Original Paper

Neuropsychobiology

Neuropsychobiology 2018/2019;78:189–199
DOI: 10.1159/000501025

Received: February 14, 2019
Accepted after revision: May 18, 2019
Published online: July 2, 2019

A Prospective Open-Label Pilot Study of Transcranial Direct Current Stimulation in High-Functioning Autistic Patients with a Dysexecutive Syndrome

Maud Rothärmel[a] Virginie Moulier[a, e] Marianne Vasse[a] Clémence Isaac[e] Mathieu Faerber[b] Bilal Bendib[a] Iris Mirea-Grivel[a] Gaëlle Opolczynski[a] Antoine Rosier[b] Olivier Guillin[a–d]

[a]University Department of Psychiatry, Centre Hospitalier du Rouvray, Sotteville-lès-Rouen, France; [b]Centre Ressource Autisme Normandie Seine Eure, Centre Hospitalier du Rouvray, Sotteville-lès-Rouen, France; [c]CHU de Rouen, Rouen, France; [d]Faculté de Médecine, Normandy University, Rouen, France; [e]EPS Ville Evrard, Unité de Recherche Clinique, Neuilly-sur-Marne, France

Keywords
Executive functions · Transcranial direct current stimulation · Autism

Abstract
Background: Executive functions (EF) are often impaired in autism spectrum disorder (ASD). Such dysfunctions are associated with anxiety, depression, and a lack of autonomy. Transcranial direct current stimulation (tDCS) has been shown to enhance EF in healthy adults and clinical populations and to improve working memory – a component of the EF – in adults with high-functioning ASD (HF-ASD). We hypothesized that tDCS could improve the EF of HF-ASD patients. Such enhancement could improve their adaptive behaviors. ***Method:*** Eight patients with HF-ASD received 10 consecutive cathodal tDCS sessions (2 mA) over the left dorsolateral prefrontal cortex (F3) for 15 min each in an open trial. EF (with the Stroop test, Trail Making Test [TMT] A and B, Modified Wisconsin Card Sorting Test [mWCST], and Verbal Fluency Test) and behavioral dysexecutive syndrome (with the Behavioral Dysexecutive Syndrome Inventory and the Repetitive and Restricted Behaviour scale) were assessed before and 10 days after treatment. ***Results:*** This study showed significant improvement in initiation (TMT-A time: $p = 0.018$) and cognitive flexibility (TMT-B time: $p = 0.009$; letter Verbal Fluency Test: $p = 0.017$; mWCST total errors: $p = 0.028$) after tDCS. Regarding behavior, the hypoactivity of the patients improved, as well as their repetitive and restrictive behaviors. In addition, this noninvasive neurostimulation technique was well tolerated. ***Conclusions:*** Flexibility and initiation are the most impaired EF in autism. These are promising results which justify a randomized and placebo-controlled study in a wider population. If these results were confirmed by a randomized controlled trial, tDCS could be an easy and well-tolerated adjunctive treatment aiming to improve the quality of life and the autonomy of ASD patients.

Introduction

Autism spectrum disorders (ASD) are neurodevelopmental disorders with different intensities but similar core symptoms: abnormalities in communications, social awareness and skills, presence of restrictive and stereo-

KARGER

E-Mail karger@karger.com
www.karger.com/nps

Maud Rothärmel, MD
University Department of Psychiatry
Centre Hospitalier du Rouvray, 4 rue Paul Eluard
FR–76300 Sotteville-lès-Rouen (France)
E-Mail maud.rotharmel@ch-lerouvray.fr and maud.rotharmel@gmail.com

typed patterns of behaviors, interests, and activities (DSM-5). Executive function deficits (EFD) are present for most people with ASD even if they do not have any intellectual disability [1, 2]. Executive functions (EF) are the cognitive functions which allow to accomplish a task in a new situation. These are functions of high-level control, occurring in many types of cognitive activities, including initiation, planning, flexibility, inhibition, and executive control (i.e., function of correction in feedback). These functions are linked to working memory and attentional processes.

In intellectually disabled patients with autism, the impairment would be persistent throughout development, especially in response inhibition and working memory [3]. In addition, the EFD, and particularly the deficit of mental flexibility and planning, are associated with anxiety and depression in autism without any intellectual disability [4, 5]. These impairments lead to a decrease in the capacity of adaptation and autonomy [6]. Until recently, the only specific treatment of EFD was cognitive remediation, but this treatment is time consuming [7]. Moreover, it requires trained professionals who are not found throughout the country.

Until now, no structural brain anomalies have been detected in adults with autism compared to healthy subjects [8, 9]. However, functional anomalies in the activation of the brain areas implied in EF, especially in the prefrontal cortex, have been noticed [10]. There could be anomalies of the GABAergic pathway with instability of the excitation/inhibition balance in favor of excitation at the prefrontal cortex level [11, 12]. At the microscopic level, alterations of the cortical inhibitory structures can be observed, resulting in an inhibitory default [13].

To cope with this inhibitory default in autism, promising results have been achieved by several noninvasive neurostimulation studies [14]. First, low-frequency repetitive transcranial magnetic stimulations (LF-rTMS) targeting the left dorsolateral prefrontal cortex (DLPFC) improved the visual discrimination in children, teenagers, and adults with high-functioning autism. To do that, LF-rTMS inhibited the response to non-target stimuli [15] and/or increased the response to target stimuli [16]. LF-rTMS improved the control of the error and the function of correction. The results concerning the efficacy of rTMS on these last 2 parameters, which represent executive control, were replicated in a study from the same team in 2012 [17]. rTMS is, therefore, an interesting therapeutic tool but has the disadvantage of being contraindicated in patients with epilepsy. Indeed, the prevalence rate of epilepsy in autism is precisely higher than in the general population, even in ASD patients without intellectual disability (approximately 5–40% vs. 0.5–1% in the general population [18]).

However, there is another noninvasive neurostimulation technique, which has the advantage of not inducing serious side effects, namely seizures, contrary to rTMS [19]: transcranial direct current stimulation (tDCS). Such stimulation improved the EF in schizophrenia [20], Parkinson disease [21], and healthy volunteers [22]. Thanks to an inhibitory effect on the DLPFC when in contact with the cathode electrode, tDCS could decrease cortical excitability and thus improve selective attention [22]. By doing so, a better selection of information is possible at a neuronal level [22]. Some authors have correlated autism and its behavioral symptoms with deficient neural inhibition in some specific cortical regions, among which is the DLPFC [12, 23]. So, in autism, we might assume that cathodal tDCS could allow an improvement in EF by restoring the inhibition/excitation balance at a cortical level. EFD may be considered an important target for interventions that are aimed at improving overall function, autonomy, and adaptation in older youth and young adults with ASD without intellectual disability [24].

To our knowledge, no study has examined the impact of several sessions of tDCS on the dysexecutive syndrome of patients with high-functioning autism. The primary outcome of the study was to assess the feasibility and safety of cathodal tDCS on the left DLPFC in high-functioning autistic patients with a dysexecutive syndrome. The secondary outcomes were to study the evolution of EF and behavioral dysexecutive syndrome before and after tDCS.

Materials and Methods

Participant Recruitment and Informed Consent

We led an interventional, prospective, and monocentric pilot study between November 2016 and September 2017 at the Rouvray Hospital, Sotteville-lès-Rouen, France. The participants in the current study were recruited via advertisements at the Centre Ressource Autisme Normandie Seine Eure and the Psychiatric University Department of the Rouvray Hospital.

Study inclusion criteria were: (1) adult patients between 20 and 50 years old; (2) patients diagnosed with autism without any intellectual disability or Asperger syndrome according to the criteria of the International Classification of Mental and Behavioral Disorders (ICD-10) codes F84.0, F84.1, and F84.5; (3) patients with a complaint about their adaptation capacities and autonomy; (4) patients with 2 impaired scores (i.e., below a pathological threshold) in the 4 tests currently used to assess EF: the Modified Wisconsin Card Sorting Test (mWCST), the Stroop Color-Word Test (SCWT), the Trail Making Test part A (TMT-A) and B (TMT-B) as well as the category and letter Verbal Fluency Test; (5) patients with usual

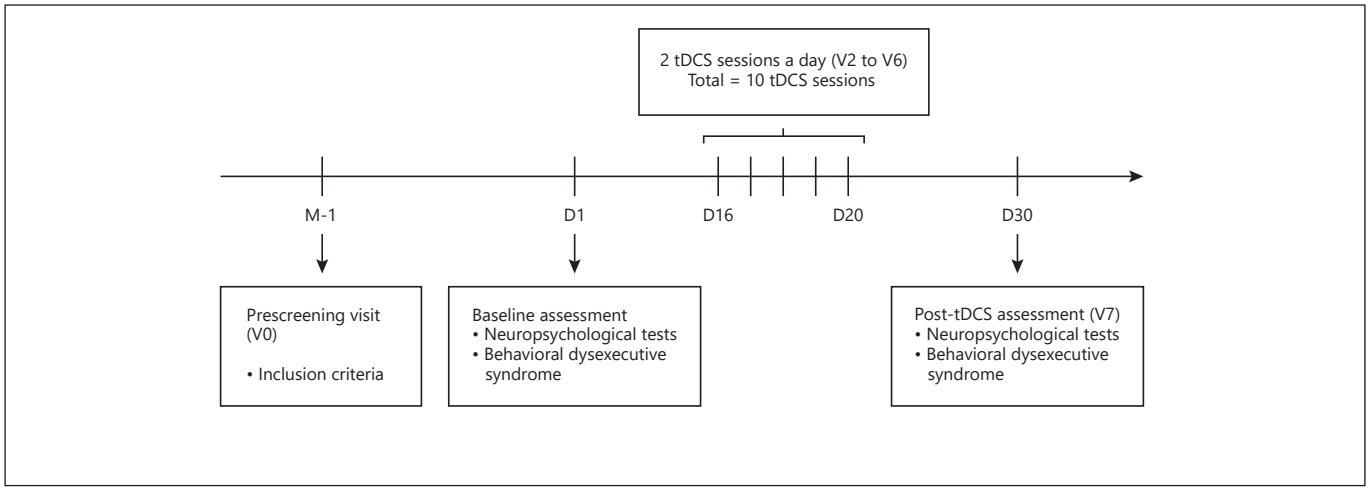

Fig. 1. The study design. V, visit.

treatment maintained for 1 month before and throughout the study; (6) patients without any tDCS experience; (7) patients affiliated to a social security system; (8) patients who took notice of the letter of information and who signed the consent form; (9) for women of childbearing age, the use of an efficient contraceptive method for 1 month was required (estrogen-progestin combination therapy, intrauterine device, or tubal ligations). Ethical approval based on the Declaration of Helsinki was provided by the Comité de Protection des Personnes Nord-Ouest 1 and the Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM) in July 2016 (number RCB2016-A00805-46).

Study Design

The study was an open-label study (Fig. 1) consisting of (1) a prescreening visit (M-1); (2) a baseline assessment with the administration of neuropsychological tests and the assessment of the behavioral dysexecutive syndrome (D1); (3) 15 days after day 1 (D16), 2 tDCS sessions a day for 5 consecutive days (10 sessions in total) with an assessment of side effects after each session (between D16 and D20); and (4) a final assessment 10 days after the end of the treatment with the same neuropsychological tests and the same assessment of the behavioral dysexecutive syndrome (D30). Indeed, Boggio et al. [25] have observed that consecutive daily sessions of tDCS were associated with an effect that lasted for 2 weeks after treatment. Thus, this study involved 30 days of participation between the first neuropsychological evaluations (D1) and the retest (D30). This 30-day interval between the 2 assessments was chosen to limit practice effects.

Transcranial Direct Current Stimulation

tDCS was performed using an electrostimulator (StarStim Noninvasive Wireless tCS Neurostimulator, Neuroelectrics®, Barcelona, Spain). It consists of a wireless Neopren headcap with 2 long-sized saline-filled electrodes. Electrode placement is based on the 10–20 EEG system allowing stimulation of various brain structures. The headcap is connected through a Bluetooth device for configuration and monitoring at a distance.

StarStim provides a constant current in accordance with the relevant data for the study: (1) the cathodal tDCS was applied over the left DLPFC in the 10/20 system (F3), and the anodal tDCS was applied on the right supraorbital area (AF8); (2) intensity: 2 mA; (3) treatment duration: 15 min; (4) gradual increase and decrease of the electric current over 10 s at the beginning and the end of stimulation, respectively; (5) number of sessions: 10; (5) frequency of treatment: 2 sessions a day with an interval of at least 2 h between the sessions for 5 consecutive days.

Neuropsychological and Clinical Measures

Modified Wisconsin Card Sorting Test

The mWCST was presented by Nelson [26]. The participants must sort the cards according to 3 possible criteria (i.e., form, color, number) following the implicit and assumed rule defined by the examiner. Then, the participants must adapt their behaviors when having to sort the cards according to another criterion. Three types of performances are notified: the number of correct categories, the total number of errors, and the number of perseverations (i.e., cards sorted out according to the previous criterion once the rule changed). Flexibility is mainly measured through the total number of errors and perseverations. The deduction of the classification rules is assessed on the basis of the number of the correct categories. Besides, an increasing number of perseverations points to a deficiency in inhibition (inhibition of a dominant response). For the mWCST, a study of the temporal stability, in which the test was performed twice at 12-day intervals, has indicated a good test-retest reliability for the perseverative errors (0.83) and nonperseverative errors (0.80) and a small learning effect thanks to measures of dispersion [27].

Trail Making Test

The TMT was first referenced in 1944 in a battery of individual tests used by the US Army [28]. This test is divided into 2 subcategories: part A, which requires the subject to connect a series of numbers (1–25) in consecutive order as quickly as possible, and part B, in which the subject alternates between numbers and letters (1-A-2-B-3 …). Part A assesses initiation, while part B tests cognitive flexibility. Other processes are involved, such as visuospatial exploration and motor speed performance. The measured scores for each part are the amount of time required to complete the task

and the total number of errors. In young adults retested after an interval of 3 weeks, reliability was low for part A (0.55) but adequate for part B (0.75) in the study of Bornstein et al. [29].

Stroop Color-Word Test

The SCWT measures initiation ("reading" and "naming" subtests) and inhibition ("interference" subtest) [30]. In the naming subtest, the subject names patches of different colors ("blue," "green," and "red"). In the reading test, the subject reads names of colors printed in black on white ("blue," "green," and "red"). In the interference test, the subject must name the color of the ink used for writing the color name. The color name and the ink are inconsistent ("red" written in green). The subject must inhibit the spontaneous response stemming from the automatic reading of the word. For each of the 3 subcategories, this test assesses speed performance ("response time" performance type) and the number of errors ("errors" performance type). An interference index can be calculated (subtest interference – subtest naming). It constitutes an easy and instructive interference score. Golden [31] reported good reliabilities for the 3 subtests: 0.86 ("reading"), 0.82 ("naming"), and 0.73 ("interference") for an individual version.

Verbal Fluency Test

In this test, the subjects have to produce as many words as they can in 1 min. There is the initial letter fluency test (words beginning with a specified letter, such as F, for example) and the semantic verbal fluency also called the category fluency test (words from the same semantic field, for example, the semantic category of animals) [32]. The number of correct words allows to assess both initiation and generation of information. Other processes are involved in the task, such as the spontaneous flexibility or the necessity to inhibit inconsistent items [33]. The test-retest reliability of the Verbal Fluency Test was good ($r > 0.7$) in the study of Strauss et al. [34].

Behavioral Dysexecutive Syndrome Inventory

The behavioral dysexecutive syndrome is assessed with the Behavioral Dysexecutive Syndrome Inventory (BDSI) [35]. This rater-administered questionnaire from the GREFEX battery takes into account the most significant sectors regarding the frontal dysfunctions or the frontal subcortical network. These sectors are represented according to 12 domains in total: hypoactivity with apathy-abulia; difficulties in anticipation, planning, and initiation of activities; disinterest and indifference to his/her own concern and others; hyperactivity-distractibility-psychomotor instability; irritability-impulsivity-aggressiveness; euphoria, emotional lability, and moria; stereotyped and perseverative behavior; environmental dependency; anosognosia-anosodiaphoria; spontaneous confabulations; social behavior disorders; and disorders of sexual, eating, and urinary behavior.

Two elements are assessed in each domain:

- the element of severity, which corresponds to the product of frequency (ranging from 1 to 4) and prevalence (ranging from 1 to 3), with data ranging thus from 1 to 12;
- the element of impact (ranging from 0 to 5) which corresponds to a disturbing behavior for the people around.

Behaviors are considered pathological when 1 of these 2 elements is pathological (either the severity element or the impact element or both).

Due to the frequency of anosognosia in this type of behavioral disorders, the inventory is based on the data given by a dependable informant who is a close relative of the patient, if possible living with him or her. Diagnosis of the behavioral dysexecutive syndrome is defined when 3 domains at least are considered pathological.

Repetitive and Restricted Behaviour Scale

The Repetitive and Restricted Behaviour scale (RRB) was specifically designed to assess the restricted and repetitive behaviors in autism [36]. It is composed of 35 items. This test analyses the severity and the presence of such behaviors in the following domains: sensorimotor stereotypes (factor 1 or F1), reaction to changes (factor 2 or F2), restricted behaviors (factor 3 or F3), and emotion regulation (factor 4 or F4). This test permits the follow-up of the symptoms and also evaluates the efficacy of the treatments. There is no threshold value for this test. This test is not part of the battery of tests of the GREFEX, but nevertheless, the RRB takes into account several behavioral domains which are also included in the BDSI. The rating is determined during the observation of the patient. Such rating can be detailed with a patient's relative or friend: spouse, close member of the family, close friend, or caregiver having a good knowledge of the patient.

Statistical Analysis of the Data

Statistical analyses were performed using SPSS Statistics software, version 21.0 (Chicago, IL, USA). The characteristics of the patients were described with means and standard deviations for quantitative data and frequencies for categorical data. Paired *t* tests were performed to compare cognitive and clinical scores between D1 (prior to any stimulation) and D30 (10 days after discontinuation of stimulation) only when the equality of variances and the normal distribution of the data (Kolmogorov-Smirnov test) were ascertained. When these assumptions were not met, the Wilcoxon signed-rank test was used. In order to control the risk of false positives due to multiple comparisons in the cognitive tasks, a Bonferroni correction was performed.

Results

Description of the Population

Sociodemographic Characteristics

A total of 22 participants with autism were screened for possible participation between August 2016 and August 2017. Eight patients did not meet the inclusion criteria (1 patient was aged 19 years and 7 patients were under guardianship); 4 patients did not have 2 impaired scores among the 5 EF tests; 1 patient refused to participate; and 1 patient was depressed. Eight patients (7 men/1 woman) aged 20–28 years met the study inclusion criteria (mean age [SD] = 24.25 [3.24] years). Regarding the level of education, 25% of the patients were at junior secondary school level, 37.5% were at senior secondary school level, while 37.5% were at university level. Regarding socioprofessional activities, all patients were jobless. Besides, they were all single patients. As regards their autonomy, 62.5% lived with their parents and 37.5% on their own.

Table 1. Performances of each cognitive test before and after tDCS

Test	Before tDCS			After tDCS			*p* value
	Score	*Z*-score	*Z*-score	Score	*Z*-score	*Z*-score	
mWCST							
Categories completed	5.75 (0.46)	–0.48 (1.25)	0.18	6.00 (0.00)	0.20 (0.02)	0.18	0.18
Total errors	6.00 (3.70)	0.89 (1.06)	0.59	3.25 (2.87)	0.09 (0.81)	0.16	0.028*
Perseverative errors	1.00 (1.60)	0.39 (1.56)	–0.47	0.75 (1.04)	0.13 (1.01)	–0.19	0.285
Stroop test							
Denomination time, s	69.25 (6.67)	1.28 (0.64)	1.19	64.50 (4.99)	0.81 (0.54)	0.77	0.067
Denomination errors	0.00 (0.00)	–0.31 (0.11)	–0.23	0.00 (0.00)	–0.31 (0.11)	–0.23	1.000
Reading time, s	49.63 (7.29)	1.43 (1.34)	1.13	49.50 (8.43)	1.35 (1.33)	1.58	0.482
Reading errors	0.00 (0.00)	–0.16 (0.08)	–0.10	0.25 (0.46)	2.34 (4.66)	–0.10	0.157
Interference time, s	128.88 (35.39)	1.37 (1.11)	1.15	114.75 (20.54)	0.15 (2.01)	0.54	0.093
Interference errors	0.25 (0.46)	–0.21 (0.49)	–0.47	0.00 (0.00)	–0.49 (0.026)	–0.47	0.157
Interference score	59.63 (31.70)	1.06 (1.43)	1.04	50.25 (17.32)	0.62 (0.75)	0.52	0.123
TMT							
TMT-A time, s	36.75 (9.74)	0.58 (0.78)	0.59	28.38 (10.91)	–0.11 (0.91)	–0.17	0.018*
TMT-A errors	0.50 (0.76)	1.88 (3.49)	–0.14	0.25 (0.46)	0.97 (2.26)	–0.21	0.540
TMT-B time, s	82.00 (32.70)	0.84 (1.32)	0.59	69.88 (32.72)	0.31 (1.34)	–0.25	**0.009****
TMT-B errors	0.00 (0.00)	–0.30 (0.00)	–0.30	0.13 (0.35)	0.16 (1.31)	–0.30	0.351
Verbal fluency test							
Initial letter	13.38 (7.27)	–1.39 (0.96)	–1.52	15.88 (6.98)	–0.97 (0.94)	–1.13	0.017*
Category	19.63 (8.62)	–1.60 (1.04)	–1.68	22.63 (5.32)	–1.23 (0.54)	–1.37	0.236

Values are means (SD) or medians. mWCST, Modified Wisconsin Card Sorting Test; tDCS, transcranial direct current stimulation; TMT, Trail Making Test. * $p < 0.05$; ** $p < 0.01$. Bold value indicates that the result remains significant after Bonferroni correction.

Clinical Characteristics

Patients were diagnosed with childhood autism (n = 4), Asperger syndrome (n = 2), or atypical autism (n = 2). Seven patients (87.5%) had at least 1 psychiatric comorbidity with an overrepresentation of the anxiety disorders or obsessive-compulsive disorder (n = 6), while 1 patient suffered from a history of depression. All patients with a psychiatric comorbidity received a medical treatment. The most represented classes of drugs were (1) antidepressants (n = 6); (2) antipsychotics (2 patients with clozapine and 2 with risperidone); (3) benzodiazepines (n = 1); and (4) mood stabilizer (valpromide, n = 1).

Tests of the EF

At the beginning, 5 patients had 2 pathological scores among the 4 EF tests and 3 patients had 3 pathological scores. For each cognitive test, performances before and after tDCS are reported in Table 1.

As regards the mWCST, the total number of errors significantly decreased after tDCS (p = 0.028). Likewise, the time to complete the TMT significantly decreased after tDCS in both TMT-A (p = 0.018) and TMT-B (p = 0.009). With regard to verbal fluency, the initial letter fluency test was significantly improved (p = 0.017) after tDCS.

Behavioral Dysexecutive Syndrome

Behaviora.l Dysexecutive Syndrome Inventory

The intensity and the impact on relatives of the 12 dysfunctional domains are reported in Table 2. The percentage of improvement of these domains is shown in Figure 2.

All patients presented at least 3 deviant domains from the BDSI before (mean [SD] = 6.125 [1.36]) and after neurostimulation (mean [SD] = 5.75 [1.04]), which corresponds to the presence of a behavioral dysexecutive syndrome for all these patients. The number of the deviant domains before and after tDCS did not change for 5 patients and decreased for the 3 other patients (p = 0.083). However, a significant improvement was shown for several domains: (1) hypoactivity with apathy-abulia (intensity: p = 0.004; impact on relatives: p = 0.021); (2) difficulties in anticipation, planning, and initiation of activities (intensity: p = 0.007; impact on relatives: p = 0.024); (3) and irritability, impulsivity, and aggressiveness (impact on relatives: p = 0.039).

Table 2. Behavioral dysexecutive syndrome (RRB and BDSI scores) before and after tDCS

Test	Before tDCS		After tDCS		*p* value
	mean ± SD	median	mean ± SD	median	
Repetitive and Restricted Behaviour scale					
F1 (sensorimotor stereotypes)	7.38 (4.07)	6.00	5.88 (3.76)	4.00	0.014*
F2 (reaction to changes)	5.00 (3.46)	4.00	4.00 (3.38)	2.50	0.007**
F3 (restricted behaviors)	7.63 (5.10)	8.00	6.88 (4.94)	7.00	0.111
F4 (emotion regulation)	6.38 (2.20)	6.50	3.63 (1.51)	4.00	<0.001***
Total score	28.13 (5.79)	29.50	21.63 (5.70)	21.50	<0.001***
Behavioral dysexecutive syndrome inventory					
Domain 1					
Intensity	7.75 (1.98)	8.00	4.25 (1.67)	4.00	0.004**
Impact on relatives	3.38 (0.92)	3.00	2.50 (0.53)	2.50	0.021*
Domain 2					
Intensity	6.63 (2.56)	6.00	3.88 (1.55)	4.00	0.007**
Impact on relatives	3.38 (0.74)	3.50	2.63 (0.52)	3.00	0.02*
Domain 3					
Intensity	7.63 (4.41)	7.50	6.63 (4.31)	6.00	0.227
Impact on relatives	3.00 (1.41)	3.50	2.75 (1.58)	3.50	0.170
Domain 4					
Intensity	2.25 (2.71)	1.00	2.50 (2.78)	2.00	0.685
Impact on relatives	1.13 (1.64)	0.00	1.50 (1.69)	1.00	0.504
Domain 5					
Intensity	2.75 (3.33)	1.50	1.00 (0.93)	1.00	0.109
Impact on relatives	1.75 (1.83)	1.50	0.75 (1.17)	0.00	0.039*
Domain 6					
Intensity	2.50 (3.66)	0.00	1.88 (3.23)	0.00	0.180
Impact on relatives	1.13 (1.64)	0.00	1.13 (1.64)	0.00	1.000
Domain 7					
Intensity	4.88 (3.36)	6.00	3.75 (3.15)	3.50	0.094
Impact on relatives	1.88 (1.36)	2.50	1.63 (1.19)	2.00	0.170
Domain 8					
Intensity	1.63 (4.21)	0.00	1.63 (4.21)	0.00	1.000
Impact on relatives	0.13 (0.35)	0.00	0.13 (0.35)	0.00	1.000
Domain 9					
Intensity	0.50 (1.41)	0.00	0.50 (1.41)	0.00	1.000
Impact on relatives	0.38 (1.06)	0.00	0.38 (1.06)	0.00	1.000
Domain 10					
Intensity	0.00 (0.00)	0.00	0.00 (0.00)	0.00	1.000
Impact on relatives	0.00 (0.00)	0.00	0.00 (0.00)	0.00	1.000
Domain 11					
Intensity	3.75 (4.17)	2.50	2.25 (2.71)	1.00	0.104
Impact on relatives	2.00 (1.51)	2.50	1.63 (1.77)	1.50	0.197
Domain 12					
Intensity	0.88 (2.10)	0.00	0.00 (0.00)	0.00	0.277
Impact on relatives	0.75 (1.49)	0.00	0.00 (0.00)	0.00	0.197

Domain 1, hypoactivity with apathy-abulia; Domain 2, difficulties in anticipation, planning, and initiation of activities; Domain 3, disinterest and indifference to his/her own concern and others; Domain 4, hyperactivity-distractibility-psychomotor instability; Domain 5, irritability-impulsivity-aggressiveness; Domain 6, euphoria, emotional lability, and moria; Domain 7, stereotyped and perseverative behavior; Domain 8, environmental dependency; Domain 9, anosognosia-anosodiaphoria; Domain 10, spontaneous confabulations; Domain 11, social behavior disorders; Domain 12, disorders of sexual, eating, and urinary behavior. BDSI, Behavioral Dysexecutive Syndrome Inventory; RRB, Repetitive and Restricted Behaviour scale; tDCS, transcranial direct current stimulation. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

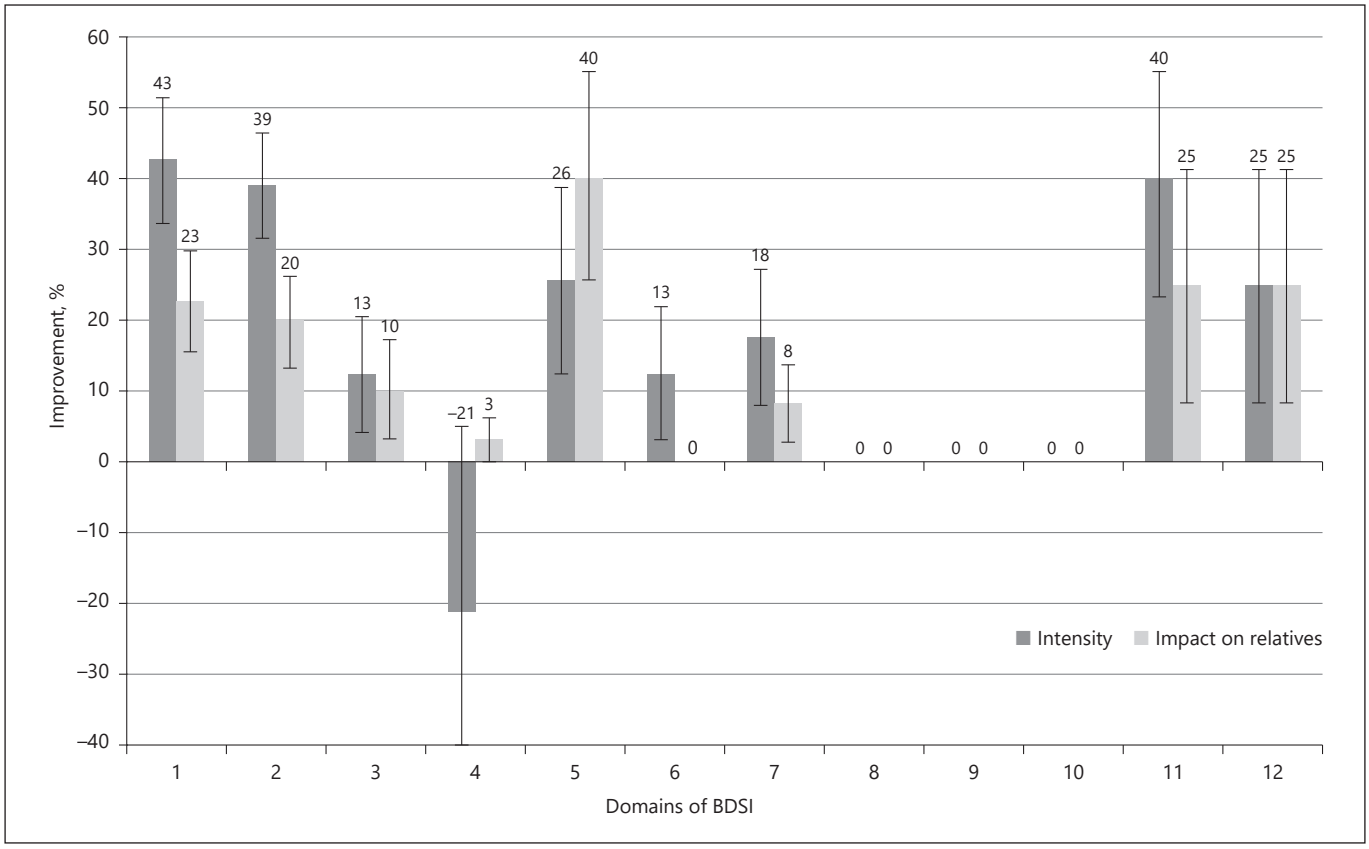

Fig. 2. The percentage of improvement in the BDSI domains after tDCS. D1: hypoactivity with apathy-abulia; D2: difficulties in anticipation, planning, and initiation of activities; D3: disinterest and indifference to his/her own concern and others; D4: hyperactivity-distractibility-psychomotor instability; D5: irritability-impulsivity-aggressiveness; D6: euphoria, emotional lability, and moria; D7: stereotyped and perseverative behavior; D8: environmental dependency; D9: anosognosia-anosodiaphoria; D10: spontaneous confabulations; D11: social behavior disorders; D12: disorders of sexual, eating, and urinary behavior.

Repetitive and Restricted Behaviour Scale

RRB scores are reported in Table 2. A decrease in the RRB scores was observed after tDCS both for the total RRB score ($p < 0.001$) and for all subcategory scores (F1, sensorimotor stereotypes: $p = 0.014$; F2, reaction to changes: $p = 0.007$; F4, emotion regulation: $p < 0.001$) except F3 (restricted behaviors). The average improvement in the total score was 23.48% (SD = 8.80%).

Tolerance

All patients experienced minor adverse effects for at least 1 session. The most frequent effects were local adverse effects where the electrodes were applied: paresthesia with sensations of buzzing, tingling, or heat ($n = 7$), pruritus ($n = 4$), or asthenia ($n = 2$). Furthermore, erythema was reported twice by the clinical examiner.

Paresthesia and pruritus developed at the beginning of stimulation with a constant moderate intensity. Sometimes, they diminished after a few seconds, but sometimes they lasted until the end of the session. These sensations were not present for every patient at every session. Eventually and less commonly, nausea and difficulty concentrating as well as sleepiness were notified during the session.

No patient experienced any serious side effect that would have required the premature ending of the sessions. There was no side effect described during the follow-up visit at D30 for the 8 patients.

Discussion

This pilot study showed that 10 sessions of tDCS were accompanied by a significant enhancement of initiation and/or generation of information (TMT-A time) and cognitive flexibility (TMT-B time, Verbal Fluency Test, and total errors score in mWCST) in adult patients with high-function-

ing autism. With regard to behavioral aspects, a significant improvement was found after tDCS for the following dimensions assessed with the BSDI: (1) hypoactivity with apathy-abulia; (2) difficulties in anticipation, planning, and initiation of activities; and (3) irritability, impulsivity, and aggressiveness (impact on relatives). In addition, sensorimotor stereotypes (F1, RRBS), reaction to change (F2, RRBS), and modulation insufficiency (F4, RRBS) were improved. The RRB total score decreased by 23% after tDCS.

These results are consistent with the first exploratory studies on the effect of tDCS in autism. Regarding the impact of tDCS on cognition in autism, Van Steenburgh et al. [37] demonstrated that both left DLPFC anodal/right DLPFC cathodal stimulation and right DLPFC anodal/left DLPFC cathodal stimulation during the cognitive tasks improved working memory performance in 12 adults with high-functioning autism. This beneficial effect persisted even 50 min after the session of right DLPFC anodal/left DLPFC cathodal stimulation (but not for left DLPFC stimulation). In a recent study, English et al. [38] examined the effect of tDCS on pseudo-neglect, i.e., on the attentional bias toward stimuli presented in the left hemisphere, driven by the greater lateralization of spatial attention to the right hemisphere [39]. In neurotypical individuals with high levels of autistic-like traits, these attentional biases were reduced [40]. In 16 neurotypical students with high levels of autistic-like traits, 1 session of anodal tDCS over the right posterior parietal cortex could restore typical attentional patterns [38].

The cognitive effects of tDCS seem to be particularly promising in autism, especially since the cognitive scores improved in our study without the number of errors increasing. This seems to indicate that patients did not change the method to complete the test but really improved their capacities of initiation and flexibility.

However, it cannot be ruled out that at least some of these improvements are due to practical effects. Indeed, even if these cognitive tests have a good reliability, an increase in the scores is possible, as has been observed in several groups of healthy subjects who were evaluated twice. In a study on the effects of rTMS, whose data have not yet been published [41], 15 healthy subjects of the control group, 25.9 (±6.4) years old on average, were cognitively assessed at a 2-week interval without having benefited from any active therapeutic intervention. In these subjects, average gains of 6.37 s in TMT-A time, 4.09 s in TMT-B time, and 2.53 words in letter fluency were observed on the second administration [41]. Similarly, in a control group of 10 healthy subjects (age: mean [SD] = 30.3 [8.0] years) who were assessed twice at a 1-month interval, a decrease of 0.5 total errors in mWCST was noticed after 1 month [42]. For the Stroop test, university students have been tested twice with a 1-month interval between test sessions [34]. On the second administration, performance improved by about 2 s on the parts "reading" and "naming" and by about 5 s on the part "interference."

If we consider the raw scores obtained by the 8 patients of the present study, they improved by about 5 s on the part "reading," by about 0.12 s on the part "naming," and by about 14 s on the part "interference" of the Stroop test; by 2.75 in total errors of the mWCST; by about 7 s on TMT-A, 12 s on TMT-B, and 2.50 words in letter fluency (Table 1). While remaining careful about the outcomes of this pilot noncontrolled study, the significant evolution of cognitive scores in the autistic patients after tDCS seems to be greater than a simple practical effect.

Regarding the impact of tDCS on dysfunctional behaviors in autism, d'Urso et al. [43] studied the effect of 10 sessions of cathodal tDCS over the left DLPFC in autistic patients with intellectual disability with the Aberrant Behavior Checklist (ABC). Several abnormal behaviors were improved after treatment: (1) irritability, agitation, crying; (2) social withdrawal and lethargy; and (3) hyperactivity and noncompliance. In addition, in 20 male children without mental retardation, aged 5–8 years, a single stimulation of anodal tDCS over the left DLPFC induced improvement in the social domain [44].

Thus, it appears that tDCS could constitute a promising therapeutic tool both cognitively and behaviorally in patients with autism. In this pilot study, we hypothesized that cathodal tDCS could be efficient in autism. We were inspired by the studies of Casanova et al. [11, 13] which found an alteration of prefrontal inhibitory structures. Indeed, the common assumption is that the anode electrode causes an enhancement of cortical excitability during stimulation, while the cathode electrode generates the opposite effect, i.e., anodal-excitation and cathodal-inhibition effects. Yet, this dual-polarity effect has not been observed in all tDCS studies and especially in cognitive studies where a lack of inhibitory cathodal effect has been found. It might reflect compensation processes as cognitive functions are supported by rich brain networks [45]. Also, direction of current flow may begin to matter less as amperage increases from 1 to 2 mA [46]. So, this new clinical indication of tDCS in autism is still in its exploratory phase, the optimal stimulation parameters (cathodal or anodal) and the best brain target remaining to be determined (right or left DLPCF, right posterior parietal cortex).

Otherwise, a good tolerance of the tDCS was found. All included patients completed the protocol. The most fre-

quent side effects were local and transitory adverse effects. Regarding the sensory hypersensitivity frequently observed in autism, the result is interesting.

The findings reported here are limited in several ways, which may inform improvements in future approaches. The important limitations of the current study are:

- Its open-label status, whitout any controlled group. Indeed, we cannot exclude that the behavioral and cognitive improvement may be due to the natural course of the disease, the learning effects of the tests, or the placebo effect.
- The small sample size.
- Regarding the EF assessment, a more ecological test, such as the Six Elements test, would have been relevant to assess dysexecutive symptoms in everyday life. In addition, the lack of a working memory task in this study is regrettable. Indeed, the recent study of van Steenburgh et al. [37] showed a significant effect of bifrontal tDCS on the dorsolateral prefontal cortex on working memory tasks.
- The lack of assessment of mood and anxiety, which could influence the results of the neuropsychological tests. Indeed, the EFD, and particularly the deficit of mental flexibility and planning, are associated with anxiety and depression in autism without any intellectual disability [4, 5]. In addition, tDCS is known to have an antidepressant effect when applied on the DLPFC [47]. So, we cannot exclude that the cognitive improvement observed would be secondary to mood improvement. However, this antidepressant effect concerns rather the anodal tDCS over the DLPFC [47], and although not assessed by scales, none of the patients were clinically depressed at inclusion and throughout the study.
- Finally, as tDCS was applied only to the DLPFC, it cannot be ruled out that any effect observed is due, not to this specific target, but rather to a nonspecific stimulation of the cortex in general. In the future, it would be interesting to compare the effects of tDCS according to the stimulated brain areas in order to address this question.

Despite these limitations, this study seems interesting because the literature about tDCS in autism remains incomplete, particularly studies related to cognition. In addition, tDCS appears to be a well-tolerated, low-cost, and accessible treatment for autistic patients. In the future, the efficacy of cathodal tDCS over the left DLPFC should be assessed in a randomized placebo-controlled double-blind trial. In this trial, it would be relevant to test the main cognitive functions, such as working memory, attention, and verbal and visual episodic memory, and to use an ecological EF task.

Conclusion

This pilot study suggests that cathodal tDCS over the left DLPFC is a possible method to enhance dysexecutive syndrome in adults with high-functioning ASD, both (1) cognitively, with an increase in initiation and/or generation of information and cognitive flexibility, and (2) behaviorally, with an improvement in initiation of activities and motivation. Further studies are necessary to assess these effects in a placebo-controlled randomized study with a larger sample.

Acknowledgments

The authors thank Miss Le Goadec for her readings and the Fondation Avenir for their contributions. They also thank Mrs. Aline Augustynen and Mrs. Jocelyne Halley for the good progress of the study.

Statement of Ethics

Ethical approval based on the Declaration of Helsinki was provided by the Comité de Protection des Personnes Nord-Ouest 1 and the Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM) in July 2016 (number RCB2016-A00805-46).

Disclosure Statement

The authors have no financial or personal conflicts of interest to declare.

Funding Sources

Part of the study was financed by the Fondation de l'Avenir whose aim is to support and promote Health Research and Innovation.

Author Contributions

M.R. designed the study, recruited patients, analyzed the data, and wrote the article. V.M. analyzed the data and wrote the article. M.V. and O.G. designed the study and recruited patients. C.I. and B.B. participated in the interpretation of the results and read the draft. M.F. and A.R. recruited patients. G.O. and I.M.-G. conducted the neuropsychological tests.

References

1 Hill EL. Evaluating the theory of executive dysfunction in autism. Dev Rev. 2004;24(2):189–233.
2 Hill EL. Executive dysfunction in autism. Trends Cogn Sci. 2004 Jan;8(1):26–32.
3 Luna B, Doll SK, Hegedus SJ, Minshew NJ, Sweeney JA. Maturation of executive function in autism. Biol Psychiatry. 2007 Feb;61(4):474–81.
4 Lawson RA, Papadakis AA, Higginson CI, Barnett JE, Wills MC, Strang JF, et al. Everyday executive function impairments predict comorbid psychopathology in autism spectrum and attention deficit hyperactivity disorders. Neuropsychology. 2015 May;29(3):445–53.
5 Wallace GL, Kenworthy L, Pugliese CE, Popal HS, White EI, Brodsky E, et al. Real-World Executive Functions in Adults with Autism Spectrum Disorder: Profiles of Impairment and Associations with Adaptive Functioning and Co-morbid Anxiety and Depression. J Autism Dev Disord. 2016 Mar;46(3):1071–83.
6 Noggle C, Thompson J, Davis J. B-21 Everyday Executive Functioning Influences Adaptive Skills in Autistic Spectrum Disorders. Arch Clin Neuropsychol. 2014;29(6):543–4.
7 Miyajima M, Omiya H, Yamashita K, Miyata T, Yambe K, Matsui M, et al. The effects of cognitive remediation therapy using the frontal/executive program for autism spectrum disorder. Int J Psychiatry Med. 2016 Apr;51(3):223–35.
8 Riedel A, Maier S, Ulbrich M, Biscaldi M, Ebert D, Fangmeier T, et al. No significant brain volume decreases or increases in adults with high-functioning autism spectrum disorder and above average intelligence: a voxel-based morphometric study. Psychiatry Res. 2014 Aug;223(2):67–74.
9 Griebling J, Minshew NJ, Bodner K, Libove R, Bansal R, Konasale P, et al. Dorsolateral prefrontal cortex magnetic resonance imaging measurements and cognitive performance in autism. J Child Neurol. 2010 Jul;25(7):856–63.
10 Luna B, Minshew NJ, Garver KE, Lazar NA, Thulborn KR, Eddy WF, et al. Neocortical system abnormalities in autism: an fMRI study of spatial working memory. Neurology. 2002 Sep;59(6):834–40.
11 Casanova MF, Buxhoeveden DP, Brown C. Clinical and macroscopic correlates of minicolumnar pathology in autism. J Child Neurol. 2002 Sep;17(9):692–5.
12 Enticott PG, Rinehart NJ, Tonge BJ, Bradshaw JL, Fitzgerald PB. A preliminary transcranial magnetic stimulation study of cortical inhibition and excitability in high-functioning autism and Asperger disorder. Dev Med Child Neurol. 2010 Aug;52(8):e179–83.
13 Casanova MF, Buxhoeveden DP, Switala AE, Roy E. Minicolumnar pathology in autism. Neurology. 2002 Feb;58(3):428–32.
14 Oberman LM, Rotenberg A, Pascual-Leone A. Use of transcranial magnetic stimulation in autism spectrum disorders. J Autism Dev Disord. 2015 Feb;45(2):524–36.
15 Sokhadze EM, El-Baz A, Baruth J, Mathai G, Sears L, Casanova MF. Effects of low frequency repetitive transcranial magnetic stimulation (rTMS) on gamma frequency oscillations and event-related potentials during processing of illusory figures in autism. J Autism Dev Disord. 2009 Apr;39(4):619–34.
16 Baruth JM, Casanova MF, El-Baz A, Horrell T, Mathai G, Sears L, et al. Low-frequency repetitive transcranial magnetic stimulation (rTMS) modulates evoked-gamma frequency oscillations in autism spectrum disorder (ASD). J Neurother. 2010 Jul;14(3):179–94.
17 Sokhadze EM, Baruth JM, Sears L, Sokhadze GE, El-Baz AS, Casanova MF. Prefrontal neuromodulation using rTMS improves error monitoring and correction function in autism. Appl Psychophysiol Biofeedback. 2012 Jun;37(2):91–102.
18 Amiet C, Gourfinkel-An I, Laurent C, Bodeau N, Génin B, Leguern E, et al. Does epilepsy in multiplex autism pedigrees define a different subgroup in terms of clinical characteristics and genetic risk? Mol Autism. 2013 Dec;4(1):47.
19 Nitsche MA, Liebetanz D, Antal A, Lang N, Tergau F, Paulus W. Modulation of cortical excitability by weak direct current stimulation–technical, safety and functional aspects. Suppl Clin Neurophysiol. 2003;56:255–76.
20 Demirtas-Tatlidede A, Vahabzadeh-Hagh AM, Pascual-Leone A. Can noninvasive brain stimulation enhance cognition in neuropsychiatric disorders? Neuropharmacology. 2013 Jan;64:566–78.
21 Doruk D, Gray Z, Bravo GL, Pascual-Leone A, Fregni F. Effects of tDCS on executive function in Parkinson's disease. Neurosci Lett. 2014 Oct;582:27–31.
22 Dockery CA, Hueckel-Weng R, Birbaumer N, Plewnia C. Enhancement of planning ability by transcranial direct current stimulation. J Neurosci. 2009 Jun;29(22):7271–7.
23 Casanova MF, van Kooten IA, Switala AE, van Engeland H, Heinsen H, Steinbusch HW, et al. Minicolumnar abnormalities in autism. Acta Neuropathol. 2006 Sep;112(3):287–303.
24 Ameis SH, Daskalakis ZJ, Blumberger DM, Desarkar P, Drmic I, Mabbott DJ, et al. Repetitive Transcranial Magnetic Stimulation for the Treatment of Executive Function Deficits in Autism Spectrum Disorder: Clinical Trial Approach. J Child Adolesc Psychopharmacol. 2017 Jun;27(5):413–21.
25 Boggio PS, Nunes A, Rigonatti SP, Nitsche MA, Pascual-Leone A, Fregni F. Repeated sessions of noninvasive brain DC stimulation is associated with motor function improvement in stroke patients. Restor Neurol Neurosci. 2007;25(2):123–9.
26 Nelson HE. A modified card sorting test sensitive to frontal lobe defects. Cortex. 1976 Dec;12(4):313–24.
27 Ingram F, Greve KW, Ingram PT, Soukup VM. Temporal stability of the Wisconsin Card Sorting Test in an untreated patient sample. Br J Clin Psychol. 1999 Jun;38(Pt 2):209–11.
28 Army Individual Test. Manual of directions and scoring. Washington, DC: War Department, Adjustant General's Office; 1944.
29 Bornstein RA, Baker GB, Douglass AB. Short-term retest reliability of the Halstead-Reitan Battery in a normal sample. J Nerv Ment Dis. 1987 Apr;175(4):229–32.
30 Stroop JR. Studies of interference in serial verbal reaction. J Exp Psychol. 1935;18(6):643–62.
31 Golden CJ. A group version of the Stroop Color and Word Test. J Pers Assess. 1975 Aug;39(4):386–8.
32 Cardebat D, Doyon B, Puel M, Goulet P, Joanette Y. Evocation lexicale formelle et sémantique chez des sujets normaux. Performances et dynamiques de production en fonction du sexe, de l'âge et du niveau d'étude. Acta Neurol Belg. 1990;90(4):207–17.
33 Clément É. Approche de la flexibilité cognitive dans la problématique de la résolution de problème. Annee Psychol. 2006;106(03):415–34.
34 Strauss E, Sherman E, Spreen O. A compendium of neuropsychological tests. 3rd ed. Oxford: Oxford University Press; 2006. pp. 514–5.
35 Cummings JL. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. Neurology. 1997 May;48(5 Suppl 6):S10–6.
36 Bourreau Y, Roux S, Gomot M, Bonnet-Brilhault F, Barthélémy C. Validation of the repetitive and restricted behaviour scale in autism spectrum disorders. Eur Child Adolesc Psychiatry. 2009 Nov;18(11):675–82.
37 van 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 Jul;8(1):40.
38 English MC, Kitching ES, Maybery MT, Visser TA. Modulating attentional biases of adults with autistic traits using transcranial direct current stimulation: A pilot study. Autism Res. 2018 Feb;11(2):385–90.
39 Siman-Tov T, Mendelsohn A, Schonberg T, Avidan G, Podlipsky I, Pessoa L, et al. Bihemispheric leftward bias in a visuospatial attention-related network. J Neurosci. 2007 Oct;27(42):11271–8.
40 English MC, Maybery MT, Visser TA. Reduced pseudoneglect for physical space, but not mental representations of space, for adults with autistic traits. J Autism Dev Disord. 2017 Jul;47(7):1956–65.

41 Moulier V, Gaudeau C, Bouaziz N, Thomas M, Schenin-King Andrianisaina P, Bertasi E, et al. Repetitive transcranial magnetic stimulation modifies the neural processing of emotional stimuli. Poster session presented at 12th World Congress of Biological Psychiatry. 2015 June 14-18; Athens, Greece.
42 Gaudeau-Bosma C, Moulier V, Allard AC, Sidhoumi D, Bouaziz N, Braha S, et al. Effect of two weeks of rTMS on brain activity in healthy subjects during an n-back task: a randomized double blind study. Brain Stimul. 2013 Jul;6(4):569–75.
43 D'Urso G, Bruzzese D, Ferrucci R, Priori A, Pascotto A, Galderisi S, et al. Transcranial direct current stimulation for hyperactivity and noncompliance in autistic disorder. World J Biol Psychiatry. 2015;16(5):361–6.
44 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 Neurol. 2015;2015:928631.
45 Jacobson L, Koslowsky M, Lavidor M. tDCS polarity effects in motor and cognitive domains: a meta-analytical review. Exp Brain Res. 2012 Jan;216(1):1–10.
46 Parkin BL, Ekhtiari H, Walsh VF. Non-invasive Human Brain Stimulation in Cognitive Neuroscience: A Primer. Neuron. 2015 Sep;87(5):932–45.
47 Boggio PS, Rigonatti SP, Ribeiro RB, Myczkowski ML, Nitsche MA, Pascual-Leone A, et al. A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. Int J Neuropsychopharmacol. 2008 Mar;11(2):249–54.