JAMA Psychiatry | Original Investigation

Transcranial Direct Current Stimulation vs Sham for the Treatment of Inattention in Adults With Attention-Deficit/Hyperactivity Disorder
The TUNED Randomized Clinical Trial

Douglas Teixeira Leffa, MD, PhD; Eugenio Horacio Grevet, MD, PhD; Claiton Henrique Dotto Bau, MD, PhD; Maitê Schneider; Carolina Prietto Ferrazza; Roberta Francieli da Silva; Marina Silva Miranda, BSc; Felipe Picon, MD, PhD; Stefania Pigatto Teche, MD; Paulo Sanches, PhD; Danton Pereira, MSc; Katya Rubia, PhD; André Russowsky Brunoni, MD, PhD; Joan A. Camprodon, MD, PhD, MPH; Wolnei Caumo, MD, PhD; Luis Augusto Rohde, MD, PhD

IMPORTANCE Transcranial direct current stimulation (tDCS) may improve symptoms of inattention in adults with attention-deficit/hyperactivity disorder (ADHD). However, previous trials are characterized by small sample sizes, heterogeneous methodologies, and short treatment periods using clinic-based tDCS.

OBJECTIVE To determine the efficacy and safety of home-based tDCS in treating inattention symptoms in adult patients with ADHD.

DESIGN, SETTING, AND PARTICIPANTS Randomized, double-blind, parallel, sham-controlled clinical trial (tDCS for the Treatment of Inattention Symptoms in Adult Patients With ADHD [TUNED]), conducted from July 2019 through July 2021 in a single-center outpatient academic setting. Of 277 potential participants screened by phone, 150 were assessed for eligibility on site, and 64 were included. Participants were adults with ADHD, inattentive or combined subtype. Exclusion criteria included current stimulant drug treatment, current moderate to severe symptoms of depression or anxiety, diagnosis of bipolar disorder with a manic or depressive episode in the last year, diagnosis of schizophrenia or another psychotic disorder, and diagnosis of autism spectrum disorder; 55 of participants completed follow-up after 4 weeks.

INTERVENTIONS Thirty-minute daily sessions of home-based tDCS for 4 weeks, 2 mA anodal-right and cathodal-left prefrontal stimulation with 35-cm^2 carbon electrodes.

MAIN OUTCOMES AND MEASURES Inattentive scores in the clinician-administered version of the Adult ADHD Self-report Scale version 1.1 (CASRS-I).

RESULTS Included in this trial were 64 participants with ADHD (31 [48%] inattentive presentation and 33 [52%] combined presentation), with a mean (SD) age of 38.3 (9.6) years. Thirty participants (47%) were women and 34 (53%) were men. Fifty-five finished the trial. At week 4, the mean (SD) inattention score, as measured with CASRS-I, was 18.88 (5.79) in the active tDCS group and 23.63 (3.97) in the sham tDCS group. Linear mixed-effects models revealed a statistically significant treatment by time interaction for CASRS-I (β interaction = −3.18; 95% CI, −4.60 to −1.75; $P < .001$), showing decreased symptoms of inattention in the active tDCS group over the 3 assessments compared to the sham tDCS group. Mild adverse events were more frequent in the active tDCS group, particularly skin redness, headache, and scalp burn.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, daily treatment with a home-based tDCS device over 4 weeks improved attention in adult patients with ADHD who were not taking stimulant medication. Home-based tDCS could be a nonpharmacological alternative for patients with ADHD.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT04003740

Visual Abstract

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Luis Augusto Rohde, MD, PhD, Department of Psychiatry, Universidade Federal do Rio Grande do Sul, Rua Ramiro Barcelos, 2350, 90035-903 Porto Alegre, RS, Brazil (lrohde@terra.com.br).

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2022.2055
Published online August 3, 2022.

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental condition with an estimated worldwide prevalence of 5.2% in school-aged children[1] and 2.5% in adults.[2] Pharmacotherapy is recommended as the initial treatment for most patients, with stimulant medication as a first-line intervention.[3] Although randomized clinical trials have determined efficacy with pharmacological treatment,[4] patient adherence is low.[5-9] Adverse effects and suboptimal response are the most commonly described reasons for treatment discontinuation.[10,11] Therefore, investigating effective nonpharmacological treatments for ADHD is a pressing concern.

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique that applies a low-intensity current over the scalp to modulate cortical excitability and induce neuroplasticity.[12,13] tDCS is easy to use and relatively inexpensive. According to the latest guidelines, no serious adverse events or irreversible injuries have been reported across more than 33 000 tDCS sessions of conventional tDCS protocols (with sessions shorter than 40 minutes using less than 4 mA).[14,15] The most common adverse effects with tDCS are skin redness, scalp burn, tingling, and headache. They are generally mild and well tolerated and occur in up to one-third of patients.[14,15] tDCS over the prefrontal cortex was associated with improvement in distinct components of higher cognitive function in healthy[16-19] and clinical[17,18,20] populations. Although a limiting factor for tDCS use is adherence due to the need for daily visits for stimulation sessions,[21] recent advances in the field led to the development of reliable home-use tDCS devices that have already been validated in clinical samples.[22]

The use of tDCS for treating ADHD has been increasingly explored in preclinical[23-25] and clinical[26,27] studies. So far, most studies have measured the effects of tDCS over the dorsolateral prefrontal cortex (DLPFC) on cognitive functions of patients with ADHD.[28,29] A recent meta-analysis[29] observed small trendwise significant effects for inhibition and processing speed, but not attention functions. However, few sham-controlled studies have evaluated the efficacy of tDCS in improving core clinical symptoms of ADHD.[30-32] Pilot studies assessing the impact of tDCS in adults[30] and children[31] with the disorder have observed a reduction in symptoms of inattention but not hyperactivity-impulsivity. However, the largest randomized clinical trial[32] of tDCS in ADHD found no improvement of symptoms in adolescent boys with the disorder. Moreover, most studies presented small sample sizes, heterogeneous methodologies, and short treatment periods.[26,27]

Therefore, the main objective of this study was to determine the efficacy and safety of 4 weeks' home-based tDCS treatment in reducing inattention symptoms in adults with ADHD. For that, we conducted a randomized, double-blind, parallel, sham-controlled trial: the tDCS for the Treatment of Inattention Symptoms in Adult Patients with ADHD (TUNED) study.

Key Points

Question Is home-based transcranial direct current stimulation (tDCS) a safe and effective treatment for inattention in adults with attention-deficit/hyperactivity disorder (ADHD)?

Findings In this randomized clinical trial including 64 adult patients with ADHD who were not taking stimulant medication, daily treatment with a home-based tDCS device over 4 weeks significantly improved symptoms of inattention compared to sham. tDCS was not associated with serious adverse events.

Meaning tDCS was a safe and well-tolerated effective treatment for inattention in adults with ADHD in this trial.

Methods

The trial was conducted in a single center at Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil, with a recruitment period from July 2019 through July 2021. The Research Ethics Committee of the Hospital de Clinicas de Porto Alegre approved the study, and all participants provided written informed consent. The entire protocol is available in Supplement 1 and the full statistical analyses in eAppendix 1 in Supplement 2. There were 4 protocol deviations, and detailed information can be found in the research project section of the trial protocol in Supplement 1 and eAppendix 1 and eTable 6 in Supplement 2.

Participants

Eligible participants were adults aged 18 to 60 years who met *DSM-5* criteria for ADHD, combined or inattentive subtypes. The diagnosis of ADHD was performed using a semistructured clinical interview conducted by trained psychiatrists (E.H.G., F.P., S.P.T.). The evaluation included a modified version of the Epidemiological Version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children, ADHD section, and the Structured Clinical Interview for *DSM-5* to assess comorbidities.

Inclusion criteria comprised moderate or severe symptoms of inattention, defined as an inattention score of 21 or higher on the clinician-administered version of the Adult ADHD Self-report Scale version 1.1 (CASRS), with the use of adult prompts.[33,34] The CASRS includes 9 questions referring to symptoms of inattention (CASRS-I) and 9 referring to symptoms of hyperactivity-impulsivity (CASRS-HI), on a scale from 0 to 4, with a score varying from 0 to 36 points for each domain (higher scores indicating increased symptoms). In addition, we included participants who were not being treated with stimulants or agreed to perform a 30-day washout from stimulants before initiating the tDCS, who had an estimated IQ score of 80 or above on the Wechsler Adult Intelligence Scale, Third Edition, and who self-reported being of European descendency. This restriction aimed to reduce the risk of population stratification bias for genetic studies.

Exclusion criteria were current moderate to severe symptoms of depression, defined as Beck Depression Inventory-II (BDI) score higher than 21; current moderate to severe symptoms of anxiety, defined as Beck Anxiety Inventory score 21 or higher; diagnosis of bipolar disorder with a manic or depressive episode in the last year; diagnosis of schizophrenia or another psychotic disorder; diagnosis of autism spectrum disorder; positive screen for substance use disorder according to the Alcohol, Smoking, and Substance Involvement

Screening Test; unstable medical condition with reduction of functional capacity; pregnancy or willingness to become pregnant in the next 3 months; inability to use the home-based tDCS device for any reason; previous history of neurosurgery; presence of any ferromagnetic metal in the head; implanted medical devices in the head or neck region; and history of noncontrolled epilepsy with seizures in the last year.

Intervention

We used a home-based tDCS device developed at Hospital de Clínicas de Porto Alegre.[35] The device has been used in previous trials[36-38] and was designed following the highest standards for at-home tDCS,[14,39] including a user-friendly interface; ability to automatically block the session in case the impedance is too high; preprogrammed number of sessions and dosage of stimulation; minimum interval between 2 consecutive sessions of 16 hours; option to abort a session if necessary; and capacity to save the number of sessions and time of stimulation performed by each participant. The current was delivered using 35-cm^2 electrodes (7 cm × 5 cm) coated with a vegetable sponge moistened with saline solution before the stimulation by 2 silicone cannulas coupled to the electrode. Each patient received a neoprene cap (small, medium, or large according to the circumference of their head) in which we fixed the electrodes, ensuring that the stimulation was provided accurately and consistently throughout the study period. Further details of the home-based device use can be found elsewhere.[35]

Participants were instructed on using the device at the baseline assessment when they received the first stimulation session while assisted by trained staff. Next, participants underwent 30-minute daily sessions of tDCS, 2-mA direct constant current, for 4 weeks for a total of 28 sessions (including weekends). The anodal and cathodal electrodes were positioned over F4 and F3, respectively, corresponding to the right and left DLPFC according to the international 10-20 electroencephalography system (eFigure 1 in Supplement 3). The right DLPFC was the target of the anodal stimulation because a meta-analysis of functional magnetic resonance imaging studies of attention demonstrated reduced activation in this region in individuals with ADHD.[40] Devices programmed for sham treatment delivered a 30-second ramp-up (0-2 mA) stimulation followed by a 30-second ramp-down (2-0 mA) at the beginning, middle, and end of the application. This was performed to mimic the tactile sensations commonly reported with tDCS and was shown to be a reliable sham protocol.[36-38] Participants were instructed to remain seated during sessions, but no other behavioral restriction was imposed. To improve adherence, each participant received a daily reminder in the form of a text message on their cell phones. This strategy has been shown to improve adherence to stimulant treatment in children[41] and adults[42] with ADHD. Each participant was encouraged to perform the stimulation sessions at the same time of the day according to their schedule.

Randomization and Blinding

Patients were randomized in a 1:1 allocation ratio to receive active or sham tDCS. Two staff members with no contact with patients generated an allocation sequence with random blocks of 6 and 4 participants kept in opaque, sealed envelopes. The same team programmed the devices to discharge sham or active stimulation according to each participant's allocation. The active and sham tDCS devices were physically indistinguishable. At the last visit, participants were asked which intervention they had received and the rate of confidence in their prediction. The blinding assessment was performed using the Bang Blinding Index,[43] ranging from −1 to 1, with 0 indicating successful blinding. A positive value suggests that participants correctly guessed their treatments beyond chance.

Outcomes

Participants were assessed at baseline and weeks 2 and 4. The prespecified primary outcome was symptoms of inattention, evaluated with CASRS-I. Secondary outcomes included hyperactivity-impulsivity symptoms evaluated with CASRS-HI, depression symptoms evaluated with BDI, anxiety symptoms evaluated with Beck Anxiety Inventory, and executive function assessed with the Behavior Rating Inventory of Executive Functions-Adult (BRIEF-A). Detailed information on the assessment with CASRS can be found in eAppendix 2 in Supplement 2.

Adverse Events

We assessed adverse events 3 times (at baseline, week 2, and week 4), relying on a commonly used questionnaire in tDCS trials.[21] Participants were instructed to report any additional adverse events experienced during or after treatment that were not included in the questionnaire.

Statistical Analysis

All participants were included in an intention-to-treat analysis according to randomized treatment assignment. We used random intercepts linear mixed-effects models to analyze continuous outcomes, which can adequately account for associations induced by repeated measurements within participants and automatically handle missing values. Independent models included treatment (2 levels: active tDCS and sham tDCS), time (continuous variable, assuming that, for each participant, measurements were linear on natural logarithm [time from baseline +1]), treatment by time interaction, and participants as random effects. Measurements closer in time were considered more associated than measurements further apart; thus, we assumed an autoregressive covariance structure. We estimate the effect size between groups using Cohen *d* and defined cutoff values for small, medium, and large effect sizes as 0.2, 0.5, and 0.8, respectively.[44] A 2-sided *P* value <.05 was considered statistically significant. All analyses were performed using Stata version 14.0 (StataCorp).

Results

We screened 277 patients by phone, assessed 150 for eligibility on site, and randomized 64 into the 2 treatment groups (32 per group). **Table 1** shows the baseline demographic and clinical characteristics. Most participants (53 [82.8%]) had been

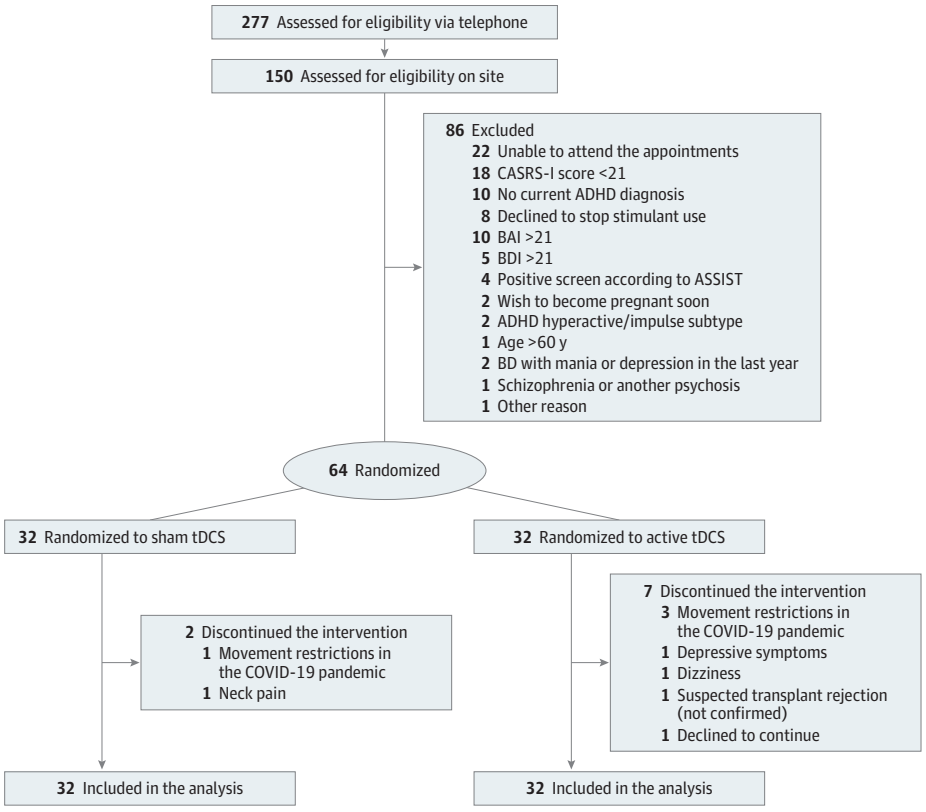
Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	No. (%)		
	Active tDCS (n = 32)	Sham tDCS (n = 32)	Total (n = 64)
Age, mean (SD), y	38.2 (10.3)	38.4 (9.1)	38.3 (9.6)
Female	19 (59.4)	11 (34.4)	30 (46.9)
Male	13 (40.6)	21 (65.6)	34 (53.1)
ADHD presentation			
Inattentive	17 (53.1)	14 (43.8)	31 (48.4)
Combined	15 (46.9)	18 (56.2)	33 (51.6)
Education, mean (SD), y	15.15 (3.36)	15.71 (2.67)	15.43 (3.02)
Brazilian criteria SES, mean (SD)	36.06 (9.29)	35.43 (7.76)	35.75 (8.49)
IQ, mean (SD)[a]	111.68 (10.33)	110.55 (10.72)	111.11 (10.45)
Lifetime diagnosis			
Any depressive disorder	9 (28.1)	10 (31.2)	19 (29.7)
Any anxiety disorder	5 (15.6)	5 (15.6)	10 (15.6)
Previous use of stimulant	27 (84.4)	26 (81.2)	53 (82.8)
Washout	5 (15.6)	3 (9.4)	8 (12.5)
Medication			
SSRI	9 (28.1)	5 (15.6)	14 (21.8)
Venlafaxine	1 (3.1)	1 (3.1)	2 (3.1)
Clomipramine	0	1 (3.1)	1 (1.6)
Desvenlafaxine	1 (3.1)	3 (9.4)	4 (6.3)
Bupropion	1 (3.1)	2 (6.2)	3 (4.7)
Benzodiazepines	2 (6.2)	1 (3.1)	3 (4.7)
Anticonvulsants	0	1 (3.1)	1 (1.6)
Buspirone	0	1 (3.1)	1 (3.1)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; SES, socioeconomic status; SSRI, selective serotonin reuptake inhibitors; tDCS, transcranial direct current stimulation.

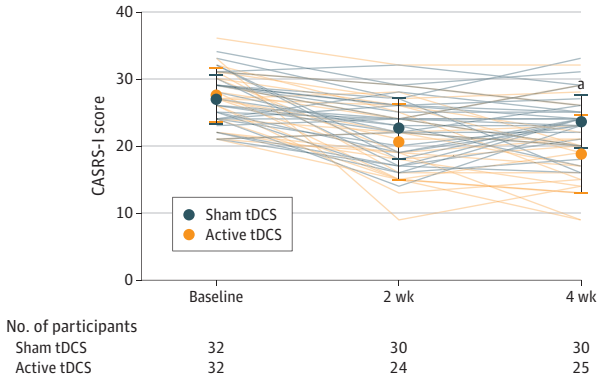
[a] Includes 29 individuals from active tDCS and 30 from sham tDCS.

Figure 1. CONSORT Diagram



ASSIST indicates the Alcohol, Smoking, and Substance Involvement Screening Test; BAI, Beck Anxiety Inventory; BD, bipolar disorder; BDI, Beck Depression Inventory-II; CASRS-I, clinician-administered version of the Adult ADHD Self-report Scale version 1.1, inattention section; tDCS, transcranial direct current stimulation.

Figure 2. Changes in Primary Outcome



No. of participants			
Sham tDCS	32	30	30
Active tDCS	32	24	25

Figure shows clinician-administered version of the Adult ADHD Self-report Scale version 1.1, inattention section (CASRS-I) scores over time. Bars represent mean scores ±1 SD of inattention symptoms measured with CASRS-I at baseline, week 2, and week 4. Lines represent individual patients' scores. CASRS-I scores range from 0 to 36, with higher scores indicating more symptoms of inattention. Two participants in sham transcranial direct current stimulation (tDCS) and 7 in the active tDCS group dropped out of the study before week 2. One participant in the active tDCS group was not available for assessment in week 2, but continued in the trial up to week 4. Linear mixed-effects models revealed a statistically significant treatment by time interaction for CASRS-I (β interaction = −3.18; 95% CI, −4.60 to −1.75; $P < .001$), showing decreased symptoms of inattention in the active tDCS group over the 3 assessments when compared to sham tDCS.

treated with stimulants in the past, and 8 (12.5%) performed washout before study initiation.

Nine patients discontinued treatment before the first 4 weeks, 2 in the sham tDCS group (1 due to restrictions to circulation during the COVID-19 pandemic and 1 for neck pain) and 7 in the active tDCS group (3 due to the same pandemic-related restrictions, 1 for depressive symptoms, 1 for dizziness, 1 for suspected transplant rejection, and 1 for declining to continue without specifying reasons) (**Figure 1**). Participants from the active tDCS group performed a mean (SD) 20.7 (9.20) sessions. In the sham tDCS group, the mean (SD) was 23.9 (5.49) sessions (eTable 1 in Supplement 2). When considering only participants who completed the 4 weeks of treatment, the mean (SD) number of sessions for the active tDCS and sham tDCS groups was 25.2 (3.01) and 24.8 (4.35), respectively (eTable 1 in Supplement 2).

Primary Outcome

At week 4, the mean (SD) inattention score, as measured with CASRS-I, was 18.88 (5.79) in the active tDCS group and 23.63 (3.97) in the sham tDCS group. Linear mixed-effects models revealed a statistically significant treatment by time interaction for CASRS-I (β interaction = −3.18; 95% CI, −4.60 to −1.75; $P < .001$), showing decreased symptoms of inattention in the active tDCS group over the 3 assessments compared to sham tDCS. The estimated Cohen *d* was 1.23 (95% CI, 0.67 to 1.78). A total of 11 patients (34.3%) in the active tDCS group achieved a 30% reduction in CASRS-I score compared to 2 patients (6.2%) in the sham tDCS group. CASRS-I values over time are presented in **Figure 2**.

Secondary Outcomes

No statistically significant differences in secondary outcomes were observed, indicating that the experimental treatment did not change symptoms of hyperactivity-impulsivity, depression, or anxiety. Values over time are presented in eTable 2 in Supplement 2. Similarly, no difference was observed in measures of executive function obtained with BRIEF-A (eTable 3 in Supplement 2).

Adverse Events

A complete list of adverse events is shown in **Table 2.** They were mostly mild (eTable 4 in Supplement 2), and no severe or serious adverse events were observed. One participant in the sham tDCS group withdrew from the trial due to an adverse event (neck pain), while 2 withdrew from the trial in the active tDCS group owing to depressive symptoms and dizziness. Four individuals presented an increase in CASRS-I scores in week 4 compared to baseline, all from the sham tDCS group. Four participants presented an increase in the overall BRIEF-A scores in the sham tDCS group, while the same was observed in 2 participants from the active tDCS group.

Blinding Integrity

eTable 5 in Supplement 2 shows the participants' guesses in the blinding assessment. The Bang Blinding Index was 0.32 (95% CI, 0.09 to 0.54) in active tDCS, suggesting a significant excess of correct guesses by about 32%. For sham tDCS, the Bang Blinding Index was -0.12 (95% CI, -0.35 to 0.10), indicating a pattern consistent with a random distribution of responses.

Additional analyses dichotomizing patients in the active tDCS group into responders (more than 30% reduction in CASRS-I from baseline to week 4, n = 11) and nonresponders (n = 14) revealed that 68% of responders correctly guessed their treatment assignment beyond chance (Bang Blinding Index = 0.68; 95% CI, 0.49 to 0.87). On the other hand, nonresponders had a pattern consistent with a random distribution of responses (Bang Blinding Index = -0.03; 95% CI, -0.36 to 0.29).

Stimulation Parameters

Data regarding current intensity and contact impedance for each stimulation session were saved in the device's software. **Figure 3** shows the mean current intensity and contact impedance from all sessions performed by each participant. Overall, the current intensity was adequately maintained at 2 mA, and the contact impedance was maintained within safety limits.[45] The time of the day each tDCS session was performed by the study participants can be found in eFigure 2 in Supplement 3.

Discussion

This randomized clinical trial assessed the efficacy of 28 daily sessions of home-based tDCS for 4 weeks in adults with ADHD. Results showed decreased symptoms of inattention after anodal compared to sham stimulation over the right DLPFC. Mild adverse events were more common in the active tDCS group, particularly skin redness and scalp burn. The study had a

Table 2. Adverse Events

Adverse event[a]	Baseline		Week 2[b]		Week 4		At least once during the study	
	Active tDCS (n = 32)	Sham tDCS (n = 32)	Active tDCS (n = 32)	Sham tDCS (n = 32)	Active tDCS (n = 25)	Sham tDCS (n = 30)	Active tDCS (n = 32)	Sham tDCS (n = 32)
Tingling	21 (65.6)	19 (59.4)	11 (34.4)	15 (46.9)	12 (48)	11 (36.7)	24 (75)	26 (81.3)
Skin redness	18 (56.3)	11 (34.4)	11 (34.4)	8 (25)	10 (40)	5 (16.7)	19 (59.4)	15 (46.9)
Headache	7 (21.9)	1 (3.1)	10 (31.3)	6 (18.8)	7 (28)	11 (36.7)	17 (53.1)	11 (34.4)
Scalp burn	12 (37.5)	6 (18.8)	6 (18.8)	2 (6.2)	6 (24)	4 (13.3)	16 (50)	10 (31.3)
Scalp pain	3 (9.4)	5 (15.6)	2 (6.2)	3 (9.4)	5 (20)	2 (6.7)	9 (28.1)	8 (25)
Sleepiness	3 (9.4)	4 (12.5)	2 (6.2)	5 (15.6)	1 (4)	6 (20)	4 (12.5)	10 (31.3)
Mood change	0	0	4 (12.5)	7 (21.9)	1 (4)	5 (16.7)	5 (15.6)	10 (31.3)
Neck pain	1 (3.1)	1 (3.1)	6 (18.8)	3 (9.4)	1 (4)	3 (10)	7 (21.9)	5 (15.6)
Trouble sleeping	0	0	1 (3.1)	1 (3.1)	2 (8)	0	3 (9.4)	1 (3.1)
Difficulty concentrating	0	0	0	1 (3.1)	0	2 (6.7)	0	2 (6.2)
Flashes of light	2 (6.2)	0	0	0	0	0	2 (6.2)	0
Mental fatigue	0	1 (3.1)	0	1 (3.1)	0	0	0	2 (6.2)
Nausea	0	0	1 (3.1)	0	0	0	1 (3.1)	0
Stiff jaw	0	0	0	1 (3.1)	0	0	0	1 (3.1)
Tingling hands	0	0	0	0	0	1 (3.3)	0	1 (3.1)
Dizziness	0	0	1 (3.1)	0	0	0	1 (3.1)	0

Abbreviation: tDCS, transcranial direct current stimulation.

[a] Adverse events were classified as mild if they did not require further action and were not classified as highly distressing by the participant; as moderate if medical evaluation or intervention was required or if the event was classified as highly distressing by the participant; as severe if the event required hospitalization or represented a serious medical threat; and as serious if the event was life-threatening or led to persistent or permanent disability. In this table, mild and moderate adverse events were combined. No severe or serious adverse events were observed.

[b] Participants who dropped out of the study before week 2 still answered the adverse events questionnaire.

dropout rate of 14%, mainly due to restrictions to circulation in the streets instituted during the COVID-19 pandemic. Nevertheless, high adherence was observed, with patients who finished the trial completing a mean 25 of 28 sessions.

This trial has key methodological differences compared to previous studies on tDCS in ADHD. First, we used a home-based tDCS device that enabled the application of a considerably higher number of sessions, with 28 sessions being the highest number of sessions so far applied to patients with ADHD. This is particularly relevant since preliminary evidence points to increased efficacy of tDCS with more extended periods of treatment.[46,47] This is further corroborated by the fact that our study showed no treatment effect after 2 weeks with 14 tDCS sessions. Most tDCS studies have used 1 to 5 sessions only.[26,27] The latest study with the largest number of sessions showed no effect after 15 sessions of tDCS over right inferior frontal cortex.[32] Our findings hence suggest that larger number of sessions seem to be necessary for tDCS to show clinical efficacy. Additionally, the need of daily visits to clinics or hospitals has been always a major challenge for the use of tDCS in clinical contexts.[14,39] Thus, the home-based device opens a new window of opportunity, especially for participants who live in geographically remote areas or have physical or cognitive disabilities that may hinder access to clinical centers. Second, most studies used a crossover design.[26] We opted for a parallel rather than crossover design since the carryover effect of tDCS is still considerably unexplored.[48] Third, while most tDCS studies used left DLPC as target region,[27] we placed the anodal excitability-increasing electrode over the right DLPFC because decreased activation in this region has been reported in adult patients with ADHD during tasks that require attention.[40] However, even though we based our target area on neuroimaging findings from the literature, there is no consensus regarding the optimal montage for ADHD. In fact, a recent study observed improved cognitive control in patients with ADHD after anodal tDCS over the left DLPFC, while no effect was observed with anodal stimulation over the right DLPFC.[49] Additional research is needed to clarify the optimal montage for patients with ADHD.

In secondary analyses, we found no effect of tDCS on hyperactivity-impulsivity, depression, or anxiety symptoms. This lack of effect may be associated with our exclusion criteria, which comprised patients from the ADHD hyperactive-impulsive presentation and individuals with current moderate to severe symptoms of depression or anxiety. Another explanation might be that hyperactivity-impulsivity symptoms involve distinct brain regions compared to inattention symptoms.[40] Hyperactivity-impulsivity in ADHD appears to be associated with a hypoactivation in the right inferior frontal cortex rather than right DLPFC.[40] Null findings were also observed for self-reported measures of executive function, which might be associated with a failure of tDCS to improve dysexecutive deficits, similarly to stimulant medication.[50]

Our findings support the use of tDCS as a safe and effective treatment for adults with ADHD with no concomitant treatment with stimulants. This is particularly relevant since a vast body of literature describes low long-term adherence rates and persistence to pharmacological treatment in patients with ADHD.[9-11] Among the reasons for treatment discontinuation are adverse events, suboptimal response, dosing inconve-

Figure 3. Stimulation Parameters

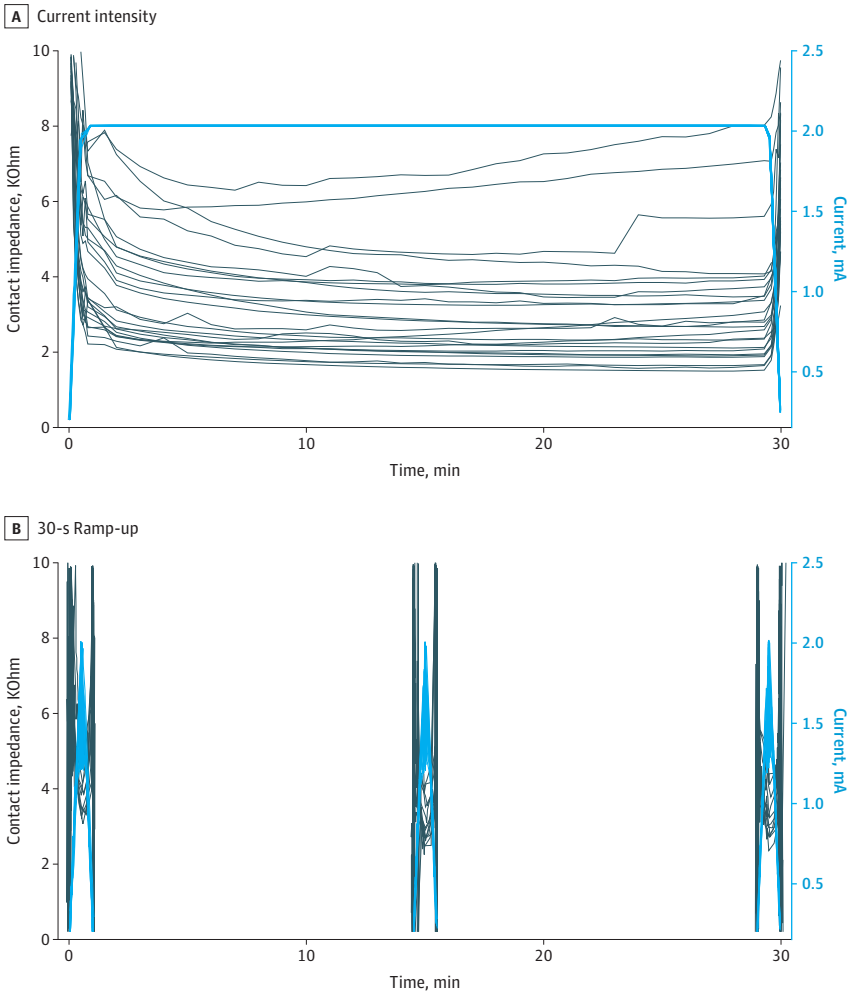


Figure shows the stimulation parameters. Each line represents the mean contact impedance (dark blue) and mean current intensity (cyan) from all sessions performed by each participant submitted to active transcranial direct current stimulation (tDCS) or sham tDCS. A, The current intensity was adequately maintained at 2 mA during the entire sessions performed by each participant. Contact impedance was maintained within safety limits. B, The 30-second ramp-up (0-2 mA) stimulation, followed by the 30-second ramp-down (2-0 mA), in the beginning, middle, and end of sessions in the sham group.

nience, social stigma, and fear of drug addiction.[10,11] There is also limited evidence for longer-term efficacy of stimulant treatment in meta-analyses[4] and epidemiological and naturalistic follow-up studies,[51] which may be associated with possible brain adaptations to ADHD medication.[52] There is, therefore, a continuous search for effective nonpharmacological interventions. Recently, a randomized clinical trial[53] demonstrated the efficacy and safety of trigeminal nerve stimulation (TNS), a noninvasive neuromodulation method, for children with ADHD. Later, TNS was the first device-based therapy for ADHD approved by the Food and Drug Administration.[54] In a conservative appraisal of our findings, the lowest limit of the 95% CI of the estimated effect size indicates at least a moderate effect, similar to the one reported with TNS,[53] as well as to the second-line treatment for ADHD, atomoxetine,[4] highlighting the potential use of neuromodulation as an effective alternative treatment for this population.

To our knowledge, this is the largest randomized clinical trial testing tDCS in patients with ADHD regarding sample size, number of sessions, and treatment length. In the sham tDCS group, we observed a slight reduction in inattention symptoms after 2 weeks, with an increase close to baseline levels after 4 weeks. This pattern is commonly observed in randomized clinical trials and is consistent with a higher expectation at the beginning of the trial combined with regression to the mean.[55] The blinding assessment showed successful blinding in the sham tDCS group. In the active tDCS group, about 68% of participants who responded to treatment could correctly guess their treatment assignment beyond chance. Although this is consistent with unblinding due to an actual effect,[56] we cannot entirely rule out the possibility that participants who perceived that they had been randomized to the active tDCS group were more likely to report in favor of improvements in their attention scores. Additionally, to our knowledge, this study is among the largest randomized trials conducted so far supporting the feasibility of a home-based tDCS device, and the first to test the use of a home-based device in patients with ADHD. A challenging task for further research is the study of individualized home-based tDCS parameters for patients with ADHD. Future trials should explore, for instance, the effects of distinct intensities and durations of sessions.

Limitations

Our findings should be viewed in light of some limitations concerning internal and external validity. Regarding internal validity, we had a higher dropout rate in the active tDCS group compared with the sham tDCS group, which might bias the interpretation of our findings. Notably, only 2 of the 7 individuals who dropped out in the active tDCS group did so due to an adverse event. Although patients received comprehensive training in using the device, no remote monitoring of sessions was performed. Therefore, there should be caution in direct comparison with studies with supervised electrode placement and exposure supervision. Regarding the study's external validity, we included a relatively homogeneous population of patients with ADHD with no current moderate to severe symptoms of depression or anxiety. This population is distinct from the usual ADHD patients treated in clinical centers, where psychiatric comorbidities are the rule rather than the exception.[57] In this study, high adherence was observed with a daily reminder. However, it is unclear whether similar rates would be obtained in real-life environments. Even though no participant in this study was being treated with stimulants during the study, it is important to keep in mind that 10 patients (3 in active tDCS and 7 in sham tDCS) were being treated for depression or anxiety with psychotropic medications that might have some mild effects on ADHD (venlafaxine, desvenlafaxine, clomipramine, or bupropion).[3,4] In addition, we included only patients with no current pharmacological treatment for ADHD, and therefore our findings might not be generalizable to patients taking stimulants or nonstimulant ADHD medications.

Conclusions

Daily treatment with a home-based tDCS device over right DLPFC compared with sham stimulation over 4 weeks improved attention in adult patients with ADHD who were not taking stimulant or nonstimulant ADHD medication. In addition, tDCS was safe and well tolerated, underlining its potential as an alternative treatment for inattention for patients with ADHD.

ARTICLE INFORMATION

Accepted for Publication: June 10, 2022.

Published Online: August 3, 2022. doi:10.1001/jamapsychiatry.2022.2055

Author Affiliations: ADHD Outpatient Program & Development Psychiatry Program, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil (Leffa, Grevet, Bau, Schneider, Ferrazza, da Silva, Miranda, Picon, Teche, Rohde); Department of Psychiatry, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil (Leffa, Grevet, Schneider, Ferrazza, da Silva, Miranda, Picon, Teche, Rohde); Department of Genetics, Institute of Biosciences, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil (Bau); Laboratory of Biomedical Engineer, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil (Sanches, Pereira); Department of Child & Adolescent Psychiatry, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom (Rubia); Service of Interdisciplinary Neuromodulation, Department and Institute of Psychiatry, Universidade de São Paulo, São Paulo, Brazil (Brunoni); Division of Neuropsychiatry and Neuromodulation, Massachusetts General Hospital, Harvard Medical School, Boston (Camprodon); Laboratory of Pain and Neuromodulation, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil (Caumo); Post-Graduate Program in Medical Sciences, School of Medicine, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil (Caumo); Department of Surgery, School of Medicine, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil (Caumo); National Institute of Developmental Psychiatry for Children and Adolescents, São Paulo, Brazil (Rohde).

Author Contributions: Drs Leffa and Rohde had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Leffa, Grevet, Bau, Teche, Rubia, Caumo, Rohde.
Acquisition, analysis, or interpretation of data: Leffa, Grevet, Schneider, Ferrazza, da Silva, Miranda, Picon, Teche, Sanches, Silva Junior, Rubia, Brunoni, Camprodon, Caumo, Rohde.
Drafting of the manuscript: Leffa, Brunoni, Rohde.
Critical revision of the manuscript for important intellectual content: Leffa, Grevet, Bau, Schneider, Ferrazza, da Silva, Miranda, Picon, Teche, Sanches, Silva Junior, Rubia, Camprodon, Caumo, Rohde.
Statistical analysis: Leffa, Picon, Brunoni, Rohde.
Obtained funding: Leffa, Rohde.
Administrative, technical, or material support: Leffa, Grevet, Bau, Schneider, Ferrazza, da Silva, Miranda, Picon, Teche, Sanches, Silva Junior, Caumo, Rohde.
Supervision: Leffa, Grevet, Bau, Rubia, Brunoni, Camprodon, Rohde.

Conflict of Interest Disclosures: Dr Leffa reported grants from Brain & Behavior Research Foundation, National Council for Scientific and Technological Development, and Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul during the conduct of the study. Dr Grevet served as a consultant to Shire/Takeda do Brasil and served on the speakers' bureau of Novartis/Sandoz and Shire/Takeda in the last 3 years. BSc Ferrazza, Ms da Silva, BSc Miranda, and Ms Schneider reported grants from National Council for Scientific and Technological Development during the conduct of the study. Dr Sanches reported grants from Financiadora de Estudos e Projetos during the conduct of the study; in addition, Dr Sanches had a patent for BR 20 2015 016450 0 licensed to Quark Medical. Dr Rubia reported grants from Takeda pharmaceuticals, National Institute of Health Research and Medical Research Council, and personal fees from Supernus outside the submitted work. The tDCS device used in this study was developed and patented by Dr Sanches, MSc Pereira, and Dr Caumo, and these authors received royalties from Quark Medical (patent for BR 20 2015 016450 0 licensed to Quark Medical). Dr Camprodon is a member of the scientific advisory board of Hyka Therapeutics and Feelmore Labs and has been a consultant for Neuronetics. Dr Rohde has received grant or research support from, served as a consultant to, and served on the speakers' bureau of Aché, Bial, Medice, Novartis/Sandoz, Pfizer/Upjohn, and Shire/Takeda in the last 3 years; the ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by Dr Rohde have received unrestricted educational and research support from Novartis/Sandoz and Shire/Takeda in the last 3 years; Dr Rhode has received authorship royalties from Oxford Press and ArtMed and grants from National Council for Scientific and Technological Development. MSc Pereira reported grants from Financiadora de Estudos e Projetos during the conduct of the study. Dr Camprodon reported other support from Hyka and other from Feelmore Labs outside the submitted work. No other disclosures were reported.

Funding/Support: This study was supported by grants 302688/2017-0 and 154116/2018-1 from the National Council for Scientific and Technological Development; 17/2551-0001 087-6, 17/2551-0001 476-6, 16/2551-0000249-5, and 19/2551-0000716-7 from Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul; NARSAD Young Investigator grant 29486 from the Brain & Behavior Research Foundation to Dr Leffa; from Fundação de Amparo à Pesquisa do Estado de São Paulo to Dr Brunoni; and 1245/13, and 0261/18 from the Brazilian Innovation Agency. Dr Brunoni receives scholarships and support from the Brazilian National Council of Scientific Development, University of São Paulo Medical School, the UK Academy of Medical Sciences (Newton Advanced Fellowship), and the International Health Cohort Consortium. Dr Grevet receives scholarship and support from the Brazilian National Council of Scientific Development.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We thank Paulo Jeng Chian Suen, BSc, Universidade de São Paulo, São Paulo, Brazil, for help with the electric field distribution model; Stephan Goerigk, PhD, Ludwig-Maximilians-University, Munich, Germany,

for support in the statistical analyses; Bruna Bellaver, PhD, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, for help with the randomized allocation sequence. There was no financial compensation.

REFERENCES

1. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *Am J Psychiatry*. 2007;194(3):204-211. doi:10.1176/ajp.2007.164.6.942

2. Simon V, Czobor P, Balint S, Meszaros A, Bitter I. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. *Br J Psychiatry*. 2009;194(3):204-211. doi:10.1192/bjp.bp.107.048827

3. Wolraich ML, Hagan JF Jr, Allan C, et al; Subcommittee on Children and Adolescents With Attention-Deficit/Hyperactive Disorder. Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*. 2019;144(4):e20192528. doi:10.1542/peds.2019-2528

4. Cortese S, Adamo N, Del Giovane C, 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 Psychiatry*. 2018;5(9):727-738. doi:10.1016/S2215-0366(18)30269-4

5. Marcus SC, Wan GJ, Kemner JE, Olfson M. Continuity of methylphenidate treatment for attention-deficit/hyperactivity disorder. *Arch Pediatr Adolesc Med*. 2005;159(6):572-578. doi:10.1001/archpedi.159.6.572

6. Adler LD, Nierenberg AA. Review of medication adherence in children and adults with ADHD. *Postgrad Med*. 2010;122(1):184-191. doi:10.3810/pgm.2010.01.2112

7. Winterstein AG, Gerhard T, Shuster J, et al. Utilization of pharmacologic treatment in youths with attention deficit/hyperactivity disorder in Medicaid database. *Ann Pharmacother*. 2008;42(1):24-31. doi:10.1345/aph.1K143

8. Perwien A, Hall J, Swensen A, Swindle R. Stimulant treatment patterns and compliance in children and adults with newly treated attention-deficit/hyperactivity disorder. *J Manag Care Pharm*. 2004;10(2):122-129. doi:10.18553/jmcp.2004.10.2.122

9. Olfson M, Marcus SC, Zhang HF, Wan GJ. Continuity in methylphenidate treatment of adults with attention-deficit/hyperactivity disorder. *J Manag Care Pharm*. 2007;13(7):570-577. doi:10.18553/jmcp.2007.13.7.570

10. Gajria K, Lu M, Sikirica V, et al. Adherence, persistence, and medication discontinuation in patients with attention-deficit/hyperactivity disorder—a systematic literature review. *Neuropsychiatr Dis Treat*. 2014;10:1543-1569. doi:10.2147/NDT.S65721

11. Khan MU, Aslani P. A review of factors influencing the three phases of medication adherence in people with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2019;29(6):398-418. doi:10.1089/cap.2018.0153

12. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol*. 2000;527(Pt 3):633-639. doi:10.1111/j.1469-7793.2000.t01-1-00633.x

13. Polanía R, Nitsche MA, Ruff CC. Studying and modifying brain function with non-invasive brain stimulation. *Nat Neurosci*. 2018;21(2):174-187. doi:10.1038/s41593-017-0054-4

14. Salehinejad MA, Nikolin S, Vicario CM, Nitsche MA, Loo CK, Brunoni AR. Safety and tolerability. In: Brunoni AR, Nitsche MA, Loo CK, eds. *Transcranial Direct Current Stimulation in Neuropsychiatric Disorders: Clinical Principles and Management*. Springer International Publishing; 2021:667-676. doi:10.1007/978-3-030-76136-3_35

15. Bikson M, Grossman P, Thomas C, et al. Safety of transcranial direct current stimulation: evidence based update 2016. *Brain Stimul*. 2016;9(5):641-661. doi:10.1016/j.brs.2016.06.004

16. de Boer NS, Schluter RS, Daams JG, van der Werf YD, Goudriaan AE, van Holst RJ. The effect of non-invasive brain stimulation on executive functioning in healthy controls: a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2021;125:122-147. doi:10.1016/j.neubiorev.2021.01.013

17. Hill AT, Fitzgerald PB, Hoy KE. Effects of anodal transcranial direct current stimulation on working memory: a systematic review and meta-analysis of findings from healthy and neuropsychiatric populations. *Brain Stimul*. 2016;9(2):197-208. doi:10.1016/j.brs.2015.10.006

18. Brunoni AR, Vanderhasselt M-A. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. *Brain Cogn*. 2014;86:1-9. doi:10.1016/j.bandc.2014.01.008

19. Dubreuil-Vall L, Chau P, Ruffini G, Widge AS, Camprodon JA. tDCS to the left DLPFC modulates cognitive and physiological correlates of executive function in a state-dependent manner. *Brain Stimul*. 2019;12(6):1456-1463. doi:10.1016/j.brs.2019.06.006

20. Sarkis RA, Kaur N, Camprodon JA. Transcranial direct current stimulation (tDCS): modulation of executive function in health and disease. *Curr Behav Neurosci Rep*. 2014;1(2):74-85. doi:10.1007/s40473-014-0009-y

21. Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *Int J Neuropsychopharmacol*. 2011;14(8):1133-1145. doi:10.1017/S1461145710001690

22. Alonzo A, Fong J, Ball N, Martin D, Chand N, Loo C. Pilot trial of home-administered transcranial direct current stimulation for the treatment of depression. *J Affect Disord*. 2019;252:475-483. doi:10.1016/j.jad.2019.04.041

23. Leffa DT, de Souza A, Scarabelot VL, et al. Transcranial direct current stimulation improves short-term memory in an animal model of attention-deficit/hyperactivity disorder. *Eur Neuropsychopharmacol*. 2016;26(2):368-377. doi:10.1016/j.euroneuro.2015.11.012

24. Leffa DT, Bellaver B, Salvi AA, et al. Transcranial direct current stimulation improves long-term memory deficits in an animal model of attention-deficit/hyperactivity disorder and modulates oxidative and inflammatory parameters. *Brain Stimul*. 2018;11(4):743-751. doi:10.1016/j.brs.2018.04.001

25. Jung DH, Ahn SM, Pak ME, et al. Therapeutic effects of anodal transcranial direct current stimulation in a rat model of ADHD. *Elife*. 2020;9:e56359. doi:10.7554/eLife.56359

26. Leffa DT, Rohde LA. Attention-deficit/hyperactivity disorder. In: Brunoni AR, Nitsche MA, Loo CK, eds. *Transcranial Direct Current Stimulation in Neuropsychiatric Disorders: Clinical Principles and Management*. Springer International Publishing; 2021:565-584. doi:10.1007/978-3-030-76136-3_28

27. Rubia K, Westwood S, Aggensteiner P-M, Brandeis D. Neurotherapeutics for attention deficit/hyperactivity disorder (adhd): a review. *Cells*. 2021;10(8):2156. doi:10.3390/cells10082156

28. Salehinejad MA, Wischnewski M, Nejati V, Vicario CM, Nitsche MA. Transcranial direct current stimulation in attention-deficit hyperactivity disorder: A meta-analysis of neuropsychological deficits. *PLoS One*. 2019;14(4):e0215095. doi:10.1371/journal.pone.0215095

29. 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*. 2021;46(1):E14-E33. doi:10.1503/jpn.190179

30. Cachoeira CT, Leffa DT, Mittelstadt SD, et al. Positive effects of transcranial direct current stimulation in adult patients with attention-deficit/hyperactivity disorder—a pilot randomized controlled study. *Psychiatry Res*. 2017;247:28-32. doi:10.1016/j.psychres.2016.11.009

31. Soff C, Sotnikova A, Christiansen H, Becker K, Siniatchkin M. Transcranial direct current stimulation improves clinical symptoms in adolescents with attention deficit hyperactivity disorder. *J Neural Transm (Vienna)*. 2017;124(1):133-144. doi:10.1007/s00702-016-1646-y

32. Westwood SJ, Criaud M, Lam S-L, et al. Transcranial direct current stimulation (tDCS) combined with cognitive training in adolescent boys with ADHD: a double-blind, randomised, sham-controlled trial. *Psychol Med*. 2021:1-16. doi:10.1017/S0033291721001859

33. Kessler RC, Adler L, Ames M, et al. The World Health Organization Adult ADHD Self-report Scale (ASRS): a short screening scale for use in the general population. *Psychol Med*. 2005;35(2):245-256. doi:10.1017/S0033291704002892

34. Mattos P, Segenreich D, Saboya E, Louzã M, Dias G, Romano M. Adaptação transcultural para o português da escala Adult Self-report Scale para avaliação do transtorno de déficit de atenção/hiperatividade (TDAH) em adultos. *Arch Clin Psychiatry (São Paulo)*. 2006;33:188-194. doi:10.1590/S0101-60832006000400004

35. Carvalho F, Brietzke AP, Gasparin A, et al. Home-based transcranial direct current stimulation device development: an updated protocol used at home in healthy subjects and fibromyalgia patients. *J Vis Exp*. 2018;(137). doi:10.3791/57614

36. Brietzke AP, Zortea M, Carvalho F, et al. Large treatment effect with extended home-based transcranial direct current stimulation over dorsolateral prefrontal cortex in fibromyalgia: a proof of concept sham-randomized clinical study. *J Pain*. 2020;21(1-2):212-224. doi:10.1016/j.jpain.2019.06.013

37. Caumo W, Alves RL, Vicuña P, et al. Impact of bifrontal home-based transcranial direct current

stimulation in pain catastrophizing and disability due to pain in fibromyalgia: a randomized, double-blind sham-controlled study. *J Pain*. 2022; 23(4):641-656. doi:10.1016/j.jpain.2021.11.002

38. Mota SM, Amaral de Castro L, Riedel PG, et al. Home-based transcranial direct current stimulation for the treatment of symptoms of depression and anxiety in temporal lobe epilepsy: a randomized, double-blind, sham-controlled clinical trial. *Front Integr Neurosci*. 2021;15:753995. doi:10.3389/fnint.2021.753995

39. Charvet LE, Shaw MT, Bikson M, Woods AJ, Knotkova H. Supervised transcranial direct current stimulation (tDCS) at home: A guide for clinical research and practice. *Brain Stimul*. 2020;13(3): 686-693. doi:10.1016/j.brs.2020.02.011

40. Hart H, Radua J, Nakao T, Mataix-Cols D, Rubia K. Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects. *JAMA Psychiatry*. 2013;70(2):185-198. doi:10.1001/jamapsychiatry.2013.277

41. Fried R, DiSalvo M, Kelberman C, et al. An innovative SMS intervention to improve adherence to stimulants in children with ADHD: Preliminary findings. *J Psychopharmacol*. 2020;34(8):883-890. doi:10.1177/0269881120908014

42. Biederman J, Fried R, DiSalvo M, et al. A novel text message intervention to improve adherence to stimulants in adults with attention deficit/hyperactivity disorder. *J Clin Psychopharmacol*. 2019;39(4):351-356. doi:10.1097/JCP.0000000000001055

43. Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. *Control Clin Trials*. 2004;25(2): 143-156. doi:10.1016/j.cct.2003.10.016

44. Kraemer HC, Kupfer DJ. Size of treatment effects and their importance to clinical research and practice. *Biol Psychiatry*. 2006;59(11):990-996. doi:10.1016/j.biopsych.2005.09.014

45. Bikson M, Datta A, Elwassif M. Establishing safety limits for transcranial direct current stimulation. *Clin Neurophysiol*. 2009;120(6):1033-1034. doi:10.1016/j.clinph.2009.03.018

46. Castillo-Saavedra L, Gebodh N, Bikson M, et al. Clinically effective treatment of fibromyalgia pain with high-definition transcranial direct current stimulation: phase ii open-label dose optimization. *J Pain*. 2016;17(1):14-26. doi:10.1016/j.jpain.2015.09.009

47. Brunoni AR, Moffa AH, Fregni F, et al. Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. *Br J Psychiatry*. 2016;208 (6):522-531. doi:10.1192/bjp.bp.115.164715

48. Biabani M, Farrell M, Zoghi M, Egan G, Jaberzadeh S. Crossover design in transcranial direct current stimulation studies on motor learning: potential pitfalls and difficulties in interpretation of findings. *Rev Neurosci*. 2018;29 (4):463-473. doi:10.1515/revneuro-2017-0056

49. Dubreuil-Vall L, Gomez-Bernal F, Villegas AC, et al. Transcranial direct current stimulation to the left dorsolateral prefrontal cortex improves cognitive control in patients with attention-deficit/hyperactivity disorder: a randomized behavioral and neurophysiological study. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2021;6(4):439-448. doi:10.1016/j.bpsc.2020.11.006

50. Biederman J, Mick E, Fried R, Wilner N, Spencer TJ, Faraone SV. Are stimulants effective in the treatment of executive function deficits? results from a randomized double blind study of OROS-methylphenidate in adults with ADHD. *Eur Neuropsychopharmacol*. 2011;21(7):508-515. doi:10.1016/j.euroneuro.2010.11.005

51. Swanson JM. Debate: are stimulant medications for attention-deficit/hyperactivity disorder effective in the long term? (against). *J Am Acad Child Adolesc Psychiatry*. 2019;58(10):936-938. doi:10.1016/j.jaac.2019.07.001

52. Fusar-Poli P, Rubia K, Rossi G, Sartori G, Balottin U. Striatal dopamine transporter alterations in ADHD: pathophysiology or adaptation to psychostimulants? a meta-analysis. *Am J Psychiatry*. 2012;169(3):264-272. doi:10.1176/appi.ajp.2011.11060940

53. McGough JJ, Sturm A, Cowen J, et al. Double-blind, sham-controlled, pilot study of trigeminal nerve stimulation for attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2019;58(4):403-411.e3. doi:10.1016/j.jaac.2018.11.013

54. Voelker R. Trigeminal nerve stimulator for ADHD. *JAMA*. 2019;321(21):2066. doi:10.1001/jama.2019.6992

55. Enck P, Klosterhalfen S. Placebos and the Placebo Effect in Drug Trials. In: Barrett JE, Page CP, Michel MC, eds. *Concepts and Principles of Pharmacology*. Springer International Publishing. 2019:399-431, doi:10.1007/164_2019_269.

56. Hróbjartsson A, Forfang E, Haahr MT, Als-Nielsen B, Brorson S. Blinded trials taken to the test: an analysis of randomized clinical trials that report tests for the success of blinding. *Int J Epidemiol*. 2007;36(3):654-663. doi:10.1093/ije/dym020

57. Faraone SV, Banaschewski T, Coghill D, et al. The World Federation of ADHD International Consensus Statement: 208 evidence-based conclusions about the disorder. *Neurosci Biobehav Rev*. 2021;128:789-818. Published online 2021. doi:10.1016/j.neubiorev.2021.01.022