Brain Stimulation 15 (2022) 414–425

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Neurophysiological and behavioral effects of multisession prefrontal tDCS and concurrent cognitive remediation training in patients with autism spectrum disorder (ASD): A double-blind, randomized controlled fNIRS study

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ARTICLE INFO

Article history:
Received 6 October 2021
Received in revised form
7 February 2022
Accepted 10 February 2022
Available online 15 February 2022

Keywords:
Autism
tDCS
Cognitive
Social
fNIRS
RCT

ABSTRACT

Background: The clinical effects and neurophysiological mechanisms of prefrontal tDCS and concurrent cognitive remediation training in individuals with autism spectrum disorder (ASD) remain unclear.
Objective: This two-armed, double-blind, randomized, sham-controlled trial aimed to investigate the beneficial effects of tDCS combined with concurrent cognitive remediation training on adolescents and young adults with ASD.
Methods: Participants were randomly assigned to either active or sham tDCS groups and received 1.5 mA prefrontal tDCS with left dorsolateral prefrontal cortex (dlPFC) cathode placement and right supraorbital region anode placement for 20 minutes over two consecutive weeks. tDCS was delivered concurrently with a computerized cognitive remediation training program. Social functioning and its underlying cognitive processes, as well as prefrontal resting-state functional connectivity (rsFC), were measured.
Results: The results from 41 participants indicated that multisession prefrontal tDCS, compared to sham tDCS, significantly enhanced the social functioning of ASD individuals [$F(1,39) = 4.75$, $p = .035$, $\eta_p^2 = 0.11$]. This improvement was associated with enhanced emotion recognition [$F(1,39) = 8.34$, $p = .006$, $\eta_p^2 = 0.18$] and cognitive flexibility [$F(1,39) = 4.91$, $p = .033$, $\eta_p^2 = 0.11$]. Specifically, this tDCS protocol optimized information processing efficiency [$F(1,39) = 4.43$, $p = .042$, $\eta_p^2 = 0.10$], and the optimization showed a trend to be associated with enhanced rsFC in the right medial prefrontal cortex ($\rho = 0.339$, pFDR = .083).
Conclusion: Multisession tDCS with left dlPFC cathode placement and right supraorbital region anode placement paired with concurrent cognitive remediation training promoted social functioning in individuals with ASD. This appeared to be associated with the enhancement of the functional connectivity of the right medial PFC, a major hub for flexible social information processing, allowing these individuals to process information more efficiently in response to different social situations.
Trial registration: ClinicalTrials.gov (ID: NCT03814083)

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https://doi.org/10.1016/j.brs.2022.02.004

1. Introduction

Autism spectrum disorder (ASD) is a pervasive neurodevelopmental disorder characterized by persistent deficits in social interaction as well as restricted, repetitive behaviors that play a major role in the social and occupational dysfunction of these individuals [1]. Approximately 45% of individuals with ASD who do not have intellectual disabilities [2] show marked impairment in essential skills for successful social interactions, including recognizing emotions [3,4] and attributing social meanings [5], despite having average verbal and performance skills [6]. Moreover, these individuals appear rigid and inflexible in daily situations; for instance, they exhibit strong preferences for rules and elaborated rituals [7]. Importantly, previous studies have shown that these social interaction deficits [6] and inflexible behaviors [8] might persist, and even deteriorate, as age increases. Thus, individuals with ASD may fall further behind their typically developing (TD) counterparts in social interactions as they grow older, creating considerable lifelong stresses for themselves, their families and the society.

Extensive research has shown that executive functioning (EF), a series of cognitive processes required for monitoring goal-directed behavior [9], is impaired in ASD [10]. Specifically, cognitive flexibility (CF), often defined as the capacity to adjust behaviors according to different environmental demands so that appropriate responses can be generated for goal attainment [11], has been shown to be key for “cold” EF (i.e., EF that involves purely cognitive processing [12]), and contributes to the behavioral manifestation of ASD individuals [13]. Daily examples of CF, such as updating one's beliefs when facing new information and shifting from one conversation to another [14], are impaired in these individuals. Furthermore, Ewing et al. [15] reported that children with ASD demonstrated reduced perceptual updating of faces, while Mo et al. [16] revealed that children with ASD have problems disengaging from and shifting between the social and nonsocial visual stimuli. More importantly, a number of studies have demonstrated that CF deficits are associated with impaired social interaction skills such as emotion recognition, which is regarded as “hot” EF (i.e., EF that involves affective processing [12]). For example, using a variant of the Wisconsin Card Sorting Test (WCST), Fabio et al. [17] showed that the performance of children with ASD decreased after the card sorting rule had changed, and this impaired performance was positively correlated with impaired emotion recognition abilities. Moreover, Strang et al. [18] showed that slower performance on the Trail Making Test (which involves rule switching) significantly correlated with more inflexible behaviors in daily life. In addition, using the Cambridge Neuropsychological Test Automated Battery (CANTAB) multitasking test (MTT), Krishnamurthy et al. [19] demonstrated that children with ASD produced more errors than TD controls after the rule changed. Taken together, these studies support the notion that both cold and hot EF are impaired in ASD, and these impairments are mediated by individuals' speed of processing during task performance.

Although the exact neurophysiological mechanism by which ASD influences EF and overall social functioning remains unclear, a prominent theory postulates that an excitation-inhibition (E:I) imbalance in local neural networks that support cognitive and affective processes impedes global brain signaling; thus, individuals with ASD may experience difficulties in modulating flexible and goal-directed behaviors [20–22]. Converging evidence from multiple neurophysiological and neuroimaging studies has shown that an E:I imbalance is evident in different regions of the prefrontal cortex (PFC) in ASD. Notably, a magnetic resonance spectroscopy (MRS) study reported that ASD individuals had a higher E:I ratio due to a higher glutamate concentration in the left frontal cortex but not the right frontal cortex [23]. Moreover, neurophysiological studies have shown that the heightened E:I ratio in ASD is specifically found in the left dorsolateral prefrontal cortex (dlPFC) during “cold” EF tasks [24] and that this heightened E:I ratio is modifiable by repeated inhibitory (low-frequency) transcranial magnetic stimulation [25,26]. Another resting-state neuroimaging study showed that a higher E:I ratio was also evident in the ventromedial PFC (vmPFC) in ASD [27]; a higher E:I ratio in this region has been associated with decreased inhibitory neurotransmitter gamma-aminobutyric acid (GABA) functioning [28] and impaired synaptic information processing and social behavior in rodent ASD models [29]. The local E:I ratio has recently been shown to play a major role in the organization of resting-state functional connectivity (rsFC [30]). Specifically, Gu et al. [31] have shown that a higher regional E:I ratio is associated with lower functional connectivity within the default mode network (DMN), a network with medial PFC as a core hub [32,33], which supports CF [14] and social-cognitive functions [34]. Structural and functional alterations in individuals with ASD were found to be associated with social-cognitive dysfunctions in these individuals [21].

Given the above premises, treatments that can reduce E:I ratios over the left dlPFC and vmPFC may be promising methods to promote EF, including CF and social communication, and reduce inflexible behaviors in individuals with ASD. Transcranial direct current stimulation (tDCS), a noninvasive neuromodulation method that influences cortical excitability [35] by promoting subthreshold changes in the resting membrane potentials of the targeted neuronal population [36], is one such approach. Previous MRS studies have reported that tDCS anodal stimulation increases cortical excitability by reducing local concentrations of GABA, whereas tDCS cathodal stimulation decreases cortical excitability by reducing local excitatory glutamate levels [37,38]. Given that the higher E:I ratio in the left dlPFC and right vmPFC in ASD are possibly due to higher glutamate and lower GABA concentrations, respectively, it is reasonable to assume that placement of the cathode over the left dlPFC (to reduce the glutamate concentration) and placement of the anode over the right vmPFC (to enhance the GABA concentration) might be more beneficial for treating ASD than other tDCS methods. Indeed, previous studies have provided preliminary evidence that tDCS with the cathode placed over the left dlPFC and the anode placed over the right supraorbital region, encompassing the right vmPFC and orbitofrontal cortex (OFC), reduces irritability, social withdrawal and hyperactivity [39], and improves processing speed and CF [40] in adults with ASD. However, given the limitations in sample size and design of these studies, the clinical, neuropsychological and neurophysiological effects of left dlPFC cathode placement and right supraorbital region anode placement in individuals with ASD remain largely elusive. In addition, given that tDCS enhances the clinical effects of behavioral treatments [41] and exhibits task-dependent effects on EF performance [42], and that multiple studies have shown that computerized cognitive remediation training focusing on “cold” EF yields clinically and cognitively beneficial effects in ASD, it might be possible that tDCS could augment conventional EF training for ASD, although this combination has not been studied in the ASD population [43]. Hence, this study aimed to investigate the beneficial effects of a montage of prefrontal tDCS (with left dlPFC cathode placement and right supraorbital region anode placement) delivered concurrently with computerized cognitive remediation training on individuals with ASD by conducting a double-blind, randomized, sham-controlled trial. We hypothesized that tDCS with left dlPFC cathode placement and right supraorbital region anode placement would enhance EF, including CF and emotional recognition, and promote rsFC in the medial PFC, a core hub of the DMN that has been shown to be affected by heightened E:I ratios in individuals with ASD.

2. Methods

2.1. Trial design and participants

This was a 2-armed, parallel randomized controlled trial (RCT) conducted in accordance with the guidelines of the Declaration of Helsinki. The main trial was registered in the ClinicalTrials.gov Protocol Registration and Results System (ID: NCT03814083), and the study was approved by the Human Subjects Ethics Subcommittee of The Hong Kong Polytechnic University (HSEARS20171230001) and The Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (CREC number: 2019.292). To be eligible for the study, individuals had to be 14–21 years old, be diagnosed with ASD by a psychiatrist (according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) prior to the study, and had an intelligence quotient (IQ) $\geq$ 60 measured by the Wechsler Intelligence Scale (4th edition; adult/child versions) conducted by a clinical/educational psychologist. The ASD diagnosis was confirmed by the Autism Diagnostic Interview – Revised (ADI-R [44]) conducted by a child psychiatrist (C.S.) who was blind to the study hypothesis. Individuals with other comorbid neuropsychiatric conditions (i.e., schizophrenia spectrum disorders and mood disorders) or neurological disorders (i.e., head trauma and epilepsy) were excluded. For more information on participants' inclusion criteria, see the *Supplementary Methods*. Assessments and treatments were performed at The Hong Kong Polytechnic University.

2.2. Randomization and blinding

Eligible participants were randomly assigned into either the intervention or control group in a 1:1 ratio by using a computer random number generator. To achieve blinding of participants, sham tDCS was performed to mimic the sensation induced by real tDCS. To blind research personnel to both patient treatment and assessment, the individual responsible for tDCS machine operation and group allocation (K.K.) did not participate in any patient contact or data analysis processes.

2.3. tDCS and computerized cognitive remediation training program

Transcranial direct current was delivered using the Starstim tDCS Device (Neuroelectrics Instrument Controller, v 1.0) through a pair of saline-soaked (NaCl 0.9% solution) circular sponge electrodes (25 cm^2) that were fastened to the scalp with a nonconductive cap. The active tDCS group received a dose of 1.5 mA tDCS five days per week for two weeks. Fig. 1 shows the electrode placement, voltage and electric field distribution of the tDCS protocol used in this study. Each session of stimulation lasted for 20 min, with 30 s of ramp-up and ramp-down before and after the 20-min stimulation, respectively. During tDCS, participants engaged in concurrent app-based cognitive remediation training (Lumosity; Lumos Labs, San Francisco, CA). The online cognitive

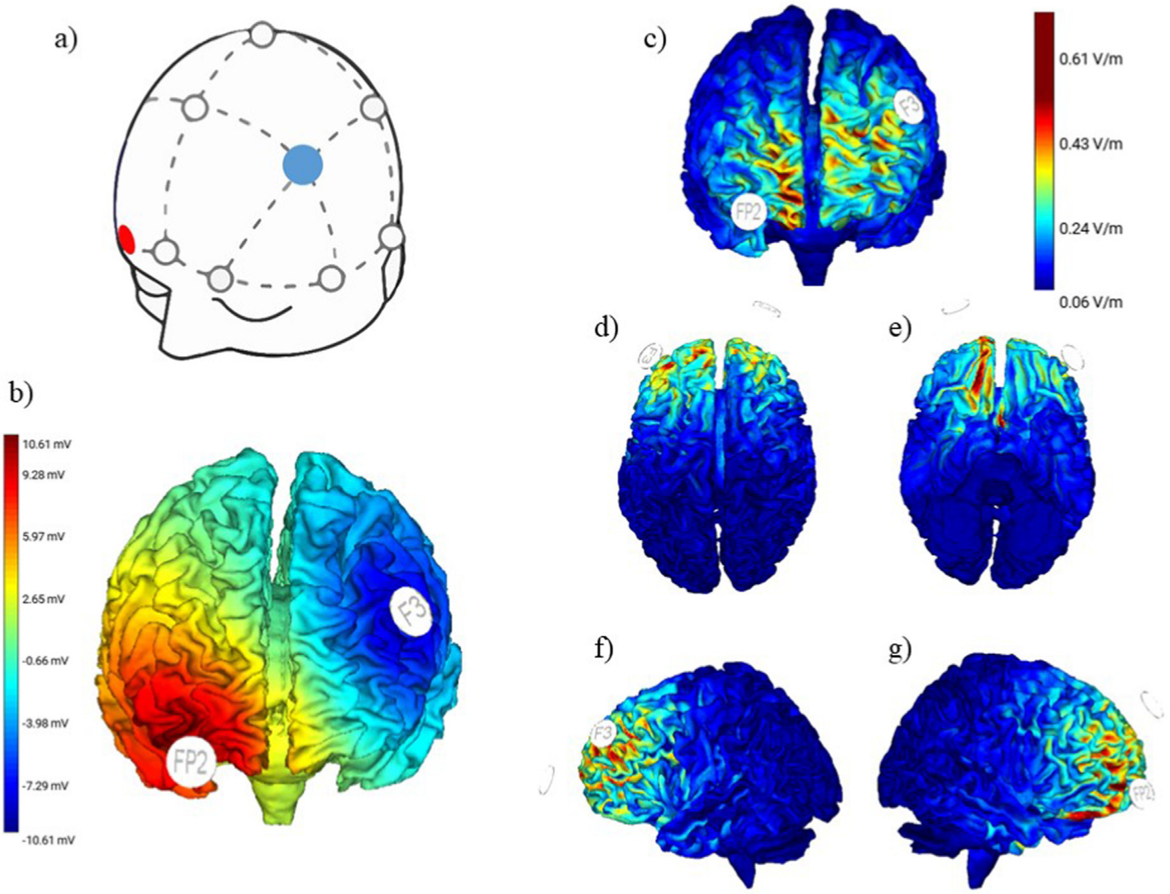

Fig. 1. Electrode placement, voltage and electric field distribution of the tDCS protocol used in this study. (a) A circular cathode electrode (25 cm^2) was placed at the F3 region of the 10–20 electroencephalogram (EEG) system, which corresponds to the left dlPFC. A circular return electrode (25 cm^2) was placed at the Fp2 region of the 10–20 EEG system, which corresponds to the right orbitofrontal area. (b) Voltage generated by 1.5 mA, left dlPFC (cathode) – right supraorbital region (anode) montage. (c–g) Electric field distribution [(c) front view; (d) top view; (e) bottom view; (f) left view; (g) right view] generated by left dlPFC (cathode) – right supraorbital region (anode) montage.

Table 1
Detailed descriptions of games incorporated in the cognitive remediation training program.

Name of the game	Descriptions	Targeted Cognitive Domain
Color Match	Color words are shown on two cards. Participants have to decide whether the text color of the bottom card matches the meaning of text of the top card. This game assembles stroop task.	Interference control
Lost in Migration	Five bird-shaped arrow heads appear on the screen. The peripheral arrow heads may appear in the same or different directions as the centre arrow head. Participants are asked to avoid distractions and swipe to the direction of the centre arrow head. This game assembles flanker task.	Interference control
Train of Thought	The object of the game is to direct an increasing number of trains to their stations changing the tracks to get the coloured train to the station with the same colour. The game is organized into 14 levels and trains of different colors may appear simultaneously on the screen, so thatparticipants have to plan ahead and divide their attention efficiently to maximize accuracy.	Planning
Trouble Brewing	Participants are asked to brew cups of coffee with various sizes according to the given orders. They have to brew multiple cups of coffee simultaneously and to avoid overflow of the coffee. Failing to do so will lead to punishments (participants are given additional order to complete). The aim of the game is to maximize the number of orders and complete the order within a limited time.	Planning
Ebb and Flow	Serval leaves are flowing on the water. When orange leaves are shown, participants have to swipe to the direction where the leaves are moving. When green leaves are shown, participants have to swipe to the direction where the tips of the leaves are pointing.	Set shifting
Brain Shift	Two cards (one at the top, another at the bottom of the screen) with each card showing an alphabet-number pair are shown. For the top card, participants are asked to focus on looking at the numbers only and decide whether it is an even number. For the bottom card, participants are asked to focus on the alphabet only and decide whether it is a vowel.	Set shifting
Highway Hazards	Participants are asked to maneuver a race car (left-right) to prevent it from colliding with the obstacles on a car-racing track. The less obstacles they hit, the faster they can drive.	Visual information processing
Speed Match	Participants are asked to decide whether the present symbol presented on the screen matches the previous symbol presented. This game assembles 1-back task.	Visual information processing
Memory Matrix	Participants are asked to memorize the location of blue tiles presented within a grid in 2 s. The blue tiles then disappear, and participants are asked to indicate the location of tiles in the grid.	Working memory capacity
Pinball Recall	Participants are asked to memorize, in 2 s, the locations of several bumpers presented within a grid. These bumpers change the direction of a ball that moves either horizontally or vertically in the given grid.After the bumpers disappear, participants are asked to predict the ending position of the ball with its starting position given.	Working memory capacity and manipulation

training program comprised 10 games targeting “cold” EF domains, including interference control, planning, set shifting and working memory. Each game lasted for approximately 2 min. Table 1 provides detailed descriptions of the games included and the cognitive domains targeted in the training package for our study. Individuals undergoing sham tDCS received the same cognitive remediation training and underwent the same tDCS protocol except for the 20-min stimulation. Given that cortical excitability and neuronal plasticity, which are associated with cognitive performance, have been shown to be significantly affected by the circadian rhythms of individuals [45], the time of the day for all treatment sessions was fixed for each participant to minimize the confounding effect of time. After each treatment session, participants were asked to complete a questionnaire adopted from Poreisz et al. [46], which contained rating scales that charted the presence and severity of uncomfortable sensations (e.g., pain, tingling, burning and itching) over the scalp where the electrodes were placed, as well as headaches and changes in arousal, mood or visual perception.

2.4. Outcome measures

To measure the change in overall social functioning and inflexible behaviors before and after treatment, the Social Responsiveness Scale – 2nd Edition (SRS-2 [47]) was used as the primary outcome measure. The SRS-2 is a parent-report, norm-referenced measure developed to measure social functioning in both clinical and nonclinical populations, including individuals with ASD [48]. It is a highly reliable and sensitive measure given its strong correlations with the DSM criterion scores and has been utilized in multiple RCTs involving individuals with ASD [49,50]. While the total SRS-2 score reflects overall social functioning, the social communication index (SCI) subscore reveals the participants' interpersonal communication performance, and the restricted repetitive behavior (RRB) domain score specifically reflects the participant's inflexible behaviors. Higher SRS-2 total score, SCI and RRB subscores indicate greater social dysfunction, greater social communication deficits, and more severe inflexible behaviors, respectively.

Secondary outcomes included changes in “cold” and “hot” EF performance, as well as changes in information processing efficiency (IPE), which were measured with the CANTAB Emotion Recognition Task (ERT), (Children's) Color Trail Test – part 2 (CTT2), CANTAB MTT and WCST. The total accuracy rate of each participant was recorded in the CANTAB ERT, with a higher score indicating better basic emotion recognition (“hot” EF). Cognitive flexibility (CF; “cold” EF) and information processing performances were represented by composite scores (see the *Supplementary Methods* for detailed calculations of the composite scores). Improved CF and information processing performance were indicated by higher CF and IPE composite scores, respectively.

2.5. rsFC measurement

Given that the existing literature (reviewed above) has suggested that the medial PFC is the core hub for flexible social-cognitive behaviors and that a heightened E:I ratio was identified in the medial PFC, we focused our rsFC investigation on the PFC, using a 52-channel fNIRS optical topography system (ETG-4000; Hitachi Medical Co., Tokyo, Japan). The arrangements of channels, near-infrared emitters and detectors, as well as the channel groupings, are illustrated in Fig. 2. The channels were grouped to represent the medial and lateral PFC in the left and right hemispheres to increase the signal-to-noise ratio [51]. A resting fNIRS measurement was collected in the eyes-open condition for 5 min, with the participants asked to focus on an image (i.e., a house) displayed on a computer screen [52].

2.6. Data analysis

The documented common side effects possibly resulted from tDCS stimulation were analyzed with chi-square test, or likelihood

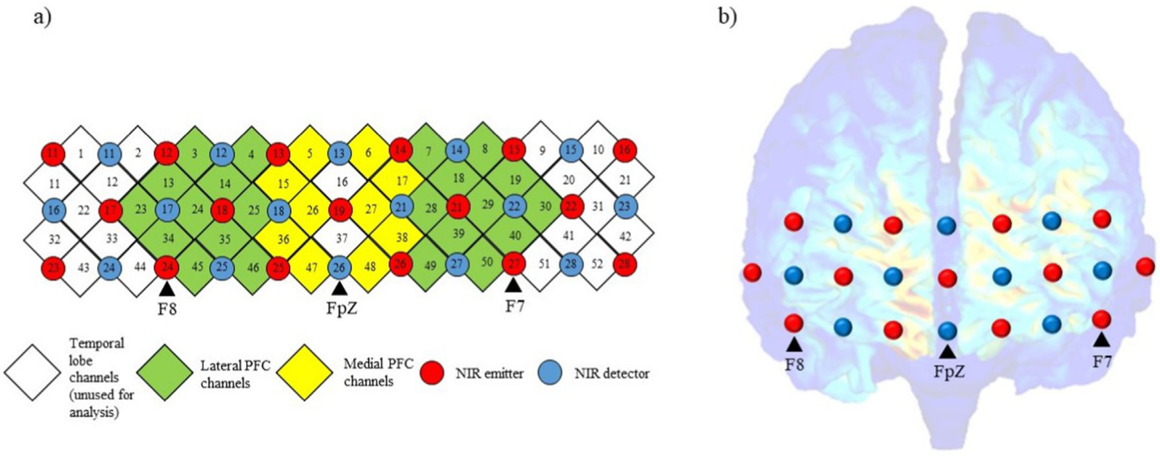

Fig. 2. Diagrams showing the NIRS probe set for rsFC measurement in this study. (a) The arrangements of near-infrared (NIR) channels, emitters and detectors, as well as the channel groupings. (b) NIR emitters and detectors for the prefrontal ROIs on a brain template. The brain template shows the electric field distribution induced by tDCS with left dlPFC (cathode) – right supraorbital region (anode) montage.

ratio test when assumptions of chi-square test were violated. To examine the effects of tDCS on social functioning in individuals with ASD, we analyzed the SRS-2 total score, SCI and RRB subscores. To examine the effect of tDCS on emotion recognition, we compared CF and information processing, the total hit rate from CANTAB ERT and the CF and IPE composites of individuals in the two groups. All of the above group comparisons were assessed using 2x2 repeated-measures ANOVAs, and any tDCS effects indicated by a significant *group*time* interaction were followed up with post hoc paired t tests with Bonferroni corrections for participants in the active tDCS group. To investigate the difference in PFC rsFC changes between the two groups before and after tDCS, a 2x2 repeated-measures ANOVA for each ROI was performed with the averaged coherence values (r) of the medial/lateral PFC of each hemisphere, with the familywise error rate maintained at alpha = .05 (i.e., for each individual ROI, p = .05/4 = 0.0125 represented a significant effect). For each of the group comparisons, partial eta squared (η_p^2) and its 90% confidence interval (CI) were reported [53]. To provide a more comprehensive understanding of a specific treatment effect [54], we also calculated Cohen's *d*, followed by post hoc t tests. To explore the relationships between the changes in social functioning and behavior, social functioning and emotion recognition, social functioning and CF, social functioning and information processing speed and social functioning and rsFC before and after the treatment, Spearman's rank order correlation analyses (two-tailed) were conducted at the whole group level. Then, subgroup correlation analyses were conducted to identify any differences in correlation patterns between the treatment arms. For correlation analyses, the false discovery rate (FDR) was maintained at alpha = .05 using the Benjamini–Hochberg procedure [55]. Due to the exploratory nature of these analyses, trends toward significance at p < .1 (FDR-corrected) were also reported [56]. All analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 ([57]; for more information, see the *Supplementary Methods*).

3. Results

3.1. Participant characteristics, tDCS safety and the quality of blinding

The Consolidated Standards of Reporting Trials (CONSORT) flowchart is shown in Fig. 3. Table 2 shows the baseline demographic and clinical characteristics for participants in each group. The participants in the active and sham tDCS groups were matched on age, IQ, sex, handedness, and baseline ASD symptom severity (ps > .098). Although a significantly more participants in the active tDCS group experienced short-term itchiness over the stimulation site (resolved within 10 min after each treatment session) than participants in the sham tDCS group (likelihood ratio test = 4.47, p < .05), other side effects were not significantly different between participants in the active and sham groups (ps > .05; Table S1). Importantly, our blinding measures were deemed successful, as the number of participants in active and sham tDCS groups who correctly identified their group assignment were not significantly different ($\chi^2(1) = 0.223$, p = .636).

3.2. Effects of tDCS on the primary outcome

As indicated by the SRS-2 total score, the improvement in overall social functioning in the active and sham tDCS groups differed significantly, as indicated by a significant *group*time* interaction determined by the 2x2 repeated-measures ANOVA [F(1,39) = 4.75, p = .035, $\eta_p^2 = 0.11$, 90% CI (0.0040, 0.27); Fig. 4a]. Post hoc paired sample t tests with a Bonferroni correction revealed that the reduction in the SRS-2 total score was highly significant in participants in the active group [t(19) = 6.51. p < .001] and nonsignificant in participants in the sham group [t(20) = 2.53, p = .02]. A significant *group*time* interaction was also found between the active and sham tDCS groups for the SRS-2 RRB subscore [F(1,39) = 4.11, p = .049, $\eta_p^2 = 0.095$, 90% CI (0.0001, 0.25); Fig. 4b]. Post hoc paired sample t tests revealed that the reduction in RRB scores was highly significant in participants in the active group [t(19) = 4.79. p < .001] and nonsignificant in participants in the sham group [t(20) = 1.03, p = .31]. Although the *group*time* interaction effect for the SRS-2 SCI subscore was nonsignificant [F(1,39) = 2.87, p = .098, $\eta_p^2 = 0.069$, 90% CI (0, 0.22); Fig. 4c], post hoc paired sample t tests revealed that the reduction in SCI score was highly significant in participants in the active group [t(19) = 5.68. p < .001] and nonsignificant in participants in the sham group [t(20) = 1.03, p = .31].

3.3. Effects of tDCS on secondary outcomes

A highly significant *group*time* interaction was found for participants' emotion recognition, as reflected by the CANTAB ERT total hit rate [F(1,39) = 8.34, p = .006, $\eta_p^2 = 0.176$, 90% CI (0.0031, 0.34)].

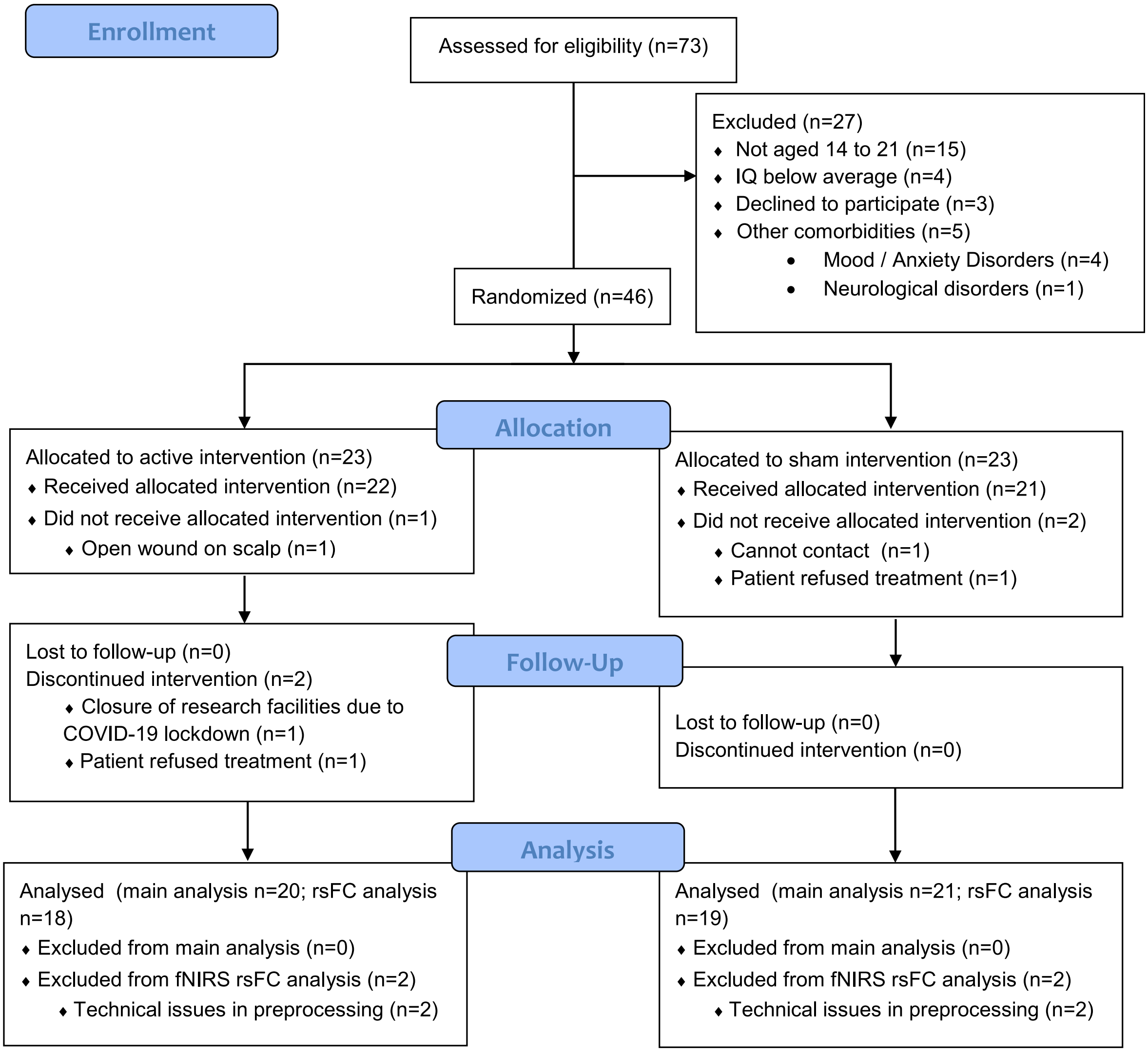

Fig. 3. The CONSORT flowchart.

Table 2
Participants' demographic information.

Demographic Details	Group		Statistics		
	Active (n = 20)	Sham (n = 21)	t/χ2	df	p
Mean chronological age in years (S.D.)	17.03 (2.55)	17.10 (2.30)	-.079	39	.937
IQ (S.D.)	84.00 (20.89)	85.33 (16.88)	-.225	39	.823
Gender (M:F)	18:2	20:1	[a].421	1	.517
Handedness (R:L)	19:1	20:1	[a].001	1	.972
Mean SRS-2 Total (S.D.)	102.85 (27.02)	108.52 (28.41)	-.655	39	.517
Mean SRS-2 SCI (S.D.)	84.55 (21.10)	89.67 (22.23)	-.755	39	.455
Mean SRS-2 RRB (S.D.)	18.30 (7.38)	18.86 (8.40)	-.225	39	.823
ADI-R social interaction subscore (S.D.)	20.45 (5.75)	22.71 (5.15)	−1.33	39	.191
ADI-R verbal communication subscore (S.D.)	16.55 (5.57)	19.33 (4.83)	−1.71	39	.095
ADI-R restricted, repetitive behavior subscore (S.D.)	4.15 (2.21)	4.14 (2.01)	.011	39	.991

Note:Abbreviations: IQ = intelligence quotient, Gender (M = male; F = female), Handedness (R = right-handed; L = left-handed), SRS-2 = Social Responsiveness Scale- 2, SCI = social communication index, RRB = restricted, repetitive behavior, ADI-R = Autism Diagnostic Interview-revised.

[a] The group comparison was conducted by Likelihood Ratio.

However, the post hoc paired t tests with a Bonferroni correction for both groups were nonsignificant [active: t(19) = −1.72. p = .10; sham: t(19) = 2.34. p = .03]. As indicated by the CF composite score, the CF improvement differed significantly between the groups, as indicated by a significant *group*time* interaction from the 2x2 repeated-measures ANOVA [F(1,39) = 4.91, p = .033, $\eta_p^2 = 0.11$, 90% CI (0.0050, 0.27)]. Post hoc paired sample t tests revealed that the enhancement in the CF composite score was highly significant in the active group [t(19) = 4.46. p < .001] and nonsignificant in the sham group [t(20) = 1.85, p = .08]. As indicated by the IPE

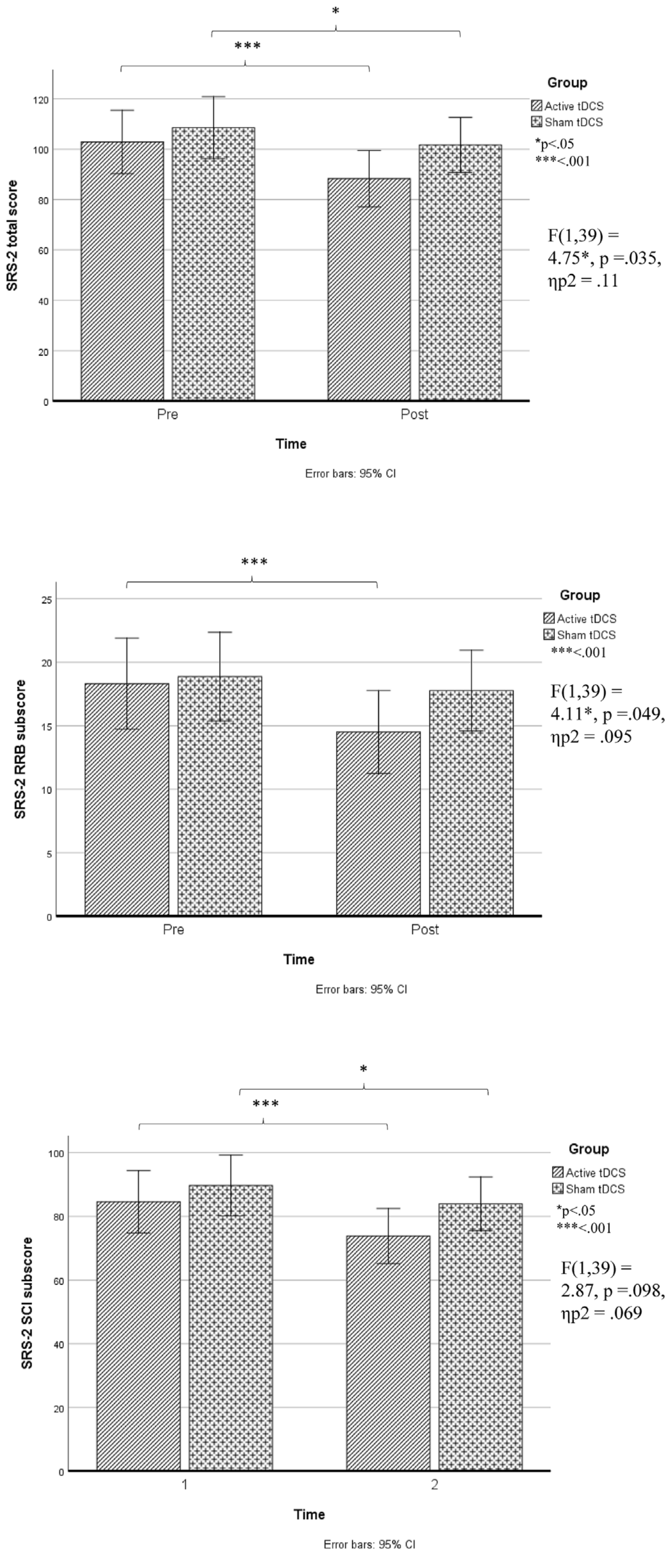

Fig. 4. Bar charts showing the changes in (a) the SRS-2 total score, (b) the restricted, repetitive behavior (RRB) subscore, and (c) the social communication index (SCI) subscore.

composite score, the change in participants' IPE differed significantly between groups, as indicated by a significant *group*time* interaction determined by the 2x2 repeated-measures ANOVA [F(1,39) = 4.43, p = .042, $\eta_p^2 = 0.10$, 90% CI (0.0020, 0.26)]. Post hoc paired sample t tests revealed that the enhancement in the IPE composite score was nonsignificant in both the active [t(19) = −1.92. p = .07] and sham [t(19) = 1.10. p = .283] tDCS groups. Table 3 shows the descriptive and inferential statistics of the CF and IPE composite scores.

3.4. Effects of tDCS on PFC rsFC

The 2x2 repeated-measures ANOVA revealed that tDCS induced highly significant differences in the changes in rsFC of the right medial PFC [F(1,35) = 7.08, p = .012, $\eta_p^2 = 0.17$, 90% CI (0.022, 0.34)] but not for the left medial PFC and lateral PFCs (ps > .49; Table 4). Post hoc paired t tests for the right medial PFC ROI showed that the increase in rsFC was highly significant in the active tDCS group [t(17) = −4.03. p = .001] and nonsignificant in the sham tDCS group [t(18) = 0.347. p = .733]. Visual inspection of individual rsFC data (Fig. 5) revealed greater interindividual variability among younger participants in rsFC raw change in the right medial PFC after the active tDCS (Fig. 5a) and sham tDCS (Fig. 5b) treatment.

3.5. Correlation analysis

Spearman's rank order correlation analyses for the whole study cohort (Table 5a) showed that the percentage reductions in SRS-2 total scores were significantly negatively correlated with the CANTAB ERT scores (ρ = -.461, pFDR = .028); these reductions also negatively correlated with CF (ρ = -.326, pFDR = .083) and IPE composite scores (ρ = -.306, pFDR = .083). The reduction in the SRS-2 SCI subscore was significantly correlated with the CANTAB ERT and CF composite scores (psFDR <.05). The right medial PFC rsFC showed a trend towards positively correlating with the IPE composite scores (ρ = 0.339, pFDR = .083). Significant correlations were found between the SCI subscore and IPE composite score (ρ = -.564, pFDR = .032) and between CF and PS composite scores (ρ = 0.586, pFDR = .028) for participants in the active tDCS group (Table 5b). None of the correlations between social functioning and rsFC measures or between cognitive measures and rsFC measures were significant for participants in the sham tDCS group (psFDR >.126, Table 5c).

4. Discussion

This double-blind, randomized, sham-controlled trial aimed to examine the effects of multisession prefrontal tDCS and concurrent cognitive remediation training in 14–21-year-old individuals with ASD; specifically, we evaluated the impact of this combined protocol on the social functioning and cognitive processes underlying social interaction as well as the possible neurophysiological mechanism underlying this effect. The results from the 41 eligible participants who completed the protocol indicated that, compared with the outcome of sham tDCS, 10 sessions of 1.5 mA tDCS with left dlPFC cathode placement and right supraorbital region anode placement delivered for 20 min concurrent with computerized cognitive remediation training significantly enhanced social communication and reduced restricted, repetitive behaviors in these individuals, yielding improvement in their overall social functioning. This improvement was associated with enhanced emotion recognition, which was previously demonstrated to be associated with CF. Specifically, prefrontal tDCS with left dlPFC cathode placement and right supraorbital region anode placement and concurrent cognitive remediation training, but not the training alone, optimized IPE that is associated with improved CF performance and social communication. Changes in IPE appeared to be associated with enhancement in the rsFC of the right medial PFC. The implications of these results are discussed below.

Table 3
Comparison of changes in neuropsychological performance (secondary outcome measures) between active and sham tDCS groups.

Scores/Group	Pre mean (S.D.)	Post Mean (S.D.)	Mean difference (S.D.)	*t*	*p*	*d*
Emotion recognition (total hit): F(1,39) = 8.34[b], p = .006, ηp2 = .18						
Active tDCS	20.45 (5.47)	21.75 (6.27)	1.30 (3.37)	−1.72	.10	.22
Sham tDCS	22.48 (5.86)	20.24 (5.66)	−2.24 (4.38)	2.34	.03	.39
Cognitive flexibility composite (Z): F(1,39) = 4.91[a], p = .033, ηp2 = .11						
Active tDCS	−1.10 (1.10)	-.27 (.93)	.84 (.18)	4.46[c]	<.001	.82
Sham tDCS	-.56 (1.07)	-.27 (1.33)	.29 (.73)	1.85	.08	.24
Information processing efficiency composite (Z): F(1,39) = 4.43[a], p = .042, ηp2 = .10						
Active tDCS	−1.23 (1.45)	-.85 (1.25)	.38 (.89)	−1.92	.070	.28
Sham tDCS	−1.20 (1.41)	−1.44 (1.68)	-.24 (.99)	1.10	.283	.16

Note.
[a] $p < .05$.
[b] $p < .01$.
[c] $p < .001$.

Table 4
Comparison of changes in prefrontal resting-state functional connectivity (rsFC) between active[a] and sham[b] tDCS groups.

Brain regions/Group	Pre mean (S.D.)	Post Mean (S.D.)	Mean difference (S.D.)	*t*	*p*	*d*
Right medial PFC: $F_{1,35} = 7.08$[c], p = .012, $\eta p^2 = .168$						
Active tDCS	.21 (.10)	.32 (.13)	.11 (.11)	−4.03[d]	.001	.95
Sham tDCS	.27 (.15)	.26 (.17)	-.01 (.16)	.347	.733	.06
Left medial PFC: $F_{1,35} = .221$, p = .641, $\eta p^2 = .006$						
Active tDCS	.28 (.13)	.27 (.14)	-.01 (.15)	.272	.789	.07
Sham tDCS	.31 (.19)	.27 (.13)	-.04 (.19)	.842	.411	.25
Right lateral PFC: $F_{1,35} = .492$, p = .488, $\eta p^2 = .014$						
Active tDCS	.22 (.08)	.25 (.12)	.02 (.16)	-.602	.555	.29
Sham tDCS	.24 (.12)	.22 (.10)	-.01 (.16)	.391	.701	.18
Left lateral PFC: $F_{1,35} = 000$, p = 1.00, $\eta p^2 = .000$						
Active tDCS	.24 (.09)	.22 (.08)	-.02 (.11)	.707	.489	.24
Sham tDCS	.26 (.11)	.24 (.11)	-.02 (.12)	.641	.530	.18

Note.
Abbreviation: rsFC = resting-state functional connectivity.
[a] N = 18; two rsFC data were missing in the active tDCS group.
[b] N = 19; two rsFC data were missing in the sham tDCS group.
[c] $p < .05$.
[d] $p < .01$.

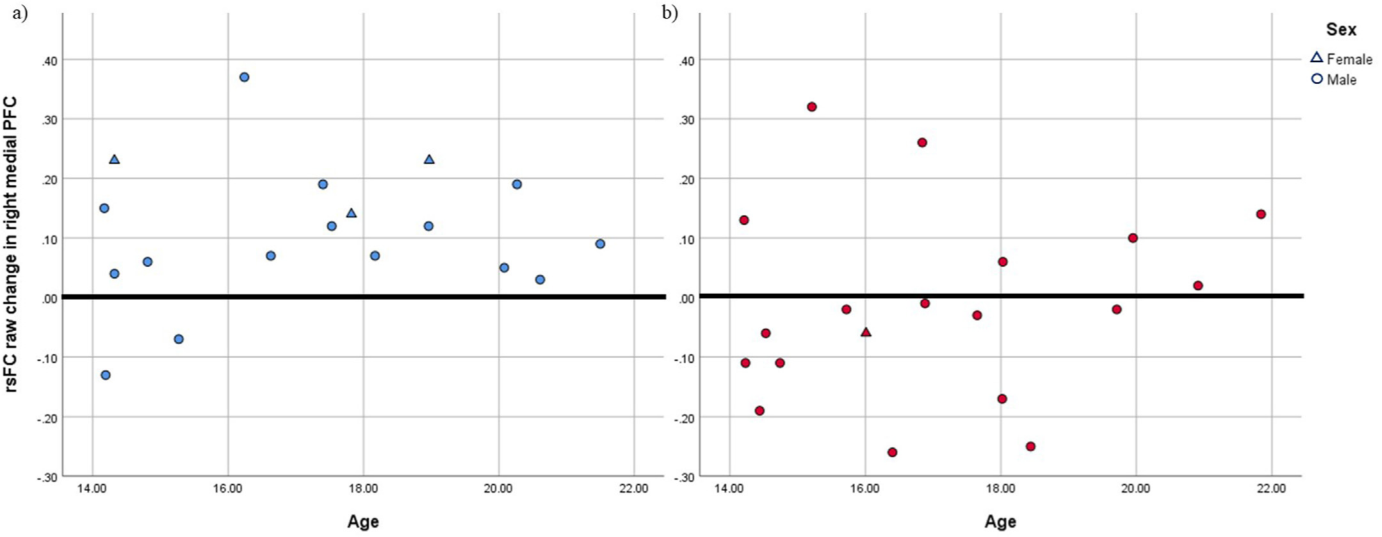

Fig. 5. Scatter plots showing the rsFC raw change in right medial PFC of individual participants in (a) active tDCS group and (b) sham tDCS group.

4.1. Clinical and cognitive effects of prefrontal tDCS with concurrent cognitive remediation

Consistent with previous preliminary studies [39,40], we found that 1.5 mA multisession tDCS with left dlPFC cathode placement and right supraorbital region anode placement, delivered concurrently with cognitive remediation training, yielded large and significant effects on social communication and restricted, repetitive behaviors in individuals with ASD. Interestingly, our results revealed that tDCS with left dlPFC cathode

Table 5a
Correlation matrix (whole group^).

SRS-2 total	1						
SRS-2 SCI	.848***	1					
SRS-2 RRB	.666***	.365*	1				
ERT	-.416*	-.398*	-.281	1			
CF	-.326†	-.378*	-.179	.256	1		
IPE	-.306†	-.313†	-.249	.131	.223	1	
R medial PFC rsFC	-.017	.002	.061	-.067	.222	.339†	1
	SRS-2 total	*SRS-2 SCI*	*SRS-2* RRB	*ERT*	*CF*	*IPE*	*R medial PFC rsFC*

Table 5b
Correlation matrix (active tDCS group§).

SRS-2 total	1						
SRS-2 SCI	.799***	1					
SRS-2 RRB	.641*	.364	1				
ERT	-.361	-.301	-.405	1			
CF	-.242	-.240	-.380	-.134	1		
IPE	-.455	-.564*	-.240	-.198	.586*	1	
R medial PFC rsFC	-.218	-.146	-.118	-.254	.337	.422	1
	SRS-2 total	*SRS-2 SCI*	*SRS-2* RRB	*ERT*	*CF*	*IPE*	*R medial PFC rsFC*

Table 5c
Correlation matrix (sham tDCS group§§).

SRS-2 total	1						
SRS-2 SCI	.916***	1					
SRS-2 RRB	.550†	.286	1				
ERT	-.407	-.462	-.031	1			
CF	-.290	-.398	.048	.488	1		
IPE	-.099	-.002	-.122	.231	-.175	1	
R medial PFC rsFC	.188	.267	.215	-.073	-.114	.081	1
	SRS-2 total	*SRS-2 SCI*	*SRS-2* RRB	*ERT*	*CF*	*IPE*	*R medial PFC rsFC*

Note.
Spearman's rank order correlational analyses were conducted.
Abbreviations: SRS-2 = Social Responsiveness Scale- 2, SCI = social communication index, RRB = restricted, repetitive behavior, ERT = CANTAB emotion recognition task, CF = Cognitive flexibility, IPE = Information processing efficiency, R = right, PFC = prefrontal cortex, rsFC = resting-state functional connectivity.
^N = 37 (listwise); four rsFC data were missing from the whole group.
§N = 18 (listwise); two rsFC data were missing in the active tDCS group.
§§N = 19 (listwise); two rsFC data were missing in the sham tDCS group.
†p < .1 (FDR-corrected).
*p < .05 (FDR-corrected).
**p < .01 (FDR-corrected).
***p < .001 (FDR-corrected).

placement and right supraorbital region anode placement enhanced both “cold” and “hot” EF, rather than only “hot” EF, as reported in a previous study [58] that paired this type of tDCS with a cognitive remediation training program targeting “cold” EF. Taking our results together with previous studies demonstrating that tDCS exhibits task-dependent effects on EF performance [42], learning and memory formation [59], it is reasonable to conclude that the effect of tDCS with left dlPFC cathode placement and right supraorbital region anode placement on the “cold” EF network is task-dependent, while it is task-independent for “hot” EF network enhancement. In addition, we showed that social communication, which was enhanced by the treatment, was significantly associated with emotion recognition, an essential skill for social interaction that previous studies have shown is deficient in individuals with ASD [4,60]. Notably, CF is associated with emotional recognition in healthy children [61] as well as in people with ASD [17], as emotion recognition has been shown to require flexible reasoning strategies in response to a situation [62]. In other words, our results may imply that tDCS with left dlPFC cathode placement and right supraorbital region anode placement and concurrent “cold” EF cognitive remediation training may promote flexible problem solving. “Cold” EF skills may generalize to “hot” EF tasks such as identifying others' emotions during social scenarios, which in turn could lead to an enhancement in overall social functioning.

4.2. Neuropsychological and neurophysiological mechanisms of prefrontal tDCS with concurrent cognitive remediation

Consistent with a meta-analysis of neuroimaging studies showing that prefrontal tDCS enhances the rsFC of the right medial prefrontal regions in the DMN [63], we showed that tDCS with left dlPFC cathode placement and right supraorbital region anode placement significantly enhanced rsFC of the right medial PFC but not the other ROIs, and had a large effect size. This effect was only observed in individuals in the active tDCS group. There are three possible explanations for the observed rsFC changes. First, the diffused electric current distribution induced by the montage of tDCS with left dlPFC cathode placement and right supraorbital region anode placement might yield the observed increase in rsFC in the medial PFC. This is in line with a previous simulation study which indicated that the electric field generated by this particular tDCS montage would induce the highest electric current density over the frontal midline regions, including the medial PFC [64].

Additionally, the electric field strength has been shown to be positively correlated with the changes of rsFC in this region [63]. However, it should be noted that the applied current most likely would affect an entire constellation of distributed brain regions, in part due to the spreading of the applied current interacting with the folded cortical surface, and indirectly through the network-level organization of the brain. Further studies that include a comparison of focal cathodal stimulation of left dlPFC with focal anodal stimulation of frontal midline cortex would be useful to elucidate the mechanisms underlying the variability of tDCS effects observed in ASD individuals. Second, it is possible that 1.5 mA left dlPFC cathodal tDCS might not produce an inhibitory effect as expected in adolescents and young adults with ASD. Previous studies in healthy individuals have shown that 1 mA cathodal tDCS produced excitatory, instead of inhibitory, effects on cortical excitability in children [65,66], similar to the effects of 2 mA cathodal tDCS in adults [67]. Third, as discussed above, performing a task (i.e., concurrent cognitive remediation training) during prefrontal tDCS might alter the hypothesized cathodal tDCS effects; although we expected that left dlPFC cathodal tDCS would be inhibitory, we instead observed a positive rsFC change in the medial PFC that is usually produced by an excitatory stimulation. When compared to another tDCS study in ASD individuals [68] that performed a reversed montage (i.e., anode placement over the left dlPFC, in contrast to our study), we revealed a right-lateralized, instead of interhemispheric, enhancement of rsFC. This implies that the direction of the electric field may play a role in promoting differential tDCS effects in brain network organization. Moreover, we found significant correlations between IPE and CF, as well as between IPE and social communication, in the active tDCS group but not in the sham tDCS group. Additionally, IPE showed a trend to be associated with enhanced rsFC in the right medial PFC. Consistent with these findings, a number of previous studies have shown that IPE is associated with functional connectivity of the brain [69,70]. People with ASD have slower processing speed [71,72], exhibit aberrant functional connectivity, including localized corticocortical connectivity in both the resting state [73] and during the performance of cognitive tasks, including CF [74]. In particular, previous studies have generally indicated hypoconnectivity within the medial PFC in individuals with ASD; importantly, this region is known to be the key hub for self-relevant information processing [32]. Given these findings, our results may imply that tDCS with left dlPFC cathode placement and right supraorbital region anode placement promotes flexible and efficient processing of social information relative to oneself within the right medial PFC, resulting in clinically observable social functioning improvements. A previous study showed that in individuals with ASD a heightened E:I ratio was found, particularly in the medial PFC [27]. Relatedly, a higher E:I ratio in the medial PFC was shown to impair synaptic information processing and social behavior in mice [29]; thus, it is reasonable to postulate that the E:I ratio of the right medial PFC would be reduced by tDCS with left dlPFC cathode placement and −right supraorbital region anode placement. Future RCTs that investigate the modulatory effects of tDCS with this montage on the E:I imbalance are needed to verify this theory.

4.3. Study significance and limitations

To the best of our knowledge, this was the first double-blind RCT to investigate the clinical, neuropsychological and neurophysiological effects of tDCS with left dlPFC cathode placement and right supraorbital region anode placement, delivered with concurrent computerized cognitive remediation training, in adolescents and young adults with ASD. By matching individuals on age, IQ, sex, and handedness in the active and sham tDCS groups, which were also matched for baseline ASD symptom severity and current social functioning, we demonstrated that our protocol was a safe and efficacious treatment. Despite contributing significantly to understanding the effects of tDCS on ASD, this study had several limitations. First, as our study involved the administration of neuropsychological tests that required an adequate level of instruction comprehension, we only included individuals with ASD who had a full-scale IQ $\geq$ 60, which only accounts for approximately 50% of the ASD population [2]. Second, visual inspection of individual fNIRS data revealed some interindividual differences regarding the treatment-related rsFC changes in right medial PFC, with greater differences observed in the younger age range (i.e. 14-18 years old) of the included participants in our study. The overrepresentation of adolescents and young adults with ASD may limit the generalization of our findings to a wider patient population of ASD. Further studies that include participants with broader ranges of age and IQ would help extend the current knowledge of the potential utility of the intervention. Third, the inclusion of female participants in our sample might have masked the true effects of tDCS with left dlPFC cathode placement and right supraorbital region anode placement, given that a previous study showed that heightened E:I was only seen in male, but not female, individuals with ASD [27]. In addition, as this study was designed as a preliminarily assessment of the effects of cathodal tDCS on individuals with ASD, the sample size was small. We minimized the possibility of false-positive results when examining group differences by employing Bonferroni corrections to adjust for multiple paired *t*-test comparisons. Similarly, we employed FDR-adjusted p values when reporting significant results from the exploratory correlation analyses. All of these data, however, have yet to be verified by a larger-scale study, and the results from this RCT should be regarded as preliminary.

5. Conclusion

This double-blind RCT was conducted to investigate the beneficial effects and underlying neurophysiological mechanism of multisession 1.5 mA tDCS with left dlPFC cathode placement and right supraorbital region anode placement delivered with concurrent computerized cognitive remediation training in 14–21-year-old individuals with ASD. The results from 41 individuals indicated that our protocol was a safe and efficacious treatment for adolescents and young adults with ASD and that it could promote their overall social functioning. This outcome appeared to be associated with the enhancement of the functional connectivity of the right medial PFC, a major hub for flexible social information processing, enabling participants to process socially relevant information in response to different social situations more efficiently. Future RCTs with neurophysiological or neuroimaging measurements that include a larger sample of male ASD with broader ranges of age and IQ, and applying focal stimulation would be helpful to deepen our understanding of the neurophysiological mechanisms of cathodal tDCS in ASD, with a specific focus on E:I modulation.

Funding

Health and Medical Research Fund (HMRF06173096)

CRediT authorship contribution statement

Yvonne M.Y. Han: Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Funding acquisition. **Melody M.Y. Chan:** Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Caroline K.S. Shea:** Resources, Project administration. **Oscar Long-hin Lai:** Investigation, Data curation. **Karthikeyan Krishnamurthy:** Investigation. **Mei-chun Cheung:** Conceptualization, Funding acquisition. **Agnes S. Chan:** Conceptualization, Funding acquisition.

Declarations of competing interest

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This study was supported by the Health and Medical Research Fund (HMRF06173096) from the Food and Health Bureau, The Government of the Hong Kong Special Administrative Region. The authors would like to thank Ms. Coco Choi for her efforts in assisting with subject recruitment and data collection, Mr. Ming Chung Chan for his efforts in data collection, and the participants and their parents who enrolled in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2022.02.004.

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