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Transcranial direct current stimulation enhances effort maintenance in ADHD

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ABSTRACT

Background: Youth with attention-deficit/hyperactivity disorder (ADHD) exhibit increased effort aversion, likely due to deficits in anticipatory dopamine firing. Previous research has shown that transcranial direct current stimulation (tDCS) targeting the right prefrontal cortex can enhance activity in dopaminergic meso-striatal regions. However, the extent to which this specific tDCS configuration effectively modulates effort behavior in anticipation of rewards in ADHD remains uncertain.
Hypothesis: We expected an increase of effort maintenance and invigoration during and following our tDCS set-up compared to sham in subjects with ADHD.
Methods: Twenty-four children and adolescents with ADHD (mean age: 11.6 years; 95 % CI [10.7, 12.4]) received 2 mA and sham tDCS for 20 min each. The anode was positioned over the ventromedial prefrontal cortex (PFC), while the cathode was placed over the right dorsolateral PFC, generating an electrical field with maximal strength in the right PFC. During and after the tDCS sessions, participants performed a button-pressing task aimed at earning delayed monetary rewards. Primary outcomes were effort maintenance (frequency of button presses) and invigoration (slopes of button presses), measuring motor task performance.
Results: We observed a significant increase in effort maintenance both during ($b = 2.66$; $p < 0.001$) and after tDCS ($b = 2.04$; $p = .007$) compared to sham. No significant difference was found for invigoration during stimulation, while after bonferroni correction ($p = 0.025$) a non-significant decrease was found after tDCS compared to sham ($b = -5.18$; $p = 0.041$).
Conclusion: tDCS targeting the ventromedial PFC (anodal) and right dorsolateral PFC (cathodal) increases effort maintenance in children and adolescents with ADHD.

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is the most common neurodevelopmental disorder in childhood and adolescence, with an estimated prevalence of 5.3 %. It is associated with an increased risk of comorbid diagnoses (e.g., depression or substance abuse disorder) and later adult occupational impairment. According to the DSM-5, the core symptoms are hyperactivity, impulsivity, and inattention [1,2]. The biological underpinnings of these symptoms are heterogeneous, but individuals with ADHD often experience motivational impairments that may be closely related to their aversion to effortful behavior in the context of a deficit in reward anticipation [3,4]. For example, compared to control children, individuals with ADHD tend to favor low-effort/low-reward options over high-effort/high-reward alternatives in activities that involve cognitive and physical demands [5]. Additionally, they may allocate less effort when faced with a high-effort trade-off and less effortful learning strategies were associated with poorer memory performance [6,7]. Structural changes and

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abnormalities of dopamine metabolism in the reward circuitry may underlie these motivational dysfunctions. For instance, a functional magnetic resonance imaging study found reduced activation in the medial frontal cortex and thalamus during reward anticipation [8]. Moreover, studies have suggested a reduction in anticipatory dopamine cell firing in individuals with ADHD [9].

First line treatment with stimulants (e.g. methylphenidate) and second line treatment with non-stimulants (e.g. atomoxetine) are effective in reducing symptoms of ADHD [10] and may increase the motivation to exert effort [5,10–13]. However, side effects such as decreased appetite, decreased growth, or insomnia, as well as treatment non-response or non-compliance are important limitations of pharmacological treatment [10,14]. In this regard, *transcranial direct current stimulation* (*tDCS*) is a promising third-line treatment approach. tDCS involves the application of a weak constant current to modulate brain activity, can be applied at home, and is associated with only mild side effects (e.g., tingling, itching, or mild burning sensation) [15,16]. A common set-up that includes an anode and a cathode is thought to enhance cortical excitability at cortical sites near the anode and decrease excitability near the cathode [17]. So far, findings on tDCS in ADHD are mixed. A decrease in delay discounting was found in a delay discounting paradigm, where children with ADHD could choose between an immediate small amount of chocolate or a delayed greater amount of chocolate [18]. Additionally, some improvements in measures of inhibitory control were found in using tasks such as the go/no-go paradigm or the flanker task. However, results were limited to subscores of the tasks and/or by very small sample sizes. The majority of studies used anodal stimulation of the left dorsolateral prefrontal cortex or right frontal cortex with currents mostly in the range of 1 mA–1.5 mA [19,20]. One reason for these mixed findings could be the application of suboptimal stimulation parameters targeting youth with ADHD.

Using tDCS, a recent study modulated subcortical dopamine levels in healthy adults by placing an anode over the ventromedial prefrontal cortex (vmPFC) and a cathode over the right dorsolateral prefrontal cortex (rDLPFC). Specifically, neuronal activity similar to that induced by L-DOPA administration was elicited in mesostriatal regions, which are involved in the regulation of reward processing [21]. Additionally, anodal stimulation of the vmPFC may upregulate the cognitive process of reward anticipation and valuation [18,22,23], especially in the context of motivational behavior in ADHD [20]. However, it has not yet been demonstrated whether this tDCS setup effectively modulates effort behavior in response to rewards, specifically in a clinical cohort of children and adolescents with ADHD. In addition, it is unclear whether effects in tDCS are only observed during stimulation or show short-term aftereffects in cortical activity. Moreover, findings in human cadaver brains showed that approximately 75 % of currents applied using tDCS are attenuated by natural barriers such as skin and skull. It has been proposed that tDCS with 4–6 mA may be needed to effectively modulate neuronal activity in adults [24]. However, in children and adolescents similar results are missing, natural barriers are smaller and current densities through tDCS are approximately 21–26 % higher compared to adults [25]. Therefore, lower currents could be sufficient to achieve neuromodulatory effects.

In light of these considerations, this study aimed to modulate effort behavior in response to delayed rewards in children and adolescents with ADHD using the described tDCS set-up that has been shown to modulate subcortical dopamine levels. Further, we used a stimulation intensity of 2 mA, given the finding of higher currents to be needed to modulate neuronal activity. During and after tDCS, children and adolescents with ADHD performed an effort allocation task in which they had to repeatedly press a button to earn rewards that were not delivered until the end of the experiment [26]. This task has the advantage of directly measuring the motor performance during effort allocation in anticipation of rewards, compared to previous studies that primarily focused on cognitive measures of reward processing. The anticipation of rewards has been proposed to be highly dopamine dependent [27]. We assessed two main outcome parameters: *effort maintenance* and *invigoration*. Effort maintenance referred to the frequency of button presses throughout the task, whereas invigoration described the increase in button presses (i.e., slope) when a prospective reward was presented. In ADHD, both the maintenance of effort and drive to initiate effortful behavior are altered by dopaminergic drugs [5,11]. Therefore both parameters may be modulated by potentially increasing dopaminergic neuronal activity.

First, we expected that tDCS with anode placement over the vmPFC and cathode placement over the rDLPFC at an intensity of 2 mA would improve effort maintenance and invigoration in children and adolescents with ADHD, compared to sham when the task was performed concurrently. Second, we hypothesized that tDCS would have a sustained effect compared to sham when the effort task was completed following stimulation and therefore aimed to investigate short-term aftereffects.

2. Methods

2.1. General procedure

The study was a pre-registered (DRKS00029410 at drks.de/search/en) cross-over, triple-blind, sham-controlled, randomized clinical trial, designed to include 24 right-handed children and adolescents with ADHD between 8 and 17 years of age. The study aimed for a statistical power of 80 % [28] at an alpha level of 0.05 and an expected medium effect size of $d = 0.69$. Subjects with autism spectrum disorder, anxiety disorder (except specific phobia), tic disorder, personality disorder, depression, eating disorder, and an IQ < 85 were excluded from participation. Long-acting stimulant medication was discontinued for 48 h, while immediate-release stimulant medication was paused for 24 h prior to the tDCS intervention. Parents, participants with ADHD, the experimenter, and the data analysist were blinded to the stimulation condition. Data were collected between November 2022 and April 2023 at the university hospital for child and adolescent psychiatry cologne. The study was approved by the Ethics Committee of the Medical Faculty of the University Hospital of Cologne (ID: 00013774) and conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Council for Harmonization [29]. European regulations for medical device ((EU) 2017/745) were met.

The study comprised three site visits, including diagnostics and two days of intervention with at least 24 h of washout period between the two stimulation sessions (Fig. 1). Each subject completed the task with both tDCS and sham stimulation on two separate days. The randomization process is detailed in the supplementary material. Participants first received 3 min of tDCS or sham stimulation and then began the effort allocation task (EfAT) with concurrent stimulation. In total stimulation lasted 20 min. The task was repeated 10 min after the end of the stimulation without stimulation (tDCS or sham).

2.2. Diagnostics

After obtaining written informed consent from each child and their legal guardians, all subjects were screened for inclusion and exclusion criteria. To confirm and classify the diagnosis of ADHD according to the DSM-5, a structured clinical interview was administered by an experienced child and adolescent psychiatrist (*Kinder-DIPS*) [30]. In addition, ADHD symptom severity was assessed using the *DISYPS-III ADHD self- and parent rating scales* [31]. Right-handedness was assessed using the *Edinburgh Handedness Inventory* [32]. The *Culture Fair Intelligence-20 Revised Test* ($n = 17$) was administered, unless subjects had already undergone IQ diagnostics in the previous 2 years [33]. If IQ had been measured previously, assessment was either based on the *Wechsler Intelligence Scale for Children* ($n = 6$) or the *Kaufman Assessment Battery for Children* ($n = 1$) [34,35].

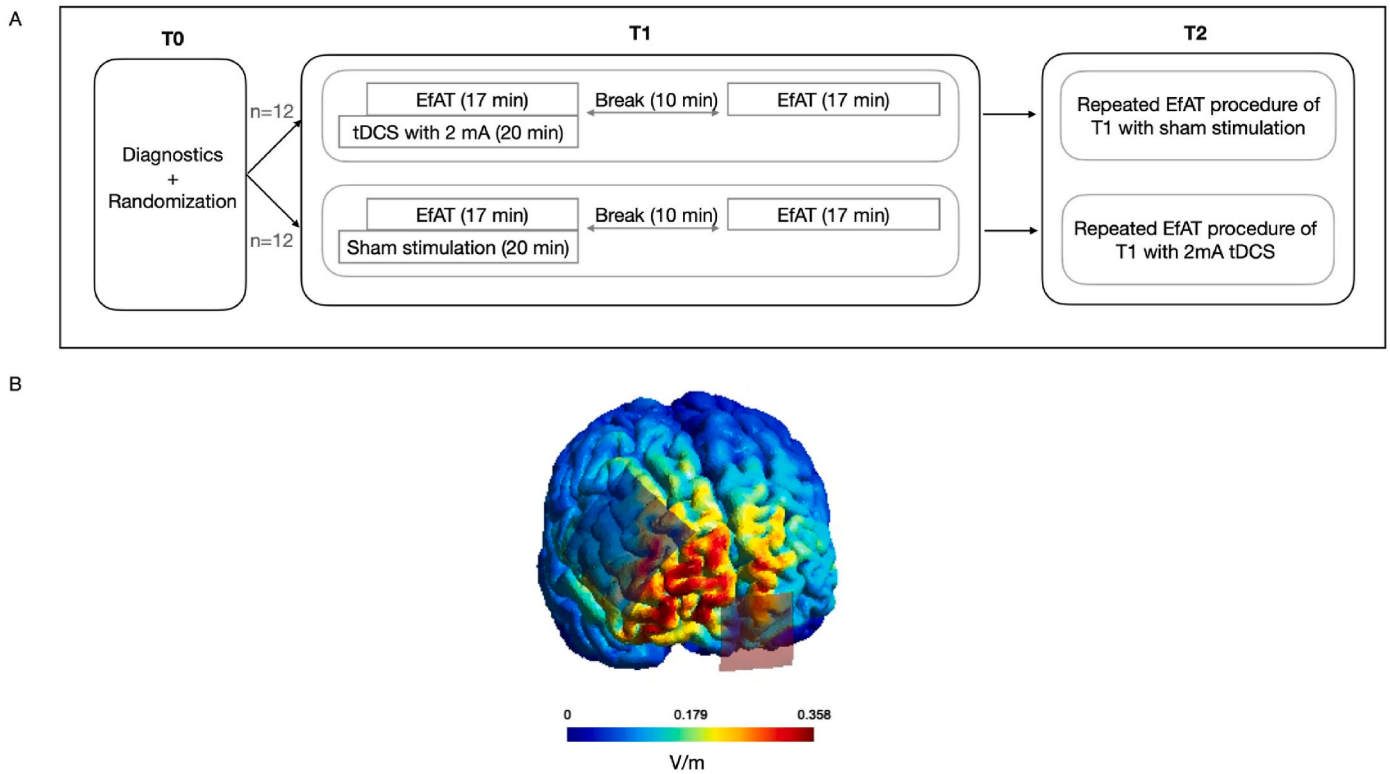

Fig. 1. A) Study procedure. **B)** Electrical field simulation of the tDCS. The anode was placed over the venteromedial prefrontal cortex (Fpz) and the cathode over the right dorsolateral pre-frontal cortex (F4). The maximum electrical current strength was generated in the right prefrontal cortex. EfAT = Effort Allocation Task, mA = milli Ampere, tDCS = transcranial direct current stimulation.

2.3. Transcranial direct current Stimulation

Each subject was stimulated with a battery-powered electrical stimulator (DC-Stimulator plus, NeuroConn, Ilmenau, Germany) at 2 mA (active) and 30 s ramp-in and ramp-out for 20 min on two different days. The order of stimulation was randomized and counterbalanced. Impedance was maintained below 5 kΩ at all times. Sham stimulation consisted of a weak current of 110 μA every 550 ms, which produces side effects similar to tDCS but has no effect on brain activity. The anode (3.5 × 3.5 cm) was placed over Fpz and the cathode (5 × 5 cm) over F4, according to the international 10–20 EEG electrode placement system [36] using a 10-10 electrode placement cap (Easycap GmbH, Wörthsee, Germany). Electrodes were placed using Ten20 conductive paste (Weaver and Company, Aurora, CO, USA). To avoid bridging between electrodes and optimize the electrical field strength, a distance of approximately 4 cm was maintained between electrodes [37], in contrast to existing recommendations [38]. Using this electrode placement, similar neuronal activity was found in fMRI after L-Dopa administration and tDCS in mesostriatal regions [21]. Side effects were systematically assessed after each stimulation session using an adjusted version of the NIBS tolerability questionnaire [15]. For blinding purposes, a code was assigned to the experimenter, who then entered it into the tDCS device. These codes indicated either sham or 2 mA tDCS, but the experimenter and subjects did not know to which setting the codes related. A random order of codes was generated by a third person not conducting any assessments. The electrical field of the stimulation was modeled using SIMNIBS 4 by placing our electrodes on the example MRI model "ernie" (Fig. 1) [39].

2.4. Effort allocation task (EfAT)

The task assessed the primary outcome parameters of *effort maintenance* and *invigoration*. It began 3 min after the tDCS initiation and lasted for 17 min (Fig. 2). The task was adapted from Neuser et al. (2020) and slightly modified to make it suitable for children and adolescents [26]. Prior to the tDCS, each participant's maximum effort was calibrated. To do this, a tube containing a blue ball appeared on the screen. Subjects were asked to move the ball to the top of the screen by repeatedly pressing a button on the X-Box controller during two trials of 10 s (s) each. To provide immediate feedback on the maximum ball position, a blue horizontal line always marked the highest position of the ball. Subjects then completed four practice trials on each day before starting the actual task. Only before the first session, these practice trials were also used to update the maximum button pressing frequency if the level reached in the calibration trials was exceeded. The assessed maximum button pressing frequency was kept constant on both intervention days and was used to adjust the level of difficulty for each subject. The level of difficulty varied between 75 % (low) and 85 % (high) of the individual's maximum frequency by varying a red threshold line shown in Fig. 2C.

The task consisted of 24 trials, each lasting 30 s. Subjects were instructed to repeatedly press a button on an X-Box controller to keep a ball over a red line in order to earn points. At the end of the task, these points were converted into monetary rewards based on a predetermined reward level (high vs. low) set at the beginning of each trial. In the high reward condition, each point earned was multiplied by 10, while in the low reward condition, points were multiplied by 1. The order of the reward levels was randomized at the start of every session. Participants had the opportunity to earn 5 cents for every 100 points accumulated, with the actual payment being made at the end of the experimental session.

A detailed experimental procedure is shown in Fig. 2 and described below. First, a fixation cross was displayed for a duration of 2 s with varying jitter time intervals to prevent anticipation of the trial onset (A). Next, a picture appeared for 1 s, indicating either the low or high reward condition (B). Next, a display with a ball in a tube and a red line was presented, and subjects had to repeatedly press the button of an X-Box

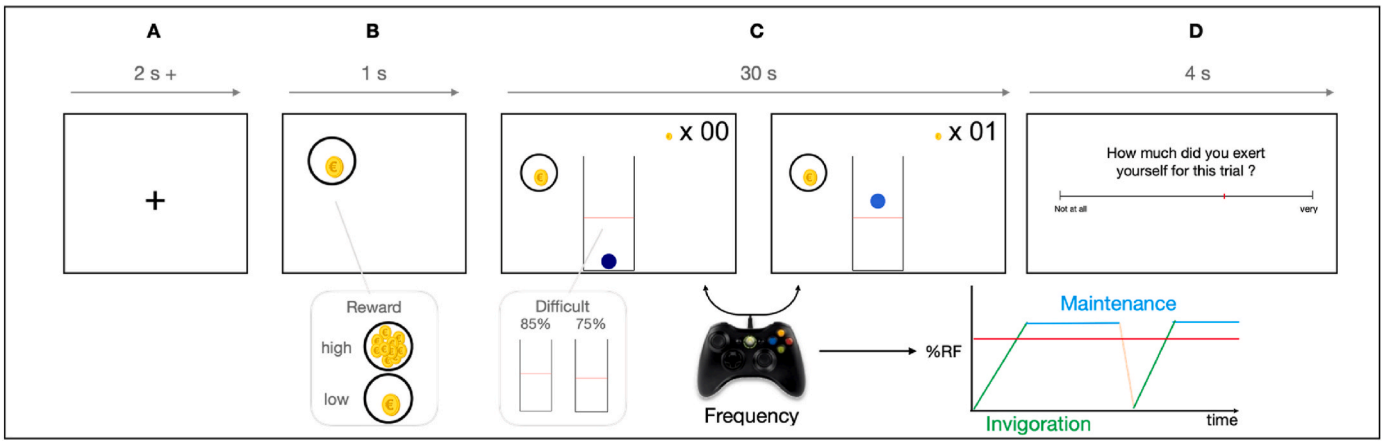

Fig. 2. Trial Sequence of the Effort Allocation Task: **(A)** Fixation cross. **(B)** Reward Condition. **(C)** Level of difficulty and 30 s (s) of repeated button pressing to obtain the reward. **(D)** Visual Analogue Scale with exertion rating. RF = relative frequency.

controller (Nacon, France) to keep the ball above the red line. For each second that the ball was held over the red line, subjects earned one point, and the total number of points earned in a trial was simultaneously displayed in a counter in the upper right corner of the screen. The level of difficulty (low vs. high) alternated every trial (C). After each trial, a visual analog scale was displayed to provide feedback on the level of exertion (D). After 12 trials, there was a 15-s rest period. At the end of the task, the points earned and the corresponding amount of money were displayed.

The same task was repeated 10 min after the tDCS without stimulation to assess possible aftereffects. It was programmed using MATLAB (The MathWorks, Massachusetts, USA) and displayed using the Psychophysics Toolbox extensions [40]. Detailed analysis of our primary outcome parameters *maintenance* (relative frequency of button presses) and *invigoration* (slope of button presses) are described in the supplementary material.

2.5. Statistics

Two repeated measures multilevel mixed-effect models were estimated, one for effort maintenance and one for invigoration, to analyze effects first during stimulation (tDCS vs. sham) and second after stimulation. We hypothesized a consistent increase in effort maintenance and invigoration during and after tDCS compared to sham. Each model included the interaction term of stimulation condition (sham vs. tDCS) by time (concurrent vs. sequential task performance), as well as the predictors difficulty (high vs. low target line), reward magnitude (high vs. low rewards), trial number (to account for motor exhaustion) and session number (to account for learning effects and the order of stimulation condition). In addition, we included the interaction terms treatment by time by reward magnitude, treatment by time by difficulty, and treatment by time by reward magnitude by difficulty. The model included random intercepts at the individual level. The treatment by time interaction term allowed us to estimate the difference-in-difference of the tDCS treatment effect. Thus, to evaluate our hypothesis of constant treatment effects, we expected a non-significant interaction between the task performance during and after tDCS compared to sham. Next, from our model we calculated the marginal effects of time (concurrent vs. sequential task performance) and stimulation condition (sham vs. tDCS) in our data set. The calculation of marginal effects allowed us to compare the effect of tDCS either during or before task performance on effort maintenance and invigoration, assuming constant covariates (reward magnitude, level of difficulty, trial, session sequence) referenced to its corresponding control condition. Significance levels were adjusted by Bonferroni correction (p = 0.025) based on our two a priori hypotheses (maintenance and invigoration). Additionally, in an exploratory analysis, we calculated marginal effects of reward magnitude (low vs. high) and the level of difficulty (low vs. high). Cohens f^2 effect sizes were calculated [41]. Statistical comparison of blinding to the stimulation condition was performed using a Chi-Squared test. Analyses were performed with Stata 17 (Stata Corp, Texas, USA).

3. Results

3.1. Study sample

Our final sample included 24 subjects with ADHD and is presented in full detail in Table 1. All subjects were right-handed with a mean handedness score of 90.36 (SD: 9.71).

3.2. Effects of transcranial direct current stimulation on effort maintenance and invigoration

Using a repeated measures mixed-effects model, we first analyzed the effects on effort maintenance (Table 2, $F_{17,2263.07} = 7.52$; $p < 0.001$). We observed an increase in effort maintenance both during task performance concurrent with ($p < 0.001$; b = 2.66; z(23) = 3.52; 95 % CI [1.18, 4.13]; $f^2 = 0.02$) and after tDCS ($p = .007$; b = 2.04; z(23) = 2.71; 95 % CI [0.56, 3.52]; $f^2 = 0.01$) compared to sham. Regression coefficients (b) indicate that tDCS resulted in a small, but significant 2.66 % increase in the frequency of button pressing during task performance concurrent with tDCS and a sustained effect for a task performance immediately following tDCS, with a 2.04 % increase in effort maintenance (Fig. 3). Moreover, as expected, participants engaged in mostly economically effective behavior during task performance. Participants increased button presses on high reward trials compared to low reward trials both during ($p < 0.001$; b = 4.11; z(23) = 5.40; 95 % CI

Table 1
Study sample.

Age in years (Mean, [95 % CI])	11.6 [10.7, 12.4]
Intelligence quotient (Mean [95 % CI])	106.5 [100.2, 112.7]
ADHD-Subtype	
Combined (n)	17
Hyperactive/impulsive (n)	2
Inattentive (n)	5
Sex (n of male/female/divers)	21/3/0
Comorbid Diagnosis	
Oppositional Defiant Disorder (n (%))	6 (25 %)
Specific Phobia (n (%))	4 (12.5 %)
Disruptive Affect Regulation (n (%))	2 (8 %)
Insomnia (n (%))	6 (25 %)
Enuresis diurnal (n (%))	1 (4 %)
Enuresis nocturna (n (%))	1 (4 %)

Table 2
Effect of tDCS (2 mA vs Sham) on task performance concurrent and after stimulation. During and after tDCS we observed a significant increase of effort maintenance compared to sham. Coefficients describe the direction of behavioral effects for tDCS compared to sham (positive coefficients being an increase and vice versa). Bonferroni corrected alpha-levels were p = 0.025. B = unstandardized beta regression coefficient, 95 % CI = 95 % Confidence Interval.

	B	z-Value	95 % CI	p-Value
Effort Maintenance				
Concurrent to stimulation	2.66	3.52	[1.18, 4.13]	**<0.001***
After stimulation	2.04	2.71	[0.56, 3.52]	**0.007***
Invigoration				
Concurrent to stimulation	−0.21	−0.09	[-5.14, 4.71]	0.933
After stimulation	−5.18	−2.05	[-10.15, −0.22]	0.04

[2.61, 5.59]; $f^2 = 0.03$) and after ($p < 0.001$, b = 5.41; z(23) = 7.12; 95 % CI [3.92, 6.89]; $f^2 = 0.04$) stimulation. During trials with a high level of difficulty compared to a low level of difficuly we found a significant decrease in effort maintencance both during ($p = .004$; b = −2.14; z(23) = -2.85; 95 % CI [−3.62, −0.66]; $f^2 = 0.01$) and after ($p = .002$; b = −2.38; z(23) = −3.16; 95 % CI [−3.85, −0.91]; $f^2 = 0.01$) stimulation. Not surprisingly, we found a small decrease in the button press frequency with increasing task duration (exhaustion effect, $p = .004$, b = −0.12; t(23) = −2.87; 95 % CI [-0.19, −0.04]). No effect of session sequence (order of tDCS or sham) was found ($p = .503$, b = 0.18; t(23) = 0.51; 95 % CI [-0.35, 0.72]). Interaction terms included in the model did not reach significance (see Supplementary Material).

An identical repeated measures mixed-effects model was used to evaluate the effect of tDCS on invigoration ($F_{17,2213.91} = 2.09$; $p = .005$). We did not observe a significant effect on task performance during tDCS ($p = .933$, b = −0.21; z(23) = −0.09; 95 % CI [−5.14, 4.71]; $f^2 < 0.01$). Performance after tDCS showed slightly reduced invigoration slopes (b = −5.18; $f^2 < 0.01$) compared to sham stimulation ($p = .041$; z(23) = −2.05; 95 % CI [−10.15, −0.22]). This reduction was not significant at the Bonferroni corrected alpha level ($p = .025$). This result indicates no significant change in the initial increase in button press rates in prospect of a reward during tDCS, and a slightly (non-significant) reduced initial drive of button presses when the task was performed after tDCS compared to sham stimulation. During high reward trials, the invigoration slope increased significantly both during ($p < 0.001$, b = 9.01; z(23) = 3.56; 95 % CI [4.04, 13.97]; $f^2 = 0.01$) and after ($p = .002$, b = 7.78; z(23) = 3.05; 95 % CI [2.78, 12.79]; $f^2 = 0.01$) stimulation. During trials with a high level of difficulty compared to a low level of difficulty, we found no significant differences in invigoration slope both during ($p = .249$, b = −2.89; z(23) = −1.15; 95 % CI [−7.81, 2.02]; $f^2 < 0.01$)

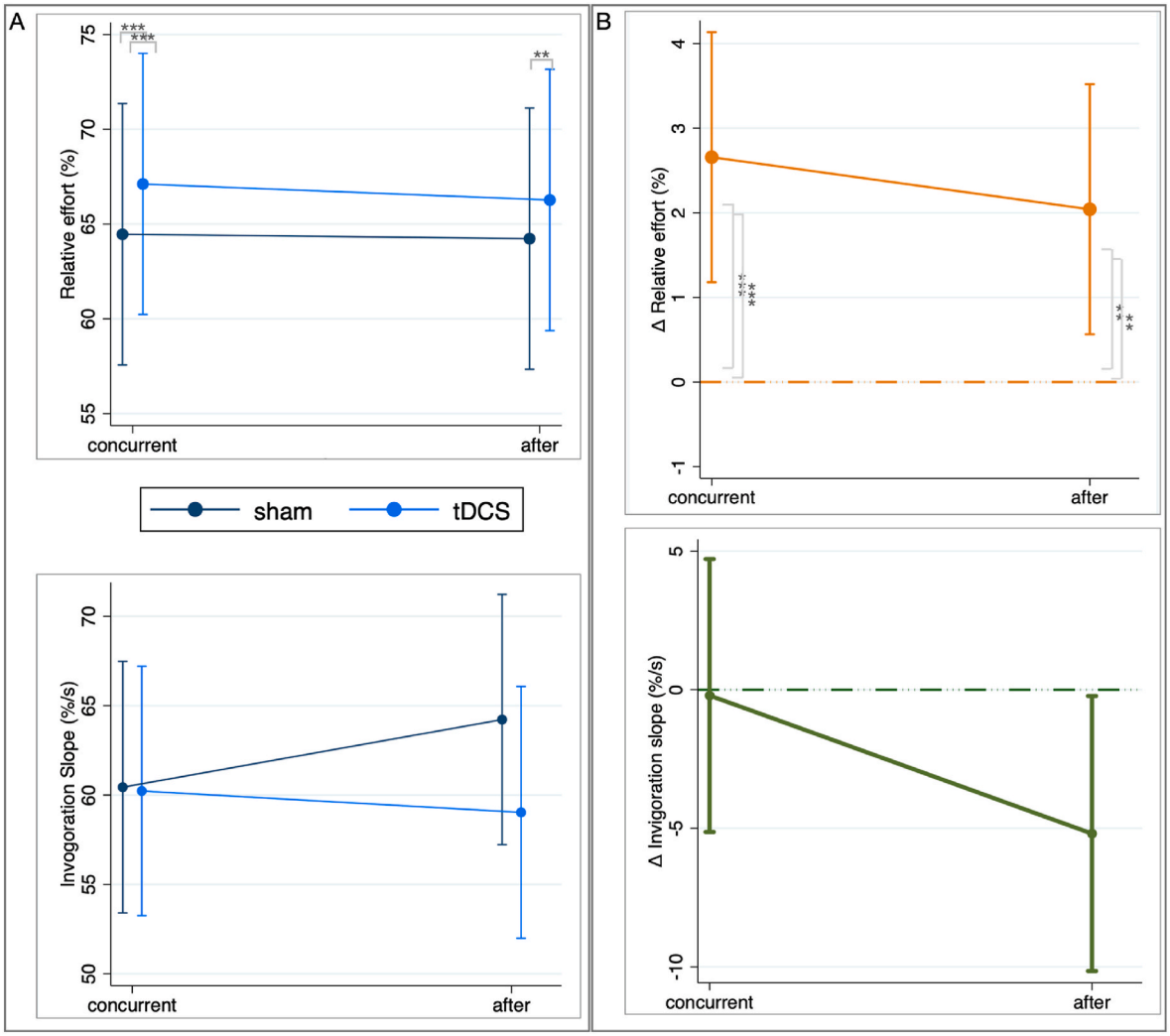

Fig. 3. Group difference **(A)** and intraindividual difference (Δ of tDCS minus sham, **B**) illustrating the effects of tDCS compared to sham on effort maintenance (relative effort) and invigoration (slope). We observed a significant 2.66 % increase in effort maintenance during concurrent task performance with tDCS compared to sham, and this effect persisted during post-stimulation task performance, with a difference of 2.04 %. Marginplots of average treatment effects with 95 % confidence intervals are shown.

and after (p=*.829*, b = 0.54; z(23) = 0.22; 95 % CI [−4.41, 5.51]; $f^2 <$ 0.01) stimulation. In addition, the invigoration slope was lower in later trials of the task (p = *.006*, b = −0.36; t(23) = −2.76; 95 % CI [-0.62, −0.11]) and was not significantly affected by session sequence (p = *.597*, b = 0.48; t(23) = 0.53; 95 % CI [−1.31, 2.28]). None of the interaction terms included into the model reached significance (Supplemental Material).

3.3. Side effects

Subjects receiving tDCS experienced tingling (87.5 %), itching (12.5 %), headache (4.2 %), nausea (4.2 %), and mild burning (87.5 %), red skin (41.7 %), and mild warming (29.2 %) under the electrode. Nausea was reported to be unrelated to the intervention. With the exception of red skin, side effects did not persist beyond 30 min following the intervention. Additionally, no side effects were reported on the day after the intervention, when we followed up with participants. Details on sham side effects, along with a table of side effects during both sham and tDCS, are provided in the supplementary material. Participants were asked to guess their stimulation condition (2 mA vs. sham) after each session, with approximately 52.1 % of the guesses being correct. This indicates that the participants were successfully blinded to the stimulation condition [$\chi 2_{(1)} = 0.08$, p = *.773*].

4. Discussion

This study aimed to enhance effortful behavior in anticipation of rewards in children and adolescents with ADHD by applying tDCS with an anode over the vmPFC and cathode over the rDLPFC. Effects on task performance were assessed concurrently and after tDCS. Effort maintenance (maintenance of the button press rate over a longer time) was significantly enhanced during and after tDCS compared to sham stimulation. This finding suggests a possible causal relationship between our specific tDCS application and increased motivational effort maintenance in children and adolescents with ADHD. Contrary to our expectations, the invigoration slope (the initial increase of the button press rate during the trial) was not significantly affected during tDCS. However, when the task was performed after tDCS, the initial motivational drive as reflected by the invigoration slope was slightly reduced.

The main finding was a significant increase in effort maintenance for both, task performance during and after tDCS compared to sham. Thereby, tDCS may have led to a reduced aversion to exerting effort. The study achieved a random balance in the order of stimulation conditions, and the statistical model adjusted for the order of task performance, independent of the stimulation condition. Additionally, we controlled for the number of trials in each task to reduce these potential confounders. Therefore, it can be assumed that the tDCS effect is not primarily influenced by motor learning or motor exhaustion.

This proof-of-principle study indicates that the effect of tDCS on effort maintenance is small and therefore may not be clinically relevant. However, the effect was intra-individually stable (see Fig. 3B), suggesting it may be well replicable. To further contextualize the small but statistically significant effects behaviorally, we compared them to the effects of reward magnitude (high vs. low) and level of difficulty (high vs. low) in our paradigm. We found that the effect of tDCS was smaller than reward magnitude but similar to the behavioral changes elicited by the difficulty levels. Additionally, the small effects align with findings from previous studies modulating motivational behavior in subjects with ADHD using dopamine agonists in neurobehavioral paradigms. For example, in a lever-pressing task aimed at gaining rewards, methylphenidate intake increased performance in subjects with ADHD on compared to off medication, with a small effect size [42]. Similarly, another study found that amphetamine increased the willingness to exert effort in subjects with ADHD compared to a placebo. Notably, consistent with the results from this study, the effect on reward magnitude was greater than the effect of the intervention [5].

In this study, an increase in effort maintenance even after controlling for reward condition (high vs. low) was observed, suggesting that the effect of an increased effort maintenance is independent of reward magnitude. To our knowledge, one previous study used tDCS to modulate anticipatory reward behavior, but not effortful behavior, in children with ADHD using tDCS. In this previous study, the cathode was positioned over the left DLPFC and the anode over the vmPFC. In a chocolate delay discounting task reduced delay discounting rates specific to high reward conditions were found, while low reward conditions remained unaffected during tDCS compared to sham [18]. This may indicate differences in the valuation of reward magnitude compared to our study. The ventral and dorsal striatum, bilateral medial prefrontal cortex (mPFC), dorsal anterior cingulate cortex, and bilateral caudate have been proposed to be sensitive to reward magnitude during the anticipation phase of reward processing [43]. Interestingly, both this study and the described study placed the excitatory anode over the vmPFC. However, here the cathode was placed over the rDLPFC, whereas the other study used a cathode placement over the left DLPFC, resulting in electrical fields pointing in opposite directions. This difference may have differentially influenced the evaluation of reward magnitude in the described cortical regions, especially the mPFC. Importantly, a study using the same electrode set-up as ours found an increased reward valuation and these valuations correlated with increased functional connectivity between the vmPFC and the ventral midbrain [22]. Therefore, upregulation of the vmPFC by anodal tDCS may have increased reward valuation and decreased delay discounting in the paradigm used. The observed increase in effort maintenance, however, might also be attributed to a downregulation of the rDLPFC through cathodal stimulation, a key hub for cold executive functions (e.g., cognitive inhibitory control) [23]. However, in this study, the cathodal stimulation was less focal, with an electrode size of 25 cm^2 compared to the anode size of 12.25 cm^2, resulting in a stronger electrical field at the anode (placed over the vmPFC) compared to the cathode (placed over the rDLPFC). Nonetheless, the additive effect of rDLPFC downregulation may contribute to our observed effects and more advanced designs are warranted to disentangle the relative influence. Previous research using a bilateral DLPFC tDCS set-up with the cathode over the rDLPFC showed improvements in executive control [44], whereas another study did not report effects of cathodal rDLPFC stimulation on cognitive control [45]. However, our task was not specifically designed to assess delay discounting or cognitive (inhibitory) control. The specific cognitive processes that best explain the increased motor performance for rewards elicited by our tDCS remain to be elucidated by future studies.

In addition to these studies, two studies in healthy adults have used tDCS over the right frontopolar cortex to affect reward-related decision-making. These studies demonstrated increased willingness to engage in cognitive and motor effort, as well as improved rewarded motor learning [46,47]. These findings are consistent with the present results and suggest that tDCS targeting the right frontal cortex may influence effort decision-making preceding the engagement of subsequent motor effort, actual motor performance in anticipation of rewards, motor learning and reward valuation.

However, it is important to note that the two latter studies used electrode set-ups that were different from the present study. In both studies, the cathode was placed over the vertex, with a size of 100 cm^2, whereas here a 25 cm^2 cathode was placed over the rDLPFC. Stimulations intensities of either 1 mA [47] or 1.5 mA [46] were used in the respective studies (in contrast to 2 mA in the present study). Additionally, both studies placed the anode over the right fronto-polar cortex, which differs from the positioning to the present study, where the anode was placed over the vmPFC. All parameters are known to influence the focality of the electrical field and thereby its neuromodulatory effect [37]. Nevertheless, taken together, these findings suggest the right frontal cortex as a promising cortical target for tDCS to enhance reward processing. In future studies, it will remain to be elucidated, whether this finding is attributed specifically to changes in motor processing (e.g.

changes in motor speed, control or responses) or is additionally mediated by other subcomponents of cognitive decision making such as delay discounting or cognitive control.

No effects on the invigoration slope concurrent with tDCS were observed. However, a decrease in invigoration slope after tDCS compared to sham was shown, which was significant only before correction for multiple testing. Whether the limited power of this initial study may explain the inconclusive effect needs to be evaluated in future larger scale studies. Interestingly, transcutaneous vagus nerve stimulation (tVNS) was found to increase invigoration, whereas no effect was observed for effort maintenance using the same task [26]. The finding could be explained by different mechanisms of action on the reward circuitry by tDCS targeting the right prefrontal cortex and tVNS. Acute tVNS might be associated with stronger effects in the initial drive, potentially by a bottom-up mechanism increasing stomach-brain coupling via the nucleus of the solitary tract pathway [48]. Whereas our tDCS set-up might favor effort maintenance via a top-down pathway, increasing the connectivity between the vmPFC and ventral midbrain [22]. However, a direct comparison is limited, given that healthy adults were stimulated in contrast to the present sample our children and adolescents with ADHD.

The study has several limitations that need to be recognized and addressed in future research. Only a limited number of subjects were included, which may have exaggerated effects of the stimulation that are not estimated at high precision. Results need proper replication in larger studies. Subjects aged between 8 and 17 years were included, encompassing various stages of brain maturation. Future studies should investigate whether tDCS effects are limited to specific age groups. However, all of our included subjects had an onset in ADHD in early childhood and fulfilled the diagnostic criteria at the time of study inclusion. No baseline data were obtained from healthy participants. Therefore, no conclusions can be drawn to what extent the investigated reward-related performance is actually affected in the investigated study sample. No conclusions can be drawn on long-term treatment effects in ADHD, as only acute and carry-over effects up to 30 min after tDCS were assessed. We were not able to conduct analysis comparing ADHD subtypes, which needs to be addressed in future studies. In addition, it remains unclear to what extent patients will benefit from this specific tDCS stimulation clinically. Furthermore, results do not generalize to cognitive tasks, as only motor performance was assessed.

In summary, the present study demonstrates the general ability of tDCS using an anode over the vmPFC and a cathode over the rDLPFC to improve effort maintenance in individuals with ADHD. These findings have implications for future research, including the exploration and optimalization of this tDCS setup for potential long-term treatment effects of repeated tDCS sessions in ADHD. Our results may point to the potential of an alternative treatment in modulating reward behavior in ADHD by using tDCS. However, larg-scaled studies including extensive follow-ups with repeated sessions are warranted, to determine whether the observed effects translate to clinically meaningful change. Additionally, our results may imply that this tDCS setup might be investigated in other pediatric disorders characterized by motivational deficits, such as depression, to ameliorate anhedonia-related deficits.

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CRediT authorship contribution statement

Jasper Vöckel: Writing – original draft, Visualization, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Anne Kühnel:** Writing – review & editing, Visualization, Methodology, Formal analysis. **Rebecca Rossberg:** Writing – review & editing, Methodology, Investigation. **Nina Geist:** Writing – review & editing, Investigation. **Christine Sigrist:** Writing – review & editing, Visualization. **Lena Pokorny:** Writing – review & editing. **Julian Koenig:** Writing – review & editing, Formal analysis. **Nils Kroemer:** Writing – review & editing, Methodology. **Stephan Bender:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

We have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2024.07.018.

References

[1] American Psychiatric Association. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. fifth ed. 2013. Washington, DC: 2013.
[2] Posner J, Polanczyk GV, Sonuga-Barke E. Attention-deficit hyperactivity disorder. Lancet Lond Engl 2020;395:450–62. https://doi.org/10.1016/S0140-6736(19)33004-1.
[3] Sonuga-Barke EJS. The dual pathway model of AD/HD: an elaboration of neurodevelopmental characteristics. Neurosci Biobehav Rev 2003;27:593–604. https://doi.org/10.1016/j.neubiorev.2003.08.005.
[4] Sergeant JA. Modeling attention-deficit/hyperactivity disorder: a critical appraisal of the cognitive-energetic model. Biol Psychiatry 2005;57:1248–55. https://doi.org/10.1016/j.biopsych.2004.09.010.
[5] Chong TT-J, Fortunato E, Bellgrove MA. Amphetamines improve the motivation to invest effort in attention-deficit/hyperactivity disorder. J Neurosci 2023;43:6898–908. https://doi.org/10.1523/JNEUROSCI.0982-23.2023.
[6] Egeland J, Nordby Johansen S, Ueland T. Do low-effort learning strategies mediate impaired memory in ADHD? J Learn Disabil 2010;43:430–40. https://doi.org/10.1177/0022219409355473.
[7] Winter Y, Ben-Pazi H, Pollak Y. Effort allocation in children with ADHD: Abnormal decision-making or poor execution? J Atten Disord 2016;23:1240–50. https://doi.org/10.1177/1087054716654569.
[8] Chen D, Jia T, Cheng W, Cao M, Banaschewski T, Barker GJ, et al. Brain Signatures during reward anticipation predict persistent attention-deficit/hyperactivity disorder symptoms. J Am Acad Child Adolesc Psychiatry 2022;61:1050–61. https://doi.org/10.1016/j.jaac.2021.11.030.
[9] Tripp G, Wickens JR. Research review: dopamine transfer deficit: a neurobiological theory of altered reinforcement mechanisms in ADHD. J Child Psychol Psychiatry 2008;49:691–704. https://doi.org/10.1111/j.1469-7610.2007.01851.x.
[10] Cortese S, Adamo N, Del Giovane C, Mohr-Jensen C, Hayes AJ, Carucci S, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. Lancet Psychiatr 2018;5:727–38. https://doi.org/10.1016/S2215-0366(18)30269-4.
[11] Rubia K, Halari R, Cubillo A, Mohammad A-M, Brammer M, Taylor E. Methylphenidate normalises activation and functional connectivity deficits in attention and motivation networks in medication-naïve children with ADHD during a rewarded continuous performance task. Neuropharmacology 2009;57:640–52. https://doi.org/10.1016/j.neuropharm.2009.08.013.
[12] Chelonis JJ, Johnson TA, Ferguson SA, Berry KJ, Kubacak B, Edwards MC, et al. Effect of methylphenidate on motivation in children with attention-deficit/hyperactivity disorder. Exp Clin Psychopharmacol 2011;19:145–53. https://doi.org/10.1037/a0022794.
[13] Addicott MA, Schechter JC, Sapyta JJ, Selig JP, Kollins SH, Weiss MD. Methylphenidate increases willingness to perform effort in adults with ADHD. Pharmacol Biochem Behav 2019;183:14–21. https://doi.org/10.1016/j.pbb.2019.06.008.
[14] Wehmeier PM, Dittmann RW, Banaschewski T. Treatment compliance or medication adherence in children and adolescents on ADHD medication in clinical practice: results from the COMPLY observational study. Atten Deficit Hyperact Disord 2015;7:165–74. https://doi.org/10.1007/s12402-014-0156-8.
[15] Zewdie E, Ciechanski P, Kuo HC, Giuffre A, Kahl C, King R, et al. Safety and tolerability of transcranial magnetic and direct current stimulation in children: prospective single center evidence from 3.5 million stimulations. Brain Stimulat 2020;13:565–75. https://doi.org/10.1016/j.brs.2019.12.025.
[16] Leffa DT, Grevet EH, Bau CHD, Schneider M, Ferrazza CP, da Silva RF, et al. Transcranial direct current stimulation vs sham for the treatment of inattention in adults with attention-deficit/hyperactivity disorder: the TUNED randomized

clinical trial. JAMA Psychiatr 2022;79:847–56. https://doi.org/10.1001/jamapsychiatry.2022.2055.
[17] Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 2000;527(Pt 3):633–9. https://doi.org/10.1111/j.1469-7793.2000.t01-1-00633.x.
[18] Nejati V, Sarraj Khorrami A, Nitsche MA. Transcranial direct current stimulation improves reward processing in children with ADHD. J Atten Disord 2021;25:1623–31. https://doi.org/10.1177/1087054720923094.
[19] Westwood SJ, Radua J, Rubia K. Noninvasive brain stimulation in children and adults with attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. J Psychiatry Neurosci JPN 2021;46:E14–33. https://doi.org/10.1503/jpn.190179.
[20] Salehinejad MA, Nejati V, Mosayebi-Samani M, Mohammadi A, Wischnewski M, Kuo M-F, et al. Transcranial direct current stimulation in ADHD: a systematic review of efficacy, Safety, and protocol-induced electrical field modeling results. Neurosci Bull 2020;36:1191–212. https://doi.org/10.1007/s12264-020-00501-x.
[21] Meyer B, Mann C, Götz M, Gerlicher A, Saase V, Yuen KSL, et al. Increased neural activity in mesostriatal regions after prefrontal transcranial direct current stimulation and l-DOPA administration. J Neurosci Off J Soc Neurosci 2019;39:5326–35. https://doi.org/10.1523/JNEUROSCI.3128-18.2019.
[22] Chib VS, Yun K, Takahashi H, Shimojo S. Noninvasive remote activation of the ventral midbrain by transcranial direct current stimulation of prefrontal cortex. Transl Psychiatry 2013;3:e268. https://doi.org/10.1038/tp.2013.44.
[23] Salehinejad MA, Ghanavati E, Rashid MHA, Nitsche MA. Hot and cold executive functions in the brain: a prefrontal-cingular network. Brain Neurosci Adv 2021;5:23982128211007769. https://doi.org/10.1177/23982128211007769.
[24] Vöröslakos M, Takeuchi Y, Brinyiczki K, Zombori T, Oliva A, Fernández-Ruiz A, et al. Direct effects of transcranial electric stimulation on brain circuits in rats and humans. Nat Commun 2018;9:483. https://doi.org/10.1038/s41467-018-02928-3.
[25] Hunold A, Haueisen J, Freitag CM, Siniatchkin M, Moliadze V. Cortical current density magnitudes during transcranial direct current stimulation correlate with skull thickness in children, adolescent and young adults. Prog Brain Res 2021;264:41–56. https://doi.org/10.1016/bs.pbr.2021.01.010.
[26] Neuser MP, Teckentrup V, Kühnel A, Hallschmid M, Walter M, Kroemer NB. Vagus nerve stimulation boosts the drive to work for rewards. Nat Commun 2020;11:1–11. https://doi.org/10.1038/s41467-020-17344-9.
[27] Webber HE, Lopez-Gamundi P, Stamatovich SN, de Wit H, Wardle MC. Using pharmacological manipulations to study the role of dopamine in human reward functioning: a review of studies in healthy adults. Neurosci Biobehav Rev 2021;120:123–58. https://doi.org/10.1016/j.neubiorev.2020.11.004.
[28] Wittes J. Sample size calculations for randomized controlled trials. Epidemiol Rev 2002;24:39–53. https://doi.org/10.1093/epirev/24.1.39.
[29] World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191–4. https://doi.org/10.1001/jama.2013.281053.
[30] Margraf J, Cwik JC, Pflug V, Schneider S. Strukturierte klinische Interviews zur Erfassung psychischer Störungen über die Lebensspanne. Z Klin Psychol Psychother 2017;46:176–86. https://doi.org/10.1026/1616-3443/a000430.
[31] Döpfner M, Görtz-Dorten A, Lehmkuhl G. Diagnostik-System für psychische Störungen nach ICD-10 und DSM-5 für Kinder und Jugendliche - III (DISYPS-III). Göttingen: Hogrefe; 2017.
[32] Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971;9:97–113. https://doi.org/10.1016/0028-3932(71)90067-4.
[33] Wiess R. Grundintelligenztest Skala-2 Revision-(CFT-20R). Göttingen: Hogrefe; 2006.
[34] Kaufman AS. Kaufman assessment battery for children. second ed. MN Am Guid Serv; 2004.
[35] Wechsler D. Wechsler intelligence scale for children-(WISC-V): Technical and interpretive manual. 2014. Bloomington, MN.
[36] Jasper HH. Ten-twenty electrode system of the international federation. Electroencephalogr Clin Neurophysiol 1958;10:371–5.
[37] Caulfield KA, George MS. Optimized APPS-tDCS electrode position, size, and distance doubles the on-target stimulation magnitude in 3000 electric field models. Sci Rep 2022;12:20116. https://doi.org/10.1038/s41598-022-24618-3.
[38] Jamil A, Batsikadze G, Kuo H-I, Labruna L, Hasan A, Paulus W, et al. Systematic evaluation of the impact of stimulation intensity on neuroplastic after-effects induced by transcranial direct current stimulation. J Physiol 2017;595:1273–88. https://doi.org/10.1113/JP272738.
[39] Thielscher A, Antunes A, Saturnino GB. Field modeling for transcranial magnetic stimulation: a useful tool to understand the physiological effects of TMS? 2015 37th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. EMBC 2015:222–5. https://doi.org/10.1109/EMBC.2015.7318340.
[40] Kleiner M, Brainard D, Pelli D. What's new in Psychtoolbox-3?. 2007.
[41] Selya AS, Rose JS, Dierker LC, Hedeker D, Mermelstein RJ. A practical guide to calculating Cohen's f(2), a measure of local effect size, from PROC MIXED. Front Psychol 2012;3:111. https://doi.org/10.3389/fpsyg.2012.00111.
[42] Chelonis JJ, Johnson TA, Ferguson SA, Berry KJ, Kubacak B, Edwards MC, et al. Effect of methylphenidate on motivation in children with attention-deficit/hyperactivity disorder. Exp Clin Psychopharmacol 2011;19:145–53. https://doi.org/10.1037/a0022794.
[43] Gadassi Polack R, Mollick JA, Keren H, Joormann J, Watts R. Neural responses to reward valence and magnitude from pre- to early adolescence. Neuroimage 2023;275:120166. https://doi.org/10.1016/j.neuroimage.2023.120166.
[44] Nejati V, Salehinejad MA, Nitsche MA, Najian A, Javadi A-H. Transcranial direct current stimulation improves executive dysfunctions in ADHD: implications for inhibitory control, interference control, working memory, and cognitive flexibility. J Atten Disord 2020;24:1928–43. https://doi.org/10.1177/1087054717730611.
[45] Cosmo C, Baptista AF, de Araújo AN, do Rosário RS, Miranda JGV, Montoya P, et al. A randomized, double-blind, sham-controlled trial of transcranial direct current stimulation in attention-deficit/hyperactivity disorder. PLoS One 2015;10:e0135371. https://doi.org/10.1371/journal.pone.0135371.
[46] Soutschek A, Kang P, Ruff CC, Hare TA, Tobler PN. Brain stimulation over the frontopolar cortex enhances motivation to exert effort for reward. Biol Psychiatry 2018;84:38–45. https://doi.org/10.1016/j.biopsych.2017.11.007.
[47] Herrojo Ruiz M, Maudrich T, Kalloch B, Sammler D, Kenville R, Villringer A, et al. Modulation of neural activity in frontopolar cortex drives reward-based motor learning. Sci Rep 2021;11:20303. https://doi.org/10.1038/s41598-021-98571-y.
[48] Müller SJ, Teckentrup V, Rebollo I, Hallschmid M, Kroemer NB. Vagus nerve stimulation increases stomach-brain coupling via a vagal afferent pathway. Brain Stimulat 2022;15:1279–89. https://doi.org/10.1016/j.brs.2022.08.019.