CHAPTER

11

Effects of anodal multichannel transcranial direct current stimulation (tDCS) on social-cognitive performance in healthy subjects: A randomized sham-controlled crossover pilot study

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Abstract

Recent studies suggest that temporoparietal junction (TPJ) modulation can influence attention and social cognition performance. Nevertheless, no studies have used multichannel transcranial direct current stimulation (tDCS) over bilateral TPJ to estimate the effects on these neuropsychological functions. The project STIPED is using optimized multichannel stimulation as an innovative treatment approach for chronic pediatric neurodevelopmental disorders, namely in children/adolescents with Autism Spectrum Disorder (ASD).

In this pilot study, we aim to explore whether anodal multichannel tDCS coupled with a Joint Attention Task (JAT) influences social-cognitive task performance relative to sham stimulation, both in an Emotion Recognition Task (ERT) and in a Mooney Faces Detection Task (MFDT), as well as to evaluate this technique's safety and tolerability.

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Twenty healthy adults were enrolled in a randomized, single-blinded, sham-controlled, crossover study. During two sessions, participants completed the ERT and the MFDT before and after 20 min of sham or anodal tDCS over bilateral TPJ. No significant differences on performance accuracy and reaction time were found between stimulation conditions for all tasks, including the JAT. A significant main time effect for overall accuracy and reaction time was found for the MFDT. Itching was the most common side effect and stimulation conditions detection was at chance level. Results suggest that multichannel tDCS over bilateral TPJ does not affect performance of low-level emotional recognition tasks in healthy adults. Although preliminary safety and tolerability are demonstrated, further studies over longer periods will be pursued to investigate the clinical efficacy in children/adolescents with ASD, where social cognition impairments are preponderant.

Keywords

Multichannel tDCS, Temporoparietal junction, Social cognition, Facial expression, Holistic face detection, Joint attention

1 Introduction

Non-invasive brain stimulation methods, including transcranial direct current stimulation (tDCS) have been suggested as a promising alternative for the treatment of neurodevelopmental disorders, namely Autism Spectrum Disorder (ASD), given the induced improvements in multiple cognitive domains for both healthy individuals as for patients with neuropsychiatric disorders (Boggio et al., 2006; Brunoni et al., 2013; Dedoncker et al., 2016; Kekic et al., 2016; Kuo et al., 2014).

TDCS is a safe, well-tolerated and non-invasive established method of modulating neuronal activity. A constant, low-intensity direct current (0.5–2 mA) is passed into the brain through anode and cathode electrodes that are placed on the scalp, generating subthreshold alterations of the resting membrane potential and, consequently inducing transient changes in cortical excitability (Nitsche and Paulus, 2000, 2011). Anodal stimulation generates depolarization of resting membrane potentials in underlying cortical tissue, increasing rates of neuronal firing and excitability; while cathodal tDCS promotes hyperpolarization, reducing firing rates and excitability (Stagg and Nitsche, 2011). Conventional tDCS techniques use predominantly bipolar montages and large sponge pad electrodes, stimulating relatively broad brain regions between the anode and the cathode (Brunoni et al., 2012). To improve focality, depth of penetration and targeting-location control, new approaches using arrays of smaller electrodes, such as multichannel montages or High-Definition tDCS (HD-tDCS) have emerged. Multichannel tDCS and HD-tDCS allow greater current density and focality (Datta et al., 2009). An $M \times N$ multichannel configuration montage is typically used for targeting cortical and deep brain structures, where N is the number of active electrodes that is placed over the target region and M is the number of return electrodes. The active electrode defines the polarity of the stimulation as either anodal or cathodal, and the limits of the return electrodes confine the area undergoing modulation (Garnett et al., 2015).

Some studies have already demonstrated that non-invasive brain stimulation techniques may be used to target core ASD traits, namely social cognition via modulation of the temporoparietal junction (TPJ) (Donaldson et al., 2015; Santiesteban et al., 2012). Social cognition concerns the processes that allow individuals to interact and understand the mental and affective states of other people (Adolphs, 2009). It involves a wide variety of skills, such as facial memory and recognition, affect recognition and interpretation, or theory of mind (the ability to infer and reflect upon the emotions, intentions, beliefs of the self and others) (Frith and Frith, 2003; Korkmaz, 2011). TPJ is a key multimodal cortical region that is emerging as an important hub in several cognitive domains, such as social cognition, attention, or language and speech (Binder et al., 2009; Corbetta and Shulman, 2002; Dunbar, 2012; Geng and Vossel, 2013; Van Overwalle, 2009).

Recent studies have explored the effects of tDCS over TPJ in a range of socio-cognitive tasks designed to be challenging in clinical groups such as ASD. Santiesteban et al. (2015) applied anodal stimulation over the right and left TPJ in healthy volunteers and observed bilateral TPJ involvement in perspective taking and imitation inhibition tasks, but no effect on a theory of mind task. Other studies investigated whether anodal or cathodal stimulation over the right TPJ could modulate the belief attribution in healthy subjects. Sellaro et al. (2015) observed that subjects who received anodal stimulation assigned less blame to accidental harms compared to participants who received cathodal or sham stimulation. Ye et al. (2015) found that inhibiting the left or the right TPJ decreased the role of beliefs in moral judgments, while Mai et al. (2016) observed that the accuracy of both theory of mind and cognitive empathy tasks also decreased after receiving cathodal stimulation. More recently, Donaldson et al. (2018, 2019) studied the potential effects of HD-tDCS on the performance and neurophysiology of mental/emotional state attribution and self-other processing tasks. They found that anodal HD-tDCS over the right TPJ can affect facial emotion recognition, thereby identifying some preliminary underlying neurophysiological correlates in healthy volunteers.

Although recent results are encouraging, the number of studies is still scarce, even in adults. Moreover, no studies are available on bilateral tDCS stimulation in either adults or children. Indeed, to the best of our knowledge, no experiments have used multichannel tDCS over bilateral TPJ to estimate the effects on social cognition, which may be particularly relevant in children and adolescents, in the context of ASD, since this is a core brain area which is involved in several neuro-cognitive impairments characterizing the disorder (van Veluw and Chance, 2014; Venkataraman et al., 2015). Recent studies have also found that the left and right TPJ stimulation effects on social cognitive abilities are comparable (Santiesteban et al., 2015; Yang et al., 2020). Even though most of the research has been focused on tDCS application in adult populations, there is evidence that tDCS can also be safely applied on children and adolescents with minor side effects (Andrade et al., 2014; Krishnan et al., 2015; Moliadze et al., 2015). The European research project

STIPED is using optimized multichannel stimulation as an innovative treatment approach for chronic pediatric neurodevelopmental disorders, including children and adolescents with ASD and Attention-Deficit/Hyperactivity Disorder (ADHD) (STIPED Consortium, 2017). Nonetheless, feasibility tests are first needed in adults to assess the practicability of the proposed stimulation protocol. The present work was carried out as part of the project STIPED (Stimulation in Pediatrics; Horizon 2020 n° 731827) and intended to explore the feasibility of the stimulation protocol in controls so that it can then be applied in a large-scale clinical study in children and adolescents with ASD. As such, a randomized, single-blinded, sham-controlled, crossover pilot study in young healthy adults was carried out. In this pilot study, we aimed at exploring whether anodal multichannel tDCS over bilateral TPJ coupled with a learning task would influence social-cognitive task performance relative to sham stimulation, both in a facial expression recognition task and in a holistic face detection task, as well as to evaluate the safety and tolerability of this technique. Based on the most directly relevant studies discussed above and in recent evidence that a tailored concurrent task might activate the same pathways of tDCS and augment neuromodulatory effects (Bikson and Rahman, 2013; Kronberg et al., 2020), we hypothesize that anodal stimulation would increase accuracy and processing speed for both paradigms compared to sham stimulation, with good tolerability in healthy individuals. By enhancing the activity of TPJ, we expect improved emotion recognition and perceptual processing. On an exploratory level, we also aimed at investigating the effects of online bilateral TPJ stimulation in the concurrent task itself, in this case a joint attention paradigm.

2 Materials and methods

2.1 Participants

Twenty healthy young adults (10 females, mean age 27.6 ± 5.58 years) were recruited and included in the study. Participants were recruited from Coimbra Institute for Biomedical Imaging and Translational Research (CIBIT)/Institute for Nuclear Sciences Applied to Health (ICNAS) private volunteers' database, by email or approached in person. Participants had never received tDCS and presented no contraindications to standard non-invasive brain stimulation. All volunteers had normal or corrected to normal vision. The inclusion criteria were: (a) young healthy subjects (b) with the age of 18 or over. The exclusion criteria included the following: (a) history of neurological or psychiatric disorders; (b) epilepsy/epileptic seizures in the past or family history of epileptic seizures; (c) migraine; (d) history of brain surgery or of craniocerebral injury with loss of consciousness; (e) history of any serious life-threatening or heart disease; (f) tuberous sclerosis, neurofibromatosis, cerebral palsy, increased intracranial pressure; (g) cardiac pacemaker or any other body electronic devices; (h) pregnancy; (i) substance or tobacco consumption; (j) concomitant medication with effects on the central nervous system and (k) dermatological diseases of the scalp.

Table 1 Demographic characteristics of participants.

Variable	Mean ± STD
Gender (M/F)	20 (10/10)
Age (years)	27.6 ± 5.58
Years education	17.00 ± 2.58
Edinburgh Handedness Inventory (EHI)	79.12 ± 24.21

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Medicine of the University of Coimbra. All participants gave their written informed consent prior to screening procedures and recruitment. The demographic characteristics of the participants are summarized in Table 1.

2.2 Study design

The study followed a randomized, single-blinded, sham-controlled, crossover design. Each participant attended a (i) screening session to obtain informed consent, assess inclusion criteria and collect demographics information, and (ii) two neurostimulation sessions which differed in the type of stimulation applied (verum/sham) during a concomitant socio-cognitive task completion. The stimulation order (verum-sham or sham-verum) was randomized and counterbalanced across participants (also considering their gender), so that for half of them the anodal stimulation was the first session, while for the other half sham stimulation was. Participants were blinded to the stimulation condition. Neurostimulation sessions were separated by a washout period of 1 week to avoid carryover effects, and the screening visit was performed either 1 day before the first tDCS session or earlier on the same day.

In each neurostimulation session, participants completed two social cognition tasks before and after 20 min of either sham or anodal multichannel tDCS over bilateral TPJ. For both stimulation conditions, multichannel tDCS was performed concurrently with a joint attention task to boost modulation of social cognition neural circuits via activity-selective mechanisms. The activity-selective mechanism states that the administration of tDCS combined with a learning task (online tDCS) can pre-activate cortical regions specific to the paired task (in this case related to social cognition) and thus, enhance the neuromodulatory potential of tDCS by improving the functional specificity of stimulation (Bikson and Rahman, 2013; Kronberg et al., 2020).

The experimental design of the neurostimulation sessions is schematized in Fig. 1.

2.3 Experimental procedure

Before the beginning of the first neurostimulation session, volunteers signed the informed consent and participated in a brief screening that included medical and psychosocial history assessment, sociodemographic data collection and tDCS safety

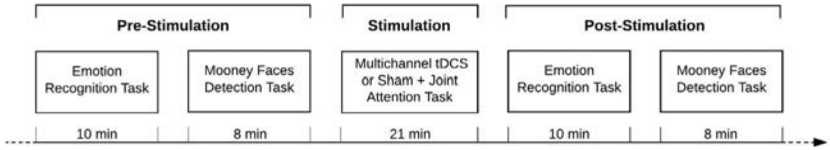


FIG. 1

Schematic of the study's experimental design for each neurostimulation session. Each participant was required to complete two social cognition tasks before stimulation. After 20 min of stimulation (sham or verum) concomitantly with a joint attention task, each participant was required to complete the same tasks performed before.

conditions evaluation to ensure inclusion criteria. Eligible participants completed the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971) to assess right (scores between +40 and +100) or left-hand dominance (scores between −100 and −40).

The experimental procedure for the two sessions was the same, except for the type of stimulation administered. To prevent effects induced by the single-blind design on the dependent variables, the instructions given to participants were the same and followed a predetermined protocol setting. The experiment included three social cognition tasks, and each participant was required to complete a facial expression task and a holistic detection task before and after receiving multichannel tDCS. During stimulation, the participants had to simultaneously perform a joint attention task, with the purpose of activating the same social cognition pathways and augment neuromodulatory effects of tDCS.

Participants were tested in a quiet room and were seated about 65 cm away from the screen (distance measured from the eyes to the center of the screen). The paradigms were presented on a 22-in. LCD monitor (frame rate of 60 Hz, 1680 × 1050 pixel resolution) and were delivered using either Matlab® (Mathworks, version R2017a), Vizard 5 (WorldViz, release 5 VR Toolkit, development edition) or Unity (Unity Technologies, r4.0), depending on the task's programming.

In the beginning of each session, participants' scalps and the right mastoids areas were exfoliated with an abrasive gel and then cleaned with alcohol to ensure low impedance levels at electrodes placement sites. The EEG reference electrodes set (CMS/DRL) was attached to the right mastoid and then a 32-channel neoprene cap with 24 EEG NG Geltrode NE032 and 8 hybrid tCS/EEG NG PiStim NE029 (Neuroelectrics, Barcelona, Spain), placed according to the international 10–10 system was fitted to the participants' heads. All the electrodes were loaded with conductive gel to maximize the scalp contact and allow for a low-resistance recording. At least two impedance checks were carried out to guarantee that all the electrodes were kept under 15 kΩ during the recordings: before initiating the first socio-cognitive task and immediately before launching the stimulation protocol. Multichannel tDCS was delivered using the StarStim® 32 device (Neuroelectrics, Barcelona, Spain) and the Neuroelectrics® Instrument Controller (NIC) software (releases 2.0.9 and 2.0.10). EEG was also recorded during stimulation and while participants were performing the social cognition tasks; nevertheless, within the context of the present work, EEG data will not be presented.

At the end of each session, participants completed a safety questionnaire to assess discomfort sensations during the stimulation and were asked to try to identify which type of stimulation they received (verum or sham). This questionnaire was adapted from Poreisz et al. (2007) and consists of six commonly reported side effects (itching, pain, warmth, burn, metallic taste and fatigue), as well as an "other" category that allows participants to report additional sensations (Brunoni et al., 2011). For each side effect, a four-step scale of intensity is defined: absent, mild, moderate and strong.

The total duration of the experimental procedure for each session was approximately 1 h 30 min, including 20 min for scalp cleaning and placement of the EEG/ tDCS cap, 60 min for the experimental tasks, neurostimulation and the safety questionnaire, and 10 min to clean up at the end.

2.3.1 Multichannel tDCS

Multichannel tDCS stimulation followed the recommended safety procedures (Poreisz et al., 2007; Woods et al., 2016) and was performed using StarStim® 32 system (Neuroelectrics, Barcelona, Spain). This device is a wireless hybrid EEG/tDCS 32-channel neurostimulator, currently certified for research use only.

A total of eight sintered silver chloride (Ag/AgCl) electrodes of 12 mm diameter (3.14 cm^2 contact area) were used and placed in a double 3×1 configuration targeting the anterior and posterior regions of left and right TPJ. These regions were demonstrated to be functionally connected to other areas involved in social cognition, attentional selection (Mars et al., 2012) and revealed significant activation for tasks involving emotion recognition and intention attribution (Schurz et al., 2014).

According to the 10–10 EEG international system, active electrodes were placed over CP5 (left) and CP6 (right) positions with three corresponding return electrodes on each side (C5, P1 and PO7 on the left and C4, T8 and P6 on the right). The reference electrodes were placed over the right mastoid. During verum stimulation, a current of 1 mA per active electrode (maximal injected current per electrode surface area of 0.318 mA/cm^2) was delivered to the brain during 20 min, with a ramp up of 30 s at the beginning and a ramp down of 30 s at the end of stimulation period. The maximal injected current into the brain at any given time was below 2 mA. During sham stimulation, the current was ramped up to a maximum of 2 mA in 30 s and then brought back again to 0 mA in 30 s, both at the beginning and at the end of the protocol; during 19 min no stimulation occurred. This procedure was used to give the participants the same sensation as a verum stimulation, during which the participant usually only perceives the initial increase and final decrease of current.

For both stimulation conditions, a joint attention task was being performed simultaneously by the participants (online/concurrent task) and EEG was also being collected by a total of 24 electrodes. The montage of electrodes used for bilateral stimulation of the TPJ is depicted in Fig. 2.

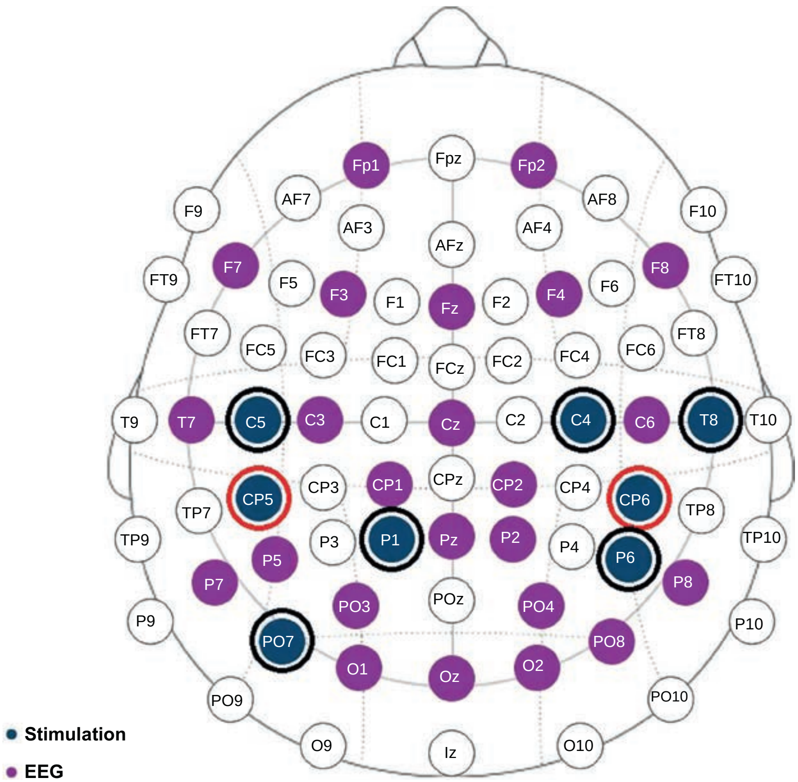


FIG. 2

Head diagram showing the positioning of the tDCS and EEG electrodes used during multichannel stimulation over bilateral TPJ. Anodal electrodes are delineated with red circles and cathodal electrodes are with black circles.

2.3.2 Social cognition tasks

Two social cognition tasks were used to investigate the effect sizes of changes in behavioral performance: the Emotion Recognition Task (ERT) and the Mooney Faces Detection Task (MFDT). A third task, corresponding to the online/concurrent task, was used to engage social cognition neural networks and potentiate the effects of neurostimulation within pre-activated circuits: the Joint Attention Task (JAT). The presentation order of the tasks was the same between and within (pre and post stimulations) participants. Within each task presentation, the order of individual stimuli was randomized. In both sessions, all the participants were provided with detailed instructions and had a brief training period to be acquainted with the protocol/tasks.

2.3.2.1 Emotion recognition task (ERT)

The ERT is based on the paradigm originally designed by Simões et al. (2018) for investigating neural correlates of emotion expression imagery networks in adolescents with ASD. The task, developed in Vizard 5 (WorldViz, release 5 VR Toolkit, development edition), was revised so that it became harder and more challenging for the participants. The ERT, depicted in Fig. 3, consists of identifying visual facial expressions in a virtual male avatar (happy, sad and neutral facial expressions), in

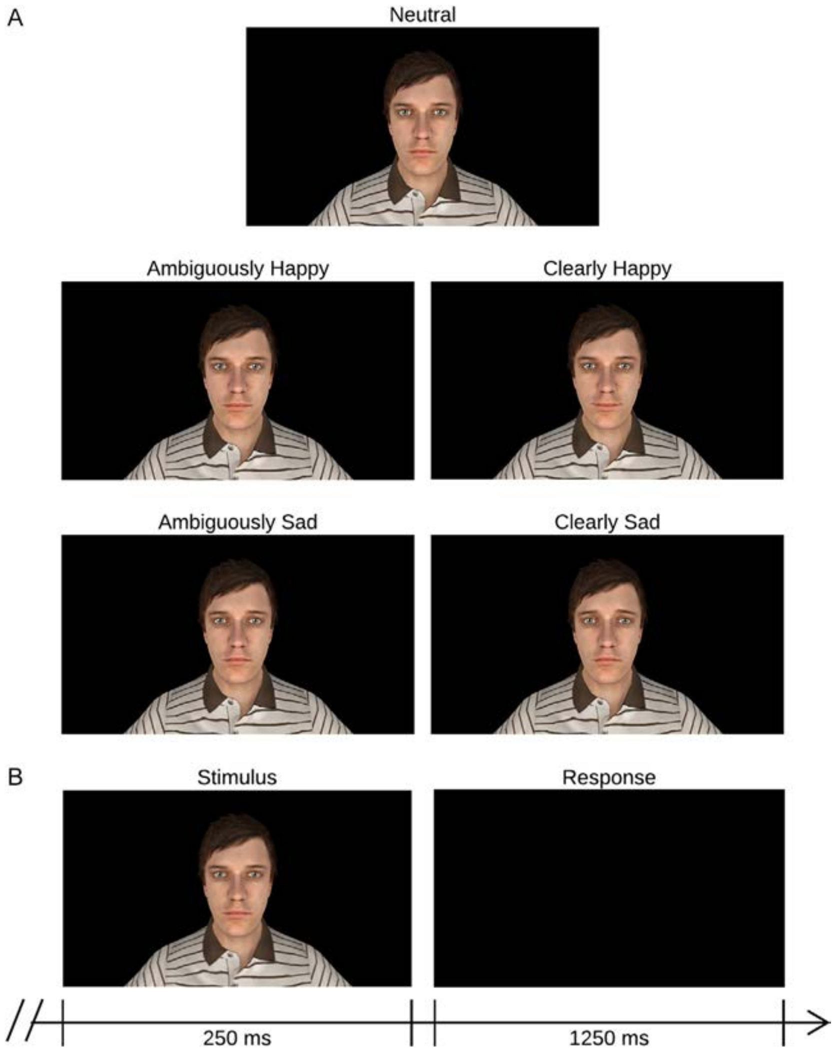


FIG. 3

Emotion recognition task. (A) Base stimuli. (B) Structure of the trials.

which the degree of intensity of the expression changes for happy and sad conditions. Two different intensity levels (departing from neutral) of sad and happy expressions are present: one clearer and another more ambiguous, resulting in five different facial expressions: clearly happy, ambiguously happy, neutral, ambiguously sad and clearly sad.

The task consists of four runs of 2.5 min (100 randomized trials per run—20 trials for each facial expression) with short pauses in between. Trials have a mean duration of 1500 ms, varying between 1250 and 1750 ms due to an inter-trial jitter (range: 0–500 ms, average: 250 ms). Each stimulus is displayed for 250 ms, followed by a black screen baseline with a mean duration of 1250 ms (range: 1000–1500 ms). Participants must observe the face of the avatar and decide whether he looked happy, sad or neutral, by pressing a specific button for each condition (Numeric Keypad Targus PAUK10). A total of 80 trials per condition are recorded and the full length of the experiment is around 10 min.

2.3.2.2 Mooney faces detection task (MFDT)

The MFDT is an adapted version of the paradigm used by Castelhano et al. (2018) and Tavares et al. (2016) for investigating the neural correlates of holistic face processing in adults with ASD using Mooney face stimuli (Mooney, 1957).

The task, programmed in Matlab® (Mathworks, version R2017a) using the Psychophysics Toolbox version 3.0 extensions (Brainard, 1997), consists of a visual closure face detection task on two-tone images (black and white). Stimuli consist of Mooney faces (upright faces and scrambled non-facial images) that were chosen from a set of images available and piloted previously at our research center (Castelhano et al., 2013). For the scrambled non-faces category, some of the stimuli present parts of a face (e.g., nose, eye, ear) that are mixed and/or inverted in the image. Each picture is presented during 1000 ms and is preceded by a black screen baseline with a fixation cross also for 1000 ms. After stimulus presentation, participants must decide whether the stimulus looked like a face or not, by pressing a specific button for each condition (Numeric Keypad Targus PAUK10). The response period lasts until there is a button press or for 1000 ms (maximum), in cases where the participant does not give an answer. As such, the minimal inter-stimulus-interval (ISI) between consecutive stimuli is 1000 ms and the maximum ISI is dependent on the participant's response. The experiment consists of 2 runs of 4 min, with different pre-defined randomized sequences of trials (80 trials per run—40 for face and 40 for scrambled stimuli) and with a short pause in between. A total of 80 trials per condition are recorded and the full length of the experiment is around 8 min. The stimuli and the structure of the trials are illustrated in Fig. 4.

2.3.2.3 Joint attention task (JAT)

A joint attention paradigm was expressly developed to be performed during multichannel tDCS (online stimulation). Joint attention is an early-developing social communication skill, usually impaired in ASD individuals, defined by the non-verbal

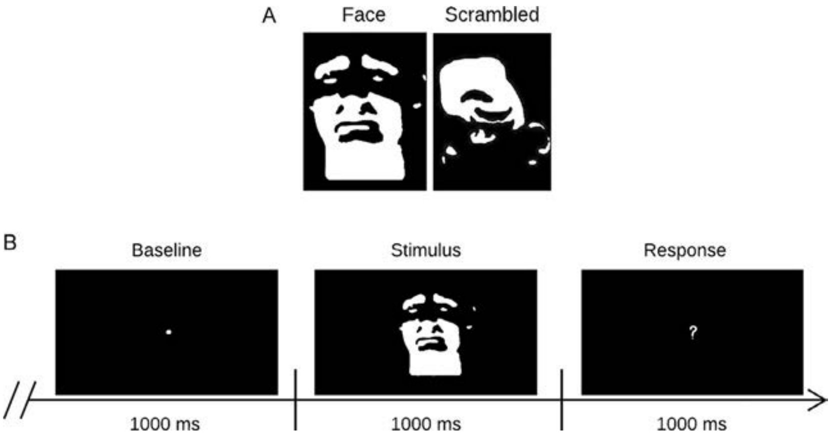


FIG. 4

Mooney faces detection task. (A) Base stimuli. (B) Structure of the trials.

coordination of attention of two individuals toward a third object or event (Bakeman and Adamson, 1984). One type of joint attention is the ability to follow the direction of the gaze and gestures of others to share a common point of reference.

The task was designed in Unity (Unity Technologies, release 4.0) and consists of a virtual scenario wherein five avatars interact among each other during a birthday party. Several distractors are placed in the setting, such as furniture, decoration, food, drinks, gifts; and some of the objects change throughout the course of the birthday party. The task is divided into three runs that represent different phases of the event: the first run corresponds to the beginning of the party, the second run to its middle and the third to its end. Each trial is composed by a moving period where one, two or three avatars turn their gaze from the participant (Fig. 5B–D) to another avatar (target), followed by another moving period where the avatar(s) move back their gaze to the initial/baseline position. The target avatar maintains its gaze at the participant during trial duration. In the baseline position, all the avatars are looking at the participant (Fig. 5A). Each stimulus has a duration of 2000 ms and the ISI between consecutive conditions is also 2000 ms. The task consists of 3 runs of 5 min and 40s (85 trials per run) with a pause of 1 min and 30 s in between. A total of 85 trials per condition are recorded and the full length of the experiment is 20 min. Participants are requested to observe the scenario and whenever one of the avatars is looking at another avatar, participants should follow its gaze and also look at the target avatar. In the case where two or three avatars are looking at another avatar, participants should follow their gaze, look at the target avatar and also press a button (Numeric Keypad Targus PAUK10).

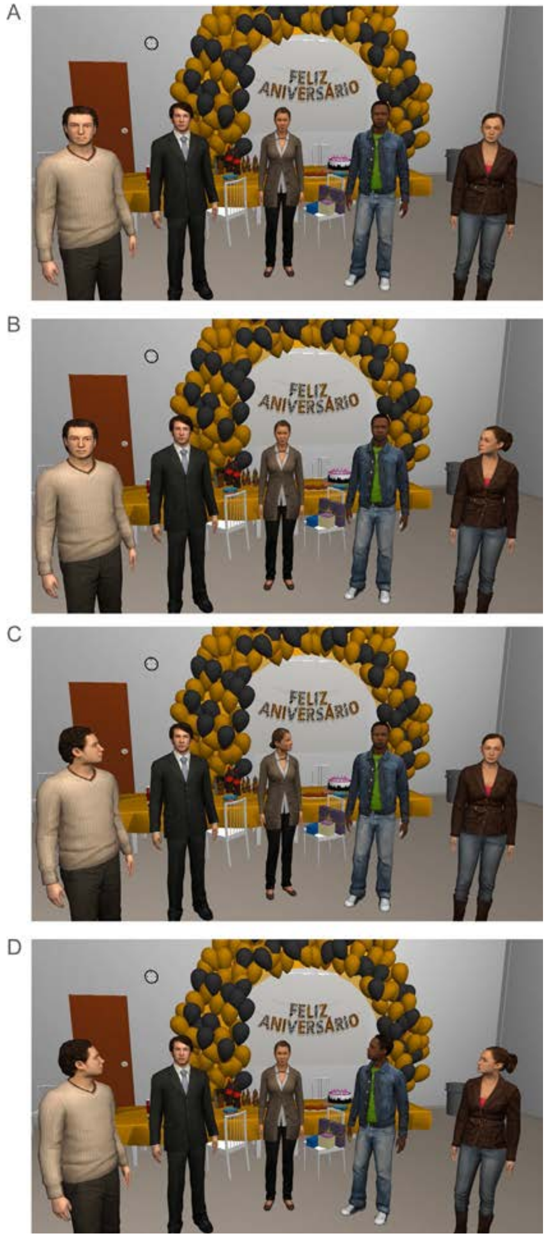


FIG. 5

Examples of stimuli types in the Joint Attention Task. (A) Baseline position for all the avatars gazing at the participant. (B) One avatar gazes at another avatar. (C) Two avatars gaze at another avatar. (D) Three avatars gaze at another avatar.

2.4 Data analysis and statistics

Data and statistical analysis were conducted in Matlab® (Mathworks, version R2017a) and SPSS (IBM SPSS Statistics 27.0). Accuracy and reaction time were used as measures of task performance. Overall accuracy and separate accuracy and reaction time scores for the different stimulus categories were calculated for the three socio-cognitive tasks (ERT, MFDT and JAT).

To detect stimulation effects on the ERT and MFDT, overall metrics and metrics for each stimulus category were subjected to a general linear model two-way repeated measure analysis of variance (ANOVA) with the within-subjects' factors $\text{stimulation}_{\text{verum,sham}}$ and $\text{time}_{\text{pre,post}}$. Simple main effects were determined by a repeated measures ANOVA if a significant interaction was present. If there was no significant interaction but only significant main effects, a post hoc analysis of multiple comparisons (Bonferroni correction) was applied. Partial eta squared (η_p^2) was calculated to report effect size estimates. In the case of the JAT, paired *t*-tests were used to investigate overall and specific stimulus category differences according to the stimulation condition.

For all tasks, an additional analysis was performed to evaluate carryover effects, i.e., if the effect of the prior treatment (i.e., stimulation condition) persisted to the subsequent treatment effect. A repeated measures ANOVA model defining two levels of the between-subjects factor order (sham-verum; verum-sham) and two levels of the within-subjects factor stimulation (verum, sham) was set up. The responses under sham and verum conditions were deviations from each participant's baseline measurement, i.e., change scores ($\text{response}_{\text{post}}$—$\text{response}_{\text{pre}}$), except for the JAT where responses were measured only during stimulation.

Furthermore, to evaluate the tolerability of the system, the adverse events associated with verum and sham stimulation procedures were also evaluated. A series of Wilcoxon signed rank tests were used to assess differences in side effects ratings between anodal multichannel tDCS and sham sessions. For safety, there were no serious adverse events and, hence, no statistical analyses were performed. Finally, to test the effectiveness of participant blinding, it was examined whether individuals could deduce the assigned condition at the end of each session, using a cross-tabulation and a Pearson chi-squared (χ^2) test. To evaluate the effect of the order in which the two stimulation conditions were administered on the overall and per session rates of correct identification of stimulation condition, Wilcoxon signed rank tests were used.

For all analyses, *p* values less than 0.05 were considered statistically significant.

3 Results

3.1 Task performance

Task performance was measured with respect to accuracy (percentage of correct trials) and reaction time. Figs. 6 and 7 represent ERT and MFDT performances for the different types of stimuli in pre and post stimulation for sham and anodal multichannel tDCS.

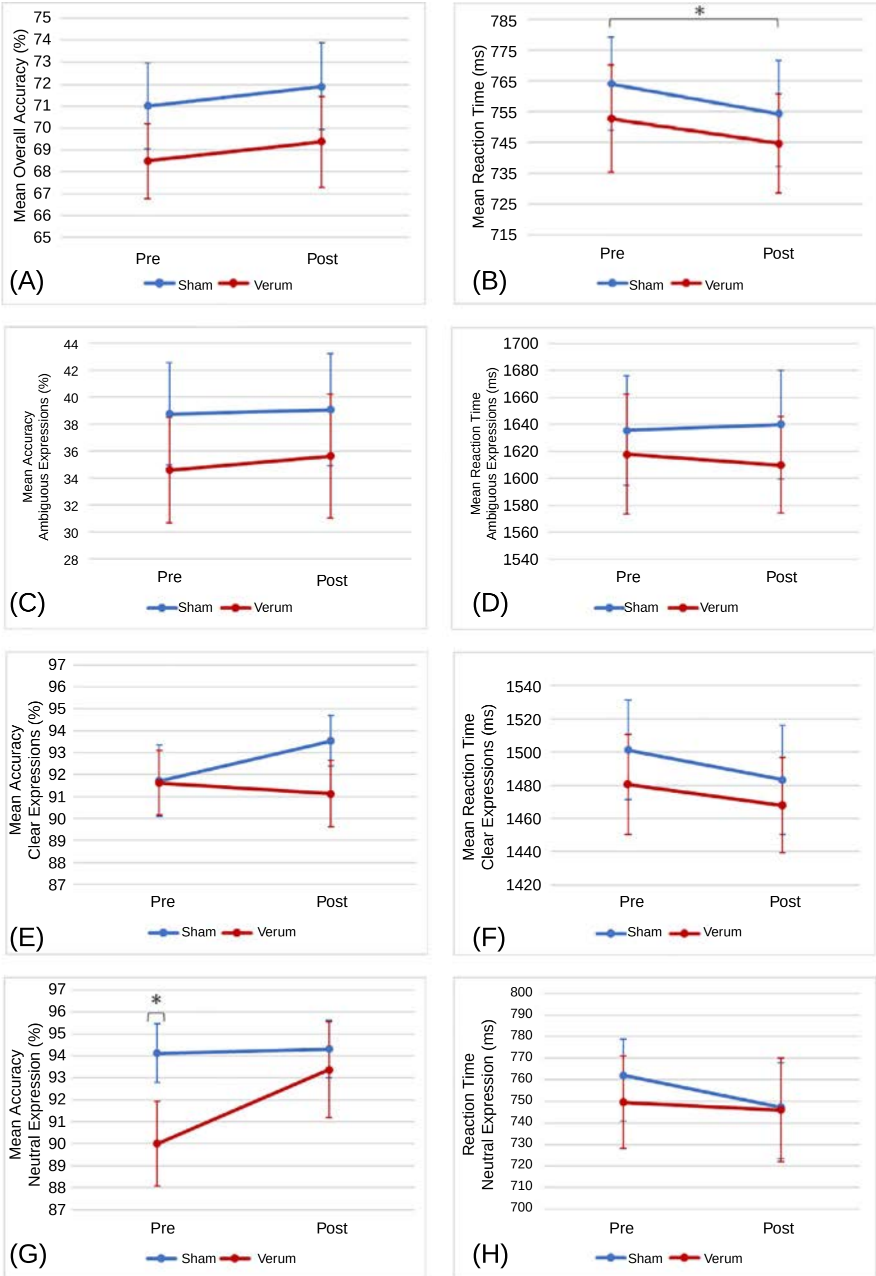


FIG. 6

Changes in the ERT performance regarding stimulation and time for each type of stimulus. (A and B) Overall mean accuracy and mean reaction time. (C and D) Mean accuracy and mean reaction time for ambiguous stimuli (ambiguously happy + ambiguously sad). (E and F) Mean accuracy and mean reaction time for clear stimuli (clearly happy + clearly sad). (G and H) Mean accuracy and mean reaction time for the neutral stimulus. *Significant effect ($p < 0.05$). Error bars depict standard errors of the mean.

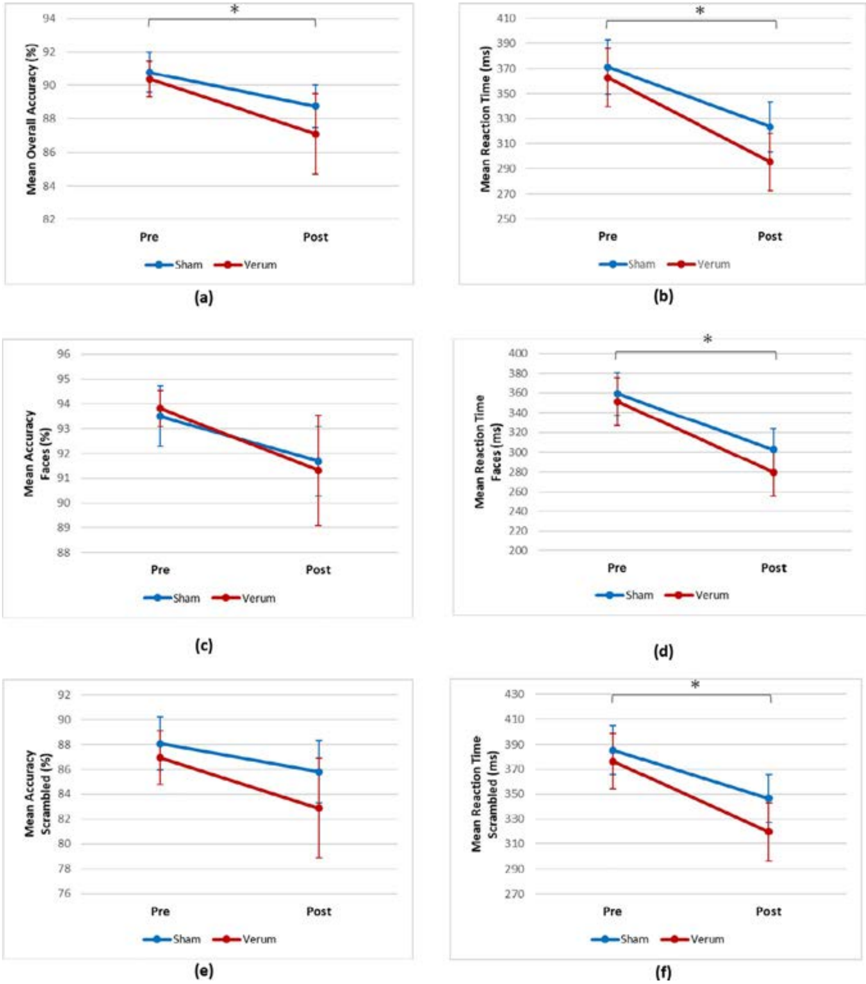


FIG. 7

Changes in the MFDT performance regarding stimulation and time for each type of stimulus. (A and B) Overall mean accuracy and mean reaction time. (C and D) Mean accuracy and mean reaction time for upright faces stimuli. (E and F) Mean accuracy and mean reaction time for scrambled non-faces stimuli. *Significant effect ($p < 0.05$). Error bars depict standard errors of the mean.

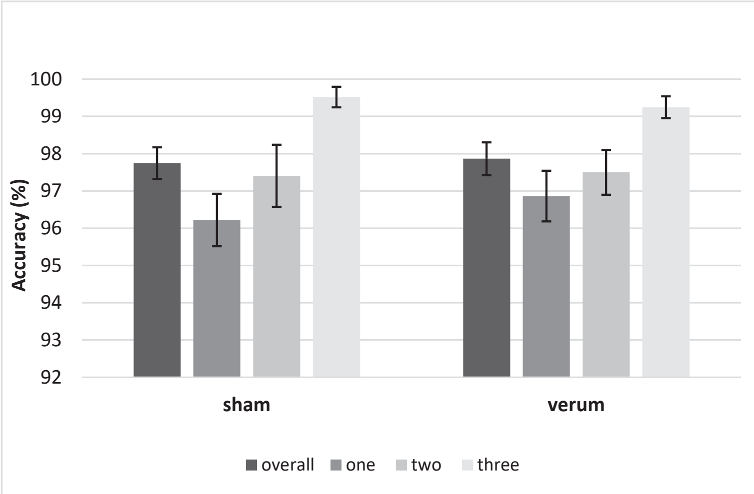
An ANOVA with the repeated-measure factors stimulation$_{verum,sham}$ and time$_{pre,post}$ was applied for each performance metric of the ERT and MFDT.

Regarding the ERT, the range of accuracy rates was 54–93.5% (mean ± SD: 70.19 ± 8.62%) for all conditions, participants, and types of stimuli. When considering each emotion category, the range of accuracy rates varied and presented lower values for the ambiguous stimuli (9.38–85.63%; mean ± SD: 37.01 ± 18.19%) and higher values for clear (73.13–100%; mean ± SD: 92 ± 6.44%) and neutral stimuli (60–100%; mean ± SD: 92.95 ± 7.80%). Nevertheless, the results revealed that there was no significant main effect for both stimulation condition [$F(1,19) = 2.52$, $p = 0.13$, $\eta_p^2 = 0.12$] and time [$F(1,19) = 1.21$, $p = 0.29$, $\eta_p^2 = 0.060$] on participants' overall accuracy. No significant interaction between stimulation type and time [$F(1,19) = 0.00$, $p = 1.00$, $\eta_p^2 = 0.00$] was also observed. Regarding reaction time, the ANOVA showed a significant effect of time [$F(1,19) = 6.24$, $p = 0.02$, $\eta_p^2 = 0.25$] (Fig. 6B), but no significant main effects for both stimulation [$F(1,19) = 1.00$, $p = 0.33$, $\eta_p^2 = 0.05$] and time × stimulation interaction [$F(1,19) = 0.04$, $p = 0.84$, $\eta_p^2 = 0.002$]. Post hoc tests using the Bonferroni correction revealed that participants reacted significantly faster to images after stimulation than before stimulation. Statistical analysis was also carried out to evaluate the performance of participants for each emotion category: ambiguous stimuli (ambiguously happy + ambiguously sad), non-ambiguous stimuli (clearly happy, clearly sad) and neutral. Nevertheless, all the results were non-significant for each within-subjects' factor and interaction (all $p > 0.11$) (Fig. 6C–H). A baseline difference between sham and verum stimulation for neutral faces accuracy was observed and investigated. An additional paired *t*-test revealed a significant baseline difference between sham and verum conditions on accuracy for the neutral stimulus [$t(19) = 2.18$, $p = 0.04$].

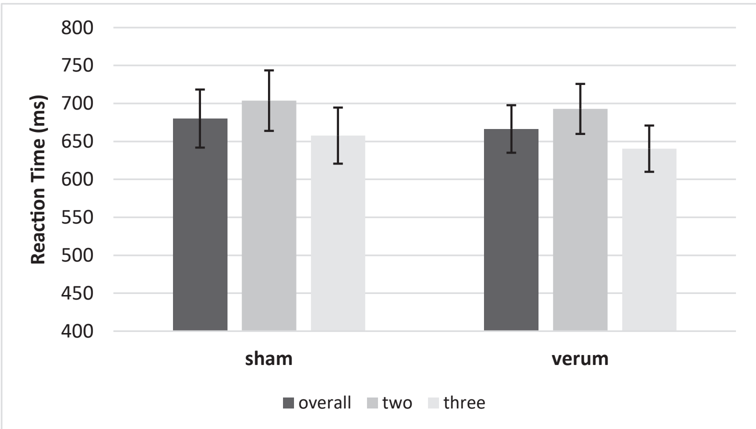
For the MFDT, the range of accuracy rates was 56.25–99.38% (mean ± SD: 89.25 ± 7.07%) for all conditions, participants, and types of stimuli. When considering each stimulus category, the range of accuracy rates showed slightly lower values for the scrambled non-faces stimuli (18.75–100%; mean ± SD: 85.92 ± 12.45%) and higher values for upright faces stimuli (60–100%; mean ± SD: 92.58 ± 6.65%). Additional analyses of MFDT performance for the different types of stimuli showed a significant main effect of time on participants' overall accuracy [$F(1,19) = 9.41$, $p = 0.01$, $\eta_p^2 = 0.33$] and reaction time [$F(1,19) = 26.44$, $p = 0.00$, $\eta_p^2 = 0.58$], as well as on participants' reaction times when detecting either faces stimuli [$F(1,19) = 31.81$, $p = 0.00$, $\eta_p^2 = 0.63$] or scrambled stimuli [$F(1,19) = 13.57$, $p = 0.002$, $\eta_p^2 = 0.42$]. Likewise, no significant main effects of both stimulation (all $p > 0.24$) and time × stimulation interactions (all $p > 0.19$) were observed on all the performance metrics. Bonferroni-corrected post hoc tests detected a decrease in accuracy from pre to post task condition and revealed that participants reacted significantly faster to images after stimulation than at pre-stimulation.

Fig. 8 shows JAT performance for the different types of stimuli in sham and anodal multichannel tDCS.

For this task, the range of accuracy rates was 92.16–100% (mean ± SD: 97.80 ± 1.91%) for all conditions, participants, and types of stimuli. When considering each stimulus category, the range of accuracy rates showed slightly lower values when one avatar (85.88–100%; mean ± SD: 96.54 ± 3.07%) or two avatars were gazing at another (86.25–100%; mean ± SD: 97.45 ± 3.20%) and higher values when three avatars were gazing at another (94.94–100%; mean ± SD: 99.38 ± 1.26%). The high overall accuracy suggests that participants stayed engaged and maintained



(a)



(b)

FIG. 8

Changes in the JAT performance regarding stimulation for each type of stimulus. (A) Overall mean accuracy and mean accuracy for one, two or three onlookers' avatars. (B) Overall mean reaction time and mean reaction time for two or three onlookers' avatars. For one onlooker avatar stimulus, participants must not press any button, so reaction time determination does not apply. Error bars depict standard errors of the mean.

attention during the task. Paired samples *t*-tests showed no significant effects between sham and verum conditions on either participants' overall accuracy [$t(19) = -0.39$, $p = 0.70$] or reaction time [$t(19) = 0.48$, $p = 0.63$]. For the three main categories of stimuli, no effects of stimulation were also detected on accuracy and reaction time when one avatar [accuracy: $t(19) = -0.39$, $p = 0.70$], two avatars [accuracy: $t(19) = -0.13$, $p = 0.90$; reaction time: $t(19) = 0.37$, $p = 0.71$] or three avatars [accuracy: $t(19) = 1.11$, $p = 0.28$; reaction time: $t(19) = 0.61$, $p = 0.55$] were gazing at another avatar. Finally, concerning carryover effects, the results of the repeated measures ANOVA showed a significant interaction between stimulation and order factors in the MFDT for overall accuracy [$F(1, 18) = 14.55$, $p = 0.001$, $\eta_p^2 = 0.45$], and for participants' accuracy when detecting either faces [$F(1, 18) = 5.60$, $p = 0.03$, $\eta_p^2 = 0.24$] or scrambled stimuli [$F(1, 18) = 11.05$ $p = 0.004$, $\eta_p^2 = 0.33$]. The JAT also showed a significant interaction between stimulation and order for overall accuracy [$F(1, 18) = 6.31$ $p = 0.02$, $\eta_p^2 = 0.26$], and for participants' accuracy when detecting two avatars [$F(1, 18) = 7.78$ $p = 0.01$, $\eta_p^2 = 0.30$] and three avatars [$F(1, 18) = 6.25$ $p = 0.02$, $\eta_p^2 = 0.26$] gazing at another avatar. Further inspection of profile plots (Figs. S1 and S2 in Supplementary Material in the online version at https://doi.org/10.1016/bs.pbr.2021.04.004) suggests that participants in the order "verum-sham" had a higher average response following the sham condition than the group in the order "sham-verum," implying that there was a carryover of benefits from initial administration of the verum stimulation. For the ERT, no significant interactions between stimulation and order for the different task metrics were found.

3.2 Tolerability and blinding

Tolerability was assessed by a safety questionnaire that evaluated undesirable sensations associated to multichannel tDCS. A total of 40 stimulation sessions were performed without any complications, serious adverse events or dropouts from the study, suggesting that multichannel tDCS meets basic safety parameters. Table 2 evaluates the frequency of each reported side effect and its severity according to stimulation condition. When combining mild, moderate, and strong scale-intensity categories, itching and fatigue were relatively commonly reported for both verum (70% and 45%, respectively) and sham conditions (35% for both sensations), while the side effects such as pain, warmth and burn were uncommonly described (less than 10%). These sensations were rated, on average, as mild. Furthermore, severely rated side effects were rare: itching was only rated as strong by one participant in an anodal multichannel tDCS session. Metallic taste was not reported in any of the sessions.

A series of Wilcoxon signed rank tests identified a significant difference in the rating of itchiness between the active and sham conditions ($Z = -2.50$, $p = 0.01$), but there were no differences for ratings of pain ($Z = -1.41$, $p = 0.157$), warmth ($Z = -1.41$, $p = 0.157$), burning ($Z = -1.00$, $p = 0.317$), or fatigue ($Z = -0.302$, $p = 0.76$).

Fig. 9 depicts the number of participants who correctly or incorrectly identified whether the stimulation session was verum or sham. Chi-squared tests revealed that

Table 2 Percentage (frequency) of reported adverse effects rated according to their intensity for each type of stimulation session. The itching sensation was reported more often for the verum sessions than for the sham sessions ($Z = -2.50$, $p = 0.01$).

	Severity							
	Absent		Mild		Moderate		Strong	
Sensation	**Sham**	**Verum**	**Sham**	**Verum**	**Sham**	**Verum**	**Sham**	**Verum**
Itching[a]	60% (n=13)	30% (n=6)	25% (n=5)	55% (n=11)	10% (n=2)	10% (n=2)	0	5% (n=1)
Pain	100% (n=20)	90% (n=18)	0	10% (n=2)	0	0	0	0
Warmth	100% (n=20)	90% (n=18)	0	10% (n=2)	0	0	0	0
Burn	95% (n=19)	90% (n=18)	5% (n=1)	10% (n=2)	0	0	0	0
Metallic taste	100% (n=20)	100% (n=20)	0	0	0	0	0	0
Fatigue	65% (n=13)	55% (n=11)	15% (n=3)	25% (n=5)	15% (n=3)	20% (n=4)	5% (n=1)	0

[a]*Significant effect* ($p < 0.05$).

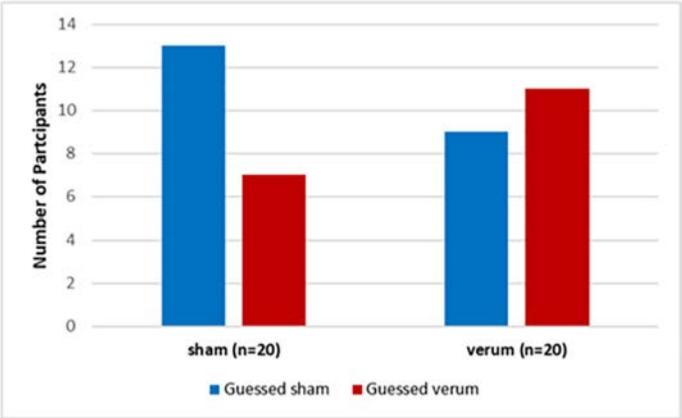


FIG. 9

Number of participants who correctly or incorrectly identified sham or anodal multichannel tDCS sessions. Order of stimulation was randomized and counterbalanced across participants.

participants were unable to accurately guess whether they received verum or sham stimulation in the first session [χ^2 (1,20) = 0.27, p = 1.00]. Tests were repeated for the second session and no significant differences in the ability to correctly judge stimulation conditions were found [χ^2 (1, N = 20) = 1.98, p = 0.35], thus reassuring the blindness of the procedure.

When considering the order in which the two stimulation conditions were administered, results of a Wilcoxon signed rank test revealed a significant difference on the rates of correct identification of stimulation condition between participants of the sequence "sham-verum" and "verum-sham" (Z = −1.99, p = 0.046). Participants in the order "sham-verum" had a higher average percentage of correct detection of stimulation condition than the group in order "verum-sham." Nevertheless, when evaluating this effect per session, only a significant difference was found on the rates of correct identification of stimulation condition between participants in the first session (session 1: Z = −2.24, p = 0.025; session 2: Z = −1.34, p = 0.18). In other words, there was an advantage at guessing the condition on the first session for "sham-verum" order, but no benefit in guessing the stimulation condition on the second session when sham was administered first, suggesting a random effect and not a carryover effect.

4 Discussion

New and effective treatment options that target the underlying mechanisms of ASD deficits are extremely important and have been widely investigated over the years, since no effective treatment for the core ASD symptoms of social cognition and communication impairments (American Psychiatric Association, 2013; Myers et al., 2007) has yet been established. Transcranial stimulation technologies have demonstrated potential in improving some of the core symptoms of conditions characterized by social-relating difficulties, such as ASD (Donaldson et al., 2018; Esse Wilson et al., 2018).

The present work was carried out in the first stage of the European research project STIPED, which is currently working toward the development of an optimized multichannel tDCS based treatment for neurodevelopmental disorders, such as ASD and ADHD. Our aim was to explore the feasibility of a multichannel stimulation protocol (designed to be used in multicenter clinical studies for children/adolescents with ASD) in an adult healthy population, by means of a randomized, single-blinded, sham-controlled, crossover study.

In this paper, we investigated modulatory effects of anodal and sham multichannel tDCS (coupled with a JAT) over bilateral TPJ on the performance of a facial expression recognition task, of a holistic face detection task and, on an exploratory level, of a joint attention paradigm (online/concurrent task).

We hypothesized that anodal stimulation leveraged by a concurrent social-cognitive task would increase the accuracy and reaction time for ERT and MFDT tasks compared to sham stimulation. However, the results of the two-way repeated measures ANOVA (Figs. 6 and 7) revealed no significant differences in accuracy and reaction time scores between stimulation conditions, as well as no significant time $\times$ stimulation interactions for both social cognition tasks. Furthermore, no stimulation effects were also detected for JAT performance metrics (Fig. 8), suggesting that behavioral measures were not modulated by multichannel tDCS.

In contrast to recent findings by Donaldson et al. (2019), Santiesteban et al. (2015) and Yang et al. (2020), we were unable to detect any significant effects of anodal stimulation in our tasks. Santiesteban et al. (2015) found that anodal tDCS of either right TPJ or left TPJ reduced the imitation effect in an imitation inhibition task (faster responses for incongruent trials) and improved performance (accuracy) in a visual perspective-taking task. Still, no effect was observed on the performance of a theory of mind task. In the study by Donaldson et al. (2019), anodal right TPJ HD-tDCS improved the performance (accuracy and reaction time) of a fear surprise task for static images of faces showing fear, but no effect was observed for static images showing surprise. More recently, Yang et al. (2020) observed that anodal tDCS over left and right TPJ increased imitation cost (measure of response times) in an imitation inhibition task (offline task) but failed to modulate behavioral measures of a visual perspective-taking (online task). In fact, our findings are mainly consistent with the results obtained by Mai et al. (2016), where no effect of anodal right TPJ tDCS was observed on the performance (accuracy and reaction time) of a theory of mind and cognitive empathy tasks. Mai's study found that the accuracy of both tasks decreased after receiving cathodal stimulation.

Due to the lack of other comparable research available, our preliminary results should be interpreted with caution. There are some potential reasons for the inexistence of a multichannel tDCS social cognition enhancement effect. The stimulation protocol itself could be one of them. In this study, we applied multichannel anodal tDCS both on the right and left TPJ using a 3 × 1 montage [active electrodes placed over CP5 (left) and CP6 (right)]. In contrast, most of the previous studies used bipolar montages, only the study by Donaldson et al. (2019) applied HD-tDCS on the right TPJ (2 mA for 20 min) using a 4 × 1 montage (active electrode placed over P6). There is a variety of different technical parameters (e.g., current intensity, density, duration, charge, laterality, montage, target region) that may influence the efficacy of stimulation. In this study, anterior and posterior regions of left and right TPJ were the target areas but considering that TPJ is a very large cortical region, stimulation may not yet be sufficiently focal and/or may cause effects that cancel each other in the different TPJ subregions. Another important aspect that could contribute to the inexistence of significant effects is the type of population and the individuals themselves. As the study was performed in healthy adults with no social deficits, their margin for progression in pre/post tasks is limited, since they already start from a high baseline. The mean rate of baseline accuracy for each type of stimulus of the MFDT and ERT are close to or above 90%, except for the ERT ambiguous expressions where detection was too difficult (mean accuracy rate of 37%). On the other hand, for a clinical ASD group, where social impairments are more significant, a lower baseline performance and a greater margin of progression is to be expected, so in this case it would be possible to better evaluate the stimulation effects. Besides that, and based on the recent study of Yang et al. (2020), not all individuals may benefit from stimulation effects. Yang et al. (2020) studied the neural and psychological predictors of cognitive enhancement/impairment from TPJ stimulation and found that participants could be classified into positive responders showing cognitive enhancement and negative responders showing cognitive impairment due to stimulation. In our study, we performed a group level analysis, but future work with larger sample sizes can potentially help individual-level effects into responder versus no-responder categories. A related factor that may also account for these results is the population age. Several studies have been demonstrating age-related changes in brain connectivity and age-related differences in terms of responsiveness to tDCS (Martin et al., 2017), so it could be possible that the effects of multichannel tDCS on social cognition may be more pronounced in pediatric populations than in adult or older adult populations. The last aspect that should also be mentioned is the single-session design. In this work, we explore cognitive effects resulting from a single multichannel tDCS session. The literature has been demonstrating that the effects of tDCS on cognitive measures are less robust and predictable compared with the more consistent effects on motor outcomes (Berryhill, 2014; Jacobson et al., 2012). However, longitudinal (repeated-sessions) designs have been showing more consistent benefits in healthy and clinical populations than a single-session design (Berryhill and Martin, 2018; Horvath et al., 2015).

Despite the lack of significant findings on task performance between stimulation conditions, we found a significant main effect of time on reaction time for the ERT and MFDT. Participants reacted significantly faster to images after stimulation than before stimulation, suggesting that learning and fatigue effects may influence the outcome. Based on Figs. 6 and 7, and on the scatter plots of reaction-time/accuracy (Figs. S3 and S4 in Supplementary Material in the online version at https://doi.org/10.1016/bs.pbr.2021.04.004) for each task, it is possible to observe a speed-accuracy tradeoff for the ERT (higher accuracy is achieved by slowing down the responses) for both stimulation sessions; however, for the MFDT increased impulsivity associated with inefficient deployment of attention or fatigue effect seems to occur in the verum session (participants respond faster, increasing the error) and a learning effect appears to occur in the sham session (participants respond faster without increasing the error). Fig. 7 also suggests an interaction between time and stimulation (crossed lines), in particular for accuracy, that deserves further exploration. This interaction did not reach significance and presents a small effect size ($\eta_p^2 = 0.01$), but we cannot exclude the possibility of both effects. Although fatigue, learning and repetition effects are expected for within-subjects tDCS designs, they could conceal potential stimulation effects that need in any case further investigation. We also detected carryover effects for the MFDT and the JAT, showing a subtle indication of some verum effect and suggesting that the washout period of 1 week was insufficient. As such, in future work it should be important to increase sample size as well as the washout period to detect direct multichannel tDCS effects. Besides the previous time and order effects, we also detected a baseline difference between sham and verum stimulation for neutral faces accuracy on ERT (Fig. 6G). Although the existence of ambiguous stimuli may be an amplification factor (most of the participants detect ambiguous stimuli as neutral), we consider that the main cause for this difference was chance since the effect does not occur in post-stimulation.

In this work, we have also evaluated the safety and tolerability of multichannel anodal tDCS over bilateral TPJ, as well as the success of the blinding procedure. No serious adverse events were observed; and itching and fatigue were the most reported side effects in those receiving verum (70% and 45%, respectively) and sham stimulation (35% for both sensations). Most of the side effects were rated as mild regardless of stimulation condition, and participants did not distinguish verum from sham at a rate better than chance, even when we considered stimulation order effects. In the first session, participants in the order “sham-verum” had a higher average percentage of correct detection of stimulation condition than the group in order “verum-sham”; however, since there was no advantage in guessing the stimulation condition on the second session when sham was administered first, this was also considered to happen by chance. Although the current study had a single-blind design with inherent risk of bias from the observer, the results of blinding procedure indicate that the fixed script was a good method to minimize/avoid influence of expectations. In general, multichannel tDCS was well-tolerated, safe, and had adequate blinding in young healthy adults, showing good prospects for its application in children/adolescents.

The present study opened new questions that should be addressed in follow-up research studies. Technically, this work investigated, for the first time, the use of multichannel anodal tDCS over bilateral TPJ to estimate the effects of low-level social cognition in healthy young adults. Nevertheless, since a very conservative analysis with tasks only requiring early level processing was performed, the understanding of potential effects may be limited. Additional work should now be pursued to explore the clinical efficacy of this technique in children/adolescents with ASD over longer treatment periods.

Author contributions

HCP, DS, MS, CA and MCB conceived and designed the study. MS, RM and CA developed the experimental paradigms. HCP, DS, VL and JC carried out the experiments with the participants. HCP and DS analyzed the data. HCP and MCB wrote the paper. All authors read, contributed, and approved the final manuscript.

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References

American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders, fifth ed. American Psychiatric Association. American Journal of Psychiatry https://doi.org/10.1176/appi.books.9780890425596.744053.

Adolphs, R., 2009. The social brain: neural basis of social knowledge. Annu. Rev. Psychol. 60, 693–716. https://doi.org/10.1146/annurev.psych.60.110707.163514.

Andrade, A.C., Magnavita, G.M., Allegro, J.V.B.N., Neto, C.E.B.P., Lucena, R.D.C.S., Fregni, F., 2014. Feasibility of transcranial direct current stimulation use in children aged 5 to 12 years. J. Child Neurol. 29, 1360–1365. https://doi.org/10.1177/0883073813503710.

Bakeman, R., Adamson, L.B., 1984. Coordinating attention to people and objects in mother-infant and peer-infant interaction. Child Dev. 55, 1278–1289. https://doi.org/10.2307/1129997.

Berryhill, M.E., 2014. Hits and misses: leveraging tDCS to advance cognitive research. Front. Psychol. 5, 800. https://doi.org/10.3389/fpsyg.2014.00800.

Berryhill, M.E., Martin, D., 2018. Cognitive effects of transcranial direct current stimulation in healthy and clinical populations: an overview. J. ECT 34, e25–e35. https://doi.org/10.1097/YCT.0000000000000534.

Bikson, M., Rahman, A., 2013. Origins of specificity during tDCS: anatomical, activity-selective, and input-bias mechanisms. Front. Hum. Neurosci. 7, 688. https://doi.org/10.3389/fnhum.2013.00688.

Binder, J.R., Desai, R.H., Graves, W.W., Conant, L.L., 2009. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. Cereb. Cortex 19, 2767–2796. https://doi.org/10.1093/cercor/bhp055.

Boggio, P.S., Ferrucci, R., Rigonatti, S.P., Covre, P., Nitsche, M., Pascual-Leone, A., Fregni, F., 2006. Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. J. Neurol. Sci. 249, 31–38. https://doi.org/10.1016/j.jns.2006.05.062.

Brainard, D.H., 1997. The psychophysics toolbox. Spat. Vis. 10, 433–436. https://doi.org/10.1163/156856897X00357.

Brunoni, A.R., Amadera, J., Berbel, B., Volz, M.S., Rizzerio, B.G., Fregni, F., 2011. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. Int. J. Neuropsychopharmacol. 14, 1133–1145. https://doi.org/10.1017/S1461145710001690.

Brunoni, A.R., Nitsche, M.A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., Edwards, D.J., Valero-Cabre, A., Rotenberg, A., Pascual-Leone, A., Ferrucci, R., Priori, A., Boggio, P.S., Fregni, F., 2012. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain Stimul. 5, 175–195. https://doi.org/10.1016/j.brs.2011.03.002.

Brunoni, A.R.A.R., Valiengo, L., Baccaro, A., Zanão, T.A., de Oliveira, J.F., Goulart, A., Boggio, P.S., Lotufo, P.A., Benseñor, I.M., Fregni, F., Zanao, T.A., de Oliveira, J.F., Goulart, A., Boggio, P.S., Lotufo, P.A., Bensenor, I.M., Fregni, F., Zanão, T.A., de Oliveira, J.F., Goulart, A., Boggio, P.S., Lotufo, P.A., Benseñor, I.M., Fregni, F., 2013. The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. JAMA Psychiat. 70, 383–391. https://doi.org/10.1001/2013.jamapsychiatry.32.

Castelhano, J., Rebola, J., Leitao, B., Rodriguez, E., Castelo-Branco, M., 2013. To perceive or not perceive: the role of gamma-band activity in signaling object percepts. PLoS One 8, e66363. https://doi.org/10.1371/journal.pone.0066363.

Castelhano, J., Tavares, P., Mouga, S., Oliveira, G., Castelo-Branco, M., 2018. Stimulus dependent neural oscillatory patterns show reliable statistical identification of autism spectrum disorder in a face perceptual decision task. Clin. Neurophysiol. 129, 981–989. https://doi.org/10.1016/j.clinph.2018.01.072.

Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev. Neurosci. 3, 201–215. https://doi.org/10.1038/nrn755.

Datta, A., Bansal, V., Diaz, J., Patel, J., Reato, D., Bikson, M., 2009. Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. Brain Stimul. 2, 201–207.e1.

Dedoncker, J., Brunoni, A.R., Baeken, C., Vanderhasselt, M.A., 2016. A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex in healthy and neuropsychiatric samples: influence of stimulation parameters. Brain Stimul. 9, 501–517. https://doi.org/10.1016/j.brs.2016.04.006.

Donaldson, P.H., Kirkovski, M., Rinehart, N.J., Enticott, P.G., 2018. Autism-relevant traits interact with temporoparietal junction stimulation effects on social cognition: a high-definition transcranial direct current stimulation and electroencephalography study. Eur. J. Neurosci. 47, 669–681. https://doi.org/10.1111/ejn.13675.

Donaldson, P.H., Kirkovski, M., Rinehart, N.J., Enticott, P.G., 2019. A double-blind HD-tDCS/EEG study examining right temporoparietal junction involvement in facial emotion processing. Soc. Neurosci. 14, 681–696. https://doi.org/10.1080/17470919.2019.1572648.

Donaldson, P.H., Rinehart, N.J., Enticott, P.G., 2015. Noninvasive stimulation of the temporoparietal junction: A systematic review. Neurosci. Biobehav. Rev. 55, 547–572. https://doi.org/10.1016/j.neubiorev.2015.05.017.

Dunbar, R.I.M., 2012. The social brain meets neuroimaging. Trends Cogn. Sci. 16, 101–102. https://doi.org/10.1016/j.tics.2011.11.013.

Esse Wilson, J., Quinn, D.K., Wilson, J.K., Garcia, C.M., Tesche, C.D., 2018. Transcranial direct current stimulation to the right temporoparietal junction for social functioning in autism spectrum disorder: a case report. J. ECT 34, e10–e13. https://doi.org/10.1097/YCT.0000000000000445.

Frith, U., Frith, C.D., 2003. Development and neurophysiology of mentalizing. Philos. Trans. R. Soc. B Biol. Sci. 358, 459–473. https://doi.org/10.1098/rstb.2002.1218.

Garnett, E.O., Malyutina, S., Datta, A., Den Ouden, D.B., 2015. On the use of the terms anodal and cathodal in high-definition transcranial direct current stimulation: a technical note. Neuromodulation 18, 705–713. https://doi.org/10.1111/ner.12320.

Geng, J.J., Vossel, S., 2013. Re-evaluating the role of TPJ in attentional control: contextual updating? Neurosci. Biobehav. Rev. 37, 2608–2620. https://doi.org/10.1016/j.neubiorev.2013.08.010.

Horvath, J.C., Forte, J.D., Carter, O., 2015. Quantitative review finds no evidence of cognitive effects in healthy populations from single-session transcranial direct current stimulation (tDCS). Brain Stimul. 8, 535–550. https://doi.org/10.1016/j.brs.2015.01.400.

Jacobson, L., Koslowsky, M., Lavidor, M., 2012. TDCS polarity effects in motor and cognitive domains: a meta-analytical review. Exp. Brain Res. 216, 1–10. https://doi.org/10.1007/s00221-011-2891-9.

Kekic, M., Boysen, E., Campbell, I.C., Schmidt, U., 2016. A systematic review of the clinical efficacy of transcranial direct current stimulation (tDCS) in psychiatric disorders. J. Psychiatr. Res. 74, 70–86. https://doi.org/10.1016/j.jpsychires.2015.12.018.

Korkmaz, B., 2011. Theory of mind and neurodevelopmental disorders of childhood. Pediatr. Res. 69, 101R–108R. https://doi.org/10.1203/PDR.0b013e318212c177.

Krishnan, C., Santos, L., Peterson, M.D., Ehinger, M., 2015. Safety of noninvasive brain stimulation in children and adolescents. Brain Stimul. 8, 76–87. https://doi.org/10.1016/j.brs.2014.10.012.

Kronberg, G., Rahman, A., Sharma, M., Bikson, M., Parra, L.C., 2020. Direct current stimulation boosts hebbian plasticity in vitro. Brain Stimul. 13, 287–301. https://doi.org/10.1016/j.brs.2019.10.014.

Kuo, M.F., Paulus, W., Nitsche, M.A., 2014. Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. Neuroimage 85, 948–960. https://doi.org/10.1016/j.neuroimage.2013.05.117.

Mai, X., Zhang, W., Hu, X., Zhen, Z., Xu, Z., Zhang, J., Liu, C., 2016. Using tDCS to explore the role of the right temporo-parietal junction in theory of mind and cognitive empathy. Front. Psychol. 7, 380. https://doi.org/10.3389/fpsyg.2016.00380.

Mars, R.B., Sallet, J., Schüffelgen, U., Jbabdi, S., Toni, I., Rushworth, M.F.S., 2012. Connectivity-based subdivisions of the human right "temporoparietal junction area": evidence for different areas participating in different cortical networks. Cereb. Cortex 22, 1894–1903. https://doi.org/10.1093/cercor/bhr268.

Martin, A.K., Meinzer, M., Lindenberg, R., Sieg, M.M., Nachtigall, L., Flöel, A., 2017. Effects of transcranial direct current stimulation on neural networks in young and older adults. J. Cogn. Neurosci. 29, 1817–1828. https://doi.org/10.1162/jocn_a_01166.

Moliadze, V., Andreas, S., Lyzhko, E., Schmanke, T., Gurashvili, T., Freitag, C.M., Siniatchkin, M., 2015. Ten minutes of 1mA transcranial direct current stimulation was well tolerated by children and adolescents: self-reports and resting state EEG analysis. Brain Res. Bull. 119, 25–33. https://doi.org/10.1016/j.brainresbull.2015.09.011.

Mooney, C.M., 1957. Age in the development of closure ability in children. Can. J. Psychol. 11, 219–226. https://doi.org/10.1037/h0083717.

Myers, S.M., Johnson, C.P., Lipkin, P.H., Cartwright, J.D., Desch, L.W., Duby, J.C., Elias, E.R., Levey, E.B., Liptak, G.S., Murphy, N.A., Tilton, A.H., Lollar, D., Macias, M., McPherson, M., Olson, D.G., Strickland, B., Skipper, S.M., Ackermann, J., Del Monte, M., Challman, T.D., Hyman, S.L., Levy, S.E., Spooner, S.A., Yeargin-Allsopp, M., 2007. Management of children with autism spectrum disorders. Pediatrics 120, 1162–1182. https://doi.org/10.1542/peds.2007-2362.

Nitsche, M.A., Paulus, W., 2000. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J. Physiol. 527 (Pt. 3), 633–639.

Nitsche, M.A., Paulus, W., 2011. Transcranial direct current stimulation—update 2011. Restor. Neurol. Neurosci. 29, 463–492. https://doi.org/10.3233/RNN-2011-0618. 252R 1135VU705H53 [pii].

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113. https://doi.org/10.1016/0028-3932(71)90067-4.

Poreisz, C., Boros, K., Antal, A., Paulus, W., 2007. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. Brain Res. Bull. 72, 208–214. https://doi.org/10.1016/j.brainresbull.2007.01.004. https://doi.org/S0361-9230(07)00011-1 [pii].

Santiesteban, I., Banissy, M.J., Catmur, C., Bird, G., 2012. Enhancing social ability by stimulating right temporoparietal junction. Curr. Biol. 22, 2274–2277. https://doi.org/10.1016/j.cub.2012.10.018.

Santiesteban, I., Banissy, M.J., Catmur, C., Bird, G., 2015. Functional lateralization of temporoparietal junction—imitation inhibition, visual perspective-taking and theory of mind. Eur. J. Neurosci. 42, 2527–2533. https://doi.org/10.1111/ejn.13036.

Schurz, M., Radua, J., Aichhorn, M., Richlan, F., Perner, J., 2014. Fractionating theory of mind: A meta-analysis of functional brain imaging studies. Neurosci. Biobehav. Rev. 42, 9–34. https://doi.org/10.1016/j.neubiorev.2014.01.009.

Sellaro, R., Güroğlu, B., Nitsche, M.A., van den Wildenberg, W.P.M., Massaro, V., Durieux, J., Hommel, B., Colzato, L.S., 2015. Increasing the role of belief information in moral judgments by stimulating the right temporoparietal junction. Neuropsychologia 77, 400–408. https://doi.org/10.1016/j.neuropsychologia.2015.09.016.

Simões, M., Monteiro, R., Andrade, J., Mouga, S., França, F., Oliveira, G., Carvalho, P., Castelo-Branco, M., 2018. A novel biomarker of compensatory recruitment of face emotional imagery networks in autism spectrum disorder. Front. Neurosci. 12, 791. https://doi.org/10.3389/fnins.2018.00791.

Stagg, C.J., Nitsche, M.A., 2011. Physiological basis of transcranial direct current stimulation. Neuroscientist 17, 37–53. https://doi.org/10.1177/1073858410386614.

STIPED Consortium, 2017. STIPED (Stimulation in Pediatrics)—H2020 Research Project [WWW Document]. URL https://www.stiped.eu/home/.
Tavares, P.P., Mouga, S.S., Oliveira, G.G., Castelo-Branco, M., 2016. Preserved face inversion effects in adults with autism spectrum disorder: an event-related potential study. Neuroreport 27, 587–592. https://doi.org/10.1097/WNR.0000000000000576.
Van Overwalle, F., 2009. Social cognition and the brain: a meta-analysis. Hum. Brain Mapp. 30, 829–858. https://doi.org/10.1002/hbm.20547.
van Veluw, S.J., Chance, S.A., 2014. Differentiating between self and others: an ALE meta-analysis of fMRI studies of self-recognition and theory of mind. Brain Imaging Behav. 8, 24–38. https://doi.org/10.1007/s11682-013-9266-8.
Venkataraman, A., Duncan, J.S., Yang, D.Y., Pelphrey, K.A., 2015. An unbiased Bayesian approach to functional connectomics implicates social-communication networks in autism. Neuroimage Clin. 8, 356–366. https://doi.org/10.1016/j.nicl.2015.04.021.
Woods, A.J., Antal, A., Bikson, M., Boggio, P.S., Brunoni, A.R., Celnik, P., Cohen, L.G., Fregni, F., Herrmann, C.S., Kappenman, E.S., Knotkova, H., Liebetanz, D., Miniussi, C., Miranda, P.C., Paulus, W., Priori, A., Reato, D., Stagg, C., Wenderoth, N., Nitsche, M.A., 2016. A technical guide to tDCS, and related non-invasive brain stimulation tools. Clin. Neurophysiol. 127, 1031–1048. https://doi.org/10.1016/j.clinph.2015.11.012.
Yang, L.Z., Zhang, W., Wang, W., Yang, Z., Wang, H., De Deng, Z., Li, C., Qiu, B., Zhang, D.R., Kadosh, R.C., Li, H., Zhang, X., 2020. Neural and psychological predictors of cognitive enhancement and impairment from Neurostimulation. Adv. Sci. 7, 1902863. https://doi.org/10.1002/advs.201902863.
Ye, H., Chen, S., Huang, D., Zheng, H., Jia, Y., Luo, J., 2015. Modulation of neural activity in the temporoparietal junction with transcranial direct current stimulation changes the role of beliefs in moral judgment. Front. Hum. Neurosci. 9, 659. https://doi.org/10.3389/fnhum.2015.00659.