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Modeling variability in tDCS-induced electric fields in depression: age-related comparisons in stratified adolescent and adult samples

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Modeling variability in tDCS-induced electric fields in depression: age-related comparisons in stratified adolescent and adult samples

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Abstract

Transcranial direct current stimulation (tDCS) has emerged as a safe, cost-effective, and scalable therapeutic strategy, with moderate effects for depression in adult patients. However, there are no published studies on tDCS in children and adolescents with depression. This study is the first to investigate the simulated regional electric fields (EF) in adolescents at risk for or currently experiencing depression. A total of 150 Brazilian adolescents (50 at low risk, 50 at high risk of developing depression, and 50 diagnosed with depression) were drawn from the Identifying Depression Early in Adolescence Risk Stratified Cohort (IDEA-RiSCo) and compared to 51 adults with depression. Employing a tDCS protocol designed for adults, we measured the simulated EF magnitude in the bilateral dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC), both key brain areas involved in depression. Statistically significant differences in EF magnitudes were observed between each adolescent group (low risk, high risk, and diagnosed with depression) and adults with depression, while no significant differences were found among the adolescent groups themselves. By focusing on a population that is often underrepresented in depression research, this study may pave the way for future trials to treat depressive disorder in adolescents with tDCS.

Keywords: transcranial direct current stimulation (tDCS), electric fields, depression, pediatric populations, brain development, computational modeling

Introduction

Depressive disorder is a mental health condition affecting nearly 300 million individuals worldwide, significantly impairing daily activities, work performance, and overall quality of life, with the potential to lead to fatal outcomes[1]. In the youth population, depression is among the leading causes of disability globally, especially during adolescence—a critical period characterized by heightened vulnerability[2]. First-line treatment options for depression, both in adults and in youth, include pharmacotherapy and psychotherapy. However, approximately one-third of these patients do not achieve remission despite multiple treatment attempts, highlighting the need for alternative therapies[3]. Over the past few decades, research has considerably advanced the application of non-invasive brain stimulation (NIBS) techniques as promising interventions for depression[4]. One of these techniques is transcranial direct current stimulation (tDCS). It involves applying a low electrical current to the scalp to alter cortical excitability and enhance neuroplasticity through γ-aminobutyric acid (GABA) and glutamatergic systems[5–7]. tDCS has emerged as a safe, cost-effective, and scalable therapeutic strategy, with moderate effects for depression in adult patients [8].

However, tDCS has been used predominantly in the adult population. Current studies applying tDCS to young populations have largely targeted autism spectrum disorders and Attention Deficit Hyperactivity Disorder[9]. While these studies indicate the safety and potential effectiveness of tDCS for these conditions[10–13], they leave a significant gap in understanding its application in adolescents—with and without risk factors for psychiatric disorders[9]. More specifically, the early assessment of depression in adolescents is vital, as it can prevent long-term consequences and improve early intervention outcomes[14]. Given that universal therapeutic approaches are less effective than targeted interventions for high-risk individuals, stratifying pre-MDD adolescents into low- and high-risk groups is essential for effective prevention[15]. Notably, there are currently no published studies on tDCS in children and adolescents with mood disorders[16].

Computational modeling using finite element method (FEM)[17] can be useful approaches to guide the optimization of tDCS protocols in children and adolescents by adapting protocol parameters derived from adult studies[18,19].

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This approach enables the investigation of the distribution and magnitude of the electric field (EF) induced by tDCS. Since the EF and the resulting neuronal changes are polarity-dependent[20], and given that anatomical properties significantly influence these effects[21], modeling the EF is valuable for understanding how variations in anatomy—such as between adolescents and adults—impact the magnitude and distribution of the EF, and consequently, the effects of tDCS.

For instance, in a study using conventional tDCS configurations (2mA current intensity and 25 cm^2 electrodes over primary motor cortex (M1)-supraorbital area), the peak EFs in the adolescent brain were approximately 1.5 times higher than in the adult brain[22]. Although 2mA currents employed in adult depression trials are positioned to penetrate cortical tissue more effectively in younger individuals, modeling studies conducted in rodents suggest that this level of current intensity does not result in tissue damage[23]. Nonetheless, due to the scarcity of studies evaluating the impact of established tDCS protocols on adolescents, researchers have recommended more conservative dosing strategies. Despite its importance, limited research, even in the adult population[24], has explored how anatomical variability during development affects the distribution of EF in critical regions associated with depression treatment, such as the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC)[25–27].

Therefore, this study is the first to investigate the EF characteristics across different age and depression risk groups by using adolescents from the Identifying Depression Early in Adolescence Risk Stratified Cohort (IDEA-RiSCo)[15,28] at risk for depression or with current depression and comparing them to adults with depression using tDCS protocols parameters that are usually considered for adult populations with depression. The primary outcome was the difference in the simulated EF magnitude in the bilateral DLPFC and ACC regions across groups (adolescents at low or high risk for depression or with current depression compared to adults with depression). The secondary outcome was the difference in the simulated EF magnitude in the bilateral DLPFC and ACC regions between groups of adults and adolescents with depression and among adolescents at risk for depression or with current depression. The significance of this study lies not only in its unique evaluation of

age- and risk-specific effects on tDCS-related electric fields but also in its potential to inform future research and clinical practices in treating depression in pediatric populations.

Materials and Methods

Study design

This cross-sectional comparative study was designed to evaluate the simulated EF magnitudes in the bilateral DLPFC and ACC across different groups (adolescents at low or high risk for depression or with current depression compared to adults with depression). Our study consisted of 150 Brazilian adolescents from the IDEA-RiSCo cohort[15,28], classified into three groups: (i) low risk and (ii) high risk of developing depression, and (iii) those diagnosed with depression. Additionally, a subset of 51 adults diagnosed with major depressive disorder (MDD) was included for comparative purposes, providing further insights into differences across age groups.

Participants

Adolescents at risk for depression or with current depression from the IDEA-RiSCo cohort[2,15]

The sample comprised 150 adolescents aged between 14 and 16 years (mean age of 15.64 ± 0.67 years, 75 males (50%)), evenly distributed into three groups: 50 classified as low risk (LR) of developing depression, 50 as high-risk (HR) and 50 with MDD, without pharmacological treatment. Each group comprised 25 females and 25 males. Screening was conducted in 7720 adolescents from public schools in Porto Alegre, in the south of Brazil, and participant selection was based on the IDEA-Risk Score (IDEA-RS)[29], a stratification tool developed to identify risk levels, as part of the IDEA-RiSCo study[15]. The stratification criteria classified the low-risk group as those with IDEA-RS scores at or below the 20th percentile; the high-risk group as those with scores at or above the 90th percentile; and the MDD group as those with a current diagnosis of MDD who also scored at or above the 90th percentile[15]. Absence of a lifetime history of depressive disorders (including dysthymia) for the low risk and high risk groups and presence of a current depressive episode for the MDD group were determined through clinical interview using the

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Brazilian Portuguese translation of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL)[15,28,30]. Depressive symptoms were assessed using the Children's Depression Rating Scale–Revised (CDRS-R), validated for use in adolescents. Data collection was approved by the Brazilian National Ethics in Research Commission (CAAE 50473015.9.0000.5327). All participants provided written assent, with additional written consent obtained from their primary caregivers.

Our study is a secondary exploration based on adolescents' available data from a well-powered study, the IDEA-RiSCo study, for which the sample size was estimated for the study of neurobiological differences between low- and high-risk adolescents. To keep the same ratio per group (n = 50) to evaluate neurodevelopmental effects, we added 51 adults with MDD, described in section 2.2.2.

Adults with depression

The adult population comprises 51 individuals aged 18 to 65 years (mean age of 40.02 ± 11.00 years, 12 males (23.5%)). All participants initially presented with a Hamilton Depression Rating Scale (HDRS) score of 17 or higher and had their diagnosis of MDD confirmed through the Mini International Neuropsychiatric Interview (MINI)[31]. Exclusion criteria included presence of other mental disorders, severe neurological or clinical diseases, severe suicidal ideation, psychotic symptoms, manic symptoms (score > 8 on the Young Mania Rating Scale), rapid cycling bipolar disorder, and contraindications to repetitive transcranial magnetic stimulation (rTMS) or magnetic resonance imaging (MRI), such as the presence of metal or electronic implants in the cephalic segment, epilepsy, and claustrophobia. The study was approved by local and national ethics committees (CAAE: 52384921.6.0000.0068).

MRI data acquisition

Structural magnetic resonance imaging (MRI) was performed for both the adolescent and adult samples. For adolescents, scans were conducted using a 3T Ingenia scanner (Koninklijke Philips N.V., The Netherlands), software version 5.3.1, at the Hospital de Clínicas de Porto Alegre, Porto Alegre (RS), Brazil. Adults underwent MRI using a 3T Achieva scanner (Philips) at the

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Instituto de Radiologia do Hospital das Clínicas, São Paulo, Brazil. All participants, regardless of age, adhered to standardized procedures prior to imaging acquisition, which included the removal of metal objects to ensure safety and image quality, and they were instructed to keep their heads still during the scan. Participants were informed about the duration of the scan and were assured that they could communicate with the experimenter at any time.

For the adolescent participants, high-resolution structural images were acquired using T1-weighted volumetric acquisition (MPRAGE) in the sagittal plane with the following parameters: TR = 8.7 ms, TE = 4 ms, TI = 900 ms, flip angle = 8°, field of view = 256 x 242 mm, with 200 slices of 0.94 mm thickness and an acquisition matrix of 272 x 255, yielding a voxel resolution of 0.94 x 0.94 x 0.94 mm^3. Notably, dynamic stabilization was not employed for adolescent scans. Dynamic stabilization was not applied because the acquisition protocol used in this study did not include this feature for structural imaging. The Philips Ingenia 3T scanner (software version 5.3.1) did not include a prospective motion correction module for anatomical scans. Head motion was minimized using foam padding and verbal instructions before and during scanning. During acquisition, real-time image previews were monitored, and the sequence was repeated whenever motion was observed. After acquisition, images were visually inspected to ensure the absence of motion artifacts and the anatomical precision required for subsequent analyses.

Adult patients had T1-weighted images collected with a different set of parameters: repetition time (TR) = 7.0 ms, echo time (TE) = 3.2 ms, excitation angle (FA) = 8°, field of view (FOV) = 240 x 240 mm^2, and a matrix of 240 x 240 pixels, resulting in 180 slices of 1 mm thickness, yielding a voxel size of 1 x 1 x 1 mm^3. Additionally, a T2-weighted sequence was utilized with TE = 287 ms, TR = 2100 ms, 180 axial slices (thickness = 1 mm), FA = 90º, and FOV = 256 x 256 mm. Dynamic stabilization was employed for the adult participants to minimize motion artifacts, along with cardiac and respiratory monitoring during image acquisition. More than 90% of the adult sample was actively medicated at the time of MRI acquisition.

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E-field modeling analysis

Creating head models

Head models were generated via *charm* from the SimNIBS (v4.0.0), a free and open-source software package developed by the Danish Research Centre for Magnetic Resonance in Copenhagen, Denmark. The charm tool enables general modeling for each subject using T1-weighted MRI facilitating the reconstruction of high-resolution head models. An examination of segmentations slice-by-slice was undertaken to ensure accurate tissue classifications. Subsequently, tetrahedral volume mesh head models were generated based on the segmentation surfaces utilizing SimNIBS[32,33].

Simulation

The simulation phase began after the individual tetrahedral volume mesh head models were created. SimNIBS was employed to conduct simulations utilizing a standard bilateral montage, wherein tDCS electrodes were positioned with the anode and cathode at F3 and F4, respectively, using the standard SimNIBS methodology to map the 10-10 EEG system (Figure 1). In the simulations, the electric current intensity was set to 2 mA for the left hemisphere and -2 mA for the right hemisphere. The electrodes, configured in a rectangular shape, measured 5 x 5 cm, with a thickness of 5 mm. The saline-soaked sponges utilized in the simulation had a thickness of 6 mm. The conductivity parameters were adjusted based on the default settings in SimNIBS, encompassing white matter (0.126 S/m), gray matter (0.275 S/m), cerebrospinal fluid (1.654 S/m), skull (0.010 S/m), skin (0.465 S/m), and eyeballs (0.500 S/m). We considered the same values for both adolescent and adult samples to focus on the morphological effects[34].

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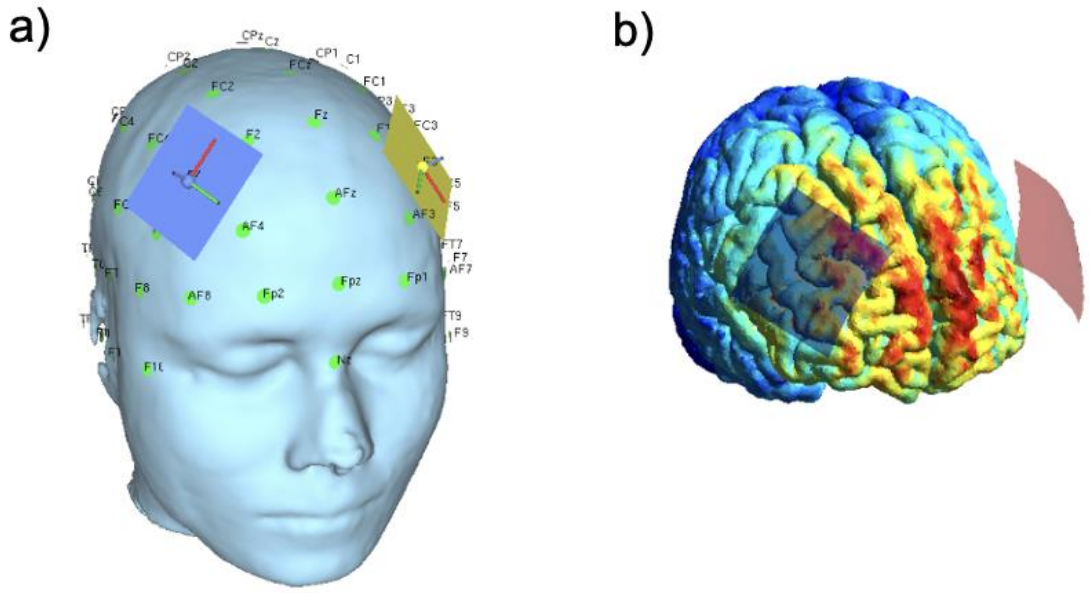


Figure 1: Illustration of the tDCS settings performed in the present study using software SimNIBS. (a) Demonstration of the stimulation site: anodal electrode positioned over the left DLPFC (F3 in 10-10 EEG system, yellow electrode) and cathodal over the right DLPFC (F4 in 10-10 EEG system, blue electrode) and (b) simulated electric field for the tDCS. The colour represents the simulated electric field magnitude according to the montage settings, with red color representing the highest values. tDCS: transcranial direct current stimulation. EEG: electroencephalography. DLPFC: dorsolateral prefrontal cortex.

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Regions of Interest (ROIs) Definition

The selected ROIs targeted for the study were the brain areas in which simulated EF strength (represented as "magnE" in SimNIBS software) was assessed. Magnitude in this context refers to the strength or intensity of the EF applied to a specific brain region. It is quantitatively represented by the variable "*magn E*" and typically measured in volts per meter (V/m). This measure reflects the extent of EF exposure a particular brain area receives during stimulation, influencing the neural activity in that region.

In order to define the DLPFC, we used the Sallet atlas (2013)[35], which provides a detailed parcellation of the area based on functional and tractography data through a cross-species comparison of both humans and primates. The atlas divides the DLPFC into 10 subregions, denominated "clusters", which are also recognized by their corresponding Brodmann areas

(BAs). The DLPFC is a critical area involved in executive functions such as working memory, cognitive control, and decision-making. The Sallet et al. atlas (2013) defines the following subregions: the Supplementary Motor Area (SMA) (cluster 1), the pre-Supplementary Motor Area (pre-SMA) (cluster 2), Brodmann area 9 (cluster 3), and Brodmann area 10 (cluster 4). Additionally, on the lateral surface, six areas were identified and labeled as follows: area 9/46d (cluster 5), area 9/46v (cluster 6), Brodmann area 46 (cluster 7), area 8A (cluster 8), anterior dorsal premotor area (PMd) (cluster 9), and area 8B (cluster 10) (Figure 2, Table 1 from Supplementary Material). These clusters, as defined by the atlas, helped to pinpoint specific functional and anatomical subdivisions within the broader DLPFC area, providing a refined understanding of its diverse roles and connectivity patterns.

The ACC ROI was assessed by using the parcellation of the Brainnetome atlas[36], a connectivity-based parcellation framework that identifies the subdivisions of the whole human brain, providing a cross-validated and multimodal anatomical and functional parcellation atlas based on structural MRI, diffusion tensor imaging and resting-state fMRI connectivity. In this study, two subregions of the ACC were analyzed in both the left and right hemispheres. Specifically, we focused on the subgenual ACC (sgACC) and pregenual ACC (pgACC) using the “A32sg” and “A32p” ROIs from the Brainnetome atlas, due to their significant roles in predicting antidepressant response[27] (Figure 2).

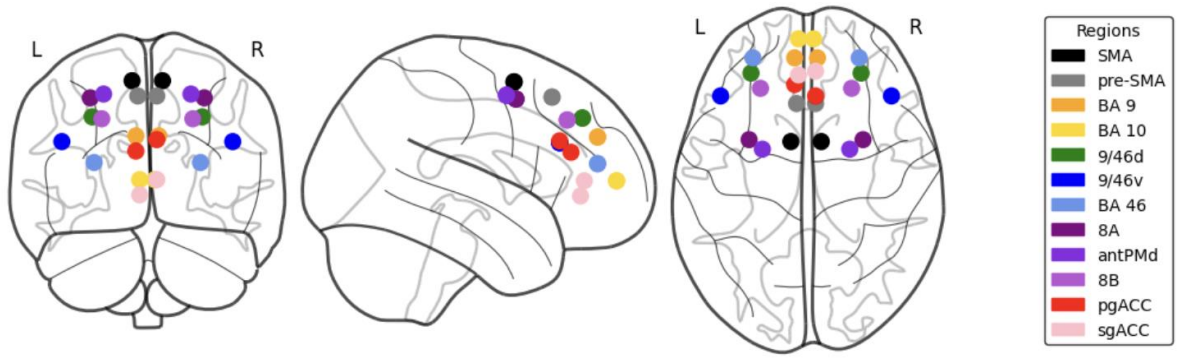


Figure 2: Regions of Interest (ROIs). For illustrative purposes, the regions were presented as circles centered on their center of mass in MNI coordinates. SMA: Supplementary Motor Area. BA: Brodmann area. ant PMd: anterior dorsal premotor

area. ACC: Anterior Cingulate Cortex. pg: pregenual. sg: subgenual. MNI: Montreal Neurological Institute.

Electric field values calculation

We first used the *mni2subject* function to transform the ROI's coordinates from MNI space into the individual participant space. Subsequently, the *nii2msh* function was applied to generate surface meshes from the transformed clusters. To quantify the Electric Field (EF) magnitudes at the individual participant level, the mesh files generated for each ROI for each participant were processed through a custom MATLAB script[37]. This script calculated the regional EF magnitudes for each ROI at the individual level.

Statistical analysis

To standardize depressive symptom scores measured using distinct tools—HDRS for adults and CDRS for adolescents—we employed Z-score transformation. This calculation was performed separately for both the adult and adolescent groups to account for potential differences in severity and scoring distribution.

Then, we conducted a series of statistical analyses to compare EF magnitudes across different brain regions between adolescents and adults. The groups were included as factors in the dataset, allowing for appropriate variance analysis between the age groups. This analysis focused on 24 predefined brain regions, as previously described. For each brain region, a one-way ANCOVA was conducted to evaluate significant differences in EF magnitudes between the predefined groups (adolescents at low or high risk for depression or with current depression compared to adults with depression), controlling for the MRI acquisition site. We also reran the models to assess the effects of gender, as the proportion of males and females differed between adults and adolescents. The p-value associated with the ANOVA F-statistic was recorded to assess significance. If the ANCOVA p-value for a region was less than 0.05, indicating significant differences between groups, then Tukey's HSD test was performed for post-hoc analysis, comparing all pairwise group means and providing adjusted p-values for each comparison.

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To mitigate the increased likelihood of Type I errors due to multiple comparisons, we applied the False Discovery Rate (FDR) correction to the ANOVA p-values. Results were presented considering region names, raw and FDR-corrected ANOVA p-values, and Tukey HSD post-hoc results with comparison groups and associated p-values, with detailed information included in the Supplementary Material. There were no missing data in our study.

Results

A total of 201 individuals were included in the study. The flow diagram with screening, inclusion and exclusion information can be seen in Figure 3. While our exclusion criteria aimed to ensure safety and diagnostic accuracy, they may have introduced selection bias by excluding individuals with psychiatric comorbidities, low IQ, or medical contraindications to MRI. This could limit the applicability of findings to more severely affected or comorbid populations. Additional exclusions during adolescents screening included: in the low-risk group, four participants were excluded after criterion re-evaluation, one due to IQ <70, two with psychiatric comorbidities, five with unconfirmed MDD, and two for other reasons (metal implant and blood collection refusal). In the high-risk group, two individuals were excluded for IQ <70, one for psychiatric comorbidities, eight with confirmed MDD, and two for other reasons. The MDD group experienced greater exclusions: eight following criterion re-evaluation, one for IQ <70, one not meeting post-pubertal criteria, twenty for psychiatric comorbidities, fifty due to unconfirmed diagnosis, and three for reasons including metal implants and MRI non-completion. Participants without lifetime depression (LR and HR) or with current MDD (MDD group) were invited for biological sampling. We also add that in the adolescent sample we have low (LR) and high (HR and MDD) levels of risk factors, which means that the findings are not necessarily generalizable to individuals with intermediate risk levels. Adult exclusions included one for medical complications, one for symptom worsening, one due to treatment non-response, one for work reasons, and four for missing MRI.

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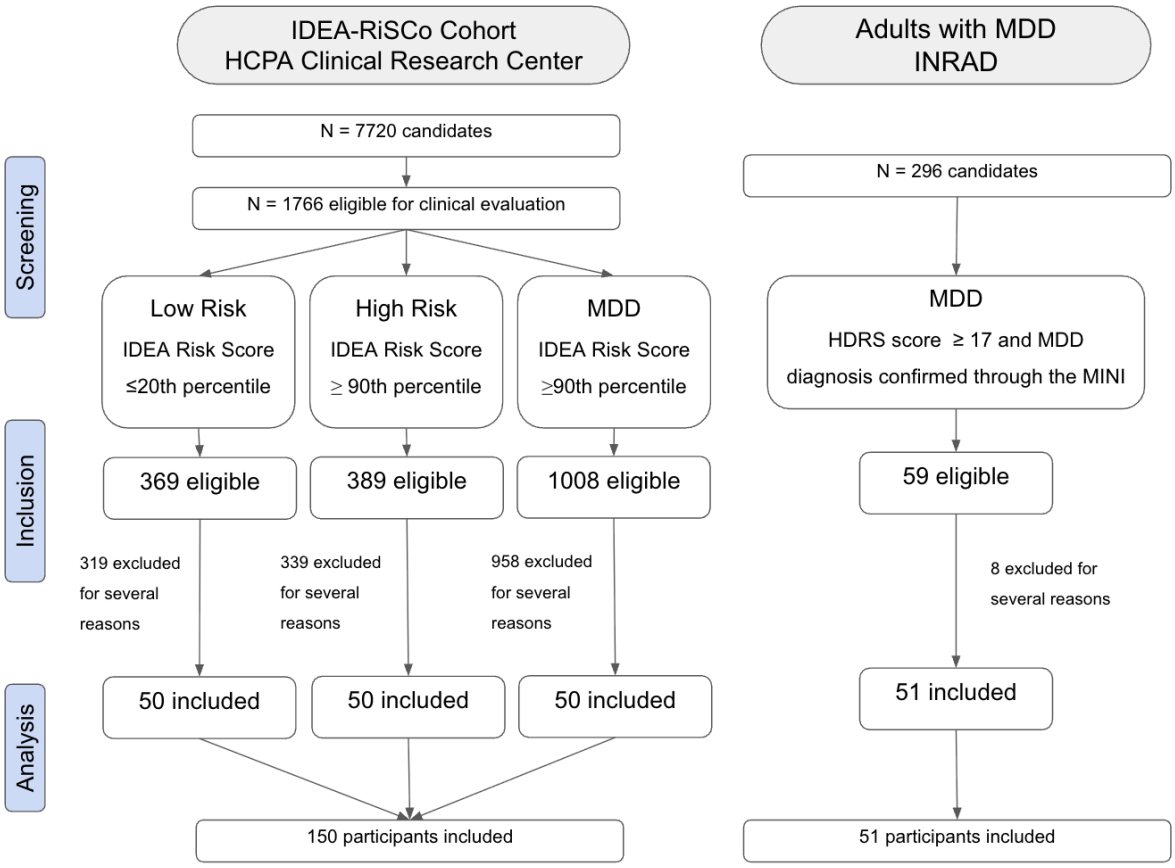


Figure 3: Flow diagram of the study. HDRS: Hamilton Depression Rating Scale. HCPA: Hospital das Clínicas de Porto Alegre. MDD: Major Depressive Disorder. IDEA: Identifying Depression Early in Adolescence. IDEA-RiSCo: Identifying Depression Early in Adolescence Risk Stratified Cohort. More details regarding adolescents group allocation and inclusion and exclusion criteria can be found in Figure S3.3 in Supplementary material from the original study.

The demographic characteristics of all subjects are shown in Table 1. It was found significant group effects on age ($p < 2e\text{-}16$), sex ($p = .012$), and z-scores ($p < 2e\text{-}16$), with adolescents in the LR, HR, and MDD groups being significantly younger and having lower z-scores compared to MDD adults, except from the MDD adolescents having higher z-scores compared to MDD adults. No significant differences among the adolescent groups in terms of age and sex were found ($p > .05$). Significant differences in z-scores were found between the MDD adolescent group compared to LR ($p < .001$) and HR ($p < .001$) groups.

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Table 1. Population description and statistics.

	LR adolescents (N = 50)	**HR adolescents (N = 50)**	**MDD adolescents (N = 50)**	**MDD adults (N = 51)**	**p**
Age (mean ± SD)	15.43 ± 0.81	15.76 ± 0.83	15.80 ± 0.75	40.02 ± 10.11	<2e-16
Female (%)	25 (50%)	25 (50%)	25 (50%)	39 (76.5%)	0.012
DS raw score (mean ± SD)	19.33 ± 2.85 (CDRS)	22.64 ± 5.44 (CDRS)	50.94 ± 9.79 (CDRS)	18.24 ± 2.70 (HDRS)	
DS z-score (mean ± SD)	-0.7 ± 0.3	-0.5 ± 0.35	1.3 ± 0.6	0.28 ± 1	<2e-16

MDD = Major Depressive Disorder, HR = High Risk of Developing MDD, LR = Low Risk of Developing MDD, DS = depression scale, HDRS = Hamilton Rating Scale for Depression, CDRS = Children's Depression Rating Scale. SD - standard deviation.

Differences in EF magnitudes across groups

There were statistically significant differences in the mean EF magnitudes across the adolescents groups (MDD, high-risk, low-risk) and adults with MDD for every ROI analyzed (p-FDR = 0.05, Figure 4). The most significant differences were observed in the right SMA area (cluster 1) and the right pregenual ACC (see Table 2 in the Supplementary Material). The smallest significant difference was observed in the left area 9/46v (cluster 6), followed by the right Brodmann area 10 (cluster 4) (see Table 2 in the Supplementary Material). The differences remained significant even after controlling for gender effects.

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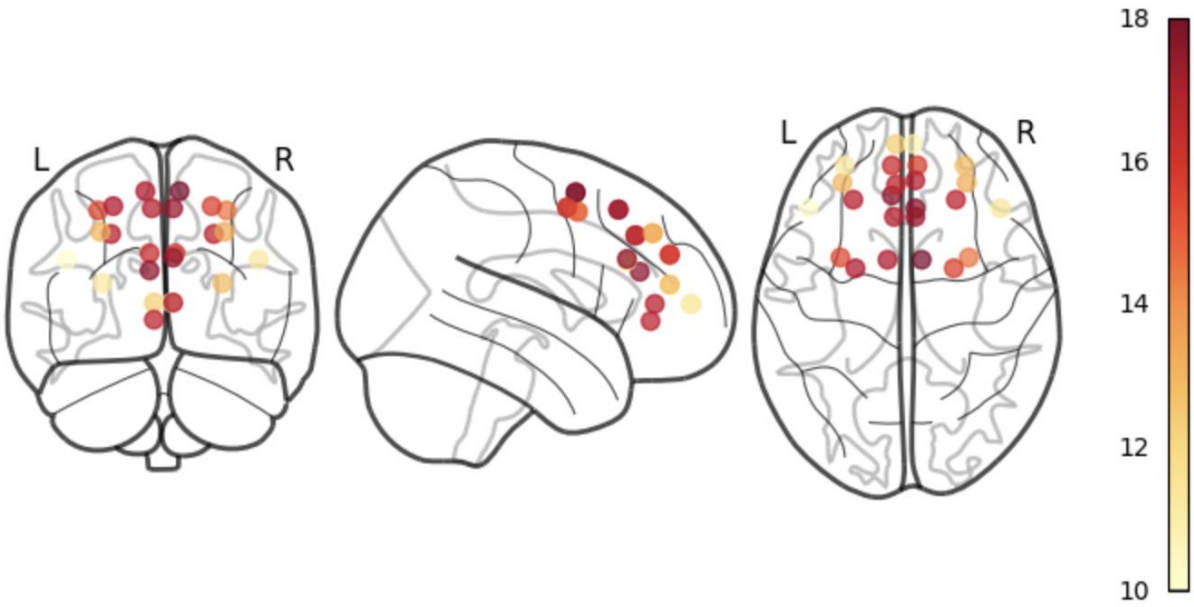


Figure 4: Differences in regional electric field magnitudes across groups (adolescents at low or high risk for Major Depressive Disorder (MDD) or with current MDD compared to adults with MDD) (p-FDR = 0.05). For illustrative purposes, the regions were presented as circles centered on their center of mass in MNI coordinates. Colorbars represent p-FDR values converted to -log10 scale. *MNI: Montreal Neurological Institute. FDR: False Discovery Rate.*

Differences in EF magnitudes between adults and adolescents with depression

Post-hoc analyses indicated MDD, HR and LR adolescent groups exhibited significantly ($p < 0.05$) higher regional EF magnitude compared to adults with MDD in both hemispheres (Figures 5a, 5b and 5c, respectively. See also Table 2 in the Supplementary Material). The adolescent group with MDD exhibited less differences in regional EF magnitudes compared to adults with MDD, followed by the HR and LR groups, respectively. The differences remained significant even after controlling for gender effects.

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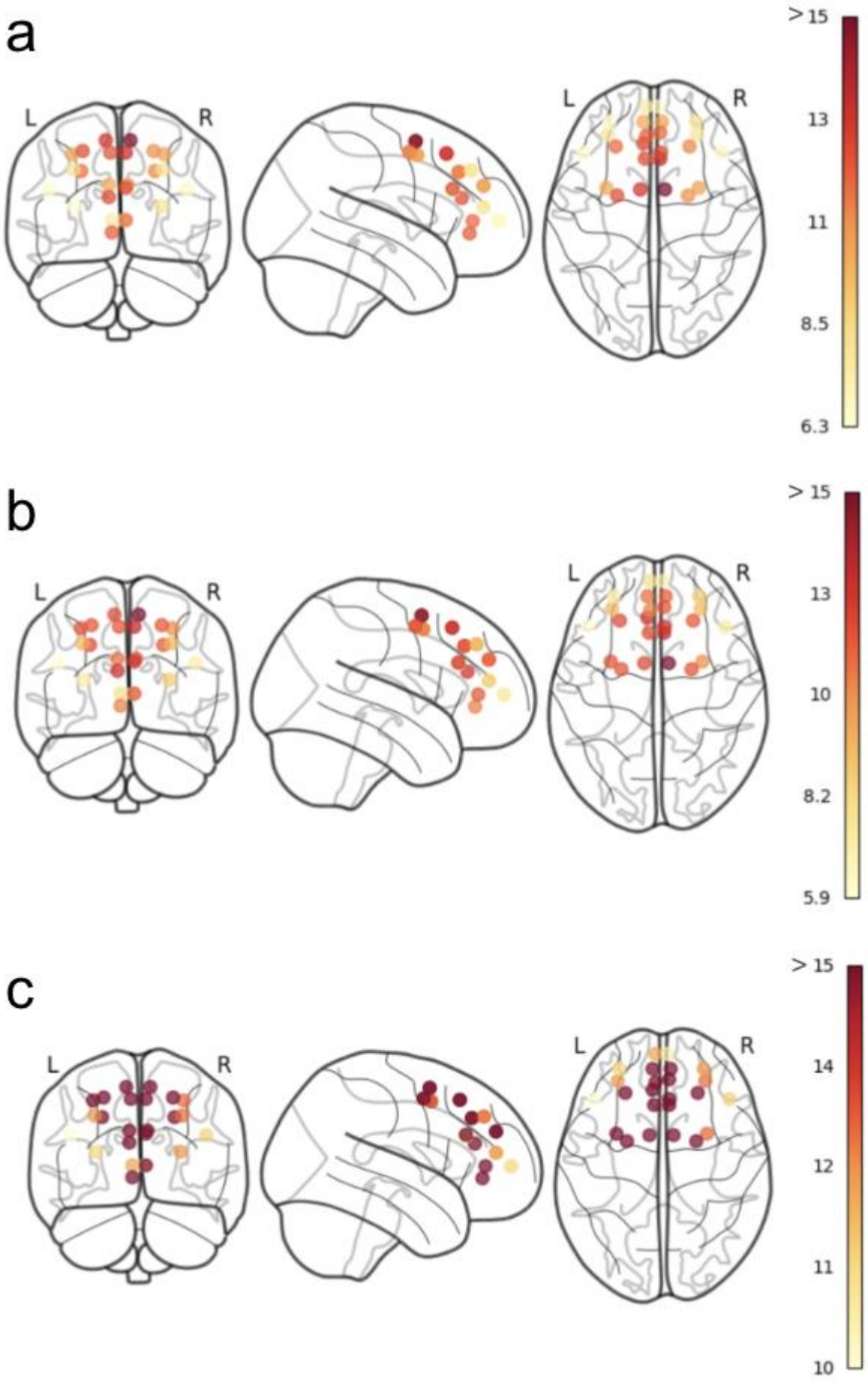

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Figure 5: Post-hoc pairwise comparisons of the differences in regional electric field magnitudes between (a) adolescents with Major Depressive Disorder (MDD) and adults with MDD; (b) adolescents at high risk of MDD and adults with MDD; and (c) adolescents at low risk of MDD and adults with MDD. Significant values were set at Tukey p-value < 0.05. For illustrative purposes, the regions were presented as circles centered on their center of mass in MNI coordinates. Colorbars represent p values converted to -log10 scale. *MNI: Montreal Neurological Institute.*

Differences in EF magnitudes among adolescents identified as low risk, high risk, and diagnosed with depression

Among adolescent groups, the regional EF magnitude did not differ significantly between risk and diagnosis groups (p > .05, see Table 2 in the Supplementary Material) in both hemispheres. The differences remained non-significant even after controlling for gender effects.

Discussion

This study aimed to investigate simulated EF magnitude in adolescents at risk for depression or with current depression compared to adults with depression using tDCS protocols parameters that are usually considered for adult populations with depression. Findings indicate that (1) depression protocols applied to the adult population induce significantly higher regional EF magnitude in adolescents with depression compared to adults with depression and (2) among adolescents, non-significant induced regional EF magnitude differences were observed.

Adolescents exhibited significantly higher EF magnitudes in all DLPFC and ACC regions compared to adults with depression. In a recent study with high definition transcranial electrical stimulation in healthy participants, an inverse linear relationship between age and EF intensity was observed across the lifespan, with anatomical factors such as skull thickness, scalp thickness, and epidural cerebrospinal fluid thickness being important in the inter-individual EF variability[34]. This inverse linear relationship was also noted when considering transcranial magnetic stimulation[38]. Our findings corroborate this relationship between age and EF, even in the case of patients with depression.

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However, the question still remains as to how this relationship influences clinical outcome.

Using a subsample of 16 adult patients who underwent tDCS in the Escitalopram versus Electrical Current Therapy for Treating Depression Clinical Study (ELECT-TDCS) trial[39], Suen and collaborators applied computational modelling considering a current intensity of 2 mA and electrode sizes of 5 × 5 cm^2, the anode and the cathode positioned over F5 and F6, respectively. They found high variability in the simulated EF strength among patients, with higher bilateral ACC and DLPFC simulated EF strength associated with bigger decrease of negative affect and higher left ACC simulated EF strength related to bigger depression scores decrease[24]. Although the findings of Suen and collaborators may suggest that higher interindividual baseline EF strength informs better behavioral outcomes after tDCS, previous studies indicate that the excitatory or inhibitory tDCS effects found in adults cannot be automatically extrapolated to younger populations. As an example, a preliminary pediatric study with participants aged between 11 to 16 years old, found that 1-mA cathodal tDCS produced an unexpected excitatory effect on cortical excitability of the motor cortex. Additionally, 0.5 mA cathodal tDCS decreased while the 0.5 mA anodal stimulation induced any change on cortico-spinal excitability, indicating age-dependent effects of tDCS on cortical excitability of the primary motor cortex [40]. Similarly, another study found that 1 mA cathodal tDCS suppressed the N100 amplitude in healthy children and adolescents compared with sham stimulation, while the N100 amplitude was not modified by 1 mA anodal tDCS[41].

Additionally, while adolescents exhibit higher EF magnitudes than adults under the same prefrontal tDCS protocol, it does not necessarily follow that the same protocol will translate into greater clinical efficacy. It is important to acknowledge that tDCS can produce non-linear effects, with higher current intensities (e.g., 2 mA versus 1 mA) not necessarily leading to stronger neurophysiological and behavioral/cognitive outcomes[42,43]. Moreover, we stress that the excitatory and inhibitory effects of tDCS cannot be directly transferred from adults to adolescents[44]. Additionally, we highlight the neurodevelopmental differences in adolescents, specifically addressing how variations in conductivity due to anatomical changes, like increased skull thickness and expanded

cerebrospinal fluid (CSF) space[45,46], contribute to the variability in EFs. These aspects highlight that responses to tDCS are often non-linear, influenced by factors beyond mere current intensity.

The regional EF magnitude did not differ significantly between adolescents at risk for depression and with current depression. In studies comparing simulated EF strength by tDCS in adults with MDD and healthy controls, some found significant reduction when considering the 99.5th percentile of the simulated EF strength[47], a specific part of the superior frontal sulcus[48], whole-brain and Sallet areas 8B and 9[49]. Csifcsák and collaborators suggested that the anatomical changes associated with depression did not influence the stimulation effects[48]. Using the same adolescent sample from our study, it was found that there were no significant differences in whole-brain cortical and subcortical volume, surface area or cortical thickness between adolescents at risk for depression or with current depression[50]. Some studies did not report changes in volume or thickness in the brains of depressed adolescents[51,52], while others pointed out significant changes in regional brain volume[53,54], cortical thickness[55] and surface area[52], calling for more research to establish more robust patterns of structural brain changes in depressed adolescent patients. It is noteworthy that both the present and Rohrsetzer and collaborators studies considered a risk-enriched cohort[15] with adolescents stratified by their risk of developing depressive disorder using a composite score that encompasses 11 sociodemographic variables[29], which can provide a more nuanced perspective towards neurobiological correlates of at risk and currently depressed adolescents. For the adult population, in contraposition, an ancillary study from the ELECT-tDCS trial found that larger left prefrontal cortex baseline gray matter volume was associated with bigger antidepressant effects after tDCS[56].

The absence of significant differences in EF magnitude among the adolescent groups (LR, HR, and MDD) represents a favorable outcome for protocol standardization. This finding indicates that even with the slight neurobiological changes linked to varying levels of depression risk, these alterations are not substantial enough to notably impact impedance or current flow. Consequently, this consistency supports the application of tDCS protocols across different clinical adolescent populations without the need for

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individualized adjustments based purely on risk status. By streamlining treatment strategies in this manner, we enhance the feasibility of tDCS implementation in real-world clinical settings, thereby promoting uniformity and potentially improving treatment outcomes across diverse adolescent subgroups.

Research focused on applying tDCS in adolescents must consider the unique aspects of neurodevelopment to ensure appropriateness and efficacy of the intervention. Studies of tDCS applied over the motor cortex of adults indicated that anodal tDCS increases excitatory neurotransmitter glutamate activity, while cathodal tDCS increases inhibitory neurotransmitter GABA[5]. Inhibitory potential of GABA increases throughout development[57], having an unexpected excitatory effect in early development[44]. Beyond the acute phase, the prolonged tDCS effects depend on modifications in the efficacy of N-methyl-D-aspartate (NMDA) receptors[5], which promotes excitatory neurotransmission in early life, while in the mature brain it is dominated by the synergy between α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-NMDA receptors[44]. In addition to alterations in the GABAergic and glutamatergic systems throughout neurodevelopment, various processes, including anatomical maturation and cortical network development, also occur[58–61]. In this context, while an important factor for evaluating the efficacy and safety of tDCS protocols, EF magnitude does not capture all brain individual variations, as it does not consider, for example, the functional dynamics or the brain networks reconfigurations[62]. When considering multimodal MRI analysis, the resting-state functional MRI has been the most robust depression onset predictor in many studies[63–65].

We considered the positioning of the anode over the left DLPFC and the cathode over the right DLPFC, since this is the most used positioning in trials that evaluated tDCS in adult depressive patients[8]. This positioning seeks to normalize the hypoactivity in the left DLPFC and hyperactivity in the right DLPFC found in the brains of adult depressive patients[66]. However, the frontal imbalance hypothesis does not seem to match the findings in the brains of depressed adolescents, who showed unexpected hyperactivation in the DLPFC when faced with tasks with negative stimuli[67], undermining usual electrode positioning for adults as the most appropriate for the adolescent population. Another relevant issue refers to the intensity of current applied, its safety and

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tolerability in adolescents[40,41,68]. In a study that evaluated different tDCS setups in two children and three adults, it was reported that a lower intensity of applied current (~1 mA) in pediatric patients could result in similar current density to those observed in adults exposed to 2 mA. Although modeling did not indicate the presence of brain damage in children's brains when applying a current intensity of 2 mA, caution was suggested, as current density tends to be higher in pediatric populations[46]. Given that replicating adult tDCS protocols in children may not produce equivalent doses due to developmental differences, careful consideration must be given when designing and adjusting protocols for future adolescent clinical trials. Tailoring stimulation parameters to account for age-related neurophysiological differences will be crucial to optimize safety and efficacy in this population.

While this study provides valuable insights, several limitations must be acknowledged. The reliance on EF simulations does not fully capture real-time brain stimulation dynamics, and the cross-sectional design limits causal inferences about depression progression. Considering that our primary finding emphasizes age-based differences in EF magnitude, it is important to address the limitation associated with utilizing standard SimNIBS conductivity parameters derived from adult data for the adolescent sample. Existing literature indicates that adolescents may exhibit distinct conductivity characteristics, such as higher water content in their skull and surrounding tissues[45,46]. This variation could significantly impact impedance and may result in either an underestimation or overestimation of the EF results in our study. By incorporating these considerations, we aim to provide a more nuanced interpretation of our findings and underscore the necessity for age-specific conductivity models in future research. Future studies could benefit from longitudinal designs integrating neuroimaging and electrophysiological data during active tDCS sessions. Employing unified diagnostic tools and symptom severity measures across age groups would improve consistency and reliability. Lastly, understanding how developmental changes in gray and white matter influence tDCS responsiveness could provide a more comprehensive framework for optimizing neuromodulation in younger populations.

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Conclusion

In conclusion, this study highlights the age and depression-dependent variability in electric fields (EFs) induced by transcranial direct current stimulation (tDCS) in critical brain regions for mood regulation, such as the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC). These findings emphasize the necessity for age and depression-specific adjustments to tDCS parameters to optimize therapeutic outcomes. Future research should prioritize several key areas: conducting age-adjusted dose-finding studies to determine optimal current intensities for adolescents, evaluating alternative electrode montages tailored specifically for this age group, and integrating computational modeling with longitudinal clinical outcomes to better understand the treatment's long-term effects. This comprehensive approach is crucial for advancing tDCS protocols aimed at effectively treating depressive symptoms in adolescents while considering the neural and psychosocial factors that may influence treatment efficacy.

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correlate with skull thickness in children, adolescent and young adults. Prog Brain Res. 2021;264:41–56.

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Supplementary material

Table 1: Regions and MNI coordinates.

Region	MNI coordinate (x, y, z)
left SMA (cluster 1)	-8, 4, 58
right SMA (cluster1)	8 , 4 , 58
left pre-SMA (cluster 2)	-5, 24, 50
right pre-SMA (cluster 2)	5, 24, 50
left Brodmann area 9 (cluster 3)	-6, 48, 29
right Brodmann area 9 (cluster 3)	6, 48, 29
left Brodmann area 10 (cluster 4)	-4, 58, 6
right Brodmann area 10 (cluster 4)	4, 58, 6
left area 9/46d (cluster 5)	-29, 40, 39
right area 9/46d (cluster 5)	29, 40, 39
left area 9/46v (cluster 6)	-45, 28, 26
right area 9/46v (cluster 6)	45, 28, 26
left Brodmann area 46 (cluster 7)	-28, 48, 15
right Brodmann area 46 (cluster 7)	28, 48,15
left area 8A (cluster 8)	-30, 5, 49
right area 8A (cluster 8)	30, 5, 49
left anterior PMd (cluster 9)	-23, 0, 51
right anterior PMd (cluster 9)	23, 0, 51
left area 8B (cluster 10)	-24, 32, 38
right area 8B (cluster 10)	24, 32, 38
left pregenual ACC	-6, 34, 21
right pregenual ACC	5, 28, 27
left subgenual ACC	-4, 39, -2
right subgenual ACC	5, 41, 6

SMA: Supplementary Motor Area. PMd: dorsal premotor area. ACC: Anterior Cingulate Cortex. MNI: Montreal Neurological Institute.

E-PROOF

Table 2: One-way ANCOVA results of the differences in simulated electric field magnitudes among the groups and post-hoc Tukey p-values. 0: Group of adults with Major Depressive Disorder; 1: Group of adolescents with Low-risk of Major Depressive Disorder; 2: Group of adolescents with High-risk of Major Depressive Disorder and 3: Group of adolescents with Major Depressive Disorder.

Region	ANOVA p-value	p-value (FDR-corrected)	Groups Comparison	Tukey p-value
left SMA (cluster 1)	1.06E-18	4.85E-18	1-0	<1.00E-15
			2-0	8.86E-13
			3-0	1.92E-13
			2-1	0.61
			3-1	0.75
			3-2	0.99
right SMA (cluster1)	1.63E-20	3.91E-19	1-0	<1.00E-15
			2-0	<1.00E-15
			3-0	<1.00E-15
			2-1	0.80
			3-1	0.93
			3-2	0.99
left pre-SMA (cluster 2)	2.69E-18	7.68E-18	1-0	<1.00E-15
			2-0	1.66E-12
			3-0	1.12E-12
			2-1	0.56
			3-1	0.60
			3-2	0.99
right pre-SMA (cluster 2)	3.31E-19	1.99E-18	1-0	<1.00E-15
			2-0	8.85E-14
			3-0	1.01E-13
			2-1	0.78
			3-1	0.77
			3-2	0.99
left Brodmann area 9 (cluster 3)	1.28E-17	2.57E-17	1-0	<1.00E-15
			2-0	6.20E-12

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			3-0	1.02E-10
			2-1	0.39
			3-1	0.17
			3-2	0.96
right Brodmann area 9 (cluster 3)	4.02E-17	7.43E-17	1-0	<1.00E-15
			2-0	2.57E-12
			3-0	5.48E-11
			2-1	0.73
			3-1	0.41
			3-2	0.96
left Brodmann area 10 (cluster 4)	1.52E-13	1.82E-13	1-0	7.09E-13
			2-0	1.36E-08
			3-0	2.88E-08
			2-1	0.33
			3-1	0.26
			3-2	0.99
right Brodmann area 10 (cluster 4)	8.19E-12	8.55E-12	1-0	3.08E-11
			2-0	1.48E-07
			3-0	3.20E-07
			2-1	0.42
			3-1	0.33
			3-2	0.99
left area 9/46d (cluster 5)	2.67E-14	3.55E-14	1-0	3.83E-13
			2-0	5.65E-10
			3-0	1.25E-08
			2-1	0.62
			3-1	0.29
			3-2	0.94
right area 9/46d (cluster 5)	1.44E-14	2.04E-14	1-0	1.31E-13
			2-0	5.43E-10

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			3-0	1.34E-08
			2-1	0.52
			3-1	0.21
			3-2	0.94
left area 9/46v (cluster 6)	3.70E-11	3.70E-11	1-0	1.10E-10
			2-0	1.16E-06
			3-0	3.51E-07
			2-1	0.31
			3-1	0.45
			3-2	0.99
right area 9/46v (cluster 6)	1.54E-12	1.76E-12	1-0	4.08E-12
			2-0	8.34E-08
			3-0	2.19E-07
			2-1	0.30
			3-1	0.21
			3-2	0.99
left Brodmann area 46 (cluster 7)	2.26E-12	2.46E-12	1-0	5.71E-12
			2-0	7.36E-08
			3-0	4.60E-07
			2-1	0.34
			3-1	0.18
			3-2	0.98
right Brodmann area 46 (cluster 7)	4.64E-14	5.86E-14	1-0	4.08E-13
			2-0	2.48E-09
			3-0	1.11E-08
			2-1	0.46
			3-1	0.30
			3-2	0.99
left area 8A (cluster 8)	8.18E-17	1.31E-16	1-0	<1.00E-15
			2-0	1.50E-12

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			3-0	9.91E-11
			2-1	0.88
			3-1	0.48
			3-2	0.90
right area 8A (cluster 8)	7.93E-16	1.19E-15	1-0	1.10E-13
			2-0	2.64E-11
			3-0	6.39E-11
			2-1	0.82
			3-1	0.74
			3-2	0.99
left anterior PMd (cluster 9)	1.21E-18	4.85E-18	1-0	<1.00E-15
			2-0	1.66E-12
			3-0	7.99E-13
			2-1	0.45
			3-1	0.52
			3-2	0.99
right anterior PMd (cluster 9)	5.32E-17	9.12E-17	1-0	<1.00E-15
			2-0	1.57E-12
			3-0	1.93E-11
			2-1	0.88
			3-1	0.66
			3-2	0.98
left area 8B (cluster 10)	2.77E-18	7.69E-18	1-0	<1.00E-15
			2-0	9.57E-13
			3-0	3.80E-12
			2-1	0.59
			3-1	0.45
			3-2	0.99
right area 8B (cluster 10)	4.79E-18	1.15E-17	1-0	<1.00E-15
			2-0	1.87E-12

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			3-0	1.22E-11
			2-1	0.51
			3-1	0.33
			3-2	0.99
left pregenual ACC	1.53E-19	1.23E-18	1-0	<1.00E-15
			2-0	2.27E-13
			3-0	7.29E-13
			2-1	0.99
			3-1	0.33
			3-2	0.43
right pregenual ACC	9.27E-19	1.11E-18	1-0	<1.00E-15
			2-0	1.96E-13
			3-0	6.53E-13
			2-1	0.38
			3-1	0.29
			3-2	0.99
left subgenual ACC	5.82E-18	1.27E-17	1-0	<1.00E-15
			2-0	1.41E-11
			3-0	1.82E-12
			2-1	0.34
			3-1	0.54
			3-2	0.99
right subgenual ACC	2.88E-18	7.69E-18	1-0	<1.00E-15
			2-0	1.74E-12
			3-0	3.25E-12
			2-1	0.51
			3-1	0.44
			3-2	0.99

SMA: Supplementary Motor Area. PMd: dorsal premotor area. ACC: Anterior Cingulate Cortex.

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