Original research

Transcranial direct current stimulation and cognitive stimulation therapy in children with autism spectrum disorder: randomized, sham-controlled, double-blind, crossover, clinical trial

Patricia Vieira de Oliveira[1]
Mariana Lessa de Castro[2]
Luanda André Collange-Grecco[3]
Sueli Rizzutti[4]
Mauro Muszkat[5]

[1]Corresponding author. Universidade Federal de São Paulo (São Paulo). São Paulo, Brazil. patricia@prvo.com.br
[2,4,5]Universidade Federal de São Paulo (São Paulo). São Paulo, Brazil.
[3]Centro Universitário de Anápolis (Anápolis). Goiás, Brazil.

ABSTRACT | BACKGROUND: Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation technic that has been researched as a therapeutic alternative to reduce symptoms and improve cognitive functioning in many disorders, including autism spectrum disorder (ASD), a neurodevelopmental disorder in which functional changes are observed in some brain structures, damaging different areas of the individual's lives. **OBJECTIVE:** To compare the effects of active and sham transcranial direct current stimulation during cognitive stimulation tasks training in children with an autism spectrum disorder. **METHODS:** A randomized, sham-controlled, double-blind, crossover clinical trial was conducted. Twelve children with ASD underwent ten cognitive training sessions combined with active and sham tDCS. Anodal tDCS was administered over the left dorsolateral prefrontal cortex (DLPFC). Executive functions and social cognition were evaluated before, after, and three months after (follow-up) the intervention. **RESULTS:** No differences were found in the effects between the two interventions. Considering the mean results before and after active tDCS, improvements were seen in the theory of mind function (pre-intervention: 14.58 ± 5.04; post-intervention: 17.08 ± 5.21 [d^2 = 0.51)]; follow-up: 16.92 ± 5.52 [d^2 = 0.46]) and inhibitory control (pre-intervention: -1.31 ± 1.90; follow-up: 0.25 ± 1.14, d^2 = 1.04). **CONCLUSION:** The administration of active tDCS over the left DLPFC during the training of cognitive stimulation tasks did not result in superior effects compared to sham tDCS combined with training in children with an autism spectrum disorder.

KEYWORDS: Autism spectrum disorder. Transcranial direct current stimulation. Social cognition. Executive functions. Neuromodulation.

Submitted 12/01/2022, Accepted 03/02/2023, Published 04/05/2023
Brain Imaging Stimul., Salvador, 2023;2:e4954
http://dx.doi.org/10.17267/2965-3738bis.2023.e4954
ISSN: 2965-3738
Assigned editors: Katia Sá, Abrahão Baptista

How to cite this article: Oliveira PV, Castro ML, Collange-Grecco LA, Rizzutti S, Muszkat M. Transcranial direct current stimulation and cognitive stimulation therapy in children with autism spectrum disorder: randomized, sham-controlled, double-blind, crossover, clinical trial. Brain Imaging Stimul. 2023;2:e4954. http://dx.doi.org/10.17267/2965-3738bis.2023.e4954

CC BY

Introduction

Autism spectrum disorder (ASD) is a condition with a multifactor etiology and high incidence throughout the world that imposes substantial limitations. In the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5), this neurodevelopmental disorder is characterized by persistent, significant deficits in communication and social interaction in multiple contexts and restrictive, repetitive patterns of behavior and interest.[1] Part of the symptoms is believed to be caused by significant impairments in social cognition skills, specifically regarding the Theory of Mind and emotional perception, as well as impairments regarding two indicators of the adequate development of social cognition: language and executive functions.[2-6]

The Theory of Mind (TOM) refers to a system of the arraignment of mental states of others and oneself. Mental states are individuals' thoughts, feelings, knowledge, desires, and beliefs. In turn, emotional perception branches into two groups: a more basic one that is related to the recognition of facial expressions and the recognition of emotions before non-facial cues, such as the interlocutor's voice tone, and another more complex group regarding both understanding and management of emotions.[7,8]

Executive Functions (EFs) are the cognitive skill set for maintaining our behavior and emotions and planning actions.9 The EFs mediate much of an individual's daily activities, and their good development is significant for adaptive, socioemotional, and cognitive functioning.[10,11] According to Miyake et al.[12] and Diamond[9], EFs have three core elements: inhibition (or inhibitory control), cognitive flexibility, and working memory.

Considering the limitations secondary to ASD, several behavioral therapeutic approaches analyzed in clinical trials have demonstrated promising effects in treating children with this condition.[13-17] Cognitive and behavioral stimulation therapies are considered the basis of treatment for children with ASD[15,18] to minimize clinical symptoms and well as the negative impacts on independence and social quality of life.

In recent years, transcranial direct current stimulation (tDCS), which is a safe, effective, noninvasive brain stimulation technique, has been used in scientific production involving individuals with a diagnosis of ASD in different life cycle stages.[19-27] The administration of tDCS over a particular brain area exerts neuromodulatory effects. The effects on cortical excitability and neuroplasticity tend to promote improvements in cognitive-behavioral aspects, such as attention, learning, memory, communication, impulsivity, and decision-making.[28-30] The left dorsolateral prefrontal cortex (DLPFC) is considered a promising target area in the treatment of children with ASD due mainly to its essential involvement in cognitive control processes related to executive functions.

Some findings applying tDCS in the DLPFC in the infant-juvenile population with ASD, for example, demonstrate promising effects, such as significant improvement in vocabulary and syntax tasks[24], decrease in the CARS scale score, as in all domains of ATEC, except the language domain, seven days after active stimulation.[19,31] Attenuation of symptoms of catatonia and behavior problems in a teenager with ASD.[20] The reduction of ASD symptoms and the effect remained until six months after the intervention.[23] Electroencephalographic changes were also identified after the application of tDCS, such as increased network flexibility and inter-hemispheric connectivity in the active tDCS group concerning control. These findings suggest that anodic stimulation in DLPFC may induce changes in cortical excitability locally and globally.[26]

However, except for the study by Schneider and Hopp[32], the other studies done in children so far investigated only the effect of tDCS on symptoms and behavior. In turn, studies with adults showed improvement in working memory[25], increase in the social functioning index[21] and better performance in verbal fluency tasks of emotion.[21,22]

Thus, anodal tDCS over this region of the brain during the execution of cognitive-behavioral stimulation tasks is believed to enhance the effects of behavioral therapy, contributing satisfactorily to a reduction

in the disorder's symptoms and improvement in the global skills of the child. Therefore, the present study aimed to investigate whether ten 20-minute sessions of anodal tDCS administered over the left dorsolateral prefrontal cortex during the training of cognitive stimulation tasks would improve executive functions, social cognition, and language in children with ASD compared to the effects achieved with the administration of sham tDCS during the same behavioral intervention.

Methods

A randomized, sham-controlled, double-blind, crossover clinical trial was conducted. This study received approval from the Human Research Ethics Committee of Universidade Federal de São Paulo (Brazil) (process number: 87656918.7.0000.5505). It was conducted according to the ethical standards of Resolution No. 466/2012 of the Nation Health Board. The study was registered in the Brazilian Clinical Trials Registry (REBEC) under number RBR-93wgtg. Written informed consent was obtained from the legal guardians and participants.

Participants

Twelve children participated in the study. All participants were diagnosed with ASD and underwent screening at the Interdisciplinary Children's Neuropsychological Care Center of the Universidade Federal de São Paulo, Brazil. The inclusion criteria were a) a diagnosis of ASD confirmed by a pediatric neurologist using the criteria of the DSM-51; b) age six to 12 years old; c) enrolled in school; c) degree of understanding and cooperation compatible with the execution of the proposed intervention; d) a threshold of 30 or more points on the Childhood Autism Rating Scale[25]; e) authorization to participate in the study through a statement of informed consent signed by a legal guardian as well as a term of assent signed by the participant. The exclusion criteria were a) epilepsy; b) metal implant in the skull or hearing aids; c) other mental or neurological disorder beyond ASD (the exclusion criteria underwent through a neuropediatric assessment according to the DSM-5 criteria); d) sensory or motor deficiency that limited the execution of the proposed procedures.

Children who met the eligibility criteria were randomly allocated to begin participation in one of the two therapeutic interventions analyzed:

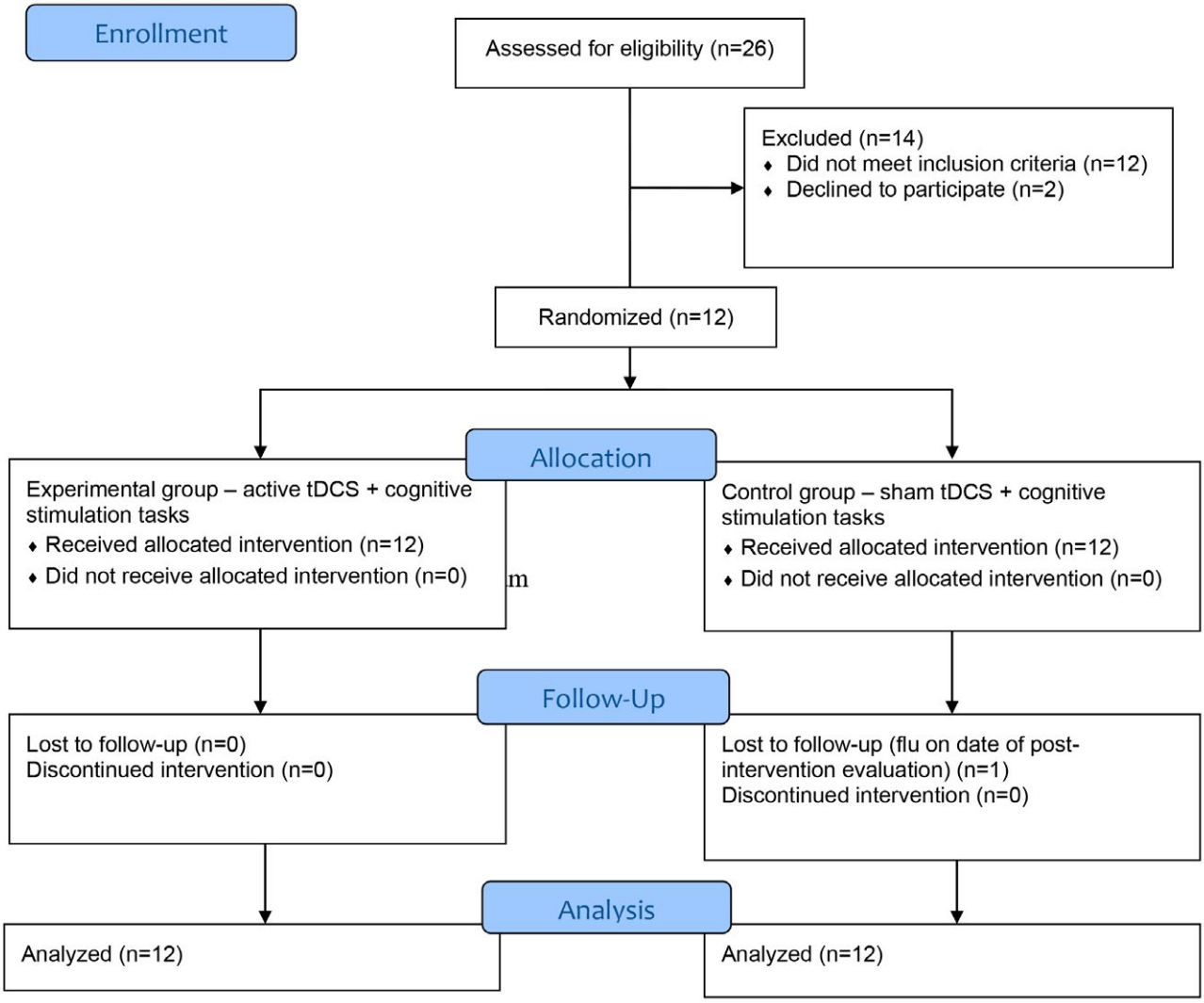
• Experimental intervention: cognitive stimulation tasks combined with anodal tDCS over the left dorsolateral prefrontal cortex;

• Control intervention: cognitive stimulation tasks combined with sham tDCS.

The allocation of the participants to the different interventions was determined using a simple randomization procedure. The results of the randomization procedure were stipulated on cards in sequentially numbered sealed opaque envelopes. After the pre-intervention evaluation, each participant was allocated to one of the interventions by opening an envelope. The allocation process was performed by a member of the research team not involved in the recruitment process or development of the study.

As this was a crossover study, a three-month washout period was respected between interventions to avoid the carry-over effect (prolongation of the residual effects of the previous intervention). The definition of the washout period was based on previous studies with a similar study design as the present investigation.[19,33]

Figure 1. Displays the flowchart of the study



Legend: CONSORT, 2010, Flow Diagram.
Source: the authors (2023).

The evaluation process (pre-intervention, post-intervention, and follow-up three months after the end of the interventions) was conducted on a single day for a maximum period of two hours. The evaluator was unaware of the study's objectives and did not participate in the interventions. To minimize the learning effect on the tests, the pre-intervention evaluation took place 20 days prior to the onset of the intervention, resulting in a one-month interval between the pre-intervention and post-intervention. Lots randomly determined the order of the evaluations.

The outcome measures are described below.

To evaluate social cognition, specifically regarding emotion recognition and the Theory of Mind, we used two subtests of the emotional perception field from the neuropsychological evaluation battery NEPSY II. It is worth mentioning that it is a broad evaluation battery that includes 32 subtests divided into six areas. NEPSY II is a foreign instrument that has undergone a process of cross-cultural adaptation, validity, and reliability for the Brazilian population. Most subtests showed strong evidence of truth, content validity, evidence based on the response process, and construct validity compared to other instruments, such as the Wechsler Intelligence Scale for children. As for the proof of reliability, we applied several strategies to secure internal consistency and test-retest stability.

In the Theory of Mind subtest, reliability is higher in children with typical younger development since, from the age of 7, most children perform all tasks successfully. However, in clinical samples, as in the case of ASD, the test was more sensitive to capture procedural measures.

The choice for NEPSY was due to the lack of standardized instruments for the Brazilian population that measure social cognition. Although it is not a specific procedure for the evaluation of individuals with ASD, we consider that it is a valuable tool for evaluations whose objective is to compare the skill in question before the intervention. Following is the description of the subtests:

NESPSY II – Social Perception Domain – Affect Recognition subtest: This subtest aims to assess emotion recognition skills (based on facial expressions) in children and adolescents between five and 16 years of age. The subtest comprises 35 items distributed among four different types of tasks with a progressive degree of difficulty. Each item has photographs of children expressing a primary emotion, such as joy, sadness, fear, anger, and disgust, along with a neutral expression.[34]

NESPSY II – Social Perception Domain – Theory of Mind subtest: This subtest evaluates the theory of mind function in children and adolescents five to 16 years of age. The test is divided into two parts. The first part is the Verbal Theory of Mind, which has items that involve short stories and vignettes that narrate a situation experienced by a character, followed by questions to determine whether the respondent is able to attribute emotional states to the character. The second part regards the Contextual Theory of Mind, which has tasks presenting figures showing a situation and the respondent is asked how the character must be feeling based on the context. The items have a progressive degree of difficulty and encompass tasks based on different ToM paradigms, such as false belief, identification of emotions based on the desire and/or situation, second-order ToM, etc.[34]

For the evaluation of language, specifically, the ability to employ expressive vocabulary, we used:

Children's naming test: This instrument evaluates vocabulary skills through the verbal naming of figures. The target population is children from three to 14 years of age. The test comprises 60 items presented one at a time, and the respondent must name the item shown. One point is attributed to each correct answer. The total is the sum of correct answers, enabling the classification of the respondents according to the standard score for each age. The TIN showed good reliability and internal consistency considering a 636 children and adolescents' sample. We found a coefficient of 0.97 Cronbach's alpha and a Spearman-Brow coefficient of 0.96. Other psychometric measures, such as development data and relationships with other tests, were attractive to this population.[35]

Finally, to measure the inhibitory control and cognitive flexibility domains, which are part of the executive functions, we applied the Five Digit Test (FDT). The FDT is a standardized instrument for the Brazilian population, which aims to measure the speed of cognitive processing, evaluate the skills of focusing and alternating attentional focus (cognitive flexibility), and deal with interferences (inhibitory control). The psychometric properties of FDT for the Brazilian population were investigated in several groups of individuals, clinical and non-clinical. Overall, the FDT has good validity indexes (evidence of convergent validity, internal structure validity, correlation with other tests) and reliability (internal consistency). One can access more details in the instrument's manual.

We chose the FDT due to the need for a standardized instrument that evaluated executive functions and because it is a resource that can be used in individuals with low education, not needing to be literate (which was the case of some children in the sample). Following is the description of the test:

Five Digit Test (FDT): The FDT aims to evaluate cognitive processing speed and efficiency – specifically, the ability to focus one's attention and switch to another focus according to an external cue, alternating between one rule and another (cognitive flexibility). This test also evaluates inhibitory control, as it is necessary to control the impulse of a more automatic answer in some test steps. The FDT consists of four different tasks. The first requires the reading of digits. Second, the respondent is asked to count the number of digits. The last two require alternating between reading and counting. According to the test's authors, the first two steps require more automatic cognitive

processes, whereas the last two require greater cognitive control. At the end of the test, it is possible to calculate reading, counting, choice, and alternance metrics as well as the score of the two main domains (inhibition and flexibility). These domains constituted an outcome measure in the present study.[36]

Adverse events. After each session, a questionnaire was administered based on previously reported adverse events to assess the safety of tDCS.[37]

The researcher in charge of the sessions also asked the participants and guardians about the occurrence of any adverse symptoms between sessions.

Intervention procedures

The interventions comprised ten 20-minute sessions of tDCS (active or sham) administered over the left dorsolateral prefrontal cortex during the training of cognitive tasks. Sessions were held at a frequency of five times per week over two consecutive weeks.

Transcranial direct current stimulation: tDCS was administered in ten sessions to facilitate behavioral changes by creating a neural network favorable to the environment. Stimulation was administered using the mobile DC-Stimulator (NeuroCom, Germany) with two sponge (non-metallic) surface electrodes (5 x 7 cm) moistened with saline solution. The anode was positioned over the left dorsolateral prefrontal cortex, following the 10-20 International Electroencephalogram System.[31] The cathode was positioned over the right deltoid muscle. A current of 1 mA was administered to the left dorsolateral prefrontal cortex for 20 minutes during the cognitive stimulation task. The current was gradually increased to 1 mA in the first 30 seconds and gradually diminished in the last 30 seconds of the session.

The same electrode placement procedure was used for sham stimulation, and the stimulator was switched on for 30 seconds to give the volunteer the initial sensation of stimulation. However, no current was delivered throughout the remainder of the session. This is a valid form of control in studies involving tDCS.

Cognitive stimulation tasks: Based on evidence in the literature that the effect of tDCS can be enhanced when combined with cognitive stimulation tasks.[38,39] The first aimed to stimulate emotion recognition skills, and the second involved odd situations and problem-solving. Cards were used for the intervention, with the following questions: “What emotion is this?” and “Where is the odd thing?”.[40,41]

For the first part of the session were used 3 cards of the deck "What emotion is this?" which consisted of 10 cards with names of emotions and 30 more cards with situations that expressed these emotions. The goal is for the child to associate the name with the equivalent feeling demonstrated in the letter. We also planned an adaptation to the game for children who needed to be literate. In this situation, we just requested the child to name the emotion he saw in the letter, not needing to associate the name with the figure. For each letter presented, the following questions were asked: 1. What is he (she) feeling?; 2. Why is he (she) feeling this emotion/feeling?; 3. How would you feel in this situation?

In the second part of the intervention, we used the deck "Where is the absurd?" which contains 40 cards showing unusual situations that have something wrong. This activity aimed to verify if the child perceives what is uncommon in the image and if they can propose a solution to that situation. In each session, we used 4 cards from the deck, and each time we asked the following questions: 1. Where is the absurdity/ strange in the situation?; 2. Why is this absurd?; 3. What would be the correct/ appropriate way?

Statistical analysis

Intra-group and inter-group analyses were conducted to determine differences between evaluation times (pre-intervention, post-intervention, and follow-up) and interventions (active vs. sham tDCS). Generalized equations estimating (GEE) was used, which is a way to calculate the correlation between repeated measures of the same individuals. GEE is known as marginal models and can be considered an extension of generalized linear models, which directly incorporate the correlation between measures of the same sampling unit. Poisson distribution, a discrete probability distribution applicable to counts, was used in the models for all tests except the FDT. Gaussian distribution (linear regression for continuous data) was used for the FDT.

The choice of method was based on the type of sample (small) and type of study (longitudinal crossover design). In small samples, GEE has statistical power around 80% greater than repeated-measures ANOVA and is a preferred model for studies in medical fields or correlates in which the clinical conditions of the participants are altered during the intervention.

Numerical variables in each group were expressed as mean and standard deviation. Cohen's d was calculated as a measure of the effect size, and the significance level was set at 5%. The tables' statistically significant results ($p \leq 0.05$) are bold. The R software (version 4.0.2) was used for all analyses.

The sample size and test power were obtained based on ANOVA with repeated measures (within and between individuals). The following assumptions were accepted:

• Type 1 error probability equal to 0.05;

• Effect size equal to 0.4;

• Test power (1 – probability of type II error) of 0.95;

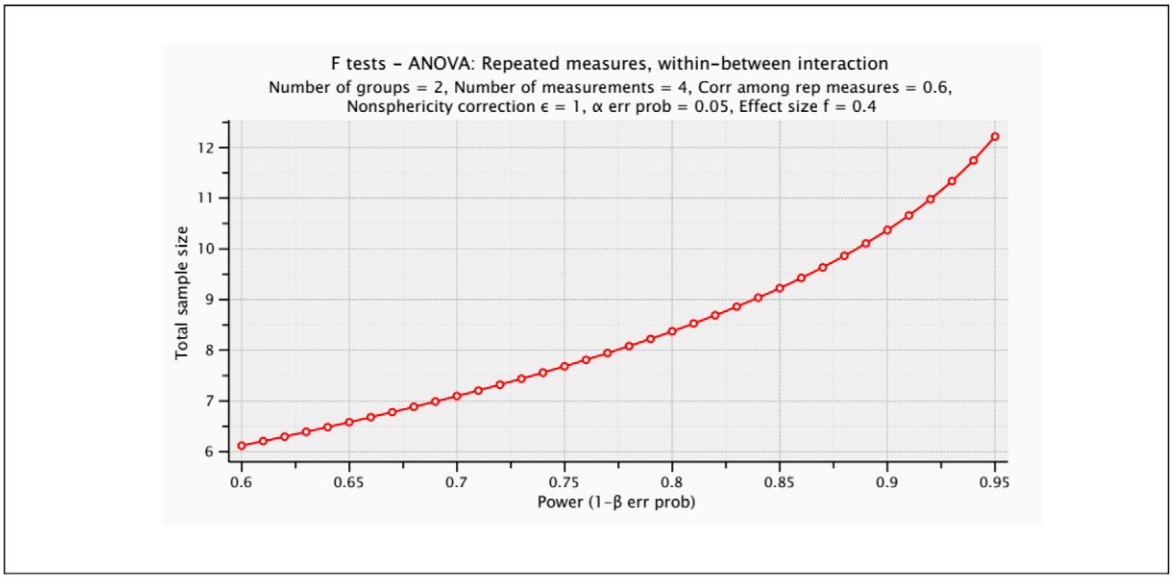
• Number of groups equal to 2;

• Number of measurements equal to 4;

• Correlation between repeated measurements of the order of 0.6.

The sample size consistent with these assumptions is equal to n=14, according to the protocol provided by the G-Power software (version 3.1). On Figure 2, it is possible to notice the relationship (increasing) between the test power function and the sample size, so that the test power reaches 0.95 when obtaining a sample size slightly above n=12.

Figure 2. Relationship between test power and sample size



Source: the authors (2023).

Results

Twenty-six children with a diagnosis of ASD were screened at the Interdisciplinary Children's Neuropsychological Care Center of the Universidade Federal de São Paulo for the present study. Twelve of these children met the eligibility criteria and participated in the study. One child did not appear for the evaluation after the active intervention due to influenza, but appeared for the three-month follow-up evaluation. All other participants took part in all evaluations and intervention sessions. Table 1 displays the clinical characteristics of the participants.

Table 1. Clinical characteristics of participants

Cases	Sex	Age	CARS	Total IQ	Verbal IQ	Execution IQ
1	M	10	30	97 (M)	87 (LM)	107 (M)
2	M	12	30	80 (T)	82 (LM)	85 (LM)
3	M	12	39	50 (D)	55 (D)	55 (D)
4	F	6	30	83 (LM)	65 (D)	104 (M)
5	M	7	30	81 (LM)	71 (T)	102 (M)
6	M	10	42	93 (M)	103 (M)	90 (LM)
7	F	7	30	84 (LM)	87 (LM)	86 (LM)
8	F	6	34	75 (T)	74 (T)	84 (LM)
9	M	7	32	52 (D)	75 (T)	45 (D)
10	M	10	33.5	79 (T)	82 (LM)	82 (LM)
11	M	7	30	69 (LM)	64 (LM)	77 (I)
12	M	8	30	95 (M)	94 (M)	98 (M)
Mean ± standard deviation	M=9 F=3	8.5±2.1	32.4±4.2	78.1±15.0	78.2±13.6	84.5±18.8

Legend: CARS: Childhood Autism Rating Scale. M = medium; LM = lower medium; T = threshold; D = deficient.
Source: the authors (2023).

Side effects. No severe side effects were found; all side effects observed and reported were categorized as mild, tolerable and transitory according to the descriptions of the children and their guardians. Eight children in the experimental group and two children in the control group reported mild itching and one child described moderate itching during the administration of active tDCS. Six children reported a tingling sensation in the initial minutes of stimulation. There were two reports of mild headache – both several hours after the administration of active tDCS. Local redness was found in six participants, which had disappeared soon after the end of the administration of active tDCS.

NESPSY II – Social Perception Domain – Affect Recognition subtest. Table 2 displays the means (standard deviation) and size effects for this variable at the different evaluation times considering the two interventions. The statistical analysis revealed no significant effects of the interventions in either the intra-group or inter-group comparisons.

Table 2. Results of emotion recognition subtest (NESPSY II – Social perception domain) before and after experimental intervention and control intervention

	Experimental intervention Active tDCS + cognitive training			Control intervention Sham tDCS + cognitive training			Experimental intervention *x* Control intervention	
	Mean (standard deviation)	p-value[1]	d[2]	Mean (standard deviation)	p-value[1]	d[2]	p-value[1]	d[2]
Pre-intervention	21.67 (7.16)	-	-	23.42 (5.92)	-	-	0.309	0.28
Post-intervention	22..2 (7.54)	0.456	0.18	23.42 (5.35)	1.000	0.00	0.743	0.08
Follow-up	23.08 (5.70)	0.383	0.23	2417 (6.07)	0.601	0.13	0.393	019

[1]Marginal models (GEE); [2]Cohen's d.
Source: the authors (2023).

NESPSY II – Social Perception Domain – Theory of Mind subtest. In the intra-group analysis of the experimental intervention, significant differences were found for the verbal Theory of Mind and total ToM score, with higher means found at the post-intervention and follow-up evaluations compared to the pre-intervention intervention. No significant differences were found in the intra-group analysis of the control intervention or the inter-group analysis ($p > 0.05$ for all analyses). Table 3 displays the means (standard deviation) and size effects for these variables at the different evaluation times considering the two interventions.

Table 3. Results of the Theory of Mind subtest (NESPSY II – Social Perception Domain) before and after experimental intervention and control intervention

Domain	Time	Experimental intervention Active tDCS + cognitive training			Control intervention Sham tDCS + cognitive training			Experimental intervention *x* Control intervention	
		Mean (standard deviation)	p-value[1]	d[2]	Mean (standard deviation)	p-value[1]	d[2]	p-value[1]	d[2]
Verbal ToM	Pre-intervention	10.58 (4.25)	-	-	11.83 (5.37)	-	-	0.130	0.27
	Post-intervention	13.17 (3.79)	**0.001**	0.67	12.5 (4.17)	0.425	0.14	0.243	0.17
	Follow-up	12.75 (4.81)	**<0.001**	0.50	12.00 (4.55)	0.812	0.03	0.182	0.17
Contextual ToM	Pre-intervention	4.00 (1.60)	-	-	4.00 (1.60)	-	-	1.000	0.00
	Post-intervention	3.92 (1.78)	0.882	0.05	4.33 (1.56)	0.072	0.22	0.462	0.26
	Follow-up	4.17 (1.47)	0.669	0.11	4.67 (1.07)	0.070	0.51	0.226	0.41
Total ToM	Pre-intervention	14.58 (5.04)	-	-	15.83 (6.45)	-	-	0.236	0.23
	Post-intervention	17.08 (5.21)	**0.017**	0.51	16.83 (5.18)	0.251	0.18	0.788	0.05
	Follow-up	16.92 (5.52)	**0.004**	0.46	16.67 (4.94)	0.303	0.15	0.702	0.05

[1]Marginal models (GEE); [2]Cohen's d; ToM = theory of mind.
Source: the authors (2023).

Children's Naming Test. No significant differences were found in the intra-group analysis of the experimental intervention or the inter-group analysis ($p > 0.05$). In contrast, significant differences were found in the means of the pre-intervention and post-intervention evaluations in the sham group ($p = 0.049$). Table 4 displays the means (standard deviation) and size effects for the Children's Naming Test at the different evaluation times considering the two interventions.

Table 4. Children's Naming Test Results before and after experimental and control intervention

Time	Experimental intervention Active tDCS + cognitive training			Control intervention Sham tDCS + cognitive training			Experimental intervention *x* Control intervention	
	Mean (standard deviation)	p-value[1]	d[2]	Mean (standard deviation)	p-value[1]	d[2]	p-value[1]	d[2]
Pre-intervention	37.25 (5.38)	-	-	37.08 (7.77)	-	-	0.884	0.03
Post-intervention	38.33 (8.34)	0.386	0.16	38.50 (7.31)	**0.049**	0.20	0.817	0.02
Follow-up	39.00 (6.94)	0.151	0.29	39.00 (7.41)	0.147	0.26	1.000	0.00

[1]Marginal models (GEE); [2]Cohen's d.
Source: the authors (2023).

Five Digit Test (FDT). A significant difference was found in the experiment group at the follow-up evaluation ($p = 0.024$), with a large effect size ($d^2 = 1.04$). No statistically significant differences were found in the intra-group analysis of the control intervention or the inter-group analysis ($p > 0.05$). Table 5 displays the means (standard deviation) and size effects for the FDT at the different evaluation times considering the two interventions.

Table 5. Results of Five Digit Test before and after experimental intervention and control intervention

Domain	Time	Experimental intervention Active tDCS + cognitive training			Control intervention Sham tDCS + cognitive training			Experimental intervention *x* Control intervention	
		Mean (standard deviation)	p-value[1]	d[2]	Mean (standard deviation)	p-value[1]	d[2]	p-value[1]	d[2]
FDT Inhibition	Pre-intervention	-1.31 (1.90)	-	-	-0.24 (2.10)	-	-	0.228	0.56
	Post-intervention	-0.29 (1.54)	*0.057*	0.62	-0.66 (2.09)	0.575	0.21	0.624	0.21
	Follow-up	0.25 (1.14)	**0.024**	1.04	-0.55 (2.07)	0.685	0.15	0.160	0.50
FDT Flexibility	Pre-intervention	-0.40 (1.33)	-	-	-0.98 (4.99)	-	-	0.668	0.17
	Post-intervention	-0.03 (1.57)	0.175	0.27	-0.93 (2.08)	0.972	0.01	0.224	0.51
	Follow-up	0.14 (1.43)	0.222	0.41	-0.55 (1.70)	0.753	0.12	0.169	0.46

Legend: FDT: Five Digit Test.
[1]Marginal models (GEE); [2]Cohen's d.
Source: the authors (2023).

Discussion

The interest in noninvasive brain stimulation techniques has increased substantially in the field of child and adolescent health in the last ten years as a promising option for reducing the symptoms of neurodevelopmental disorders and favoring the results of behavioral or physical rehabilitation. Specifically for the population diagnosed with autism spectrum disorder (ASD), transcranial direct current stimulation (tDCS) has been highlighted in the scientific literature as a therapeutic resource capable of favoring the activity of the left frontal lobe.[42]

The neurophysiological effects of tDCS have been studied, especially considering anodal stimulation of the dorsolateral prefrontal cortex (DLPFC) and temporoparietal junction, which are areas of the brain with compromised activation in individuals with ASD, as demonstrated in studies involving functional magnetic resonance.[42,43] Previous studies consider the left DLPFC to be a target area for favoring executive functions[19,25,31,44], significantly working memory. In contrast, the temporoparietal junction was selected in one study investigating social communication skills.[21]

Systematic reviews published to date have begun to demonstrate that the administration of tDCS over these areas of the brain, especially in the left hemisphere, results in promising effects regarding improvements in cognitive skills and social communication in this population.[42,43,45] In the present study, although no statistically significant differences were found, the results demonstrate that anodal tDCS over left DLPFC was superior to sham tDCS, as promising effects were observed in the comparative analysis of the evaluations performed before and after active tDCS combined with cognitive stimulation therapy. The experimental intervention (anodal tDCS + and cognitive stimulation therapy) favored increased skills related to the global theory of mind, with substantial results regarding the verbal Theory of Mind as well as cognitive processing speed and efficiency, especially the skill of inhibitory control. These effects were found after the end of the intervention. However, the most exciting results were identified at the follow-up evaluation performed three months after the end of the experimental intervention. These findings corroborate the theoretical reference developed in the field with the publication of clinical trials in recent years.

The findings make sense from the theoretical standpoint, as studies indicate that these two constructs are related, considering that good inhibitory control functioning favors the Theory of Mind[4,21,22]; this may be due to the high inhibition demand required when putting oneself in the place of another, as one must control the natural impulse to respond from one's own perspective and offer a response that considers the point of view of another person.[46] Both Theory of Mind and inhibitory control are fundamental skills for socioemotional adjustment and have direct implications regarding the behavior of individuals.

With the statistical results of the present analyses, we clearly cannot declare superior effects favoring anodal tDCS, as we did not find significant differences in the comparisons of the two interventions (anodal tDCS + cognitive stimulation therapy and sham tDCS + cognitive stimulation therapy). However, we believe that some aspects should be highlighted. The present study analyzed the effects of ten sessions of anodal tDCS administered during cognitive stimulation therapy at a frequency of five sessions per week over two consecutive weeks through pre-intervention, post-intervention and follow-up (three months after the end of the intervention) evaluations.

Among the six controlled clinical trials identified in the literature[19,21,25,31,44,47], only one study analyzing anodal tDCS over the left DLPFC addressed the combination with cognitive training.[25] The study reported results favoring active tDCS over sham tDCS, but involved adults (20 to 66 years of age) with a diagnosis of ASD and only had a single intervention session. Another clinical trial analyzing the combined effects of tDCS and cognitive therapy also involved adults with ASD submitted to a single session of anodal stimulation over the temporoparietal junction.[21]

As for the skills evaluated here, we can discuss some hypotheses to understand the results better. As already pointed out, we found no studies that investigated the effects of tDCS on CS in children and adolescents with ASD. However, the two studies with adults who evaluated social skills found interesting results.[21,22] In both of these studies, the target region chosen for stimulation was the right parietal-temporal junction (PTJ), which suggests that this may

be a more appropriate area when the objective is to improve CS. Here is an important caveat, in the study of Wilson et al.[22], the conclusion of improvement in social functioning was taken from the ATEC scale, that is, from broader and non-specific social skills of CS. Their study used the TASSK-M that evaluates the participant's knowledge about diverse social skills, such as what means someone who is "popular" or "intimidating, in other words, a broader social knowledge.

Regarding language, it was believed that anodic tDCS in the left CPFDL could bring benefits. This assumption was based on theoretical and empirical assumptions. First, by the functional connectivity between CPFDL and cognitive functions, such as Fes and language[48], and second by the empirical evidence shown in the studies of Schneider and Hopp[32] with children with ASD who, after a 30-minute session of anodic stimulation in this region, showed significant improvement in vocabulary and syntax skills. Contrary to what was expected, in the naming test, there was no effect of the type of stimulation, only a time effect between the pre and post-evaluations in the placebo group. A similar result was found in the study by Amatachaya et al.[31], in which there was no significant reduction in language problems measured by the ATEC scale after stimulating the left CPFDL.

This result may be due to the difference in language skills assessed. In the study of Schneider and Hopp[32], they conducted syntax and receptive vocabulary tasks. In this study, we used an expressive vocabulary task. Another possible explanation may be related to the heterogeneity of the sample. Schneider and Hopp[32] evaluated pre-linguistic competencies that were considered a requirement for evaluating the outcome (syntax and vocabulary) and only considered participants who scored above the threshold established by the researchers. This inclusion criterion helps to make the sample more homogeneous since it ensures that everyone has a minimum knowledge of the skill that will be evaluated. Finally, one can think of the stimulated area because, although the CPFDL is a region that acts in the organization of higher cognitive functions, including the executive components of language, it is not a primary area of the functioning of this skill. Thus, we suggest that future studies aiming to investigate the effects of anodic tDCS on oral language stimulate the lower frontal lobe region, corresponding to the Broca area and/or the posterior portion of the temporal lobe in the Wernicke area.

The last objective of this study was to investigate the effects of tDCS on Fes, specifically inhibitory control and cognitive flexibility. As presented in the results section, we found a time effect but not a type of stimulation in the inhibition domain in the active group. We observed a significant effect between pre- and follow-up with a large size effect, which did not occur in the placebo group. In theory, this effect of time would be expected, according to the literature, since Fes are skills that develop rapidly in this period of life of children and adolescents.[10,11] However, if this were the only explanation for the effect found, something similar would have been noticed in the placebo group, which did not happen. Thus, we can raise a hypothesis similar to that discussed in the Tom evaluation that there may have been an effect of tDCS on inhibitory control since the size effect of the difference was considerable. However, perhaps due to the small sample size, this effect may have been lost in the comparison between the group.

We found similar results in studies that applied protocols similar to ours, but in individuals with Attention deficit hyperactivity disorder (ADHD), which show that despite the promising results on the main symptoms of ADHD and cognitive functions such as working memory and selective attention, when dealing specifically with inhibitory control, the anodic tDCS applied on the left CPFDL, as in the present study, was not superior to placebo stimulation[30,33] evidenced an increase in interference inhibition that can be considered an executive/cognitive component of inhibitory control.

On the other hand, cathodic stimulation in F3 and anodic in the supraorbital region resulted in increased inhibitory control (impulse control).[33,49] These findings have coherence from the neuroanatomical perspective because due to the acknowledgment that several areas of the prefrontal cortex are involved in Fes, including the frontal cortex-orbital, which, according to some theories, would be related to a more emotional component of inhibitory control and connected to more limbic regions, while CPFDL is associated with a more cognitive component.[10,50] Therefore, it is possible to assume that the choice of region and type of stimulation will depend on the main complaints of the patient and can be the anodic stimulation in the left and cathodic CPFDL in the orbitofrontal when intending to achieve a more cognitive control effect (e.g., inhibition of interferences), and anodic stimulation in the

orbitofrontal and cathodic region in the CPFDL, when the expected effect is a greater impulse control.

Moreover, we believe that it is of fundamental importance to develop parallel clinical trials analyzing the effects of anodal tDCS combined with cognitive therapy in children and adolescents with ASD, but considering models that are closer to the therapeutic interventions performed in clinical practice, such as a frequency of five sessions per week over two consecutive weeks. We need to understand how the interaction of the therapeutic interventions influences the cognitive-behavioral performance of children and adolescents with ASD; whether there is a "ceiling effect" of any of the interventions; what types of cognitive and behavioral training are the most appropriate during the administration of tDCS over one of the areas of the brain involved in the physiopathology of ASD; and whether tDCS indeed results in clinical effects on executive functions and social communication in this population in the medium and long terms.

To the best of our knowledge, this is the first controlled clinical trial to analyze the effects of anodal tDCS over the left DLPFC during cognitive training in children with a diagnosis of ASD involving a follow-up evaluation three months after the end of the intervention. Thus, this study contributes to developing the theoretical reference of this promising therapeutic intervention. However, no definitive conclusions can be drawn based on our results due to the limitations of this study, such as the small number of participants and the crossover study design. We believe it is essential to develop parallel, randomized, controlled clinical trials with an adequate sample size to prove the effects of anodal tDCS combined with cognitive training for this population.

Conclusion

Anodal transcranial direct current stimulation over the left dorsolateral prefrontal cortex during the training of cognitive tasks did not increase the effect of cognitive training in the children with autism spectrum disorder who composed the sample compared to sham tDCS and cognitive training. However, promising effects of the intervention with anodal tDCS were identified in the comparison of pre-intervention evaluation and evaluations conducted after the interventions (one week and three months after the final session) with regards to the theory of mind as well as cognitive processing speed and efficiency, especially the skill of inhibitory control.

Authors' contributions

Oliveira PV participated in the methodology, validation, investigation, writing- Original draft preparation. Castro ML participated in the investigation, Validation. Collange-Grecco LA participated in the writing-Reviewing and Editing. Rizzutti S participated in the conceptualization and methodology. Muszkat M participated in the conceptualization, methodology and supervision.

Conflicts of interest

No financial, legal or political conflicts involving third parties (government, companies and private foundations, etc.) were declared for any aspect of the submitted work (including, but not limited to grants and funding, participation in an advisory board, study design, preparation manuscript, statistical analysis, etc.).

Funding

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001.

References

1. APA. AMERICAN PSYCHIATRIC ASSOCIATION. Manual Diagnóstico e Estatístico de Transtornos Mentais - DSM-5. 5th ed. Porto Alegre: Artmed; 2014.

2. Baldimtsi E, Nicolopoulou A, Tsimpli IM. Cognitive and Affective Aspects of Theory of Mind in Greek-Speaking Children with Autism Spectrum Disorders. J Autism Dev Disord. 2021;51:1142–56. https://doi.org/10.1007/s10803-020-04595-0

3. Berenguer C, Roselló B, Colomer C, Baixauli I, Miranda A. Children with autism and attention deficit hyperactivity disorder. Relationships between symptoms and executive function, theory of mind, and behavioral problems. Res Dev Disabil. 2018;83:260–9. https://doi.org/10.1016/j.ridd.2018.10.001

4. Kouklari E-C, Tsermentseli S, Monks CP. Developmental trends of hot and cool executive function in school-aged children with and without autism spectrum disorder: Links with theory of mind. Dev Psychopathol. 2019;31(2):541–56. https://doi.org/10.1017/S0954579418000081

5. Peterson CC, Wellman HM, Slaughter V. The Mind Behind the Message: Advancing Theory-of-Mind Scales for Typically Developing Children, and Those With Deafness, Autism, or Asperger Syndrome. Child Dev. 2012;83(2):469–85. https://doi.org/10.1111/j.1467-8624.2011.01728.x

6. Valeri G, Casula L, Napoli E, Stievano P, Trimarco B, Vicari S, et al. Executive Functions and Symptom Severity in an Italian Sample of Intellectually Able Preschoolers with Autism Spectrum Disorder. J Autism Dev Disord. 2020;50:3207–15. https://doi.org/10.1007/s10803-019-04102-0

7. Happé F, Cook JL, Bird G. The Structure of Social Cognition: In(ter)dependence of Sociocognitive Processes. Annu Rev Psychol. 2017;68:243–67. https://doi.org/10.1146/annurev-psych-010416-044046

8. Pinkham AE, Penn DL, Green MF, Buck B, Healey K, Harvey PD. The Social Cognition Psychometric Evaluation Study: Results of the Expert Survey and RAND Panel. Schizophr Bull. 2014;40(4):813–23. https://doi.org/10.1093/schbul/sbt081

9. Diamond A. Executive functions. Annu Rev Psychol. 2013;64:135–68. https://doi.org/10.1146/annurev-psych-113011-143750

10. Carlson SM, Zelazo PD, Faja S. Executive function. In: Zelazo PD. The Oxford handbook of developmental psychology, Vol. 1. 1st ed.. Oxford: Oxford University Press; 2013. p. 706–43.

11. Dias NM, Seabra AG. Intervention for executive functions development in early elementary school children: effects on learning and behaviour, and follow-up maintenance. Educ Psychol (Lond). 2017;37(4):468–86. https://doi.org/10.1080/01443410.2016.1214686

12. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The Unity and Diversity of Executive Functions and Their Contributions to Complex "Frontal Lobe" Tasks: A Latent Variable Analysis. Cogn Psychol. 2000;41(1):49–100. https://doi.org/10.1006/cogp.1999.0734

13. Brignell A, Chenausky KV, Song H, Zhu J, Suo C, Morgan AT. Communication interventions for autism spectrum disorder in minimally verbal children. Coch Datab Syst Rev. 2018;11:CD012324. https://doi.org/10.1002/14651858.CD012324.pub2

14. Liang X, Li R, Wong SHS, Sum RKW, Wang P, Yang B, et al. The Effects of Exercise Interventions on Executive Functions in Children and Adolescents with Autism Spectrum Disorder: A Systematic Review and Meta-analysis. Sports Med. 2022;52:75–88. https://doi.org/10.1007/s40279-021-01545-3

15. Sharma S, Hucker A, Matthews T, Grohmann D, Laws KR. Cognitive behavioural therapy for anxiety in children and young people on the autism spectrum: a systematic review and meta-analysis. BMC Psychol. 2021;9:151. https://doi.org/10.1186/s40359-021-00658-8

16. Tan BWZ, Pooley JA, Speelman CP. A Meta-Analytic Review of the Efficacy of Physical Exercise Interventions on Cognition in Individuals with Autism Spectrum Disorder and ADHD. J Autism Dev Disord. 2016;46:3126–43. https://doi.org/10.1007/s10803-016-2854-x

17. Virues-Ortega J, Julio FM, Pastor-Barriuso R. The TEACCH program for children and adults with autism: A meta-analysis of intervention studies. Clin Psychol Rev. 2013;33(8):940–53. https://doi.org/10.1016/j.cpr.2013.07.005

18. Weston L, Hodgekins J, Langdon PE. Effectiveness of cognitive behavioural therapy with people who have autistic spectrum disorders: A systematic review and meta-analysis. Clin Psychol Rev. 2016;49:41–54. https://doi.org/10.1016/j.cpr.2016.08.001

19. Amatachaya A, Auvichayapat N, Patjanasoontorn N, Suphakunpinyo C, Ngernyam N, Aree-Uea B, et al. Effect of anodal transcranial direct current stimulation on autism: A randomized double-blind crossover trial. Behav Neurol. 2014;2014:173073. https://doi.org/10.1155/2014/173073

20. Costanzo F, Menghini D, Casula L, Amendola A, Mazzone L, Valeri G, et al. Transcranial Direct Current Stimulation Treatment in an Adolescent with Autism and Drug-Resistant Catatonia. Brain Stimul. 2015;8(6):1233–5. https://doi.org/10.1016/j.brs.2015.08.009

21. Wilson JE, Trumbo MC, Wilson JK, Tesche CD. Transcranial direct current stimulation (tDCS) over right temporoparietal junction (rTPJ) for social cognition and social skills in adults with autism spectrum disorder (ASD). J Neural Transm. 2018;125:1857–66. https://doi.org/10.1007/s00702-018-1938-5

22. Wilson JE, Quinn DK, Wilson JK, Garcia CM, Tesche CD. Transcranial Direct Current Stimulation to the Right Temporoparietal Junction for Social Functioning in Autism Spectrum Disorder. J ECT. 2018;34(1):e10–3. https://doi.org/10.1097/YCT.0000000000000445

23. Gómez L, Vidal B, Maragoto C, Morales L, Berrillo S, Cuesta HV, et al. Non-Invasive Brain Stimulation for Children with Autism Spectrum Disorders: A Short-Term Outcome Study. Behav Sci. 2017;7(3):63. https://doi.org/10.3390/bs7030063

24. Schneider HD, Hopp JP. The use of the Bilingual Aphasia Test for assessment and transcranial direct current stimulation to modulate language acquisition in minimally verbal children with autism. Clin Linguist Phon. 2011;25(6-7):640–54. https://doi.org/10.3109/02699206.2011.570852

25. Steenburgh JJ, Varvaris M, Schretlen DJ, Vannorsdall TD, Gordon B. Balanced bifrontal transcranial direct current stimulation enhances working memory in adults with high-functioning autism: a sham-controlled crossover study. Mol Autism. 2017;8:40. https://doi.org/10.1186/s13229-017-0152-x

26. Zhou T, Kang J, Li Z, Chen H, Li X. Transcranial direct current stimulation modulates brain functional connectivity in autism. Neuroimage Clin. 2020;28:102500. https://doi.org/10.1016/j.nicl.2020.102500

27. Wilson J, Andrews G, Hogan C, Wang S, Shum DHK. Executive function in middle childhood and the relationship with theory of mind. Dev Neuropsychol. 2018;43(3):163–82. https://doi.org/10.1080/87565641.2018.1440296

28. Costanzo F, Varuzza C, Rossi S, Sdoia S, Varvara P, Oliveri M, et al. Reading changes in children and adolescents with dyslexia after transcranial direct current stimulation. Neuroreport. 2016;27(5):295–300. https://doi.org/10.1097/WNR.0000000000000536

29. 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. 2017;124:133–44. https://doi.org/10.1007/s00702-016-1646-y

30. Sotnikova A, Soff C, Tagliazucchi E, Becker K, Siniatchkin M. Transcranial Direct Current Stimulation Modulates Neuronal Networks in Attention Deficit Hyperactivity Disorder. Brain Topogr. 2017;30:656–72. https://doi.org/10.1007/s10548-017-0552-4

31. Amatachaya A, Jensen MP, Patjanasoontorn N, Auvichayapat N, Suphakunpinyo C, Janjarasjitt S, et al. The short-term effects of transcranial direct current stimulation on electroencephalography in children with autism: A randomized crossover controlled trial. Behav Neur. 2015;2015:928631. https://doi.org/10.1155/2015/928631

32. Schneider HD, Hopp JP. The use of the Bilingual Aphasia Test for assessment and transcranial direct current stimulation to modulate language acquisition in minimally verbal children with autism. Clin Linguist Phon. 2011;25:640–54. https://doi.org/10.3109/02699206.2011.570852

33. 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. 2017;24(13):1928–43. https://doi.org/10.1177/1087054717730611

34. Brooks BL, Sherman EMS, Strauss E. NEPSY-II: A Developmental Neuropsychological Assessment, Second Edition. Child Neuropsychology 2009;16(1):80–101. https://doi.org/10.1080/09297040903146966

35. Trevisan BT, Dias NM, Seabra AG. Teste Infantil de Nomeação. Avaliação Neuropsicológica Cognitiva: Linguagem Oral . 1st ed. São Paulo: Memnon; 2012.

36. Sedó M, Paula JJ, Malloy-Diniz LF. FDT - Teste dos Cinco Dígitos. São Paulo: Hogrefe; 2015.

37. 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. Inter J Neuropsychopharm. 2011;14(8):1133–45. https://doi.org/10.1017/S1461145710001690

38. Gill J, Shah-Basak PP, Hamilton R. It's the Thought That Counts: Examining the Task-dependent Effects of Transcranial Direct Current Stimulation on Executive Function. Brain Stimul. 2015;8(2):253–9. https://doi.org/10.1016/j.brs.2014.10.018

39. Segrave RA, Arnold S, Hoy K, Fitzgerald PB. Concurrent Cognitive Control Training Augments the Antidepressant Efficacy of tDCS: A Pilot Study. Brain Stimul. 2014;7(2):325–31. https://doi.org/10.1016/j.brs.2013.12.008

40. Claro R. Onde está o absurdo? Cartas para identificar situações fora do comum. 1st ed. São Paulo: Matrix; 2017.

41. Claro R. Que emoção é esta? Cartas com desenhos para criança identificar as emoções. 1st ed. São Paulo: Matrix; 2018.

42. Luckhardt C, Boxhoorn S, Schütz M, Fann N, Freitag CM. Brain stimulation by tDCS as treatment option in Autism Spectrum Disorder—A systematic literature review. Prog Brain Res. 2021;264:233–57. https://doi.org/10.1016/bs.pbr.2021.03.002

43. Khaleghi A, Zarafshan H, Vand SR, Mohammadi MR. Effects of Non-invasive Neurostimulation on Autism Spectrum Disorder: A Systematic Review. Clin Psychopharma Neuro. 2020;18(4):527–52. https://doi.org/10.9758/cpn.2020.18.4.527

44. Hadoush H, Nazzal M, Almasri NA, Khalil H, Alafeef M. Therapeutic Effects of Bilateral Anodal Transcranial Direct Current Stimulation on Prefrontal and Motor Cortical Areas in Children with Autism Spectrum Disorders: A Pilot Study. Autism Res. 2020;13(5):828–36. https://doi.org/10.1002/aur.2290

45. García-González S, Lugo-Marín J, Setien-Ramos I, Gisbert-Gustemps L, Arteaga-Henríquez G, Díez-Villoria E, et al. Transcranial direct current stimulation in Autism Spectrum Disorder: A systematic review and meta-analysis. Euro Neuropsychopharma. 2021;48:89–109. https://doi.org/10.1016/j.euroneuro.2021.02.017

46. Pineda-Alhucema W, Aristizabal E, Escudero-Cabarcas J, Acosta-López JE, Vélez JI. Executive Function and Theory of Mind in Children with ADHD: a Systematic Review. Neuropsychol Rev 2018;28:341–58. https://doi.org/10.1007/s11065-018-9381-9

47. Mahmoodifar E, Sotoodeh MS. Combined Transcranial Direct Current Stimulation and Selective Motor Training Enhances Balance in Children With Autism Spectrum Disorder. Percept Mot Skills. 2020;127(1):113–25. https://doi.org/10.1177/0031512519888072

48. Panikratova YR, Vlasova RM, Akhutina T v., Korneev AA, Sinitsyn VE, Pechenkova E v. Functional connectivity of the dorsolateral prefrontal cortex contributes to different components of executive functions. Int J Psychophys. 2020;151:70–9. https://doi.org/10.1016/j.ijpsycho.2020.02.013

49. Soltaninejad Z, Nejati V, Ekhtiari H. Effect of Anodal and Cathodal Transcranial Direct Current Stimulation on DLPFC on Modulation of Inhibitory Control in ADHD. J Atten Disord. 2015;23(4):325–32. https://doi.org/10.1177/1087054715618792

50. Cristofori I, Cohen-Zimerman S, Grafman J. Executive functions. Hand Clin Neuro. 2019;163:197–219. https://doi.org/10.1016/B978-0-12-804281-6.00011-2