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Research Paper

Differential effects of left DLPFC anodal and cathodal tDCS interventions on the brain in children with autism: A randomized controlled trial

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ABSTRACT

Background: Autism spectrum disorder (ASD) is a complex and heterogeneous neurodevelopmental disorder with few effective treatment options. In recent years, transcranial direct current stimulation (tDCS) has been applied in interventions for ASD, often targeting the left dorsolateral prefrontal cortex (DLPFC). However, studies investigating anodal and cathodal tDCS interventions have reported differing outcomes. Therefore, this study aimed to compare and analyze the effects of these two stimulations through a randomized controlled trial, utilizing both behavioral assessments and EEG proxy markers capable of characterizing the brain's excitatory-inhibitory balance.

Methods: This study recruited a total of 24 children with ASD (20 males and 4 females; mean age ± SD: 5.5 ± 1.2 years), who were randomly divided into two groups receiving either anodal or cathodal tDCS targeting the DLPFC. The stimulation intensity was set at 1 mA, administered five times per week for a total of 20 sessions. Behavioral intervention outcomes were assessed using the Social Responsiveness Scale (SRS) and the Autism Behavior Checklist (ABC). Additionally, the study evaluated the effects of tDCS on the brain's excitatory-inhibitory balance by analyzing corrected periodic alpha oscillation power and bandwidth, as well as non-periodic exponent and offset derived from EEG data.

Results: Following anodal tDCS intervention, results from the SRS scale indicated a decrease in overall scores, with significant differences observed in social communication and social motivation among children. On the ABC scale, overall scores also decreased, with significant differences noted in sensory behavior, social relating, body and object use, and language and communication skills. Non-periodic exponent and offsets increased following anodal tDCS stimulation, whereas they decreased after cathodal tDCS stimulation. Regarding alpha oscillation power, there was a significant increase following anodal tDCS and a significant decrease following cathodal tDCS. In terms of alpha oscillation bandwidth, there was a reduction following anodal tDCS and an increase following cathodal tDCS. Further correlation analysis revealed that in children who received anodal tDCS intervention, non-periodic exponent showed correlations with behaviors such as social communication.

Conclusion: Our study results demonstrated that anodal and cathodal tDCS targeting the left DLPFC had distinct effects on the behavior and excitatory-inhibitory balance of children with ASD. Anodal tDCS intervention appeared to have a more positive impact compared to cathodal intervention. However, the sample size was small, and we focused solely on the effects of tDCS, with our experimental design perhaps not being able to generalize to all external manipulations of excitability in our study. In future research, we will continue to improve the experiments to address these limitations.

Introduction

Autism spectrum disorder (ASD) is a complex heterogeneous neurodevelopmental disorder characterized primarily by repetitive behavior patterns and deficits in social communication (McMahon et al., 2021). This disorder typically persists throughout the patient's lifetime, posing significant challenges for families. However, the etiology of autism remained unclear to date, and the effectiveness of various medications (Zhou et al., 2021) and behavioral therapies was moderate (Amiri et al., 2022). Therefore, there is an urgent need for safe and

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effective treatment methods to alleviate ASD symptoms.

Given the genetic heterogeneity of ASD, recent research and therapeutic approaches have focused on addressing shared neurocircuitry dysfunctions arising from known genetic abnormalities (Rubenstein and Merzenich, 2003). Brain function emerged as a balance between excitatory and inhibitory (E/I) activities, with regulatory changes potentially altering normal human traits and disrupting underlying spectra of neurodevelopmental and psychiatric disorders (Robert, 2022; Oren, 2014). Previous studies indicated that E/I imbalance may impair sensory (Chen-Engerer et al., 2022), memory (He et al., 2022), social (Lopatina et al., 2018), emotional (Said et al., 2013), and other forms of neurocognitive functions, depending on the affected neural networks. As these symptoms were common in ASD, E/I imbalance may explain the pathophysiology of this neurodevelopmental disorder (Trakoshis et al., 2020; Hollestein et al., 2023).

Rubenstein et al. proposed that certain forms of autism may stem from defects in GABAergic interneurons, reducing inhibition in the cortex and hippocampus, thereby altering the E/I balance of circuits (Rubenstein and Merzenich, 2003), a hypothesis supported by subsequent genetic and animal studies (Lee et al., 2017). γ-Aminobutyric acid (GABA) served as a critical inhibitory neurotransmitter in the central nervous system, crucial for regulating brain rhythms and spontaneous neural activity during brain development. Cumulative evidence suggested that reduced GABAergic function in neural circuits may underlie the E/I imbalance in ASD (Thomson et al., 2024), potentially correlating with the pathophysiology of ASD clinical symptoms. Other animal studies indicated that mouse models relevant to autism (Kat et al., 2024) or mutations in autism-related genes (Geng et al., 2022) may also involve disruptions in inhibitory function.

Neuroimaging evidence indicated that the left dorsolateral prefrontal cortex (DLPFC) was impaired in individuals with ASD, a crucial center for cognitive control. Meta-analyses of neuroimaging studies revealed that the left DLPFC in ASD patients showed overactivation during cognitive tasks requiring attentional control, response inhibition, and cognitive flexibility, indicating an imbalance in E/I dynamics detrimental to both behavior and cognition (Salehinejad et al., 2022). Therefore, therapeutic approaches aimed at modulating E/I balance were hypothesized to improve disrupted brain dynamics, facilitate efficient and flexible information processing, and consequently reduce symptoms in individuals with ASD.

Transcranial direct current stimulation (tDCS) has provided a new tool for cognitive neuroscience and neuropsychology research, with several studies demonstrating its ability to modulate cortical excitability and affect a range of sensorimotor (Rizvi et al., 2023) and cognitive functions (Narmashiri and Akbari, 2023) in the human brain. Indeed, both anodal and cathodal tDCS can modulate E/I balance by regulating glutamatergic and GABAergic signaling, albeit through different mechanisms. Previous interventions using anodal tDCS over the left DLPFC have shown improvements in social and language abilities (Amatachaya et al., 2015), as well as enhanced working memory (Habib, 2019) and inhibitory control (Chen et al., 2024) in children with ASD. However, studies involving cathodal tDCS over the left DLPFC in ASD have also demonstrated effects; some research indicated that cathodal tDCS over the left DLPFC enhanced executive functions in adults with ASD (D'Urso et al., 2015) and reduced irritability (Rothärmel et al., 2019). When combined with cognitive remediation, cathodal tDCS over the left DLPFC has been shown to enhance flexible social cognition and information processing abilities (Han et al., 2022). Research has also concluded that modulating E/I balance through cathodal tDCS can enhance cognitive functions and achieve symptom reduction in ASD patients (Zemestani et al., 2022). However, to date, there has been no comparative research on the efficacy of cathodal versus anodal tDCS interventions for ASD.

Using electroencephalography (EEG) to record brain electrical signals directly reflects the activity of cortical neuron populations and may aid in estimating global as well as regional E-I balance. The power spectrum of electrophysiological signals measured by EEG includes both periodic components (Buzsáki et al., 2012). Historically, non-periodic activity has been attributed to instrument noise or frequency-dependent filtering by extracellular media (Beck, 2023). However, recent research has identified non-periodic activity as closely correlating with age-related cognitive decline (Tröndle et al., 2023), consciousness states (Rabuffo et al., 2022), and being considered a reliable neurophysiological indicator of synaptic excitation-inhibition ratio (Zsido et al., 2020).

Another notable issue was that current assessments of electrophysiological neural activity typically used conventionally defined frequency bands, often neglecting non-periodic signals. This standard approach conflated periodic parameters (such as power and bandwidth) with non-periodic parameters (like exponent and offset), which could obscure the physiological significance of these metrics. Therefore, when exploring tDCS interventions in children with ASD, correcting for non-periodic activity in the power spectrum could distinguish between periodic and non-periodic neural activities. This correction helped avoid confusion about the physiological meanings of these two components, thereby providing a more accurate characterization of neurophysiological oscillatory activities that could better reflect physiological information. Alpha oscillations, initially associated with the absence of external or internal processing demands, could reduce cortical excitability (Sauseng et al., 2009) and metabolic demands (Scheeringa et al., 2011). They were widely recognized as markers of E/I balance (Pellegrino et al., 2021), where higher alpha band power corresponded to lower E/I ratios.

In conclusion, this randomized controlled trial aimed to examine the effects of anodal and cathodal tDCS over the left DLPFC on the E/I balance in children with ASD. Specifically, recruited ASD children were randomly assigned to receive either anodal or cathodal tDCS interventions. Changes in the E/I balance were assessed by calculating corrected periodic alpha band power and bandwidth, as well as non-periodic exponent and offset. Additionally, recent studies have interpreted non-periodic signals as biologically significant (Molina et al., 2020), characterized by a 1/f-like distribution and two indices: (1) offset, reflecting uniform shifts in power; and (2) exponent, the negative slope of the power spectrum, believed to reflect shifts in the E/I balance (Aguilar-Velázquez and Guzmán-Vargas, 2019). We hypothesized that cathodal and anodal stimulation may have differential effects on behavior and cortical excitability in ASD children, providing meaningful insights for future applications.

Materials and methods

Subjects

Twenty-four children with ASD (20 males and 4 females; mean age ± SD: 5.5 ± 1.2 years) were recruited at Ningbo Rehabilitation Hospital and randomly assigned into two groups. Twelve children (2 females and 10 males; mean age ± SD: 5.3 ± 1.2 years) received 20 sessions of tDCS intervention with the anode placed over the left DLPFC and the cathode over the right supraorbital area. The remaining twelve children (2 females and 10 males; mean age ± SD: 5.8 ± 1.2 years) received 20 sessions of tDCS intervention with the cathode placed over the left DLPFC and the anode over the right supraorbital area.

All children were diagnosed with ASD by experienced psychiatrists based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders-V (First and Wakefield, 2010). Exclusion criteria included a history of epilepsy, brain implants, and physical disabilities. Informed consent was obtained from all parents, and they were informed about the entire process before participation. The trial was conducted in accordance with the Helsinki Declaration and approved by the Ethics Committee of Ningbo Rehabilitation Hospital.

tDCS conditions

Direct current was generated by a stimulator (JX-tDCS-1, Huaheng Jingxing Medical Technology Co., Ltd., Nanchang, China) and applied through rubber electrodes covered with saline-soaked sponges. One group received 20 sessions of stimulation (1 mA, 20 min per session, ramp-up of 30 s, ramp-down of 30 s, 5 sessions per week). The anode electrode was placed over the left DLPFC (F3), and the cathode electrode was placed over the right supraorbital area, according to the 10–20 EEG international system. The other group also received 20 sessions of stimulation (1 mA, 20 min per session, ramp-up of 30 s, ramp-down of 30 s, 5 sessions per week). In this group, the cathode electrode was placed over the left DLPFC (F3), and the anode electrode was placed over the right supraorbital area. At the end of each session, participants were queried about any adverse effects experienced during the stimulation process. Throughout the entire experimental procedure, neither children nor their parents reported any discomfort, and there were no withdrawals from the study.

Behavioral evaluation

In this study, the Autism Behavior Checklist (ABC) (Eaves, 2006) and the Social Responsiveness Scale (SRS) were administered before and after tDCS intervention. The ABC was completed by parents to assess a range of behaviors. It consists of 57 items categorized into 5 subscales: sensory, social relating, body and object use, language and communication skills, social and adaptive skills. The SRS includes 65 items across 5 dimensions: social awareness, social cognition, social communication, social motivation, and autistic mannerisms. Scores were calculated for each item, with higher scores typically indicating more severe behavioral issues.

EEG data collection and analysis

In this study, EEG data from all participants were recorded twice: once before tDCS intervention and again after 20 sessions of tDCS intervention. During data collection, children remained relaxed, seated comfortably in a quiet room with their eyes open. An eight-channel EEG recording system was used, with electrodes placed at F3, F4, T3, C3, C4, T4, O1, and O2. Impedance for all electrodes was maintained below 20 kΩ, with Cz serving as the reference electrode, and a sampling rate of 1000 Hz was employed. Each child's resting-state EEG data were recorded for approximately 5 min per session. Following EEG collection, caregivers were guided by professionals to complete the ABC and the SRS. An overview of the study process was illustrated in Fig. 1.

Offline data analysis was conducted using Matlab R2016a and EEGlab. Variations in external environment and experimental conditions can introduce noise and artifacts into EEG signals. To preprocess the data, a notch filter at 50 Hz was first applied to mitigate power line interference, followed by a bandpass filter from 0.5 to 45 Hz to address other sources of interference. Due to the presence of blinking, muscle artifacts and myoelectric components in the collected EEG signals, we used independent component analysis (ICA) to eliminate these interferences. The data were then visually inspected to remove noisy segments. Finally, the EEG data were re-referenced as part of the preprocessing steps. The processed data were subsequently used for further computational analysis.

Periodic and non-periodic signals in E/I estimation

Based on Donoghue et al. (2020) spectral parameterization method and toolbox, we computed the non-periodic exponent. Initially, we employed the Welch method to calculate the power spectral density of eight channels (using a 2-second Hamming window with 50 % overlap). This approach allowed the power spectrum to be modeled as a combination of periodic and non-periodic components. The power spectral density at each frequency point f can be expressed as:

$$P = L + \sum_{n} G_n \quad (1)$$

Where L represented the non-periodic component, and G_n denoted an individual Gaussian function. L can be further parameterized as:

$$L = b - \log_{10}\left(f^X\right) \quad (2)$$

Where b represented the offset of the non-periodic signal, and X denoted the non-periodic exponent.

For the periodic component, it can be viewed as a combination of multiple Gaussian functions G_n, where a single Gaussian function was expressed as:

$$G_n = a \times \exp\left[\frac{-(f - C)^2}{2\omega^2}\right] \quad (3)$$

Where a represented amplitude, ω denoted bandwidth for each peak, and C indicated the center frequency.

The model fitting was based on these components, with algorithm parameters setting peak width limited from 0.5 to 12 Hz, fitting frequencies from 1 to 40 Hz, and the aperiodic mode set to 'fixed' without a 'knee' parameter. Models retaining all fitting indices R^2 greater than 0.95 were retained for further analysis. Finally, subtracting the aperiodic component from the fitted spectrum yielded the oscillatory periodic components. The algorithm's final output included non-periodic parameters (exponent, offset) and periodic parameters (amplitude, bandwidth).

Statistical analyses

For statistical analysis, the Shapiro-Wilk test was used to assess the

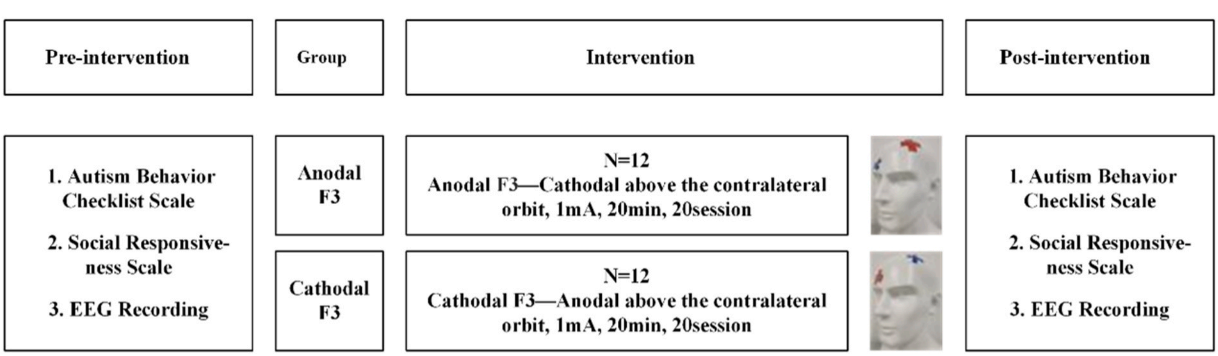

Fig. 1. The course of study. This study had a randomized design. Twenty-four children with autism were randomly assigned to the groups and received 20 sessions of intervention with above-mentioned parameters.

normality of data distribution. For comparisons of both periodic and non-periodic parameters before and after tDCS stimulation, a two-way ANOVA was employed. Grouping was based on stimulation type (anodal and cathodal) with within-group conditions being pre-stimulation and post-stimulation. Non-periodic exponents and offsets were found to adhere to normal distribution and were therefore suitable for ANOVA. However, parameters related to alpha oscillation bandwidth and alpha power did not follow a normal distribution. Consequently, non-parametric Mann-Whitney U tests were utilized for these comparisons. Regarding scores from the SRS and ABC scales, items conforming to normal distribution underwent two-way ANOVA. The grouping criteria were anodal and cathodal stimulation, with within-group conditions of pre- and post-stimulation. Conversely, items not conforming to normal distribution underwent non-parametric Mann-Whitney U tests. To analyze correlations between non-periodic exponent and ABC scale scores, Pearson correlation analysis was applied for indices correlating with sensory, social, motor, and daily living skills scores, which were normally distributed. For language scores, which did not follow a normal distribution, Spearman correlation analysis was used. All statistical analyses were conducted using SPSS 27.0.1 with a significance level set at 0.05.

Result

Scale score results

In this study, we first compared the changes in ABC and SRS scale scores before and after intervention with anodal tDCS and cathodal tDCS in children with ASD. As shown in Fig. 2-A, the results from the SRS scale indicated that following anodal tDCS intervention, overall scores decreased. Significant differences were found in social communication ($p = 0.028$, $Z = -2.199$) and social motivation ($p = 0.012$, $Z = -2.549$) among children. The ABC scale results showed that following anodal tDCS intervention, overall scores decreased. Significant differences were observed in four aspects: sensory ($p = 0.017$, $Z = -2.373$), social relating ($p = 0.018$, $Z = -2.381$), body and object use ($p = 0.028$, $Z = -2.171$), and language and communication skills ($p = 0.014$, $Z = -2.429$). In contrast, for the group of children with autism who received cathodal tDCS intervention, no significant changes were found, and the overall score trend was inconsistent.

Non-periodic neural activity

We calculated the non-periodic exponents and offsets of all channels for two groups of subjects who received anodal tDCS and cathodal tDCS interventions respectively, and constructed corresponding brain topography maps, as shown in Fig. 3. From the topography maps, it was evident that the differences in non-periodic exponents were distributed across the whole brain. Specifically, following anodal tDCS intervention, both the non-periodic exponent and offset increased, whereas following cathodal tDCS intervention, both the non-periodic exponent and offset decreased.

The average 1/f-like non-periodic components of neural activity for groups of subjects undergoing anodal and cathodal tDCS interventions were shown in Fig. 4-A and D, respectively. Statistical analysis revealed that following anodal tDCS intervention, the non-periodic exponent significantly increased compared to pre-intervention levels, whereas following cathodal tDCS intervention, the non-periodic exponent significantly decreased compared to pre-intervention levels. There was a significant within-group difference in the non-periodic exponent ($p < 0.001$, $F = 11.488$), with no significant between-group effect, but a significant interaction between stimulation type and time ($p < 0.001$, $F = 22.588$). The non-periodic offset after anodal tDCS intervention showed an increasing trend, but there was no significant difference before and after intervention, as shown in Fig. 4-B and C. Conversely, the non-periodic offset after cathodal tDCS intervention showed a decreasing trend, with no significant difference before and after intervention, as depicted in Fig. 4-E and F.

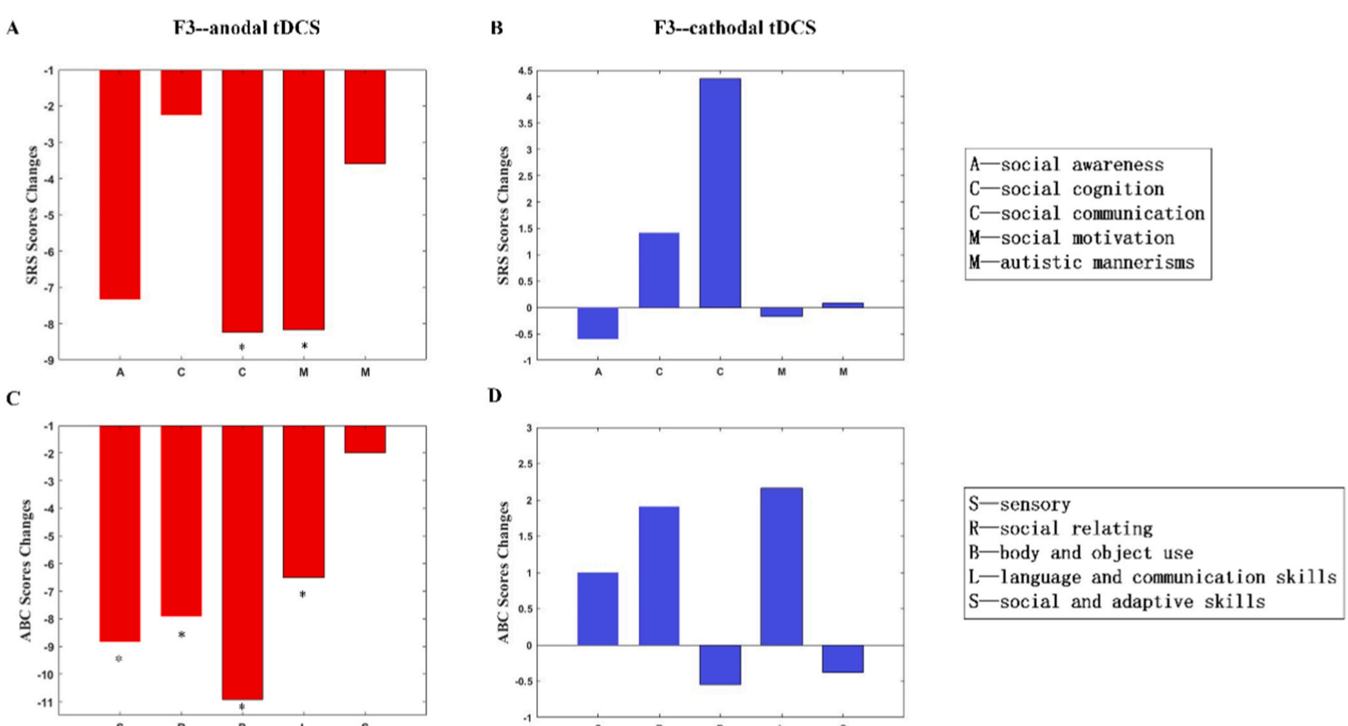

Fig. 2. The changes in SRS and ABC scale scores of the two groups of subjects who underwent anodal tDCS and cathodal tDCS interventions. A: Changes in SRS scale scores before and after anodal tDCS intervention; B: Changes in ABC scale scores before and after anodal tDCS intervention; C: Changes in SRS scale scores before and after cathodal tDCS intervention; D: Changes in ABC scale scores before and after cathodal tDCS intervention.

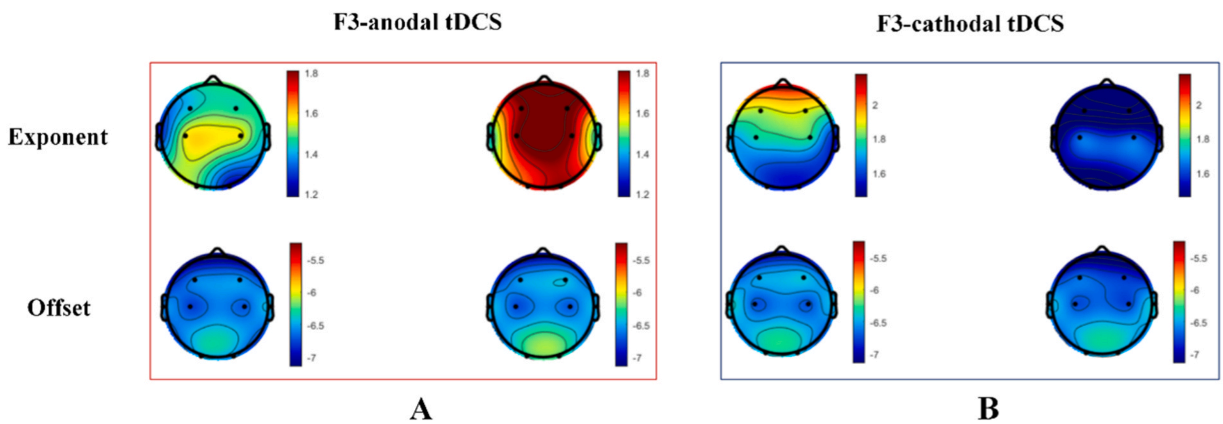

Fig. 3. The topography maps of non- periodic neural activity for two groups of subjects undergoing anodal tDCS and cathodal tDCS interventions. A: Changes in non-periodic exponent and offset before and after anodal tDCS intervention for two groups of subjects at F3; B: Changes in non-periodic exponent and offset before and after cathodal tDCS intervention for two groups of subjects at F3.

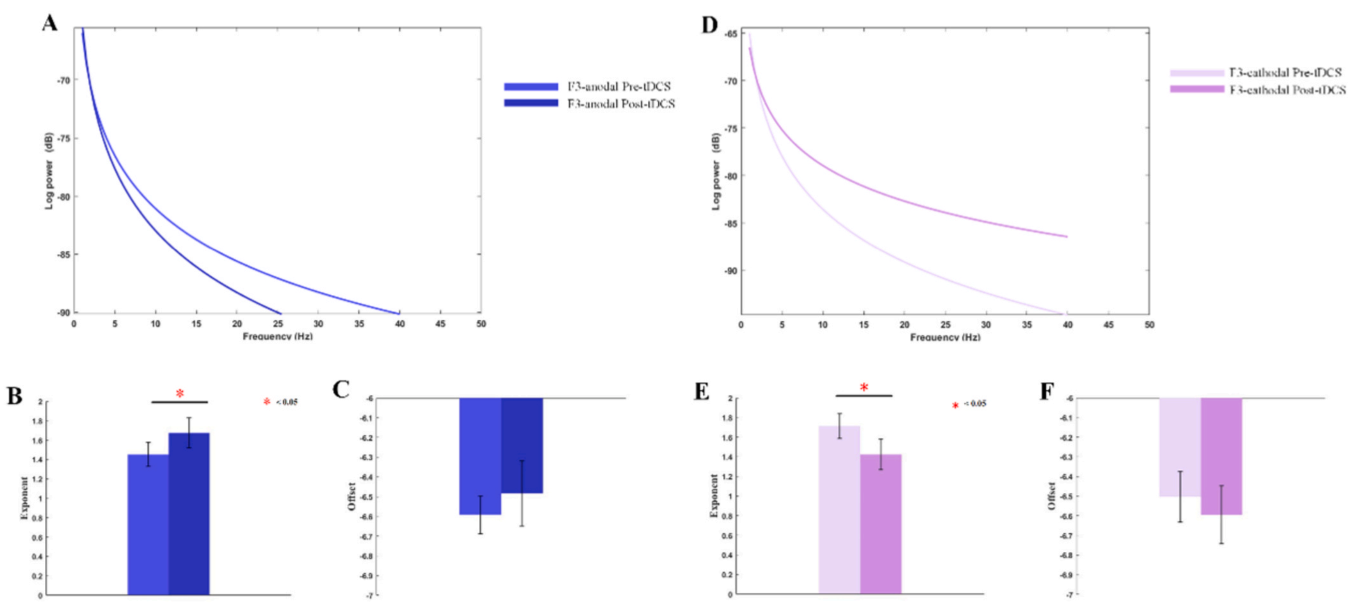

Fig. 4. Comparison of non-periodic neural activity before and after tDCS intervention. A: Schematic of 1/f-like non-periodic components before and after anodal tDCS intervention; B: Non-periodic component results before and after anodal tDCS intervention; C: Non-periodic offset results before and after anodal tDCS intervention; D: Schematic of 1/f-like non-periodic components before and after cathodal tDCS intervention; E: Non-periodic component results before and after cathodal tDCS intervention; F: Non-periodic offset results before and after cathodal tDCS intervention.

Corrected alpha oscillations after adjusting for non-periodic neural activity

Through correction of non-periodic activity and calculation of the corrected resting-state EEG power spectrum, the influence of corrected 1/f-like non-periodic activity on the power spectrum and the characteristics of corrected alpha oscillations were obtained. First, the power spectra of all channels across the whole brain were averaged, and the power spectra before and after correction of non-periodic activity were presented to visually display the changes, as shown in Fig. 5.

Through statistical analysis of alpha oscillation power and bandwidth, it was found that after anodal tDCS intervention, alpha power increased compared to before intervention, with significant differences observed ($p = 0.001$, $Z = -3.046$). After cathodal tDCS intervention, alpha power decreased compared to before intervention, also showing significant differences ($p = 0.003$, $Z = -2.836$). After anodal tDCS intervention, alpha oscillation bandwidth decreased compared to before intervention, with significant differences observed ($p = 0.01$, $Z = -2.521$). After cathodal tDCS intervention, alpha oscillation bandwidth increased compared to before intervention, with significant differences noted ($p < 0.001$, $Z = -3.361$). These specific results were illustrated in Fig. 6.

Correlation analysis

Through correlation analysis, further insights into the relationship between non-periodic exponent and behavior in ASD children were revealed. The results showed that for children who received anodal tDCS intervention: non-periodic exponent of channel C4 was negatively correlated with social cognition ($p = 0.037$, $R = -0.534$) and social communication ($p = 0.027$, $R = -0.568$). Non-periodic exponent of channel O2 was negatively correlated with social cognition ($p = 0.028$, $R = -0.563$). Non-periodic exponent of channel O1 was negatively correlated with social cognition ($p = 0.043$, $R = -0.515$), social motivation ($p = 0.038$, $R = -0.529$), and body and object use ($p = 0.043$, $R = -0.529$). This indicated that as children's abilities in social communication and cognition improving, their non-periodic activity tended to

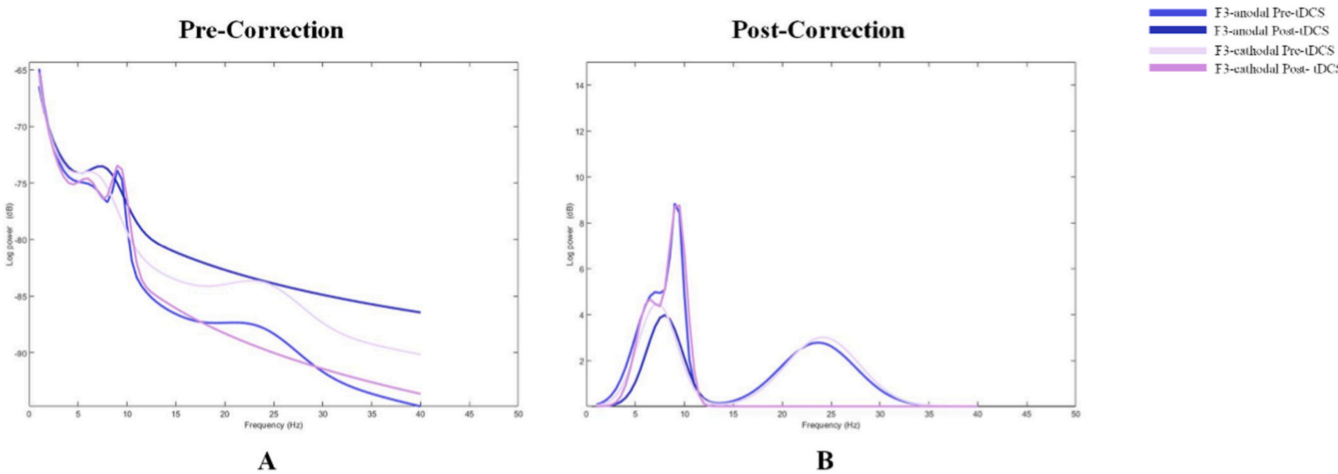

Fig. 5. A: Resting-state power spectrum before correction of non-periodic neural activity; B: Resting-state power spectrum after correction of non-periodic neural activity.

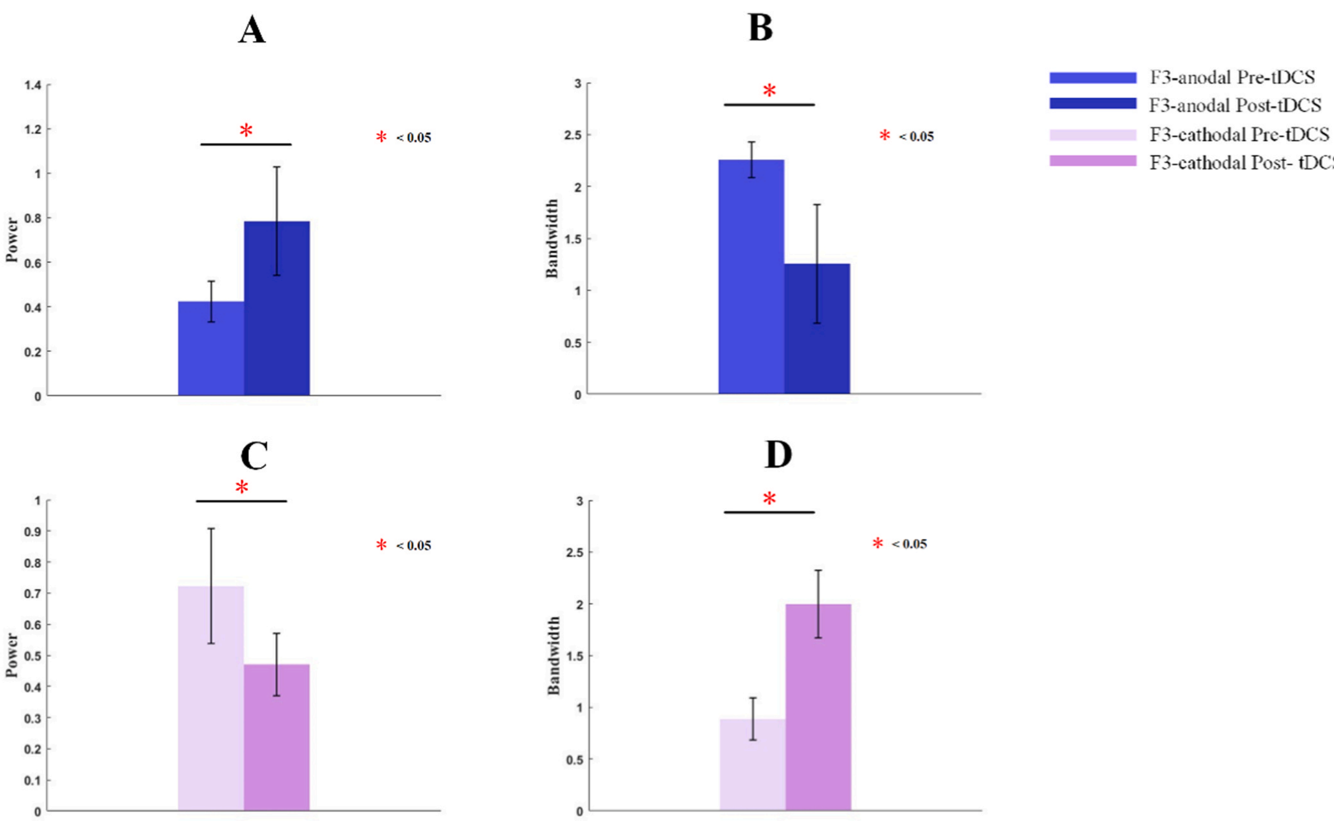

Fig. 6. The change in power spectrum after correcting for non-periodic neural activity before and after tDCS intervention. A: Statistical analysis results of alpha oscillation power following anodal tDCS intervention; B: Statistical analysis results of alpha oscillation bandwidth following anodal tDCS intervention; C: Statistical analysis results of alpha oscillation power following cathodal tDCS intervention; D: Statistical analysis results of alpha oscillation bandwidth following cathodal tDCS intervention.

decrease. However, for children who received cathodal tDCS intervention, no significant correlations were observed between non-periodic exponents and behavior. This highlighted the positive behavioral improvements brought about by anodal tDCS intervention, as depicted in Fig. 7.

Discussion

In this study, we aimed to investigate the effects of left DLPFC anodal and cathodal tDCS on behavior and the E/I balance in children with ASD. Twenty-four children with ASD were randomly divided into two groups, receiving either anodal or cathodal tDCS intervention 20 times. Behavioral assessments and EEG signal analysis were conducted to examine changes in power spectrum, non-periodic activity, and corrected alpha power. Firstly, behavioral assessments indicated that after anodal tDCS intervention, children with ASD showed significant improvements in social communication, social motivation, sensory behavior, body and object use, and other self-related behaviors. In

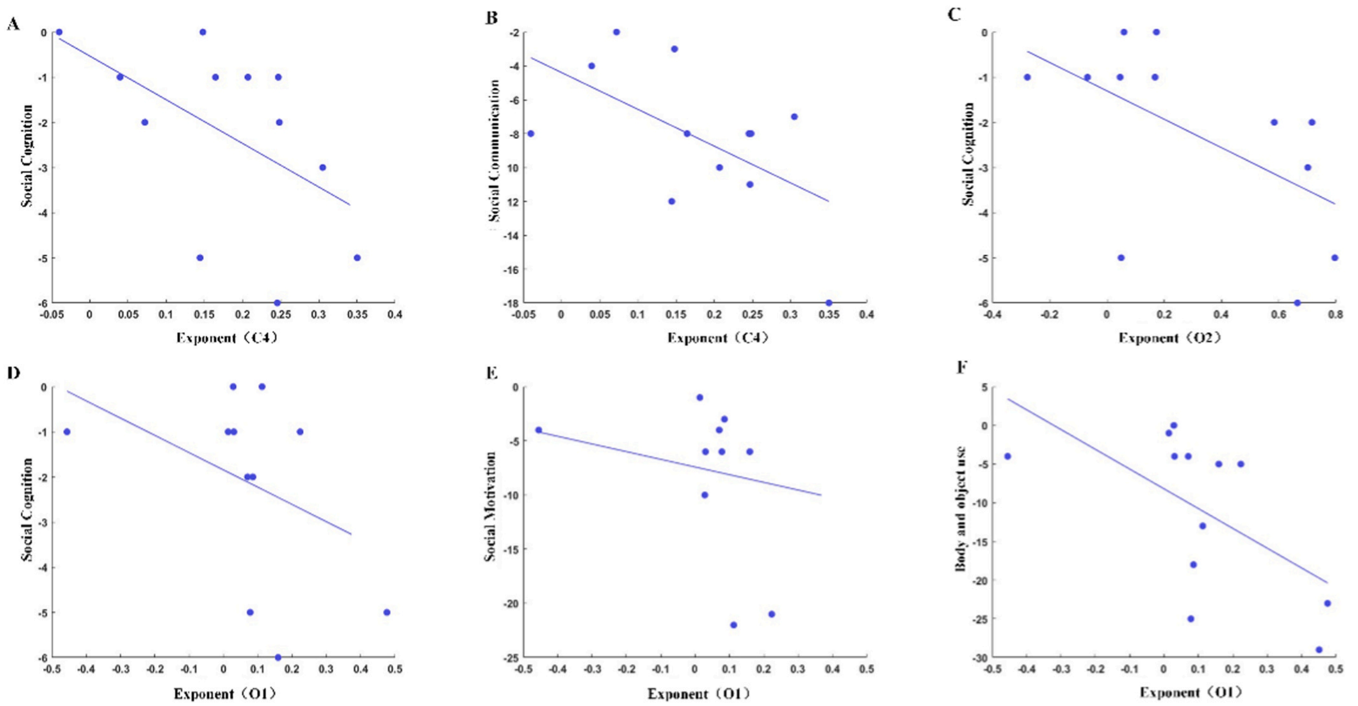

Fig. 7. Results of the correlation between non-periodic exponents and behavior in the anodal tDCS intervention group. A: Correlation between non-periodic exponent of channel C4 and social cognition; B) Correlation between non-periodic exponent of channel C4 and social communication; C) Correlation between non-periodic exponent of channel O2 and social cognition; D) Correlation between non-periodic exponent of channel O1 and social cognition; E) Correlation between non-periodic exponent of channel O1 and social motivation; F) Correlation between non-periodic exponent of channel O1 and body and object use.

contrast, there were no improvements observed in the behavioral aspects of children who received cathodal stimulation. Furthermore, it was observed that children who underwent anodal tDCS intervention exhibited significant increases in non-periodic neural activity (both exponent and offset) across the entire brain. Conversely, children who received cathodal tDCS showed the opposite trend. Additionally, after anodal tDCS intervention, there was a significant increase in alpha oscillation power among children with ASD, while cathodal tDCS intervention resulted in a decrease in alpha oscillation power. Lastly, correlation studies indicated that anodal tDCS intervention was significantly associated with negative correlations between non-periodic exponents and behavioral capabilities such as social communication in children with ASD. These findings collectively suggested that both anodal and cathodal tDCS over the left DLPFC indeed influenced behavior and the E/I balance in children with ASD. Anodal tDCS intervention appeared to have a more positive impact compared to cathodal intervention.

The EEG power spectrum exhibited both periodic and non-periodic characteristics, each carrying distinct physiological information. Non-periodic exponent and offset have been shown to relate to synaptic currents (Read and Siegel, 1996) and neuronal population spike responses (Ye and Hang Chan, 2023). Lower offsets and shallower slopes were associated with slower firing rates and fewer synchronous spike activities, reflecting the asynchrony of background neuronal discharges (Arutiunian et al., 2024). A reduction in non-periodic components indicated changes in synaptic E/I balance, possibly reflecting increased excitation and/or decreased inhibition within neural circuits. Studies involving patients and postmortem evidence suggested that inhibitory control played a crucial role in maintaining E/I balance, and its alterations were implicated in psychiatric disorders (Ulanov and Shtyrov, 2022; Qian et al., 2022). Previous research indicated a link between relative deficiency in inhibitory GABA and corresponding glutamate-mediated overexcitation in the pathogenesis of ASD (Sun et al., 2021). Neuroimaging studies have shown decreased Hurst indices in ASD cortex, where lower Hurst indices reflected increased cortical E/I ratios (Pretzsch and Floris, 2020). An animal study further demonstrated that reducing prefrontal cortex E/I ratio can rescue impaired social functions in ASD mouse models (Kratsman et al., 2016). Furthermore, numerous studies suggested that ASD affected not just specific brain regions but involved widespread connectivity across the brain (Schmitz et al., 2007; Chen, 2022; Kana et al., 2016). Therefore, the results of this study suggested that anodal tDCS intervention targeting the DLPFC enhances non-periodic activity across the entire brain in individuals with autism. This intervention effectively reduced the E/I ratio throughout the brain, thereby modulating neural activity in individuals with autism.

Previous studies have found that alpha neural oscillations played a crucial role in resting-state EEG research, with alpha band power widely regarded as a marker of E/I balance, where higher alpha power correlated with lower E/I ratios (Sauseng et al., 2009; Romei et al., 2008). Research on alpha oscillations typically linked them to attention, suggesting their underlying mechanism involved sensory suppression during selective attention (Clayton et al., 2015). Studies on selective attention and working memory tasks have indicated that increased alpha power enhanced the ability to suppress distracting information (Ku, 2018). Further research has associated alpha band neural activity in the frontal cortex with information gating and functional inhibition during working memory (Kim et al., 2024). Therefore, following the correction of non-periodic activity, we observed that anodal tDCS intervention helped increase alpha power in children with ASD. This finding elucidated the neural mechanisms of anodal tDCS intervention, further supporting tDCS as a potential therapeutic approach capable of improving symptoms in ASD patients by modulating the balance of brain excitation and inhibition.

In addition, we found a correlation between non-periodic neural activity and behavioral performance in children with ASD. Specifically, non-periodic exponents in ASD children who underwent anodal tDCS intervention were negatively correlated with aspects such as social communication and self-ability, whereas no such correlation was observed in children who received cathodal tDCS intervention. This suggested that anodal tDCS may have a positive impact on social abilities, self-awareness, and object use skills in children with ASD. Schneider's study demonstrated that a single 30-minute anodal tDCS intervention over the left DLPFC cortex improved language acquisition in 33 autistic individuals (Schneider and Hopp, 2011). Another study applied anodal tDCS to the right temporoparietal junction (rTPJ) in conjunction with social function and cognition interventions, resulting in significant improvements in social function and language fluency among patients (Esse Wilson et al., 2018). Amatachaya's study, using only scale assessments, found significant improvements in social function, perception, and cognition in children with ASD following left DLPFC anodal tDCS intervention (Amatachaya et al., 2015). Our study results provided strong evidence that anodal tDCS can improve behavioral capabilities in children with ASD.

In summary, we provided scientific evidence for the effectiveness of anodal tDCS intervention in ASD children. The findings also offered new insights into the regulation mechanisms of brain E/I balance in autism, providing a basis for future large-scale clinical research and the development of new therapeutic approaches.

However, this study had several limitations. Firstly, the sample size was small, and sensitivity to various estimates of E/I was not guided by previous research. In future experiments, we will gradually increase the sample size for further research. Another limitation was the focus solely on the effects of tDCS, while other neuromodulation strategies such as repetitive TMS and paired associative stimulation can induce changes in brain excitability through modulation of other cortical circuits. Our experimental design may not generalize to all external manipulations of excitability, as different estimates of E/I modulation may be sensitive to different cortical circuits. A third limitation was the small number of EEG channels. Due to the high proportion of non-compliant, low-functioning autistic children in our study, too many channels could not be reliably collected or ensured data quality. Fourthly, our study did not take into account the impact of potential confounding factors, such as baseline EEG activity, on the experiment. Individual differences in baseline EEG activity were an important confounder that can influence tDCS study results. In future research, we will use more refined statistical methods to better control for baseline EEG variability in order to improve the stability and reliability of the results. Additionally, we will increase the sample size to reduce the impact of individual differences on the study outcomes. Finally, not all potential EEG-based E/I estimation were considered in this study.

Compliance with ethical standards

This research was conducted in accordance with the Helsinki Declaration and approved by the Ethics Committee of Ningbo Rehabilitation Hospital.

CRediT authorship contribution statement

Xiaoli Li: Writing – review & editing, Funding acquisition. **Jiannan kang:** Writing – original draft, Methodology, Investigation, Conceptualization. **Juanmei Wu:** Software, Methodology, Data curation. **Xinping Huang:** Supervision, Formal analysis. **Wenqin Mao:** Writing – review & editing, Project administration.

Conflicts of Interest

The authors declare that there are no conflicts of interest in this research. None of the authors have any competing interests that could have potentially affected the conduct or reporting of this study.

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