

Distinct Effects of rTMS and High-Definition tDCS on Clinical Symptoms and Functional Connectivity in Adolescent Mood Disorders

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Abstract

Introduction:

Repetitive transcranial magnetic stimulation (rTMS) and high-definition transcranial direct current stimulation (HD-tDCS) are promising neuromodulation treatments for youth with mood disorders. However, evidence remains limited on which patients are more likely to benefit from each modality, and objective biomarkers to support individualized treatment selection are lacking. In this longitudinal study, we aimed to compare post-intervention changes in brain functional connectivity (FC) between rTMS and HD-tDCS, identify treatment-specific biomarkers, and inform the personalized selection of neuromodulation strategies.

Methods

A total of 109 patients finished the treatment, with 67 patients in rTMS group and 42 patients in HD-tDCS group. Clinical assessments and resting-state functional MRI were acquired at baseline and after two-weeks of treatment. Both interventions targeted the left dorsolateral prefrontal cortex. Treatment-related changes in FC were examined for the association with the improvement of depressive symptoms using partial least squares correlation. We further assessed the spatial correspondence of treatment-related FC patterns with brain-wide gene expression profiles, neurotransmitter receptor density maps, and receptor similarity architecture. A connectome-based machine learning model was trained to predict individual treatment response. To assess generalizability, the rTMS model was further tested in an independent validation cohort of 27 patients.

Results

Both treatments significantly reduced depressive symptoms; HD-tDCS showed greater improvement in manic and psychotic symptom. rTMS primarily modulated visual–default mode networks, while HD-tDCS produced broader network effects. Imaging transcriptomic analyses revealed rTMS-related FC patterns were linked to gene expression of synaptic signaling process, and HD-tDCS-related patterns related genes involved myelination and metabolic pathways. Neurotransmitter mapping further showed that the rTMS-related pattern was associated with histamine H3 receptor distribution, whereas no significant receptor association was observed for HD-tDCS. A connectome-based model accurately predicted responders, with higher efficacy in matched treatments. In the independent rTMS validation cohort, the model maintained robust performance.

Conclusions

rTMS and HD-tDCS engage distinct connectomic signatures in youth with mood disorders. FC-based biomarkers may help identify which patients are more suitable for rTMS versus HD-tDCS, advancing biomarker-guided and individualized neuromodulation treatment.

Introduction

Noninvasive neuromodulation is increasingly used as a treatment option for youth with mood disorders presenting with depressive episodes, primarily due to its favorable efficacy and tolerability (1). In evidence-based guidelines for mood disorders, repetitive transcranial magnetic stimulation (rTMS) is positioned as a first-line neuromodulation protocol (2, 3), whereas transcranial direct current stimulation (tDCS) is generally considered a second-line neuromodulation option (4, 5). The key clinical challenge, however, lies both in establishing the clinical benefits of neuromodulation and in determining which modality is most suitable for which patient. At present, this selection is still driven largely by availability and practical considerations rather than by predictive biomarkers.

Clinically, the treatment effect evidence base for rTMS is more mature, which is reflected in major guideline recommendations (6, 7). In contrast, tDCS has shown modest treatment effects with substantial heterogeneity across trials (8–10). Nevertheless, it offers pragmatic advantages including low cost, portability, and scalability, with potential for supervised home-based delivery (11, 12). HD-tDCS has renewed interest by improving current focality and target engagement, and early randomized evidence supports its potential antidepressant benefit (13, 14). Beyond depressive symptoms, both approaches have also been studied in symptom domains relevant to mood disorders, including manic/hypomanic and psychotic symptoms, but findings remain mixed and highly protocol-dependent (15, 16). As a result, clinically useful profiles for selecting one modality over the other are still insufficiently defined.

This uncertainty matters because rTMS and tDCS are not interchangeable technologies. rTMS delivers focal electromagnetic pulses that can modulate cortical excitability and synaptic plasticity (17), while high-definition tDCS (HD-tDCS) delivers weak electrical currents with improved focality compared with conventional tDCS, enabling more targeted cortical engagement (18, 19). Even when similar left prefrontal protocols are used in practice (20), the two modalities may produce different functional connectivity (FC) effects, which may in turn relate to differences in short-term symptom improvement (21, 22). Yet direct comparative studies of rTMS and HD-tDCS in youth with mood disorders remain limited (23). By parsing the distinct brain functional connectivity patterns induced by rTMS and HD-tDCS neuromodulation, and further identifying biological markers that are adaptive to individual clinical interventions, it may provide new guidance for clinical precision intervention in youth with mood disorders.

The primary challenge in personalized neuromodulation currently lies in the incomplete understanding of the underlying neurobiological mechanisms and the lack of reliable biomarkers. In adolescents, depression is increasingly conceptualized as a disorder of distributed functional network dysregulation

(24–26). Neuromodulation effects are therefore expected to propagate beyond the stimulation site and reshape large-scale networks, including systems implicated in internally directed cognition and sensory processing (27, 28). In parallel, multiscale neuroimaging frameworks now allow FC patterns to be interpreted using spatial biological annotations, including transcriptomic organization and neurotransmitter-related maps (29, 30).

Accordingly, this study aimed to compare the short-term therapeutic effects of left Dorsal Lateral Prefrontal Cortex (DLPFC) –targeted rTMS versus HD-tDCS in adolescents with mood disorders presenting with depressive episodes. Specifically, we: (i) quantified symptom improvement following short-term intervention; (ii) characterized and contrasted treatment-related functional connectivity changes and their network-level organization; (iii) tested whether these connectivity features align with molecular annotations (transcriptomic and neurotransmitter-related spatial patterns); and (iv) evaluated the predictive utility of connectivity-based features for individualized treatment response. By integrating clinical outcomes with circuit-level and molecular-level interpretations, we seek to advance objective biomarker development, inform modality selection between rTMS and HD-tDCS for depressed adolescents, and support the precision translation of neuromodulation therapies in youth mood disorders.

Method

Participants

This study included 135 mood disorders adolescents and young adults (aged 13–25 years) in depressive episodes, including 64 individuals with bipolar disorder (BD) and 71 with major depressive disorder (MDD). Patients were derived from two independent clinical cohorts: treated with either rTMS (n = 80) or HD-tDCS (n = 55) at the Early Intervention Unit of the Affiliated Brain Hospital of Nanjing Medical University.. Diagnoses were independently established by two trained psychiatrists, using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) for participants aged ≥ 18 years and the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL) for those < 18 years. All participants had a 17-item Hamilton Depression Rating Scale (HAM-D-17) score ≥ 17 at baseline. Exclusion criteria included: i) contraindications to MRI; ii) history of head trauma and loss of consciousness for 5 minutes or more; iii) comorbidities with other axial I disorders. All participants received stable pharmacotherapy, primarily consisting of antidepressants and mood stabilizers, which remained unchanged during the 2-week intervention period. Benzodiazepines were also permitted as needed for symptom management.

Clinical assessments were conducted at baseline (T0), after 10 sessions (T1), and after 20 sessions (T2), including HAM-D-17, Hamilton Anxiety Scale (HAMA), Young Mania Rating Scale (YMRS), and Brief Psychiatric Rating Scale (BPRS). Resting-state fMRI scans were acquired at T0 and T2. Written informed consent was obtained from all participants or their legal guardians. The study was approved by the Ethics Committee of Nanjing Brain Hospital (2020KY027-01 for rTMS, 2021KY134-02 for HD-tDCS).

Intervention Parameters

rTMS was performed using a Magneuro 60 magnetic stimulator (VISHEE), equipped with a figure-of-eight coil. The left DLPFC was localized using the F3 of the 10–20 EEG system. Each session consisted of forty 10-Hz trains at 110% of the resting motor threshold, totaling 1200 pulses. Participants received 20 sessions over 2 weeks, with two sessions daily, separated by ≥ 6 hours.

HD-tDCS was administered using the VC-8000F stimulator (Wogao Medical) with a 4×1 ring configuration for focal stimulation (31). The anode center electrode was positioned at F3 of the EEG 10–20 system, with four return electrodes placed 3.5 cm around the center. Each session involved 2 mA stimulation for 20 minutes, conducted twice daily over 2 weeks. All patients underwent an assessment of adverse events after each session.

fMRI Data Acquisition and Preprocessing

The details of fMRI scanning parameters and acquisition protocols are presented in Supplementary Material. The Human Connectome Project Multimodal Parcellation (HCP-MMP) atlas was used, segmenting the brain into 360 regions across Yeo's 7 network (32). Mean framewise displacement (FD) was computed and included as a covariate in subsequent statistical analyses to control for head motion (33).

Statistical Analysis

Clinical Outcomes

All statistical analyses were performed in R (version 4.4.0). Baseline differences in demographic and clinical characteristics were computed using independent-sample *t* tests for continuous variables and χ^2 tests for categorical variables. Treatment response was defined as a $\geq 50\%$ reduction in the HAMD-17 total score from T0 to T2. Group-wise response rates were compared using chi-square tests.

Latent Growth Curve Modeling for Symptom Trajectories

Longitudinal symptom trajectories were examined using latent growth curve modeling (LGCM) implemented in the *lavaan* package. Separate models were fitted for total and factor scores of HAMD-17, HAMA, YMRS, and BPRS across three time points (34). The intercept factor represented baseline symptom severity, and the slope factor captured linear changes over time. Group, sex, age, medication status, and illness duration were included as time-invariant covariates to assess interindividual differences in symptom trajectories, allowing for an evaluation of treatment effects while adjusting for demographic and clinical confounders.

Functional Connectivity Analysis

Functional connectivity analyses were conducted using the Human Connectome Project (HCP) atlas, which parcellates the brain into 360 regions spanning Yeo's 7 functional networks (32). Regional mean time series were extracted, and pairwise Pearson correlations were computed to generate individual FC matrices. Fisher's *r*-to-*z* transformation was applied to normalize the correlation values for subsequent statistical analyses.

To identify treatment-related FC, paired *t* tests were conducted from T0 to T2 within each treatment group. Connections exhibiting significant changes were considered as potential treatment-responsive connectivity. After regressing out age, sex, medication, duration and FD, residualized connectivity values were then submitted to partial least squares correlation (PLSC) analysis to examine associations with depressive symptom improvement.

Partial Least Squares Correlation Analysis

PLSC was able to identify latent variables (LVs) representing maximal covariance between changes in connectivity and clinical outcomes (35, 36). Significance of LVs was tested using permutation (1,000 iterations), and stability of connection loadings was evaluated via bootstrap resampling (threshold: $|Z| > 2$). A 10-fold cross-validation assessed generalizability. Significant connections from the first LV (LV1) were extracted and subsequently mapped onto Yeo's 7 network. See Supplementary Material for details.

Gene Expression Analysis

The treatment-related connections identified through PLSC analysis were mapped onto their corresponding brain regions (37), the spatial contributions maps were then aligned with transcriptomic data from the Allen Human Brain Atlas (AHBA), restricted to the left hemisphere (38). PLS regression linked regional gene expression to connectivity alterations (39, 40), and enrichment analysis for biological processes was performed using Metascape (<https://metascape.org/>). Genes with $|Z| > 3$ and FDR-corrected $P < .05$ were considered significant (41). For more details, see Supplementary Material.

Neurotransmitter-informed spatial annotation

To probe the neurochemical architecture underlying treatment-relevant connectivity remodeling, we performed PET-informed spatial annotation using a normative atlas of 19 neurotransmitter receptor maps spanning nine neurotransmitter systems (derived from > 1,200 healthy individuals) (30). For each treatment group, we performed spatial linear correlation analyses between brain features and neurotransmitter receptor densities across regions that have passed bootstrap, followed by spin tests at significance level of $p < 0.05$.

In addition, to test whether treatment-relevant connectivity changes preferentially occurred between parcels with similar neurochemical fingerprints, we constructed a receptor similarity matrix by correlating, for each parcel pair, their 19-feature receptor density profiles. We then assessed the

correspondence between the treatment-relevant FC pattern and the receptor similarity matrix, with significance evaluated by permutation testing.

Treatment Response Predictive Model

Baseline connectivity features significantly associated with symptom improvement were used to train support vector machine (SVM) classifiers for each treatment. Least absolute shrinkage and selection operator (LASSO) regression identified the 15 most frequently selected connection across 1000 iterations (42). A radial basis function (RBF) kernels was used, and model performance was assessed using 10-fold cross-validation. Further details are provided in Supplementary Material.

To explore treatment preference, both models were applied to all patients, estimating likelihood of response under each modality. Patients were categorized as two groups: preferred treatment group — patients who received the treatment predicted to yield the higher remission probability, and non-preferred treatment group — patients who received the treatment predicted to be less effective. Response rates between these groups were compared using χ^2 tests.

Validation

To validate the robustness of the predictive model, an independent rTMS-treated sample (n = 27) were recruited. Detailed are provided in Supplementary Material.

Results

Patient Demographics

Of the 135 patients initially enrolled, 12 patients were excluded due to excessive head motion (exceeding 3mm displacement or 3° rotation), and 14 patients were excluded for incomplete data. The final sample comprised 109 individuals, with 67 in the rTMS group and 42 in the HD-tDCS group. The two groups did not differ significantly in age, sex, diagnosis, medication status, or illness duration, and there were no significant differences in HAM-D, HAMA, YMRS, and BPRS scores between groups at baseline (Table 1).

Table 1
Demographic Characteristics and Clinical Variables of the Two Groups

	Mean (SD)			
	rTMS (n = 67)	tDCS (n = 42)	t/ χ^a	p
Demographic				
Age, years	15.69 (2.14)	15.21 (1.63)	1.22	0.22
Female, No. (%)	53 (79.10)	30 (71.43)	0.84	0.36
Male, No. (%)	14 (20.90)	12 (28.57)		
BD, No. (%)	30 (44.78)	23 (54.76)	1.03	0.31
MDD, No. (%)	37 (55.22)	19 (45.24)		
Duration, months	28.46 (25.41)	25.05 (18.49)	0.75	0.45
Clinical variables				
HAMD-17 score	26.04 (6.54)	24.79 (6.00)	1.03	0.31
HAMA score	25.10 (8.60)	23.55 (6.21)	1.1	0.28
YMRS score	9.58 (7.30)	7.79 (5.83)	1.42	0.16
BPRS score	43.06 (10.84)	45.29 (11.00)	-1.03	0.3
History Medication				
Antidepressant, No. (%)	32 (47.76)	19 (44.24)	0.07	0.80
Mood stabilizer, No. (%)	37 (55.22)	22 (52.38)	0.08	0.77
Benzodiazepine, No. (%)	10 (14.93)	8 (19.05)	0.32	0.57
Current Medication				
Antidepressant, No. (%)	22 (32.84)	14 (33.33)	0.01	0.96
Sertraline, No. (%)	10 (14.93)	7 (16.67)	0.06	0.81
Escitalopram, No. (%)	3 (4.48)	3 (7.14)	0.35	0.55
a. The baseline group differences in age, duration and all scale were analyzed using t-tests, while differences in gender, diagnosis, response rate and medication were assessed using chi-square tests.				
Abbreviations: rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; BD, bipolar disorder; MDD, major depression disorder; HAMD-17, 17-item Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; YMRS, Young Mania Rating Scale; BPRS, Brief Psychiatric Rating Scale				

	Mean (SD)			
	rTMS (n = 67)	tDCS (n = 42)	t/ χ^a	p
Demographic				
Fluoxetine, No. (%)	7 (10.45)	2 (7.14)	1.10	0.30
Fluvoxamine, No. (%)	3 (4.48)	2 (4.76)	0.01	0.95
Duloxetine, No. (%)	2 (2.99)	1 (2.38)	0.04	0.85
Venlafaxine, No. (%)	2 (2.99)	1 (2.38)	0.04	0.85
Other, No. (%)	3 (4.48)	2 (4.76)	0.01	0.95
Mood stabilizer, No. (%)	67 (100)	42 (100)	--	--
Lithium, No. (%)	66 (98.51)	40 (95.24)	1.03	0.31
Quetiapine, No. (%)	62 (92.54)	40 (95.24)	0.31	0.58
Lamotrigine, No. (%)	35 (52.24)	21 (50.00)	0.05	0.82
Valproate, No. (%)	13 (19.40)	11 (26.19)	0.69	0.41
Benzodiazepine, No. (%)	44 (65.67)	30 (71.43)	0.39	0.53
a. The baseline group differences in age, duration and all scale were analyzed using t-tests, while differences in gender, diagnosis, response rate and medication were assessed using chi-square tests.				
Abbreviations: rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; BD, bipolar disorder; MDD, major depression disorder; HAMD-17, 17-item Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; YMRS, Young Mania Rating Scale; BPRS, Brief Psychiatric Rating Scale				

Clinical Symptom Improvement and Treatment Efficacy

There were no significant differences in HAMD, HAMA, YMRS, and BPRS scores between groups at baseline. Both rTMS and HD-tDCS groups showed significant symptom improvement, except for YMRS scores in the rTMS group (Table S2). The incidence of adverse events did not differ significantly between groups.

Latent Growth Curve Modeling of Symptom Trajectories

LGCM revealed a significantly steeper decline in YMRS ($p = 0.023$) and BPRS ($p = 0.016$) scores in the HD-tDCS group compared with the rTMS group (Fig. 2). No group differences emerged for trajectories of depressive symptoms. Exploratory factor-level analyses indicated that the group effect on BPRS was primarily driven by changes in the Thought Disorder factor ($p = 0.039$) and Hostility factor ($p = 0.010$), in contrast, no significant group differences were observed in the trajectories of other factors (Table S3).

Functional Connectivity Changes Related to Clinical Improvement

Paired t-test revealed 3,465 connections in the rTMS group and 2,721 connections in the HD-tDCS group which exhibited significant changes after treatment ($p < 0.05$, uncorrected). PLSC revealed robust associations between connectivity changes and symptom improvement in both groups. In the rTMS group, the first latent variable (LV1) explained 41.27% of variance in HAMD change, comprising 203 significant connections (109 positively correlated and 94 negatively correlated, Fig. 3A). A significant association was found between connectivity changes and clinical improvement for LV1 ($r = 0.782$, $p < 0.001$, Fig. 3C). In the HD-tDCS group, LV1 explained 49.40% of variance, comprising 205 connections (107 positive correlated and 98 negative correlated; Fig. 3B). The association between connectivity alteration and clinical improvement was also significant ($r = 0.874$, $p < 0.001$, Fig. 3D). Permutation testing confirmed the statistical significance of LV1 in the two groups. (Fig. S1b and S2b). Model robustness was assessed via 10-fold cross-validation. In the rTMS group, predicted LV1 brain scores demonstrated a strong correlation with observed scores ($r = 0.656$, $p < 0.001$), whereas predicted LV1 clinical scores exhibited strong alignment with actual values ($r = 0.945$, $p < 0.001$; Fig. S1). Similarly, in the tDCS group, predicted LV1 brain scores were significantly correlated with observed scores ($r = 0.633$, $p < 0.001$), while predicted LV1 clinical scores showed a high correlation with observed values ($r = 0.963$, $p < 0.001$; Fig. S2).

Network-level analysis showed distinct treatment-specific patterns. In the rTMS group, the changes of connections were mainly localized within DMN and VIS, with 38 connections positively associated with clinical reduction. In contrast, 11 connections in DMN–ventral attention network (VAN) and 18 connections between sensorimotor network (SMN)–VAN were negatively associated with symptom improvement. However, the HD-tDCS group exhibited a more distributed pattern of alterations across multiple networks. Notably, symptom improvement was positively associated with 10 significant increased connections between the DMN and VIS, while 13 decreased connections within the DMN itself was linked to better clinical outcomes (Table S4). These findings suggest that rTMS and HD-tDCS induce engage distinct neural circuits, potentially reflecting different mechanisms of action.

Additionally, we performed PLSC analyses to examine the associations between functional connectivity changes and the four HAMD factors: (1) Anxiety, (2) Depression, (3) Insomnia, (4) Somatic symptom (43). Bootstrap validation confirmed the robustness of these factor-level associations, with all four factors demonstrating significant contributions to LV1, as indicated by bootstrap ratios exceeding the threshold of 2 in both treatment groups.

Transcriptomic Correlates of Functional Connectivity

To explore the biological underpinnings of the observed connectivity alterations, we conducted partial least squares regression between regional connectivity changes and gene expression profiles from the AHBA. The LV1 explained 27.5% of the variance in the rTMS group and 28.9% in the HD-tDCS group, with

significant spatial correspondence between LV1-derived gene expression and connectivity loadings. (Fig. S4)

To further validate the biological relevance of PLS1, we examined the correspondence between PLS1-derived weights and regional brain loadings. In both treatment groups, the PLS1-weighted gene expression maps were significantly correlated with the connectivity loading maps (rTMS: $r = 0.414$, $p < 0.0001$; tDCS: $r = 0.534$, $p < 0.0001$), indicating a robust relationship between the identified genetic component and its associated neuroimaging features

Genes contributing most strongly to LV1 ($|Z| > 3$) were subjected to Gene Ontology enrichment analysis, revealing distinct biological pathways for each modality. In the rTMS group, the candidate genes were predominantly involved in postsynaptic processes, glutamatergic synapse function and regulation of trans-synaptic signaling. In contrast, candidate genes identified in the HD-tDCS group were mainly associated with organophosphate biosynthesis process, protein catabolic and myelin sheath formation. See the Fig. 4 and Table S5.

Neurotransmitter associations of treatment-relevant connectivity patterns

In the rTMS group, the region-wise involvement fingerprint showed significant negative spatial associations with histamine (H3) receptor density ($r = -0.353$, $p_{\text{spin}} = 0.004$). In the tDCS group, no neurotransmitter receptor map showed a significant association with the region-wise involvement fingerprint. See the Fig. 5A and 5B.

Matrix correlation analyses revealed that, in the rTMS group, the treatment-relevant FC pattern was significantly correlated with the receptor similarity matrix ($r = 0.520$, $p < 0.001$). In contrast, the corresponding association in the tDCS group was not significant ($r = 0.099$, $p = 0.340$). See the Fig. 5C.

Connectivity-Guided Prediction of Treatment Response

Using LASSO regression based on the significant functional connectivity identified in the PLSC analysis, 15 robust connections were selected in each group (Table S6). These connections were used to train binary classifiers for treatment response. The rTMS model achieved a mean area under the receiver operating characteristic curve (AUC) of 0.902 (95% CI: 0.807–0.973) and an accuracy of 85.4%, whereas the HD-tDCS model yielded a mean AUC of 0.914 (95% CI: 0.813–0.980) and an accuracy of 85.7% (Fig. 6C).

Application of both models to the full cohort revealed that 57 patients were predicted to benefit more from rTMS, and 52 from HD-tDCS. Among those predicted to be optimal candidates for rTMS, the response rate was significantly higher in patients who received rTMS (75.0%, 27/36) compared to those who received HD-tDCS (19.0%, 4/21). Conversely, among patients predicted to benefit from HD-tDCS, those treated with HD-tDCS exhibited a response rate of 85.7% (18/21), whereas only 9.7% (3/31) of those receiving rTMS achieved response (Fig. 6A, 6B).

Validation of Predictive Models

To validate generalizability, we tested the rTMS model in an independent sample of 27 patients receiving rTMS. The model maintained robust performance, with an AUC of 0.804 and an accuracy of 81.5% (Fig. 6D).

Discussion

In this study, we used PLSC to investigate the differential neurobiological effects of rTMS and HD-tDCS in adolescents with mood disorders and to evaluate whether FC patterns could serve as predictive biomarkers of treatment response. Our findings revealed distinct networks-level modulation profiles associated with symptom improvement between rTMS and HD-tDCS. Furthermore, predictive models derived from modality-specific connectivity features accurately identified optimal treatment for each patient, supporting the potential of connectome-based biomarkers to guide personalized neuromodulation strategies.

Although both treatments reduced depressive symptoms, HD-tDCS appeared more effective in attenuating manic or hypomanic symptoms, as indicated by greater reductions in YMRS scores. While the incidence of adverse events did not significantly differ between groups, the divergence in YMRS trajectories raises important clinical considerations. Prior literature has documented the potential for high-frequency rTMS to induce hypomanic or manic episodes, particularly in individuals with BD or mixed features (44, 45). Our findings are consistent with these concerns and suggest that HD-tDCS may represent a safer alternative for patients with subthreshold manic symptoms (46). However, given the exploratory nature of these results, future studies with larger, diagnostically stratified cohorts are needed to confirm these effects.

Beyond symptom changes, treatment response was associated with distinct patterns of functional connectivity. In the rTMS group, therapeutic effects were mainly linked to changes in DMN, which were linked to maladaptive self-referential processing and persistent rumination (47, 48). DMN has been consistently implicated in the pathophysiology of depression, with hyperconnectivity within this network—especially involving the subgenual anterior cingulate cortex (28, 48). Moreover, dysfunctional integration between the DMN and VIS has been associated with impaired affective-sensory coupling, a hallmark of depressive states (49–51). Our findings establish a link between depressive symptoms and altered network connectivity of the DMN with the VIS.

In contrast, HD-tDCS produced more diffuse effects via sustained weak currents (52), suggesting that HD-tDCS offers a more extensive modulation of network connectivity (53). Connectivity patterns of HD-tDCS showed prominent effects observed in the SMN and FPN. Modulation of SMN connectivity may help normalize aberrant interoceptive that contribute to affective dysregulation (54), and enhancements in FPN connectivity may thus facilitate improved cognitive regulation of mood (55). These findings suggest that HD-tDCS exerts its therapeutic effects by engaging a broader constellation of brain

systems, while rTMS provides precise, localized stimulation that can be beneficial in specific therapeutic contexts. This distinction highlights the complementary roles of both techniques in neuroscience research and clinical applications (22).

The spatial convergence between treatment-relevant FC patterns and gene expression profiles further underscores the mechanistic divergence of rTMS and HD-tDCS. In the rTMS group, the involvement of candidate genes in postsynaptic processes, glutamatergic synapse function, and trans-synaptic signaling regulation is aligning with the known role of modulating excitatory neurotransmission and synaptic plasticity (56, 57). This synaptic signature aligns with the neurochemical analyses showing that the rTMS-related connectivity remodeling fingerprint was not only associated with specific PET-derived molecular maps (H3), but also exhibited a robust correspondence with the receptor similarity network. In contrast, the transcriptional profile associated with HD-tDCS highlighted biological processes related to myelin sheath formation, protein catabolism, and cellular metabolism. These findings align with preclinical evidence showing that HD-tDCS can promote oligodendrocyte proliferation and myelination in animal models (58). Furthermore, HD-tDCS has been shown to alter cerebral metabolic profiles, influencing bioenergetic pathways such as glycolysis and mitochondrial function (59). Within this framework, the absence of FDR-significant spatial associations between the HD-tDCS connectivity fingerprint and the 19 neurotransmitter maps—and the lack of significant correspondence with the receptor similarity matrix—may indicate that, at the group level and on the short-term timescale examined, HD-tDCS-related connectivity changes are less tightly coupled to stable cortical receptor-density gradients and may instead reflect broader neuromodulatory influences involving glial activity and metabolic homeostasis. Together, these results suggest that HD-tDCS may exert its therapeutic effects through broader neuromodulatory mechanisms involving glial activity and metabolic homeostasis (60), in contrast to the more synapse-focused actions of rTMS.

A major contribution of this study is the development of accurate, modality-specific predictive models using connectome-based features, which aligns with emerging evidence that the functional connectome contains individual variability relevant to treatment stratification (61, 62). Our models not only classify responders with high accuracy, but also inform optimal treatment selection for individual patients. Patients receiving the model-predicted optimal modality showed significantly greater symptom improvement, underscoring the translational potential of neuroimaging biomarkers in real-world treatment planning. Unlike traditional predictors such as symptom severity or demographics, functional connectivity patterns may reflect individualized neural responsiveness to specific neuromodulatory mechanisms (35, 63). To our knowledge, this is the first studies to directly compare rTMS and HD-tDCS in adolescents using functional neuroimaging and machine learning-based outcome prediction. By integrating systems-level imaging with molecular and clinical data, our findings contribute to the growing momentum toward precision psychiatry.

Several limitations should be acknowledged. First, the sample size was modest, and the study employed a nonrandomized design, with treatment allocation based on clinical considerations. In addition, external validation was conducted only for the rTMS model using an independent cohort, and replication of the

HD-tDCS model in independent samples is needed, which may limit the generalizability of our findings. Second, although all participants were experiencing depressive episodes, the inclusion of both MDD and BD introduces diagnostic heterogeneity that may influence neurobiological profiles and treatment effects. Third, while all patients received rTMS or HD-tDCS as their primary intervention, most were concurrently receiving pharmacotherapy, the potential confounding effects of medications on both clinical outcomes and functional connectivity changes cannot be entirely ruled out. Finally, while we identified treatment-predictive connectivity signatures, their mechanistic interpretations remain preliminary. Multimodal imaging, longitudinal trajectories, and molecular characterization will be essential to elucidate the biological underpinnings and durability of these effects.

In sum, this study provides converging evidence for distinct neural and molecular correlates of rTMS and HD-tDCS in adolescents with mood disorders. Leveraging functional connectivity biomarkers, we developed personalized predictive models with demonstrated translational relevance. These findings support the feasibility of precision-guided neuromodulation and lay the groundwork for future work to refine individualized interventions based on neural circuitry and molecular targets.

Abbreviations

AHBA	
Allen Human Brain Atlas	
BPRS	
Brief psychiatric rating scale	
DLPFC	
Dorsolateral prefrontal cortex	
FC	
Functional connectivity	
HAMA	
Hamilton anxiety scale	
HAMD	
Hamilton depression rating scale	
HD-tDCS	
High-definition transcranial direct current stimulation	
MDD	
Major depressive disorder	
PLS	
Partial least square	
rTMS	
Repetitive transcranial magnetic stimulation	
YMRS	
Young Mania Rating Scale	

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Nanjing Brain Hospital (Ethical approval number: 2020KY027-01 for rTMS, 2021KY134-02 for HD-tDCS). All participants or their legal guardians signed a written informed consent prior to the study.

Consent for publication

All authors have read the manuscript and provided consent for publication.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

Concept and design: ZJS, BB, LJ, GXH, ZRX, DW, ZJJ, WF; Acquisition, analysis, or interpretation of data: All authors; Drafting of the manuscript: ZJS, BB, LJ, ZJJ; Statistical analysis: ZJS, BB, LJ, DJ, ZPF, DW, ZJJ; Review and editing: ZJS, BB, LJ, GXH, ZRX, WLF, ZPF, ZJJ, WF. All authors critically reviewed the content and approved the final version for publication.

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Data Availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

References

1. Tang M, Zheng Y, Zhang X, Fan X. Non-invasive neuromodulation treatment for depression in adolescents: A systematic review and meta-analysis. *Psychiatry Res.* 2025;344:116329.
2. Lam RW, Kennedy SH, Adams C, Bahji A, Beaulieu S, Bhat V, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2023 Update on Clinical Guidelines for Management of Major Depressive Disorder in Adults: Réseau canadien pour les traitements de l'humeur et de l'anxiété (CANMAT) 2023: Mise à jour des lignes directrices cliniques pour la prise en charge du trouble dépressif majeur chez les adultes. *Can J psychiatry Revue canadienne de psychiatrie.* 2024;69(9):641–87.
3. Lefaucheur JP, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin Neurophysiol.* 2017;128(1):56–92.
4. Hameed MQ, Dhamne SC, Gersner R, Kaye HL, Oberman LM, Pascual-Leone A, et al. Transcranial Magnetic and Direct Current Stimulation in Children. *Curr Neurol Neurosci Rep.* 2017;17(2):11.
5. Sigrist C, Vöckel J, MacMaster FP, Farzan F, Croarkin PE, Galletly C, et al. Transcranial magnetic stimulation in the treatment of adolescent depression: a systematic review and meta-analysis of aggregated and individual-patient data from uncontrolled studies. *Eur Child Adolesc Psychiatry.* 2022;31(10):1501–25.
6. De Risio L, Borgi M, Pettorruso M, Miuli A, Ottomana AM, Sociali A, et al. Recovering from depression with repetitive transcranial magnetic stimulation (rTMS): a systematic review and meta-analysis of preclinical studies. *Transl Psychiatry.* 2020;10(1):393.
7. Berlim MT, van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. *Psychol Med.* 2014;44(2):225–39.
8. Fregni F, El-Hagrassy MM, Pacheco-Barrios K, Carvalho S, Leite J, Simis M, et al. Evidence-Based Guidelines and Secondary Meta-Analysis for the Use of Transcranial Direct Current Stimulation in Neurological and Psychiatric Disorders. *Int J Neuropsychopharmacol.* 2021;24(4):256–313.
9. Brunoni AR, Moffa AH, Sampaio-Junior B, Borrión L, Moreno ML, Fernandes RA, et al. Trial of Electrical Direct-Current Therapy versus Escitalopram for Depression. *N Engl J Med.* 2017;376(26):2523–33.
10. Palm U, Schiller C, Fintescu Z, Obermeier M, Keeser D, Reisinger E, et al. Transcranial direct current stimulation in treatment resistant depression: a randomized double-blind, placebo-controlled study. *Brain Stimul.* 2012;5(3):242–51.
11. Borrión L, Cavendish BA, Aparicio LVM, Luethi MS, Goerigk S, Ramos MRF, et al. Home-Use Transcranial Direct Current Stimulation for the Treatment of a Major Depressive Episode: A Randomized Clinical Trial. *JAMA Psychiatry.* 2024;81(4):329–37.

12. Woodham RD, Selvaraj S, Lajmi N, Hobday H, Sheehan G, Ghazi-Noori AR, et al. Home-based transcranial direct current stimulation treatment for major depressive disorder: a fully remote phase 2 randomized sham-controlled trial. *Nat Med.* 2025;31(1):87–95.
13. Jog MA, Norris V, Pfeiffer P, Taraku B, Kozikowski S, Schneider J, et al. Personalized High-Definition Transcranial Direct Current Stimulation for the Treatment of Depression: A Randomized Clinical Trial. *JAMA Netw Open.* 2025;8(9):e2531189.
14. Zhang L, Li Q, Du Y, Gao Y, Bai T, Ji GJ, et al. Effect of high-definition transcranial direct current stimulation on improving depression and modulating functional activity in emotion-related cortical-subcortical regions in bipolar depression. *J Affect Disord.* 2023;323:570–80.
15. Tee MMK, Au CH. A Systematic Review and Meta-Analysis of Randomized Sham-Controlled Trials of Repetitive Transcranial Magnetic Stimulation for Bipolar Disorder. *Psychiatr Q.* 2020;91(4):1225–47.
16. Sabé M, Hyde J, Cramer C, Eberhard A, Crippa A, Brunoni AR, et al. Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation Across Mental Disorders: A Systematic Review and Dose-Response Meta-Analysis. *JAMA Netw Open.* 2024;7(5):e2412616.
17. Di Lazzaro V, Oliviero A, Pilato F, Saturno E, Dileone M, Mazzone P, et al. The physiological basis of transcranial motor cortex stimulation in conscious humans. *Clin Neurophysiol Pract.* 2004;115(2):255–66.
18. Jannati A, Oberman LM, Rotenberg A, Pascual-Leone A. Assessing the mechanisms of brain plasticity by transcranial magnetic stimulation. *Neuropsychopharmacology.* 2023;48(1):191–208.
19. Qi S, Cao L, Wang Q, Sheng Y, Yu J, Liang Z. The Physiological Mechanisms of Transcranial Direct Current Stimulation to Enhance Motor Performance: A Narrative Review. *Biology (Basel).* 2024;13(10).
20. Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018). *Clin Neurophysiol.* 2020;131(2):474–528.
21. Jog MV, Wang DJJ, Narr KL. A review of transcranial direct current stimulation (tDCS) for the individualized treatment of depressive symptoms. *Pers Med Psychiatry.* 2019;17–18:17–22.
22. Sale MV, Mattingley JB, Zalesky A, Cocchi L. Imaging human brain networks to improve the clinical efficacy of non-invasive brain stimulation. *Neurosci Biobehav Rev.* 2015;57:187–98.
23. Grimm S, Beck J, Schuepbach D, Hell D, Boesiger P, Bermpohl F, et al. Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder. *Biol Psychiatry.* 2008;63(4):369–76.
24. Xiong Y, Yu RQ, Wang XY, Liang SS, Ran J, Li X, et al. Hemispheric asymmetries and network dysfunctions in adolescent depression: A neuroimaging study using resting-state functional magnetic resonance imaging. *World J Psychiatry.* 2025;15(2):102412.
25. Lee Y, Chahal R, Gotlib IH. The default mode network is associated with changes in internalizing and externalizing problems differently in adolescent boys and girls. *Dev Psychopathol.* 2024;36(2):834–43.

26. Chahal R, Gotlib IH, Guyer AE. Research Review: Brain network connectivity and the heterogeneity of depression in adolescence - a precision mental health perspective. *J Child Psychol Psychiatry*. 2020;61(12):1282–98.
27. Ge R, Humaira A, Gregory E, Alamian G, MacMillan EL, Barlow L, et al. Predictive Value of Acute Neuroplastic Response to rTMS in Treatment Outcome in Depression: A Concurrent TMS-fMRI Trial. *Am J Psychiatry*. 2022;179(7):500–8.
28. Weigand A, Horn A, Caballero R, Cooke D, Stern AP, Taylor SF, et al. Prospective Validation That Subgenual Connectivity Predicts Antidepressant Efficacy of Transcranial Magnetic Stimulation Sites. *Biol Psychiatry*. 2018;84(1):28–37.
29. Burt JB, Demirtaş M, Eckner WJ, Navejar NM, Ji JL, Martin WJ, et al. Hierarchy of transcriptomic specialization across human cortex captured by structural neuroimaging topography. *Nat Neurosci*. 2018;21(9):1251–9.
30. Hansen JY, Shafiei G, Markello RD, Smart K, Cox SML, Nørgaard M, et al. Mapping neurotransmitter systems to the structural and functional organization of the human neocortex. *Nat Neurosci*. 2022;25(11):1569–81.
31. Edwards D, Cortes M, Datta A, Minhas P, Wassermann EM, Bikson MJN. Physiological and modeling evidence for focal transcranial electrical brain stimulation in humans: a basis for high-definition tDCS. *NeuroImage*. 2013;74:266–75.
32. Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol*. 2011;106(3):1125–65.
33. Power JD, Mitra A, Laumann TO, Snyder AZ, Schlaggar BL, Petersen SE. Methods to detect, characterize, and remove motion artifact in resting state fMRI. *NeuroImage*. 2014;84:320–41.
34. Yu X, Zhang Z, Herle M, Banaschewski T, Barker GJ, Bokde ALW, et al. Relationships of eating behaviors with psychopathology, brain maturation and genetic risk for obesity in an adolescent cohort study. *Nat Mental health*. 2025;3(1):58–70.
35. Gallucci J, Yu JC, Oliver LD, Nakua H, Zhukovsky P, Dickie EW, et al. Neural Circuitry and Therapeutic Targeting of Depressive Symptoms in Schizophrenia Spectrum Disorders. *Am J Psychiatry*. 2024;181(10):910–9.
36. Abdi H, Williams LJ. Partial least squares methods: partial least squares correlation and partial least square regression. *Methods in molecular biology*. (Clifton NJ). 2013;930:549–79.
37. Zheng J, Womer FY, Tang L, Guo H, Zhang X, Tang Y, et al. Integrative omics analysis reveals epigenomic and transcriptomic signatures underlying brain structural deficits in major depressive disorder. *Transl Psychiatry*. 2024;14(1):17.
38. Arnatkevičiūtė A, Fulcher BD, Fornito A. A practical guide to linking brain-wide gene expression and neuroimaging data. *NeuroImage*. 2019;189:353–67.
39. Romero-Garcia R, Seidlitz J, Whitaker KJ, Morgan SE, Fonagy P, Dolan RJ, et al. Schizotypy-related magnetization of cortex in healthy adolescence is colocated with expression of schizophrenia-

- related genes. *Biol Psychiatry*. 2020;88(3):248–59.
40. Li M, Santpere G, Imamura Kawasawa Y, Evgrafov OV, Gulden FO, Pochareddy S, et al. Integrative functional genomic analysis of human brain development and neuropsychiatric risks. *Science*. 2018;362(6420):eaat7615.
41. Zhou Y, Zhou B, Pache L, Chang M, Khodabakhshi AH, Tanaseichuk O, et al. Metascape provides a biologist-oriented resource for the analysis of systems-level datasets. *Nat Commun*. 2019;10(1):1523.
42. Tibshirani R. Regression shrinkage and selection via the lasso. *J Royal Stat Soc Ser B: Stat Methodol*. 1996;58(1):267–88.
43. Shafer AB. Meta-analysis of the factor structures of four depression questionnaires: Beck, CES-D, Hamilton, and Zung. *J Clin Psychol*. 2006;62(1):123–46.
44. Rachid F. Repetitive transcranial magnetic stimulation and treatment-emergent mania and hypomania: a review of the literature. *J Psychiatr Pract*. 2017;23(2):150–9.
45. Xia G, Gajwani P, Muzina DJ, Kemp DE, Gao K, Ganocy SJ, et al. Treatment-emergent mania in unipolar and bipolar depression: focus on repetitive transcranial magnetic stimulation. *Int J Neuropsychopharmacol*. 2008;11(1):119–30.
46. Brunoni AR, Moffa AH, Sampaio-Junior B, Galvez V, Loo CKJBS. Treatment-emergent mania/hypomania during antidepressant treatment with transcranial direct current stimulation (tDCS): a systematic review and meta-analysis. *Brain Stimul*. 2017;10(2):260–2.
47. He H, Sun X, Doose J, Faller J, McIntosh JR, Saber GT et al. TMS-induced modulation of brain networks and its associations to rTMS treatment for depression: a concurrent fMRI-EEG-TMS study. *medRxiv*. 2024:2024.12.24.24319609.
48. Liston C, Chen AC, Zebley BD, Drysdale AT, Gordon R, Leuchter B, et al. Default mode network mechanisms of transcranial magnetic stimulation in depression. *Biol Psychiatry*. 2014;76(7):517–26.
49. Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA. Large-Scale Network Dysfunction in Major Depressive Disorder: A Meta-analysis of Resting-State Functional Connectivity. *JAMA Psychiatry*. 2015;72(6):603–11.
50. Zhu M, Chen Y, Zheng J, Zhao P, Xia M, Tang Y, et al. Over-integration of visual network in major depressive disorder and its association with gene expression profiles. *Transl Psychiatry*. 2025;15(1):86.
51. Chai Y, Sheline YI, Oathes DJ, Balderston NL, Rao H, Yu M. Functional connectomics in depression: insights into therapies. *Trends Cogn Sci*. 2023;27(9):814–32.
52. Milighetti S, Sterzi S, Fregni F, Hanlon CA, Hayley P, Murphy MD, et al. Effects of tDCS on spontaneous spike activity in a healthy ambulatory rat model. *Brain Stimul*. 2020;13(6):1566–76.
53. Jog MS, Kim E, Anderson C, Kubicki A, Kayathi R, Jann K, et al. In-vivo imaging of targeting and modulation of depression-relevant circuitry by transcranial direct current stimulation: a randomized clinical trial. *Transl Psychiatry*. 2021;11(1):138.

54. Wen K, Zhao Y, Zhang F, Lui S, Kemp GJ, Gong Q. Large-scale dysfunctional white matter and grey matter networks in patients with social anxiety disorder. *iScience*. 2022;25(10):105094.
55. Gao Y, Guo X, Wang S, Huang Z, Zhang B, Hong J, et al. Frontoparietal network homogeneity as a biomarker for mania and remitted bipolar disorder and a predictor of early treatment response in bipolar mania patient. *J Affect Disord*. 2023;339:486–94.
56. Lenz M, Platschek S, Priesemann V, Becker D, Willems LM, Ziemann U, et al. Repetitive magnetic stimulation induces plasticity of excitatory postsynapses on proximal dendrites of cultured mouse CA1 pyramidal neurons. *Brain Struct Funct*. 2015;220(6):3323–37.
57. Lenz M, Galanis C, Müller-Dahlhaus F, Opitz A, Wierenga CJ, Szabó G, et al. Repetitive magnetic stimulation induces plasticity of inhibitory synapses. *Nat Commun*. 2016;7:10020.
58. Maas DA, Angulo MC. Can Enhancing Neuronal Activity Improve Myelin Repair in Multiple Sclerosis? *Front Cell Neurosci*. 2021;15:645240.
59. Agrawal B, Boulos S, Khatib S, Feuermann Y, Panov J, Kaphzan H. Molecular Insights into Transcranial Direct Current Stimulation Effects: Metabolomics and Transcriptomics Analyses. *Cells*. 2024;13(3).
60. Pelletier SJ, Cicchetti F. Cellular and molecular mechanisms of action of transcranial direct current stimulation: evidence from in vitro and in vivo models. *Int J Neuropsychopharmacol*. 2014;18(2).
61. Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, et al. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nat Med*. 2016;23(1):28–38.
62. Duan J, Li Y, Zhang X, Dong S, Zhao P, Liu J, et al. Predicting treatment response in adolescents and young adults with major depressive episodes from fMRI using graph isomorphism network. *NeuroImage Clin*. 2023;40:103534.
63. Elbau IG, Lynch CJ, Downar J, Vila-Rodriguez F, Power JD, Solomonov N, et al. Functional Connectivity Mapping for rTMS Target Selection in Depression. *Am J Psychiatry*. 2023;180(3):230–40.

Figures

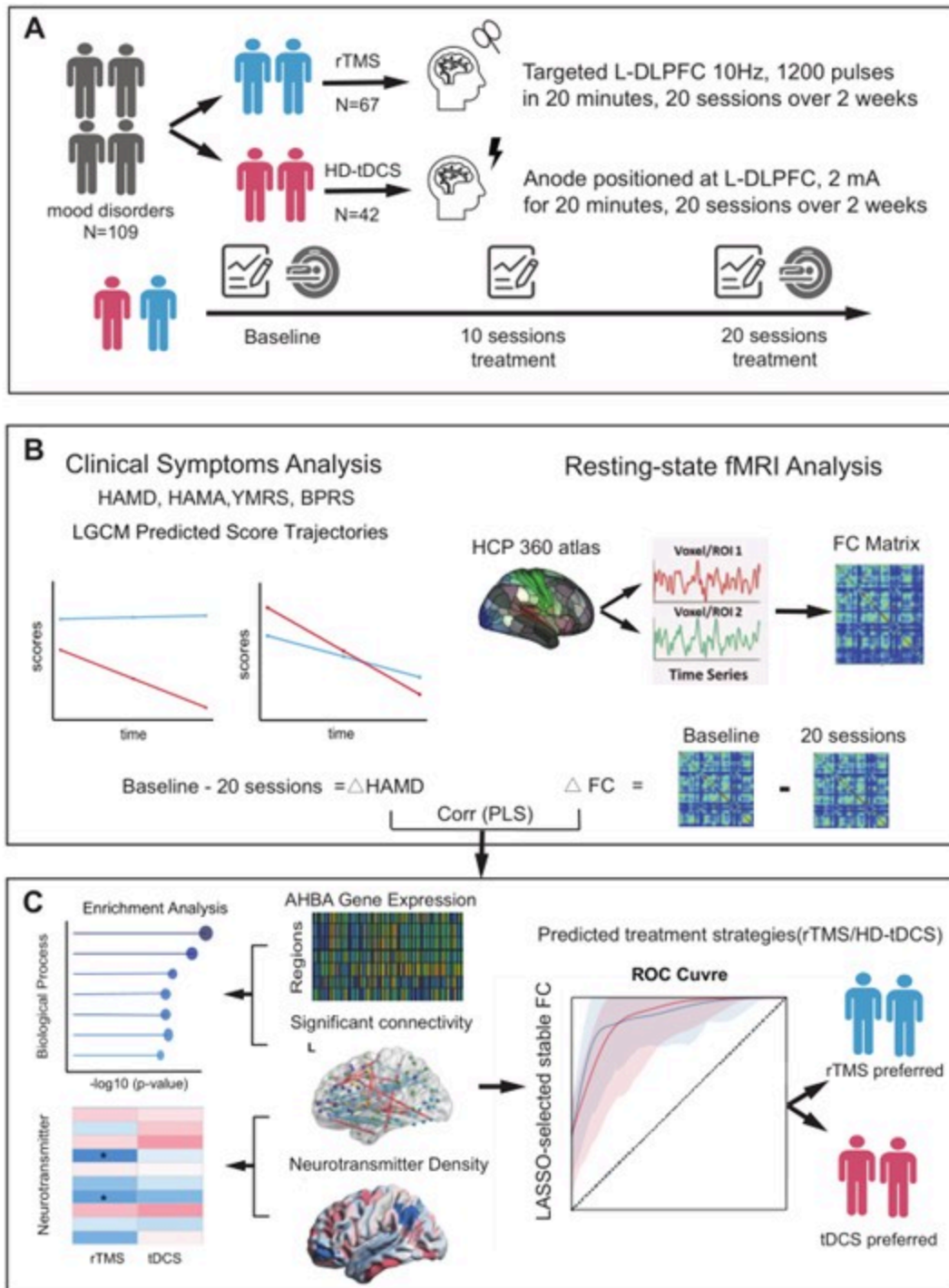


Figure 1

Schematic Overview of the Study Design. (A) A total of 109 patients with mood disorders were included, with 67 patients receiving rTMS and 42 receiving tDCS. All patients underwent clinical assessments at baseline, after 10 sessions, and after 20 sessions. Resting-state fMRI scans were acquired at baseline and after 20 sessions. (B) Symptom trajectories were assessed using latent growth curve modeling (LGCM) based on clinical assessments. Functional connectivity (FC) matrices were constructed for each subject based on resting-state fMRI data. FC changes following treatment were identified within each group using paired t-tests ($p < 0.05$). Partial least squares (PLS) correlation analysis was conducted to

examine the relationship between functional connectivity alterations and changes in the HAMD-17 scores. (C) The identified functional connections were further examined in relation to transcriptomic data from the Allen Human Brain Atlas (AHBA) using PLS regression. Biological process enrichment analysis was performed to explore molecular pathways associated with connections. In parallel, the same connectivity pattern was spatially annotated using normative neurotransmitter receptor density maps, and the correspondence between treatment-relevant FC patterns and neurotransmitter co-expression architecture was assessed Least absolute shrinkage and selection operator (LASSO) regression was used to identify stable functional connectivity features predictive of treatment outcomes. Machine learning models were applied to classify treatment response, facilitating individualized treatment selection based on neuroimaging biomarkers.

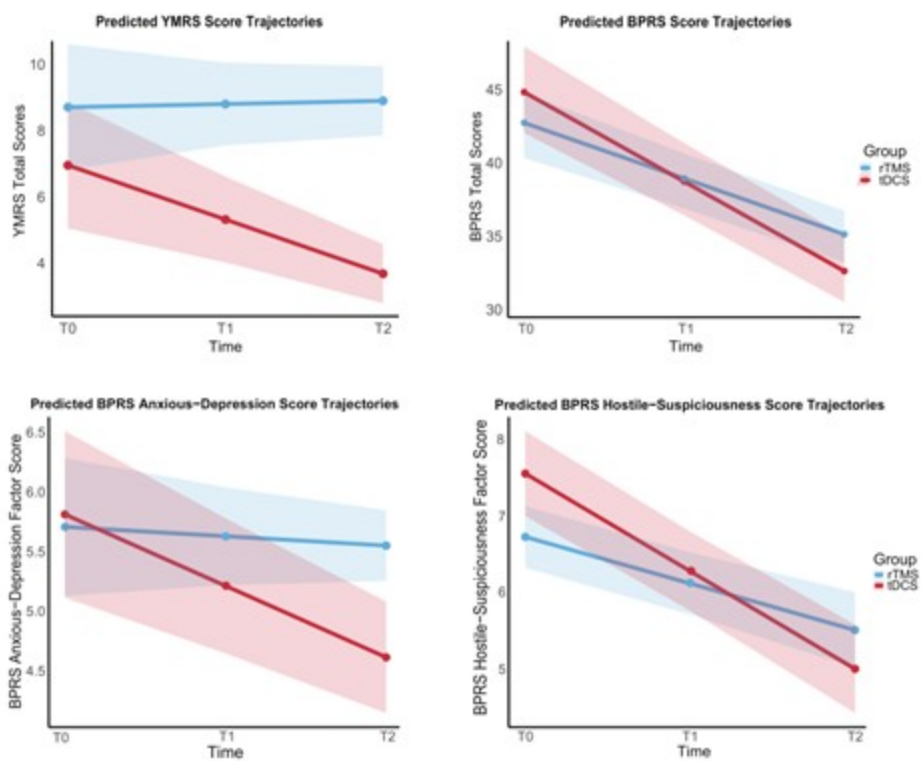


Figure 2

Latent Growth Curve Modeling of Symptom Trajectories. Predicted trajectories of Brief Psychiatric Rating Scale (BPRS), Young Mania Rating Scale (YMRS), BPRS Anxious-Depression factor and Hostile-Suspiciousness factor scores over time for the rTMS and tDCS groups. Data points represent the estimated mean scores at each time point, with shaded areas indicating 95% confidence intervals.

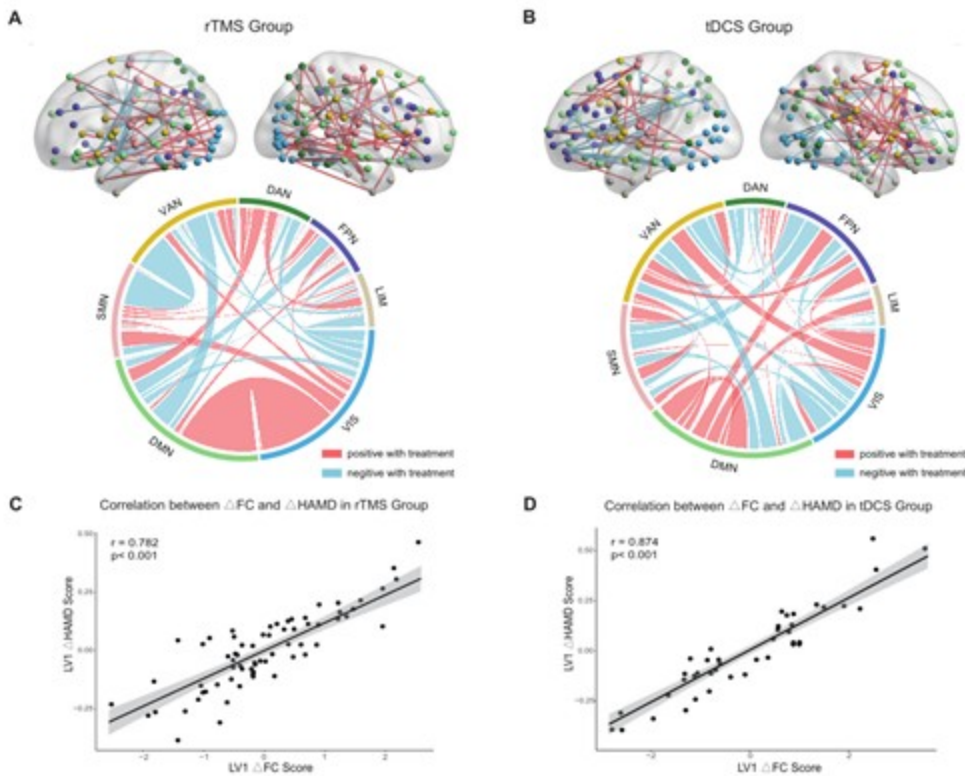


Figure 3

Functional Connectivity Associated with Depressive Symptom Improvement via Partial Least Squares Correlation Analysis. (A-B) display significant functional connectivity from the first latent variable in the rTMS group(A) and tDCS groups(B), with connection thickness proportional to their loadings. The corresponding chord diagrams illustrate the distribution of these connections across Yeo's 7 functional networks, with line thickness reflecting the number of connections within each network. Positive and negative correlations with treatment response are indicated in red and blue, respectively. (C-D) showing the correlation between FC change and symptom improvement from the first latent variable in rTMS group(C) and tDCS groups(D).

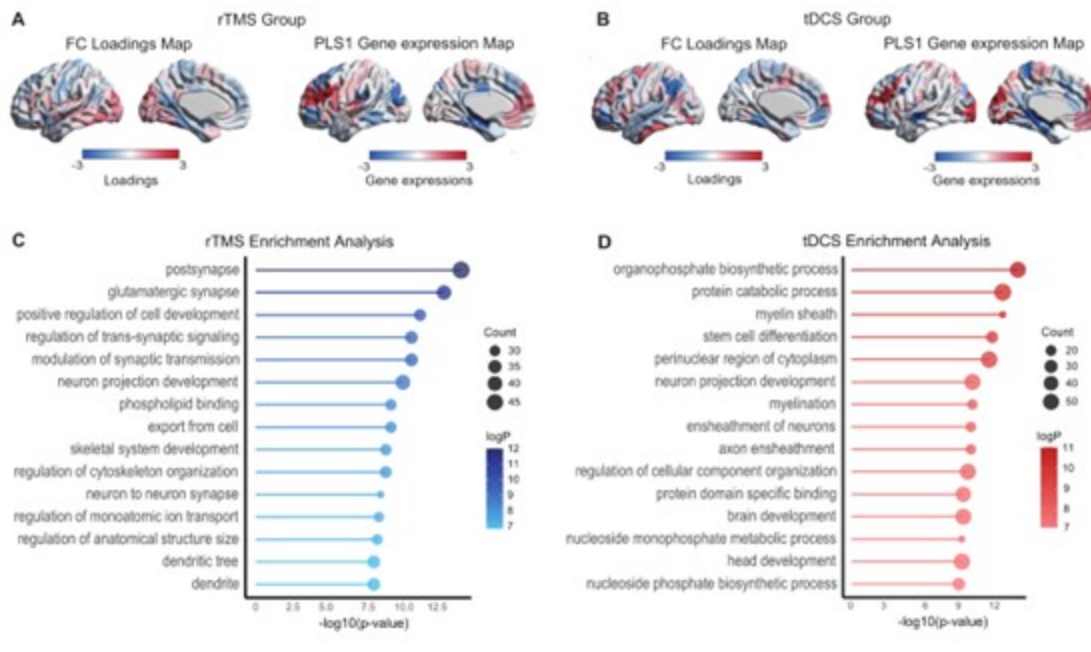


Figure 4

Functional Connectivity Loadings and Gene Enrichment Analysis in rTMS and tDCS Groups. (A and B) illustrate the group averaged functional connectivity loadings and the first latent variable (PLS1) gene expression maps in the left hemisphere for the rTMS and tDCS groups respectively. (C and D) display the top 15 Gene Ontology (GO) biological processes (FDR-corrected $P < 0.05$) enriched from PLS1-associated genes in the rTMS and tDCS groups, respectively. Dot size represents the number of genes in each category, and color intensity corresponds to the log-transformed enrichment score.

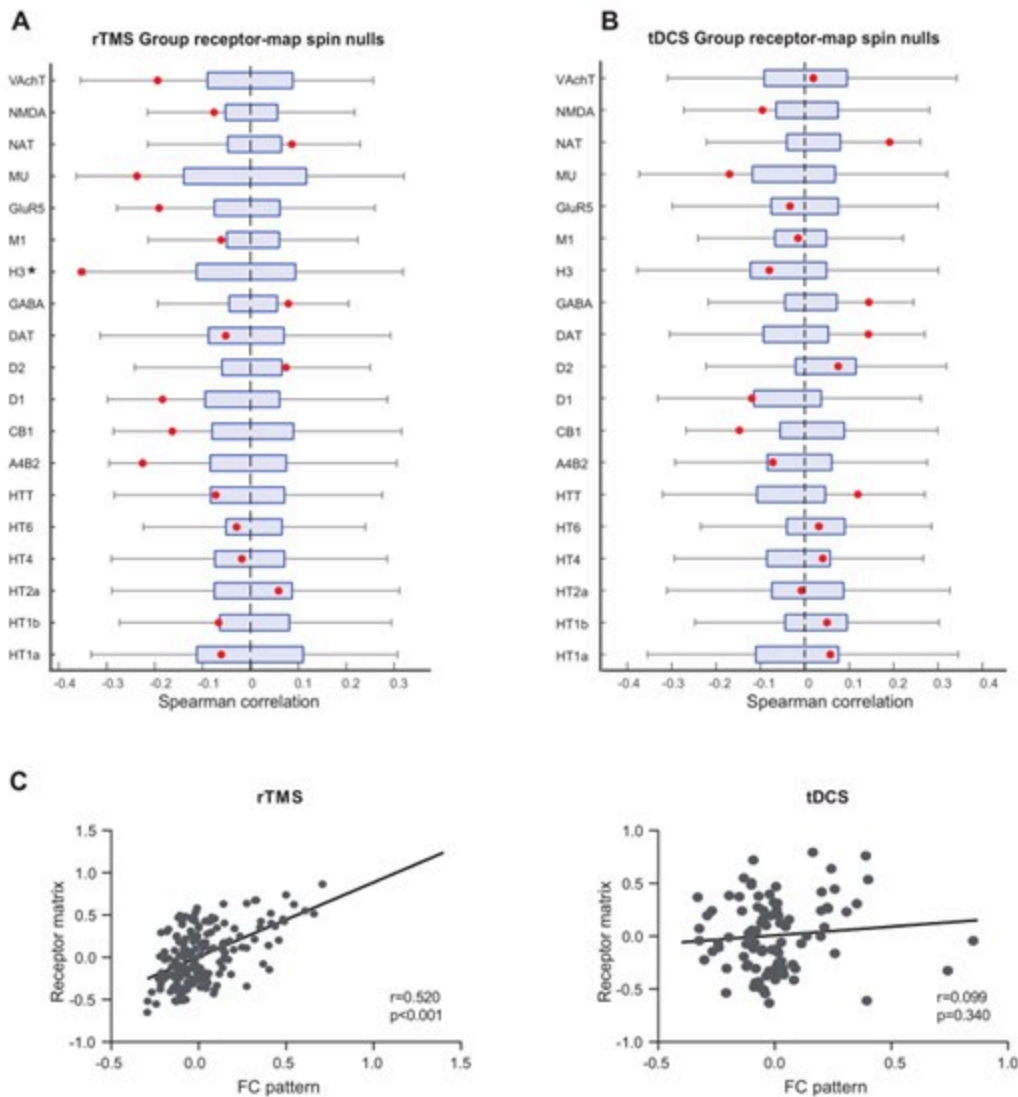


Figure 5

Neurotransmitter mapping of treatment-relevant functional connectivity patterns in rTMS and tDCS Groups. (A and B) Spatial correlations between the treatment-relevant FC pattern and 19 normative neurotransmitter receptor/transporter density maps in the rTMS (A) and HD-tDCS (B) groups. Red dots represent the observed Spearman correlation coefficients between FC patterns and receptor density maps. Blue boxes indicate the interquartile range of the null distribution derived from spin permutation testing, while grey horizontal lines denote the full range of the null distribution. Asterisks indicate associations surviving false discovery rate correction across the 19 receptor maps ($p_{\text{spin}} < 0.05$). (C) Correspondence between treatment-relevant FC patterns and neurotransmitter co-expression architecture. Scatterplots show the Spearman correlation between the FC pattern vector and the neurotransmitter receptor similarity matrix in the rTMS (left) and tDCS (right) groups. Each point represents one inter-regional connection.

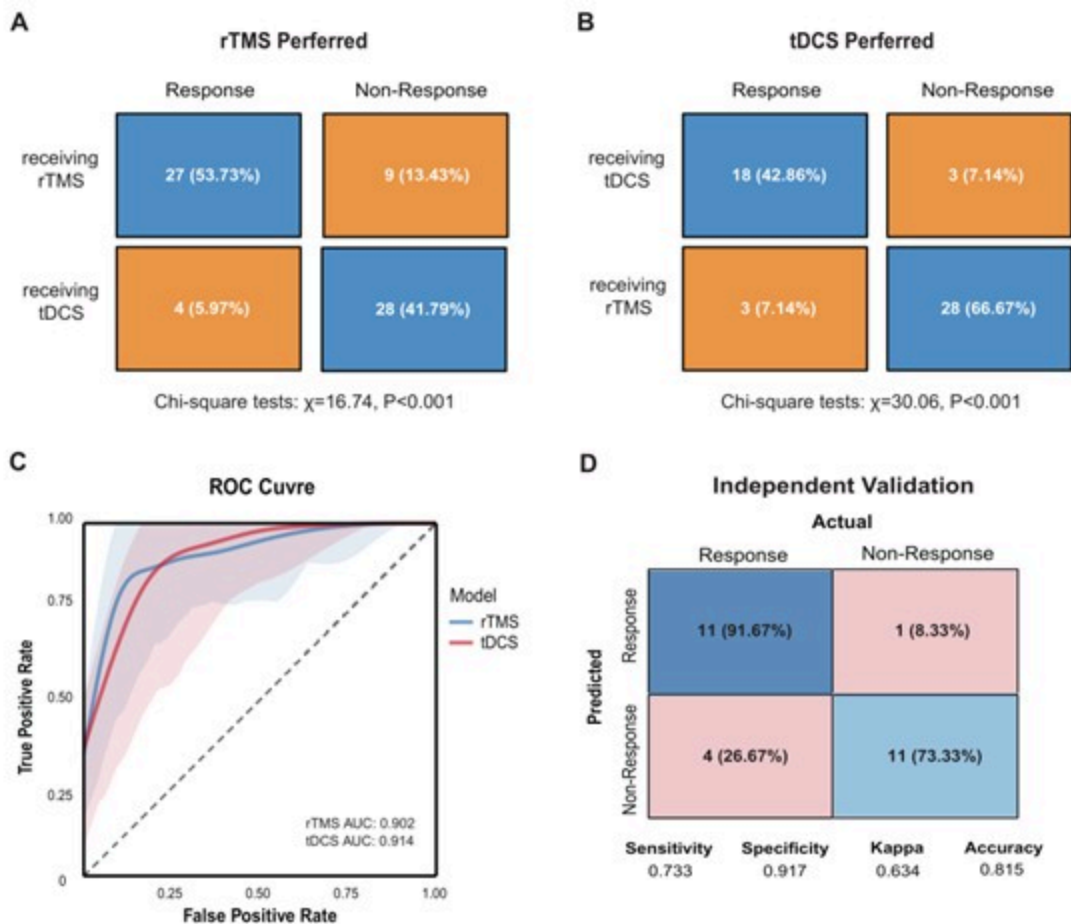


Figure 6

Predictive Performance of SVM Models for Treatment Response. (A-B) show the distribution of responders and non-responders stratified by predictive model. Panel A shows patients predicted to benefit more from rTMS, while Panel B shows patients predicted to benefit more from tDCS. Chi-squared tests were used to determine whether patients who received preferred treatment exhibited better clinical outcomes. (C) Receiver operating characteristic (ROC) curves for SVM models predicting treatment response in the rTMS and tDCS groups. The area under the curve (AUC) values indicate classification performance, with shaded regions representing 95% confidence intervals. (D) Confusion matrix depicting the model's predictive performance in the independent rTMS validation cohort. The matrix presents the number of correctly and incorrectly classified responders and non-responders.

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