessary to increase the stimulation intensity to achieve relevant results in that region. In their recent study, Breitling *et al.* [64] compared the 4 × 1 electrode montage (0.5 mA) with the conventional montage (1 mA) over the r-IFG in ADHD patients (Table 1). Although they reported more responders to the focal stimulation montage than the conventional montage, the protocols had no significant effect on behavioral performance. The use of large electrodes (5 × 7 cm^2) in the conventional montage, relatively low stimulation intensity in the 4 × 1 electrode montage, small sample size, and use of a working memory task that may be more closely related to dlPFC than r-IFG activation could be reasons for their null effects. The null effect of r-IFG tDCS could also be due to contributions of different prefrontal regions to different aspects of response inhibition (i.e., cognitive *vs* motor aspects) shown in previous studies [78–80]. Accordingly, it is reasonable to speculate that ADHD subtypes, which differ regarding cognitive and motor-related symptoms (i.e., inattentive *vs* hyperactive types), and specific components of response inhibition (i.e., motor *vs* cognitive response inhibition), also affect the efficacy of tDCS over the respective target areas. This hypothesis was partially supported by the Breitling *et al.* study [64] where it was shown that in patients with fewer hyperactive symptoms

Table 2 Effect size of the outcome measures (both significant and non-significant) of included studies.

Study	Outcome variable		*P*	Cohen's *d*	Size
Prehn-Kristensen *et al.* [45]	Working memory	Digit span*	**0.004**	−0.575	Medium
Munz *et al.* [41]	Response inhibition	RT*	**0.03**	0.91	Large
		RT variability*	**0.04**	0.855	Large
Cosmo *et al.* [43]	Response inhibition (letters)	Correct responses	0.69	0.073	Very small
		Omission error	0.89	0.272	Small
		Commission error	0.98	−0.069	Very small
	Response inhibition (fruits)	Correct responses	0.78	−0.104	Small
		Omission error	0.79	−0.133	Small
		Commission error	0.68	−0.035	Very small
Soltaninejad *et al.* [62]	Response inhibition (Go/NoGo)	Go accuracy	0.07	−0.028	Very small
		No-go accuracy*	**0.03**	0.054	Very small
		RT	0.09	0.249	Small
	Response inhibition (Stroop)	accuracy	0.10	0.594	Medium
		RT	0.31	0.249	Small
Bandeira *et al.* [44] [1]	Selective attention	Omission errors*	**0.03**	0.376	Small-to-medium
	Response inhibition (NEPSY-II)	Total error*	**0.012**	0.165	Small
		Completion time*	**0.016**	0.588	Medium
	Digit span forward	Accuracy	0.125	−0.82	Very small
	Digit span backward	Accuracy	0.531	−0.356	Medium
	Corsi cube forward	Accuracy	0.281	−0.401	Medium
	Corsi cube backward	Accuracy	0.813	0.125	Very small
Breitling *et al.* [42]	Response inhibition (Flanker task) – anodal stimulation	Omission error	n/r	−0.088	Very small
		Commission error*	**0.02**	0.476	Medium
		RT	n/r	−0.122	Small
		RT variability*	**0.05**	0.153	Small
	Response inhibition (Flanker task) – cathodal stimulation	Omission error	n/r	−0.58	Very small
		Commission error	n/r	0.187	Small
		RT	n/r	0.152	Small
		RT variability	n/r	0	–
Cachoeira et al. [48]	ADHD symptoms (ASRS)	Inattention*	**0.001**	0.85	Large
		Hyperactivity/ impulsivity	0.01	0.60	Medium
		total	0.003	0.81	Large
Nejati *et al.* [46]	Response inhibition (Go/NoGo)	Go accuracy	0.66	0.157	Small
(Exp 1) Anodal left DLPFC – cathodal right DLPFC		No-go accuracy	0.32	0.112	Small
		RT	0.14	0.263	Small
	Response inhibition (Stroop)	Accuracy*	**0.01**	0.726	Large
		RT*	**0.02**	1.119	Large
	Working memory	Accuracy	0.65	0.109	Small
		RT*	**0.01**	1.42	Large
	Cognitive control / flexibility (WCST)	Completion time*	**0.01**	0.577	Medium
		Perseverative errors	0.86	0.063	Very small
		Categories completed	0.81	0.063	Very small
		Total errors	0.69	0.115	Small

Table 2 continued

Study	Outcome variable		*P*	Cohen's *d*	Size
Nejati *et al.* [46]	Response inhibition (Go/NoGo)	Go accuracy	0.16	0.451	Medium
(Exp 2) – Anodal left DLPFC tDCS		No-go accuracy	0.50	0.699	Medium
		RT	0.15	−0.196	Small
	Working memory - anodal stimulation	Accuracy*	**0.01**	1.197	Large
		RT*	**0.04**	1.003	Large
	Cognitive control / flexibility (WCST) - anodal stimulation	Completion time	0.07	0.915	Large
		Perseverative errors*	**0.01**	−2.545	Large
		Categories completed*	**0.01**	1.666	Large
		Total errors*	**0.01**	−2.579	Large
Cathodal left DLPFC tDCS	Response inhibition (Go/NoGo) - cathodal stimulation	Go accuracy	n/r	0.451	Medium
		No-go accuracy*	**0.01**	1.248	Large
		RT	n/r	−0.64	Medium
	Working memory - cathodal stimulation	accuracy	0.345	0.578	Medium
		RT	0.108	0.587	Medium
	Cognitive control / flexibility (WCST) - cathodal stimulation	Completion time	n/r	−0.465	Medium
		Perseverative errors*	**0.04**	−0.943	Large
		Categories completed*	**0.01**	0.960	Large
		Total errors*	**0.01**	−1.157	Large
Soff *et al.* [47] [1,2]	ADHD symptoms (FBB-ADHD)	Inattention*	**0.03**	1.241	Large
		Hyperactivity	n/r	0.694	Medium
		Impulsivity	n/r	1.177	Large
	ADHD symptoms (QB-test)	Inattention*	**0.05**	0.221	Small
		Hyperactivity*	**0.03**	0.336	Small-to-medium
		Impulsivity	n/r	0.125	Small
Sotnikova *et al.* [40]	Working memory – 1-back	Accuracy	n/r	−0.96	Large
		RT	n/r	−0.022	Very small
		RT variability	n/r	0.214	Small
	Working memory – 2-back	Accuracy*	**0.001**	−1.11	Large
		RT*	**0.021**	0.682	Medium
		RT variability*	**0.026**	1.094	Large
	Response inhibition (Go/NoGo)	Accuracy*	**0.013**	−0.652	Medium
		RT	n/r	0.271	Small
		RT variability	n/r	−0.017	Very small
Jacoby *et al.* [63]	ADHD symptoms (MOXO CPT)	Attention RT	0.86	0.011	Very small
		Hyperactivity*	**0.013**	0.483	Medium
		Timing score	n/r	0.104	Small
Allenby *et al.* [49]	Response inhibition (CPT)	False positive error*	**0.01**	0.425	Medium
		True positive error	0.05	-0.051	Very small
	Response inhibition (SST)	Response time	> 0.05	−0.101	Small
		RT	> 0.05	−0.177	Small

Table 2 continued

Study	Outcome variable		*P*	Cohen's *d*	Size
Breitling *et al.* [64]	Working memory (2-back)	Accuracy	n/r[3]	−0.240	Small
Conventional montage		RT	n/r[3]	0.009	Very small
		Accuracy	n/r[3]	−0.088	Very small
4 × 1 electrode-montage		RT	n/r[3]	0.172	Small

Cohen's *d* was calculated (using mean and average SDs) between active *vs* sham tDCS for each outcome measure; *significant measures reported in the studies are bold. n/r, no report of *P* value; ASRS, Adult ADHD Self-Report Scale Symptom Checklist; WCST, Wisconsin Card Sorting Test; QbTest, Quantified Behavior Test; FBB-ADHD, German adaptive ADHD Diagnostic Checklist; CPT, Conners Continuous Performance Task; SST, Stop Signal Task. 1, Cohen's *d* in these studies are calculated based on the pre-post measurement difference according to the reported data analysis; 2, in the Soff *et al.* study [47], the difference is calculated based on baseline *vs* 7-day post-measurement; 3, in Breitling *et al.* [64], *P* value is reported for the ANOVA results (0.570 for WM accuracy and 0.100 for RT) and no *P*-value for *t*-tests is reported.

the focal stimulation over the r-IFG had larger positive effects. Nevertheless, the involvement of the r-IFG in ADHD should be further explored in future tDCS studies.

Other potentially involved but less-explored sites are the ventromedial prefrontal cortex and OFC that are involved in motivational/emotional processes and social cognition [25, 33, 81], which are impaired in ADHD. These areas are parts of the reward network and show reduced activation during tasks involving "hot" executive functions (involving emotional/motivational components) in ADHD [7, 82] and their activity differs in ADHD depending on the type of deficit, task, and ADHD subtype [83, 84].

Stimulation Polarity

The pathophysiology of ADHD includes under-activation of the lateral, orbital, and inferior prefrontal cortex. Along this line, anodal tDCS-generated excitability enhancement was used in most of the tDCS studies of ADHD (Table 1). Although cognition-enhancing and symptom-alleviating effects of anodal tDCS in ADHD are partially supported in this review, it might be that cathodal tDCS over pathologically hyperactive regions, especially areas involved in emotion processing or in hyperactive ADHD subtypes, is also beneficial. However, this has not been systematically explored so far. In this context, a recent neuroimaging study showed that the connectivity of ADHD-related brain networks differs between subtypes, with more hyperconnectivity in the default mode network in the combined, but not the inattentive subtype [8].

Another relevant point is the laterality of the stimulation protocols. As a caveat, most of the tDCS studies in ADHD so far applied bipolar stimulation over areas relevant to ADHD. Conceptually, unilateral protocols that merely target a region of interest without positioning the return electrode over a potentially similarly involved region might show better efficacy, especially if the region over which the cathodal return electrode is placed shows pathological hypoactivity. In this case, the effects of the cathodal return electrode might compromise performance, and thus partially antagonize anodal tDCS effects over the target region. One last point about cathodal tDCS is that changing conventional stimulation parametrs can add complexity or even reverse to the expected tDCS aftereffects which should be considered (for a review on this see [85]).

Stimulation Intensity, Duration, and Repetition Rate

The stimulation intensities applied in the included studies ranged from 1 mA (seven experiments) to 2 mA (three experiments) and two experiments used 1.5 mA and 1.8 mA. As our 3D modeling of the electrical fields showed (Fig. 3), the field density induced by 1 mA is approximately half of that induced by 2 mA tDCS, and might have been too low to induce relevant effects in the hypo-active targeted region in the adult ADHD population. This is in line with previous findings from other clinical populations, for example in tinnitus [86], cognitive impairment in Parkinson's disease [87], and cognitive performance and auditory hallucinations in schizophrenia [88, 89]. In children, however, increasing the stimulation intensity should be considered cautiously as shown in our computational modeling of current flow in the brain. Furthermore, results of titrating anodal [90] and cathodal [24] stimulation intensity show that increasing intensity does not always enhance neuroplastic aftereffect, especially in cathodal tDCS and should be considered with respect of duration and repetition rate [85].

The effects of different stimulation durations have not been addressed systematically in ADHD studies so far. Prolonging stimulation to increase the efficacy of the intervention is similar to enhancing the intensity and depends on the targeted cortical area [91, 92]. One advantage of increasing the duration rather than the intensity is that it does not increase the probability of side-effects like itching and tingling [93, 94], which might

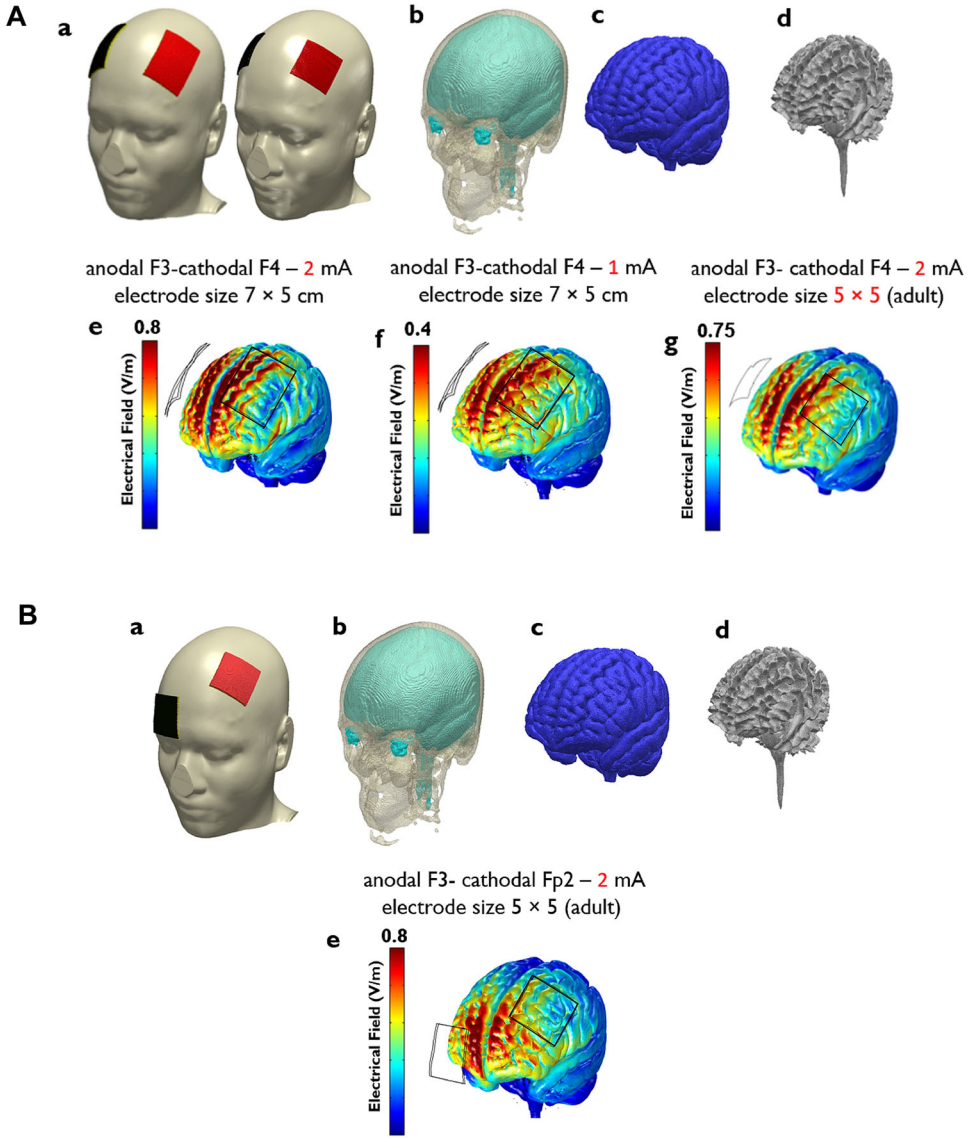

Fig. 4 Three-dimensional models of electrical current flow in the head induced by common montages applied to ADHD patients with the head sizes of an adult (1 and 2; the New York (ICBM-NY) head [69]) and a 9 year-old child (3 and 4; open-source ABIDEII-OHSU child MR datasets). MR images were first segmented into 6 tissue types: gray matter (GM), white matter (WM), CSF, skull, scalp, and air cavities using the SPM8 software package (Welcome Trust Center for Neuroimaging, London, UK) with an improved tissue probability map. A custom MatLab script was then used to correct for segmentation errors made by SPM [70]. Then, a 3D model of the segmented images, with addition of the electrodes and saline-soaked sponges, was designed using the Simpleware software package version 5 (Synopsys, Mountain View, CA). Finally, the current flow distribution inside the head was calculated based on the finite element method using COMSOL Multiphysics software package version 5.2 (COMSOL Inc., Burlington, MA). The conductivity values used for each tissue type were as follows (in S/m): GM: 0.276; WM: 0.126; CSF: 1.65; skull: 0.015; scalp: 0.465; air: 2.5×10^{-14}; saline-soaked sponge: 1.5; electrode rubber: 29 [71, 72]. Electrical fields throughout the gray matter are shown for stimulation intensities of 2.0 mA (Ae) and 1.0 mA (Af) with an F3 anodal–F4 cathodal montage and electrode sizes of 35 cm^2 and 25 cm^2 (Ag), 2.0 mA with an F3 anodal–Fp2 cathodal montage (Be), 1.0 mA (Ce) and 2 mA (Cf) with an F3 anodal–Fp2 cathodal montage in children and electrode sizes of 25 cm^2 and 35 cm^2, respectively, and 1 mA with an F8 anodal–A1 cathodal montage (De). F3, left dorsolateral prefrontal cortex; F4, right-left dorsolateral prefrontal cortex; Fp2, right supraorbital area; F8, right inferior frontal gyrus; A1, left mastoid. The figures also depict electrical fields induced in adjacent non-target areas, which should not mislead the interpretation of the electrical field under the target electrodes. The current flow under the electrode area is of interest.

be specifically relevant for studies in children. However, similar to the intensity [95], the non-linear relation of duration and the effects on cortical excitability should be taken into consideration [85, 92, 96]. An overview of the stimulation polarity, intensity, and duration used in the studies included in the present review is presented in

Fig. 4 continued

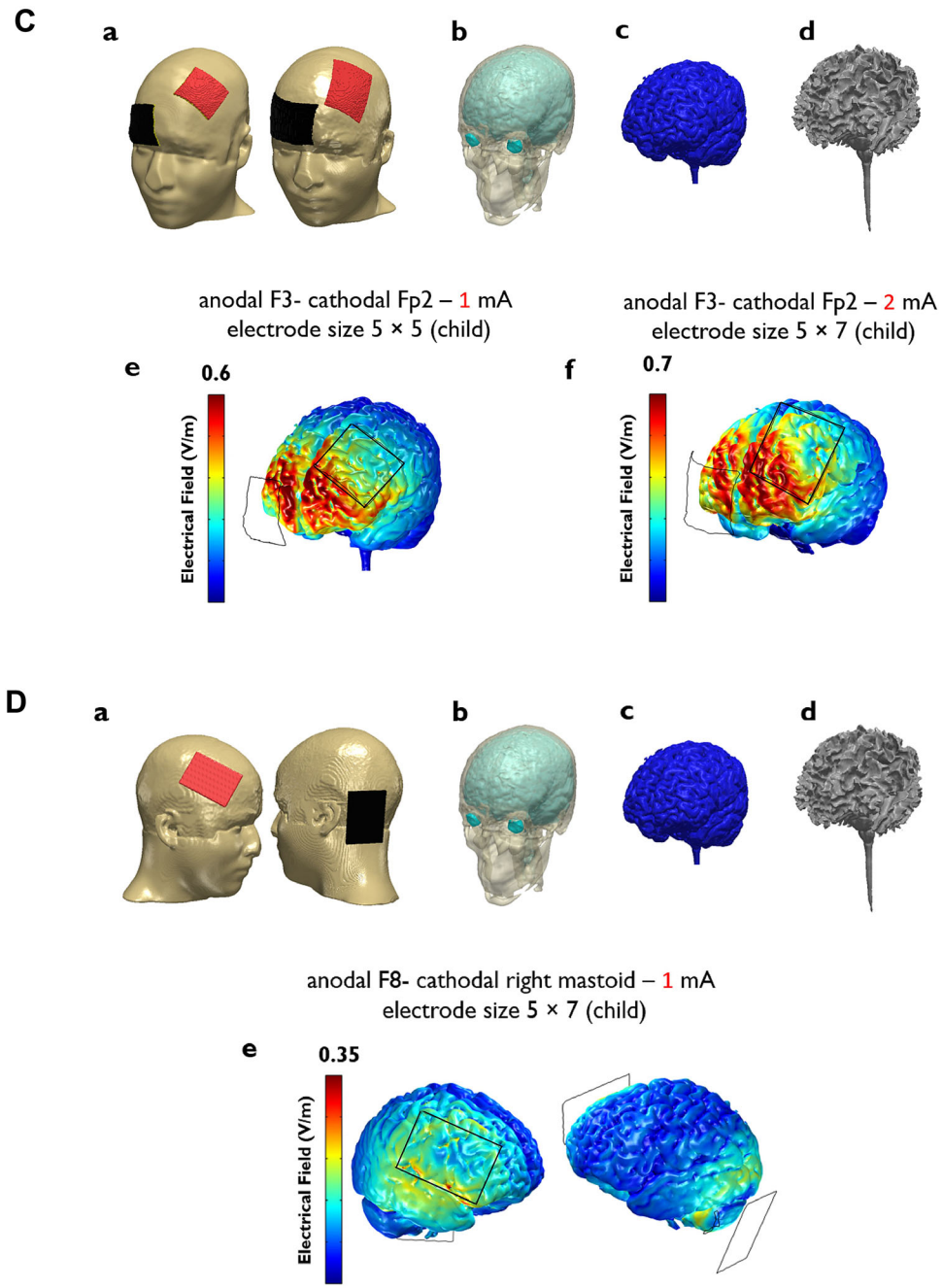

Fig. 3. Repetition rate is another parameter relevant to tDCS efficacy which was explored in only 3 tDCS studies [44, 47, 48], all of which reported significant reduction in ADHD symptoms or improvement of cognitive deficits. This is in line with previous studies that showed that tDCS efficacy is boosted by repeated tDCS sessions over motor and prefrontal regions [97, 98].

Electrode Size

Electrode size is another parameter that has an impact on the effects of tDCS. Motor cortex tDCS studies have shown that larger electrodes (e.g. 35 cm^2) result in greater changes in motor cortical excitability than smaller electrodes (e.g. 16 cm^2) [98], but such an electrode-size effect has not been found in other studies [99, 100]. Computational modeling of electrical current has shown that electrode size and inter-electrode distance affect the current density at the level of the brain, focality, and current

shunting through the scalp [98, 101]. These parameters can explain the modulatory effects of tDCS and have been found to be associated with the electrical field strength [55]. Larger electrodes generate less focal electrical fields at the brain level. In the included studies, 35 cm^2 and 25 cm^2 were most commonly used in both adults and children. These electrode sizes do not significantly differ with respect to the current density generated over the motor area in the adult brain [98]. However, the target areas in ADHD are prefrontal regions, and slight differences in electrode size might be important over this functionally more heterogeneous region. According to our modeling results, the electrical field induced by bilateral dlPFC protocol with 35 cm^2 electrodes was slightly larger (0.50) than with 25 cm^2. The use of smaller electrodes increases the focality of stimulation effects [99, 101] but whether enhanced current focality is indeed helpful for increasing clinical efficacy is still an unanswered question and depends on the pathophysiological networks involved in ADHD. A recent study [64] that compared 4 × 1 (1 cm diameter) and conventional stimulation montages found no significant differences between these protocols on working memory, which speaks against a different effect and should be taken with caution, because in that study neither protocol significantly altered performance. Systematic investigation of different electrode sizes in ADHD symptoms and cognitive deficits is needed. Finally, the distance between electrodes, which is also determined by electrode size, might be another important parameter. As a rule of thumb, there should be at least 6 cm between electrode edges to prevent excessive current shunting *via* the skin [102]. This parameter might be more critical in childhood ADHD because of the smaller head size of children. As shown in our modeling results (Fig. 4Ce,f), the larger electrode size, and decreased distance between the electrodes in the Bandeira *et al.* study (2 mA) caused an electrical field of 0.7 V/m, which is almost identical to that induced by 1 mA (0.6 V/m) in the Nejati *et al.* study with smaller electrodes.

Sham Methodology

Establishing an effective sham condition is challenging in brain stimulation studies. All studies included in this review, except for two, used sham-controlled designs for the control condition. In two studies, including one with 2 mA intensity [49], participants could discern sham from active stimulation. A potential solution for ensuring proper sham control, especially for intensities > 1 mA, is the application of anesthetic cream under the stimulation area, as suggested in previous studies [96, 103].

Childhood ADHD and Developmental Aspects of tDCS

Most of the included studies were conducted on childhood ADHD. There are unique practical considerations about the application of tDCS in the developing brain. It is crucial to consider the developmental aspects of tDCS in childhood ADHD, which might also have implications for other neurodevelopmental disorders and pediatric populations. Here, we discuss the stimulation parameters outlined above in childhood ADHD.

Previous studies have suggested that stimulation parameters should be adjusted in children and adolescents [104]. Beyond the targeted cortical regions (stimulation sites) discussed above, it is of foremost importance to consider that the developing brain in childhood ADHD is believed to be more plastic than the adult ADHD brain [51]. This might make the effects of plasticity-inducing interventions stronger, especially during sensitive developmental periods [105]. Moreover, the smaller head size of children and adolescents likely results in a stronger electrical field than in adults. Since non-linear effects of tDCS have been found dependent on stimulation intensity and duration [24, 92, 96], adapting stimulation parameters is therefore critical.

Along this line, stimulation intensity, duration, and repetition rate should be carefully considered. As our modeling results show, the stimulation intensity required to generate an electrical field comparable to that achieved in adult ADHD (2 mA, 0.8 V/m) is almost half in children (1 mA, 0.6 V/m), under otherwise identical conditions. Therefore, stimulation intensity might have to be adjusted in children to achieve effects similar to those in adults, also in light of the consideration that higher stimulation intensities might modulate areas beyond the target electrode, with possibly unintended effects on the clinical symptoms being tackled. However, a reduction of intensity might not be warranted for all targets. The intensity that modulates the dlPFC, which is relatively near the surface, might not be sufficient to reach deeper regions, such as the r-IFG. This might be one reason why the studies that targeted r-IFG found null effect in childhood ADHD [42, 64].

Regarding polarity-specific effects, cathodal tDCS at 1 mA, which has excitability-diminishing effects in adults, has excitatory effects in children and adolescents, with otherwise identical stimulation parameters [106]. Such a conversion of the directionality of tDCS after-effects has been described in adults when the intensity is enhanced to 2 mA [96]. This conversion of after-effects might be beneficial in ADHD when the return electrode is positioned over prefrontal regions, which are hypo-active in this disease. If an excitability-diminishing effect of the relevant

electrode cannot be ruled out, extracephalic positioning might be advantageous.

Electrode size is also an important aspect in this respect. A smaller electrode has the principal advantage of generating the current density aimed for at the brain level with a lower current intensity [101], and with higher focality, which is relevant for tDCS application in pediatrics because of the smaller head size compared to adults. The distance between electrodes should be sufficient to minimize current shunting through the skin. Using 35 cm^2 electrodes in children can reduce the current intensity reaching the brain if target regions are close. As our modeling shows, the use of 35 cm^2 electrodes over the left dlPFC and right Fpz or bilateral dlPFC does not guarantee the minimum required distance between electrodes, resulting in current shunting (Fig. 4D, Cf), and therefore 25 cm^2 electrodes are preferable. Finally, there are important ethical and practical challenges regarding the application of tDCS in childhood ADHD due to the relatively small number of available studies, which warrants further systematic investigation. For a relevant and detailed discussion of ethics in childhood ADHD tDCS, see Sierawska *et al.* [107].

Clinical and Methodological Implications

Optimized and Personalized Stimulation Protocols in ADHD

The results of the included studies show that the effects of tDCS on ADHD symptoms and deficits are strongly dependent on not only the nature of the symptoms/deficits but also the stimulation parameters (i.e., site, polarity, intensity, duration, and repetition rate). This is in line with the therapeutic guidelines for tDCS in other neuropsychiatric disorders [94], which suggest the adaptation of stimulation parameters to symptoms and deficits, as well as individually, if applicable. Considering the heterogeneous pathophysiology, symptoms, deficits, and treatment response of ADHD, it might be beneficial to adopt this approach in future tDCS studies in ADHD and shape the stimulation protocols to the relevant factors. ADHD subtype, for example, is an important but under-studied inter-individual factor which is identified by specific deficit patterns and their pathophysiological foundations [74]. In addition, symptoms and especially cognitive impairments are heterogeneous in ADHD [4, 7], which suggests adapting the stimulation protocols accordingly.

Combined Interventions

Recent studies have shown that combining tDCS with other interventions such as cognitive training [108, 109], pharmacological treatment [110, 111], and psychological interventions [112, 113] can boost and prolong its clinical efficacy. These findings could have implications for ADHD treatment. For example, tDCS can be combined with pharmacological interventions, which sometimes only have short-lasting effects and suffer from partial or no response in some patients[114], or cognitive training and neurofeedback, major non-pharmacological interventions in ADHD that have yielded inconsistent effects when applied alone [115]. Physical exercise, especially in a cognitively-demanding context has stronger effects on children's executive functions [116] and has recently been proposed as a novel cognitive enhancement paradigm in ADHD [117]; its combination with tDCS could be promising.

Limitations and Future Directions

The following limitations should be taken into account. First, from the currently available studies, it is difficult to rate the clinical utility of tDCS in ADHD due to a lack of systematic titration of stimulation parameters. Most of the studies reported so far are under-dosed regarding these parameters. Second, individualization and adaptation of stimulation protocols based on symptom subtypes, ADHD subtypes, specific cognitive deficits, and neuroanatomical differences are lacking in currently available studies. Future studies should: (1) systematically investigate stimulation parameters at the group level, (2) explore the effects of tDCS in different neurodevelopmental periods to determine the optimal developmental window in which to initiate interventions, especially in childhood ADHD, and (3) develop personalized stimulation approaches.

Conclusions

The findings of this systematic review suggest at least a partial improvement of symptoms and cognitive deficits in ADHD by tDCS. They further suggest that stimulation parameters such as polarity and site are relevant to the efficacy of tDCS in ADHD. Anodal tDCS over the dlPFC, compared to cathodal stimulation, seems to have a superior effect on both the clinical symptoms and cognitive deficits. However, the routine clinical application of this method as an efficient therapeutic intervention cannot yet be recommended based on these studies, but requires optimizing the stimulation parameters to improve clinical efficacy, and the exploration of clinical symptoms in addition to surrogate parameters.

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