Title: Using Prefrontal EEG Derived Theta Cordance to Predict Response to Anodal Transcranial Direct Current Stimulation (atDCS) in Female Patients with Treatment Resistant Depression

Running Title: EEG Theta Cordance Predict Response to tDCS in TRD

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Abstract

Purpose: This exploratory, proof-of-concept study investigated whether prefrontal theta cordance could serve as a candidate early indicator of response to anodal transcranial direct current stimulation (atDCS) in treatment-resistant depression (TRD), focusing on a homogeneous sample of young adult females. All findings are strictly hypothesis-generating and require external validation.

Method: Thirty female TRD patients were assessed using the Beck Depression Inventory-II (BDI-II) and resting-state EEG at baseline, after seven atDCS sessions (week 1), and after 14 sessions (week 2). Early response was defined as a 30% or greater reduction in BDI-II scores at week 1. Theta cordance was computed for the prefrontal (PF), midline left frontal (MLF), and midline right frontal (MRF) regions.

Results: Significant reductions in theta cordance were observed in the PF and MLF regions at week 1, with MLF changes showing a very large effect size (Cohen's d = 4.77) and robust group differentiation. This effect size is likely sample-specific and unstable. Exploratory logistic models combining week-one symptom improvement (ΔBDI) with changes in cordance were significant. The ΔBDI+ΔMLF model showed the strongest within-sample association with the outcome (AUC = .897). However, this estimate is likely inflated due to the small sample (N = 30) and the absence of internal validation (e.g., cross-validation); it should be interpreted as a preliminary, hypothesis-generating finding only.

Conclusion: Preliminary results suggest that early MLF theta cordance reduction is a prominent electrophysiological correlate of concurrent clinical improvement in this specific cohort of young adult females with TRD. These associative findings are strictly preliminary and demographic-specific. They underscore a need for validation in larger, sham-controlled trials with prospective designs before any consideration of clinical translation.

Keywords: Brain Stimulation, Electroencephalography, Theta cordance, Treatment-Resistant Depression

Introduction

Major Depressive Disorder (MDD) is a common, recurrent, and debilitating psychiatric condition that imposes a substantial burden on global public health. Its etiology is multifactorial, stemming from a complex interplay of genetic predispositions, early-life experiences, and underlying neurobiological disturbances (Leuchter et al., 2021). With a prevalence of 10.9% in females versus 5.1% in males, MDD accounts for a major proportion of mental health disorders and frequently serves as a precursor to various psychiatric comorbidities (Takahashi et al., 2021; Volgsten et al., 2008).

Despite considerable scientific reports, the exact neurobiological mechanisms underlying major depression are still not fully clarified. Several cortical and sub-cortical structures, particularly the limbic system, prefrontal, and anterior cingulate cortex, have been identified as key players in the complex pathophysiology of this disorder (Cui et al., 2020; Ji et al., 2021; Sheena et al., 2021; Takahashi et al., 2021; Uchida et al., 2021; Xiong et al., 2019; Zhang et al., 2020). Given their essential roles in emotion regulation, cognitive functions such as decision-making, these regions have become central targets in the ongoing effort to uncover the neural underpinnings of depression.

Neurophysiological indicators, including frontal alpha asymmetry and heightened theta power, have demonstrated potential utility in the characterization of MDD (Gollan et al., 2014; Newson & Thiagarajan, 2019). Alpha asymmetry between the two frontal hemispheres reflects imbalances in emotional processing, while increased theta oscillatory activity, especially in frontal structures, indicates altered neural synchrony and cognitive performance. These markers contribute to explaining some of the neurobiological alterations that manifest clinically in MDD.

Aberrant patterns of cerebral blood flow within the frontal cortex and anterior cingulate cortex have repeatedly been documented in MDD (Ho et al., 2013; Ota et al., 2014). A consistent observation across multiple studies is the presence of reduced metabolic activity in the left dorsolateral prefrontal cortex (DLPFC) alongside increased activity in the right frontal hemisphere (Cirillo et al., 2017; Dalby et al., 2021; Davidson, 1998). Such alterations are thought to underlie cognitive and emotional impairments observed in patients and suggest potential targets for therapeutic intervention.

Pharmacological treatment with antidepressants (ADs) leads to symptomatic and functional improvement in only about half of the patients initially. The chance of remission significantly

declines after two unsuccessful AD trials (Rush et al., 2006). Patients exhibit a spectrum of responses, ranging from partial response depression (PRD) to treatment-resistant depression (TRD) (Cipriani et al., 2018), with approximately one-third of depressed patients classified as treatment-resistant due to insufficient response to at least one antidepressant (Fava, 2003).

Transcranial Direct Current Stimulation (tDCS) is a non-invasive neuromodulation technique that alters brain neuroplasticity and cortical excitability by applying weak direct electrical currents (Olgiati & Malhotra, 2022). Anodal stimulation is capable of elevating neuronal excitability in the vicinity of the electrode placement through increased regional perfusion, thereby inducing metabolic and neurophysiological alterations (Yamada & Sumiyoshi, 2021). Such modifications within the prefrontal cortex have been associated with symptom reduction in MDD.

Cordance is a critical neurophysiological marker that uses absolute and relative EEG power measurements taken at rest to assess how active different parts of the brain are (Haghighi et al., 2017). It is thought to reflect integrative neural activity. It has been empirically correlated with regional cerebral perfusion (Leuchter et al., 1994), suggesting it may serve as a proxy for cortical metabolic demand. It may also index network-level oscillatory regulation within prefrontal-limbic circuits implicated in mood disorders. A number of investigations have employed frontal theta (4–8 Hz) cordance as a predictor of therapeutic outcomes in MDD patients receiving diverse antidepressant regimens. Early reductions in prefrontal theta cordance have been reported following administration of antidepressants such as escitalopram, bupropion, fluoxetine, and venlafaxine, marking it as a potential early biomarker of treatment efficacy (Bares et al., 2010, 2015, 2016; Baskaran et al., 2018). These reductions are hypothesized to reflect a normalization of hyperactive or dysregulated activity within prefrontal-limbic circuits, a core pathophysiological feature of MDD. However, findings regarding changes in theta cordance following neuromodulation treatments like repetitive transcranial magnetic stimulation (rTMS) are mixed (Hunter et al., 2010), with some studies reporting decreases (Bares et al., 2016) and others increase (Hunter et al., 2018). Similarly, increased theta cordance has been observed in early responders after electroconvulsive therapy (ECT) for late-life depression (Ward et al., 2020), whereas reductions have correlated with symptom improvement after eye movement desensitization and reprocessing (EMDR) therapy in unipolar depression (Baptist et al., 2021).

Given the heterogeneity of these findings and the lack of research on tDCS, the present study aims to conduct an initial investigation into these neural predictors. To reduce biological

heterogeneity and increase the internal validity of our findings for this proof-of-concept study, we focused on a single-sex cohort. We chose to recruit only female participants due to the well-documented approximately 2:1 sex difference in the prevalence of MDD, making TRD in women a highly prevalent and clinically significant public health issue. Furthermore, sex differences in the neurophysiology and anatomy of the brain, as well as treatment response, are well-established and could confound the identification of reliable biomarkers if not controlled. Therefore, this initial, proof-of-concept study aims to explore preliminary associations and assess the within-sample predictive potential of theta cordance measures from different prefrontal regions (frontal, midline left, and midline right cortex), as candidate early indicators of response to anodal tDCS in a specific, homogeneous population of female patients with TRD. It offers initial insights that are strictly specific to this demographic and are intended to inform the design of future, larger-scale studies capable of testing predictive models.

Materials and Methods

Participants

The present study utilized a quasi-experimental framework featuring three assessment time points: baseline (prior to treatment initiation), week 1 (following seven tDCS sessions), and week 2 (after 14 tDCS sessions). A total of thirty female patients diagnosed with MDD were intentionally selected through purposive sampling from outpatient psychiatric clinics located in Tehran province, Iran. Participants were selected based on purposive sampling to ensure that all individuals met the specific inclusion criteria for the study. Diagnosis was confirmed using the Structured Clinical Interview for DSM-5 – Clinical Version (SCID-5-CV). Prior to the tDCS intervention, all participants underwent a six-week course of citalopram at a fixed daily dose of 20 mg.

Participants were required to be female, of Iranian nationality, literate in Persian, right-handed, and aged between 18 and 40 years. As previously mentioned in the introduction, only females were selected so that we could control for known gender-based variations in the prevalence, neurobiology, and response to treatment of major depressive disorder. Participants had to score 29 or higher on the Beck Depression Inventory-II (BDI-II), which indicates severe depression. After six weeks of pharmacotherapy, all patients were evaluated and diagnosed with treatment-resistant depression by two experienced psychiatrists.

Participants were excluded if they presented with any of the following: a history of bipolar disorder, major neurocognitive impairment, substance use disorders, epilepsy or seizure episodes, cerebrovascular accident, head injury, learning disabilities, ongoing psychotherapy, or substance abuse (including alcohol) within the preceding six months. Additional exclusion criteria comprised prior exposure to tDCS, cranial bone abnormalities, presence of intracranial electrodes, vascular clips or shunts, cardiac pacemakers or other implanted biomedical devices, as well as pregnancy.

Ethical Considerations

Ethical approval for this study was granted by the Research Ethics Committee of Ferdowsi University of Mashhad (Approval Code: ***IR.UM.REC.1404.384***). The research was carried out in compliance with the ethical standards set forth in the Declaration of Helsinki. Comprehensive details concerning the study protocol, possible risks, and anticipated benefits were furnished to all participants. Written informed consent was secured from every individual prior to their enrollment in the study. To protect participant privacy, all collected data were anonymized.

Measures

The *Structured Clinical Interview for DSM*-5-Clinician Version (SCID-5-CV)

The SCID-5-CV is a widely utilized diagnostic instrument aligned with DSM-5 criteria for the assessment of severe psychiatric disorders (Shabani et al., 2021). In the present study, it was employed to evaluate current depressive episodes and to conduct screening for psychosis, mania, and substance-related disorders. Previous research conducted in Iran has reported Kappa coefficients of approximately .6 for the reliability of these diagnoses (Shabani et al., 2021).

Beck's Depression Inventory II (BDI-II)

This scale consists of 21 items, each scored from 0 to 3, with total scores ranging from 0 to 63—higher scores indicating more severe depression. Its three-factor structure (cognitive, affective, and somatic) has been well-documented (Beck et al., 1996). In Iranian samples, the scale has shown strong reliability, with Cronbach's alpha between .87–.91 and test-retest Kappa of .74 (Ghassemzadeh et al., 2005; Mohammadkhani et al., 2020). In the current study, internal consistency was excellent (α = .85).

EEG recording and pre-processing

Prior to each EEG recording, the distance from the nasion to the inion was measured to select the correct cap size. Head dimensions were carefully assessed before every session to guarantee uniformity across recordings. Mild abrasive alcohol was applied to the forehead and ears to cleanse the skin of oils and impurities. Each electrode location was injected with electro gel, resulting in prepared impedances of less than 5 kΩ between each electrode and the ear. 19 electrodes from the standard international 10–20 system were used for the EEG recording. These electrodes were Fp1, Fp2, F3, F4, Fz, F7, F8, C3, C4, Cz, T3, T4, T5, T6, P3, P4, Pz, O1, and O2. The earlobes were used as the reference electrodes, and a ground electrode was placed on a neutral area of the body to reduce electrical noise and ensure stable EEG recordings. EEG data were acquired through a Mitsar-201 amplifier system, with a sampling frequency of 250 Hz, while participants remained in an eyes-closed resting state. Standard tin cup electrodes, measuring 9 mm in diameter, were utilized for the recordings. Participants were asked to remain still and regulate the action of their tongues and the muscles in their foreheads, necks, and mouths during the recording sessions to reduce the generation of extracranial artifacts. The EEGLAB toolbox was employed to filter the recorded row EEG using a linear Finite Impulse Response (FIR) bandpass filter (1–80 Hz) and a notch filter at 50 Hz. Muscular activity and auditory disturbances were manually removed from the recordings, after which independent component analysis (ICA) was applied to improve the signal-to-noise ratio. On average, 2.4 ± .8 (Mean ± *SD*) ICA components per participant were identified and removed, corresponding to typical artifacts from eye blinks, eye movements, and cardiac activity. A minimum of 100 seconds of artifact-free recording was required from each participant for inclusion in the analysis (Taremian et al., 2023).

Computation of Theta Cordance

Cordance values were derived following the procedure developed by the Laboratory of Brain, Behavior, and Pharmacology at UCLA (Leuchter et al., 2017). Theta cordance was obtained via a three-stage normalization procedure that combines both absolute and relative power measurements across electrode positions and frequency ranges. The procedure begins with calculating absolute power for each bipolar electrode pair. Subsequently, these values are allocated to each electrode by computing the mean power across all neighboring pairs that share that particular electrode. Next, relative power is computed for each frequency band by expressing its power as a percentage of the total power spectrum (.5–30 Hz). In the second

step, both absolute ($A_{(s, f)}$) and relative ($R_{(s, f)}$) power values are normalized by dividing them by their respective means across all 19 electrodes, converting them into z-scored values (A_{norm} (s, f) and R_{norm} (s, f)). In the final step, cordance ($Z_{(s, f)}$) is calculated for each electrode (s) and frequency band (f) by summing these normalized values:

$$Z\,(s, f) = A_{norm}\,(s, f) + R_{norm}\,(s, f)$$

The absolute and relative normalized results were aggregated across each individual electrode site (Fp1, Fp2, Fz, F3, F4, F7, and F8) within the theta frequency band [4–8 Hz]. For the next set of statistical tests, we used the average concordance values from the two prefrontal electrodes (Fp1, Fp2), the Midline Left Frontal (MLF) region (Fz, Fp1, F3, F7), and the Midline Right Frontal (MRF) region (Fz, Fp2, F4, F8) in the theta frequency band.

Transcranial direct current stimulation (tDCS)

The Segal Stim tES device was used to administer transcranial direct current stimulation (tDCS). All participants received an identical stimulation protocol. The anode was positioned over the left dorsolateral prefrontal cortex (F3), while the cathode was placed over the right dorsolateral prefrontal cortex (F4). The dimensions of the conducting electrodes were 35 cm^2 (7 × 5 cm). Each session delivered stimulation at an intensity of 2 mA over a 20-minute period, beginning with a 30-second gradual increase and ending with a 30-second gradual decrease. Participants received 14 daily sessions over 14 consecutive days to ensure consistent treatment delivery.

Procedure

All participants completed the BDI-II at three time points: baseline (pre-treatment), week 1 (following 7 tDCS sessions), and week 2 (following 14 tDCS sessions). EEG recordings were likewise obtained at baseline, week 1, and week 2 for every patient. At the conclusion of week 1, patients were divided into two categories—early responders and non-responders—according to the magnitude of BDI score reduction, with early response defined as a decline of 30% or more from the baseline value.

Statistical Assessment

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS, version 26) and MedCalc Software (version 14.8.1, Ostend, Belgium). To compare demographic characteristics between early responders and non-responders, independent samples *t*-tests were used (two-sided, $p < .05$), and Cohen's d was calculated as a measure of

effect size. To analyze the longitudinal changes in theta cordance values (PF, MLF, MRF) and BDI-II scores, we conducted separate 2 × 3 mixed-model Analyses of Variance (ANOVAs) for each measure. Each model included Time (Baseline, Week 1, Week 2) as a within-subjects factor and Group (Responder, Non-responder) as a between-subjects factor. The primary effect of interest was the Group × Time interaction. Mauchly's test was employed to evaluate the sphericity assumption, and the Greenhouse-Geisser adjustment was applied whenever the assumption was violated. When a significant interaction effect emerged, post-hoc independent-samples *t*-tests were performed at each time point, with Bonferroni adjustment applied to maintain an overall alpha level of .025. The resulting *p*-values from these post-hoc tests, which have been evaluated against this corrected alpha level, are reported as *p*-corr in the results to distinguish them from uncorrected *p*-values. Partial Eta-Squared (ηp^2) was reported as the effect size for ANOVA results, and Cohen's *d* was reported for post-hoc *t*-tests. Readers are cautioned that effect sizes, particularly in this modest-sized, homogenous sample, should be interpreted as preliminary estimates of the observed associations rather than as stable population parameters.

To examine the predictive value of these variables, multiple logistic regression models were constructed by combining ΔBDI with each cordance index (ΔBDI + ΔPF, ΔBDI + ΔMLF, ΔBDI + ΔMRF). Multicollinearity among predictors within each combined model was assessed using the Variance Inflation Factor (VIF). All VIF values were below 2.0, well under the common threshold of 5–10, indicating that multicollinearity was not a significant concern in our models. These models served to evaluate the role of each combined predictor in classifying treatment response status. Receiver Operating Characteristic (ROC) curve analyses were carried out to determine the Area Under the Curve (AUC) for each individual predictor as well as for combined models, with exact binomial 95% confidence intervals (CIs) computed for each estimate. Given the sample size (N = 30), we were acutely aware of the substantial risks of overfitting in the logistic regression and ROC analyses. Therefore, we restricted our models to a maximum of two predictors (e.g., ΔBDI + ΔMLF) to maintain a favorable events-per-variable ratio and to conduct an exploratory proof-of-concept analysis. No internal validation (e.g., cross-validation, bootstrapping) was performed, which means the reported predictive accuracy metrics (AUC, sensitivity, specificity) are likely optimistic and subject to inflation. Consequently, all cut-off values and model coefficients should be considered unstable and illustrative rather than clinically prescriptive. A post-hoc power analysis for the key ROC analysis indicated a power of .91. While this suggests sufficient

power for the primary AUC finding, the precision of the estimates and the generalizability of the specific cut-off values are necessarily limited by the sample size, and the results should be considered preliminary until validated in a larger, independent cohort. No missing data were present, as all 30 participants completed the full protocol. Due to the exploratory nature and small sample size, adjustment for multiple confounders was not feasible; instead, demographic homogeneity was enforced by design (all female, age-restricted, right-handed, same antidepressant background).

To assess the performance of the classification models, we calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy. The Clopper–Pearson method was used to compute exact 95% CIs for sensitivity, specificity, and accuracy, while the logit transformation was applied to calculate 95% confidence intervals (CIs) for Positive Predictive Value and Negative Predictive Value (Mercaldo et al., 2007). Finally, pairwise comparisons of AUCs were performed using the z statistic to determine whether the predictive performance of the models differed significantly.

Results

Demographic and clinical characteristics of the female participants, classified as either early responders or non-responders, are summarized in Table 1. No significant group differences were found between early responders and non-responders with respect to age ($t(28) = 1.21$, $p = .23$), years of education ($t(28) = .96$, $p = .34$), or age at MDD onset ($t(28) = 1.31$, $p = .19$). Baseline BDI scores did not differ significantly between early responders and non-responders ($t(28) = .75$, $p = .46$). However, at week 1, early responders showed substantially lower BDI scores (reflecting greater improvement) relative to non-responders.

Table 1 *Demographic and clinical profile of early responders versus non-responders (Mean ± SD)*

	Total Sample (N = 30)	Early responders (N = 16)	Non-responders (N = 14)	Statistical Analysis, p	Effect Size (Cohen's d)
Age	34.77(11.93)	32.31(12.09)	37.57(11.52)	$t(28) = 1.21$, $p = .23$	-.45
Education (years)	12.7(2.97)	13.18(3.29)	12.14(2.56)	$t(28) = .96$, $p = .34$	.35
Onset MDD	27.43(8.74)	29.37(10.23)	25.21(6.29)	$t(28) = 1.31$, $p = .19$	.48
BDI Baseline	47.16(7.10)	46.25(6.14)	48.21(8.16)	$t(28) = .75$, $p = .46$	-.28
BDI Week 1	42.73(7.71)	38.93(5.24)	47.07(7.94)	$t(28) = 3.34$, $p \leq .01$	**-1.22**
BDI Change from Baseline to Week 1 (%)	-4.43(-9.39 %)	-7.32(-15.82 %)	-1.14(-2.36 %)	$t(28) = 11.23$, $P \leq .001$	**-1.27**

Note. Values are presented as Mean (*SD*) for all rows except the last row. The last row presents Absolute Change in BDI-II points, with Percentage Change shown in parentheses. Negative percentage indicates improvement (reduction in BDI-II scores).

Cordance (PF, MLF, and MRF) measures

The mixed-model ANOVA for MLF cordance revealed a significant main effect of Time (F (2,56) = 11.23, $p < .001$, $\eta p^2 = .29$), a significant main effect of Group (F (1,28) = 4.72, $p = .039$, $\eta p^2 = .14$), and a significant Group × Time interaction (F (2,56) = 10.18, $p < .001$, $\eta p^2 = .27$). Post-hoc analyses with Bonferroni correction confirmed that while groups did not differ at baseline (t(28) = 1.32, p-corr = .396, Cohen's d = .49), early responders showed a significantly greater decrease in MLF cordance at Week 1 compared to non-responders (t(28) = 12.86, p-corr < .001, Cohen's d = 4.77). This effect size is likely sample-specific and unstable. So, this extraordinarily large effect size should be interpreted with extreme caution. It is likely influenced by the small, homogeneous sample and the concurrent assessment of Week 1 cordance change and Week 1 responder status, which may introduce overlap in the measurements, rather than representing a stable, population-level effect.

A similar pattern was observed for PF cordance, which showed a significant main effect of Time (F(1.5, 41.5) = 9.65, $p = .001$, $\eta p^2 = .26$) and a significant Group × Time interaction (F(1.5, 41.5) = 4.35, $p = .023$, $\eta p^2 = .13$). Post-hoc tests indicated a significant difference between groups at Week 1 (t (28) = 9.07, p-corr < .001, Cohen's d = 3.20, a large effect), but not at baseline (t(28) = 2.08, p-corr = .094, Cohen's d = .75).

In contrast, the ANOVA for MRF cordance showed a significant main effect of Time (F(2,56) = 5.62, $p = .009$, $\eta p^2 = .17$) but no significant Group × Time interaction (F(2,56) = 1.12, $p = .339$, $\eta p^2 = .04$), indicating that longitudinal changes in this region did not robustly differentiate the groups (Table 2).

Table 2 *Results of mixed-model ANOVA and post-hoc tests for theta cordance across measurement time points (Baseline, Week 1, Week 2)*

Brain Region	ANOVA Effect	*F*-value (*df*)	*p*-value	Partial Eta-Squared (ηp^2)	Post-Hoc Comparison (Week 1)	*t*-statistic (*df* = 28)	Cohen's *d*
PF	Group	$F(1, 28) = 2.21$	.15	.073	Responder vs. non-responder	***p* < .001**	**3.20**
	Time	$F(1.5, 41.5) = 9.65$	**.001**	.26			
	Group × Time	$F(1.5, 41.5) = 4.35$	**.02**	.13			
MLF	Group	$F(1, 28) = 4.72$	**.04**	.14	Responder vs. non-responder	***p* < .001**	**4.77**
	Time	$F(2, 56) = 11.23$	**<.001**	.29			
	Group × Time	$F(2, 56) = 10.18$	**<.001**	.27			
MRF	Group	$F(1, 28) = .47$	.51	.02			
	Time	$F(2, 56) = 5.62$	**.009**	.17			
	Group × Time	$F(2, 56) = 1.12$	.34	.04			

Note. PF = Prefrontal; MLF = Midline Left Frontal; MRF = Midline Right Frontal.

Development of Combined Predictor Models (ΔBDI+ΔPF, ΔBDI+ΔMLF, and ΔBDI+ΔMRF) for tDCS Treatment Outcome

To examine the relationships within this sample, we performed exploratory logistic regression analyses incorporating changes in cordance and BDI scores from baseline to week 1 (ΔBDI+ΔPF, ΔBDI+ΔMRF, ΔBDI+ΔMLF) to predict the concurrently determined responder versus non-responder classification. All combined predictor models reached statistical significance: ΔBDI + ΔPF ($\chi^2[2] = 10.33$, $p < .001$, Nagelkerke $R^2 = .39$), ΔBDI + ΔMRF ($\chi^2[2] = 9.68$, $p < .01$, Nagelkerke $R^2 = .37$), and ΔBDI + ΔMLF ($\chi^2[2] = 16.41$, $p < .001$, Nagelkerke $R^2 = .57$). Overall, these findings indicate that the combination of BDI change with decreasing cordance values in the MLF region (ΔBDI + ΔMLF) outperformed both ΔBDI + ΔMRF and ΔBDI + ΔPF in predicting treatment outcome. It should be noted that all predictive analyses remain exploratory, and the reported performance metrics are likely inflated due to the modest sample size and absence of independent validation.

Predictive Performance Metrics for Individual Variables (ΔPF, ΔMRF, ΔMLF, and ΔBDI) and Combined Predictor Models (ΔBDI+ΔPF, ΔBDI+ΔMRF, and ΔBDI+ΔMLF)

Figures 1 and 2 present the ROC curves for both individual predictors (changes in PF cordance [ΔPF], MRF cordance [ΔMRF], MLF cordance [ΔMLF], and BDI scores [ΔBDI]) as well as for the combined predictor-variable models. Table 3 summarizes the corresponding AUC values (with exact binomial 95% CIs) and predictive accuracy metrics, including

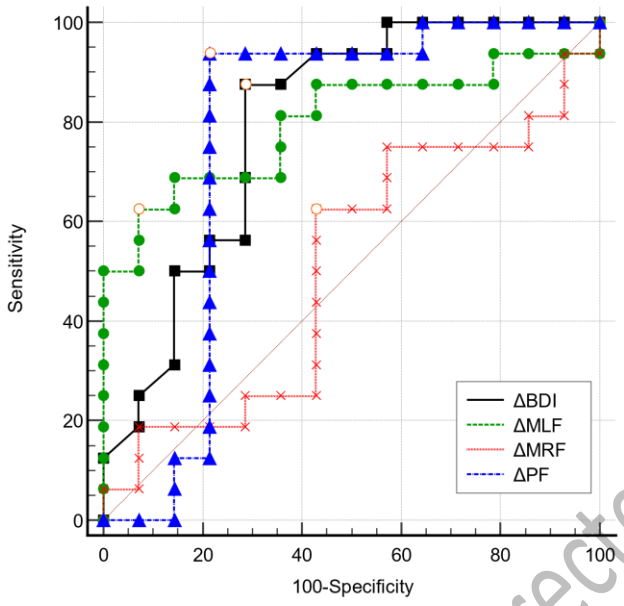
sensitivity, specificity, positive predictive value, and negative predictive value. The following ROC analyses are exploratory and are presented to describe initial predictive signals within this specific sample. The associated accuracy metrics are likely inflated due to overfitting and the absence of internal validation. As presented in Table 3, the lowest AUC value belonged to ΔMRF (.509), while the highest was observed for ΔBDI+ΔMLF (.897). Consistent with its exploratory aim, this analysis indicated that the ΔBDI+ΔMLF combination showed the strongest within-sample association with treatment outcome. In contrast, changes in ΔMRF were not meaningfully associated with response.

Table 3 *Predictive accuracy metrics for week 1 treatment response (95% CI)*

Variable	Threshold Cut-off	AUC	Sensitivity	Specificity	PPV	NPV
ΔBDI	≤ 43	.79	87.50	71.43	77.8	83.3
		.611 -.921	61.7 - 98.4	41.9 - 91.6	60.0 - 89.1	56.7 - 95.0
ΔPF	≤-.0403	.768	93.75	78.57	83.3	91.7
		.578 - .901	69.8 - 99.8	49.2 - 95.3	64.5 - 93.2	61.8 - 98.7
ΔMRF	>-.2702	.509	62.50	57.14	62.5	57.1
		.321- .695	35.4 - 84.8	28.9 - 82.3	44.9 - 77.3	38.0 - 74.4
ΔMLF	≤-.2823	.799	62.50	92.86	90.9	68.4
		.613- .922	35.4 - 84.8	66.1 - 99.8	59.3 - 98.6	53.1 - 80.6
ΔBDI+ΔPF	>.40126	.830	93.75	64.29	75.0	90.0
		.649 -.942	69.8 - 99.8	35.1 - 87.2	59.5 - 86.0	56.5 - 98.4
ΔBDI+ΔMRF	>.47805	.795	87.50	71.43	77.8	83.3
		.608- .919	61.7 - 98.4	41.9 - 91.6	60.0 - 89.1	56.7 - 95.0
ΔBDI+ΔMLF	>.60720	.897	75.00	92.86	92.3	76.5
		.731 -.978	47.6 -92.7	66.1- 99.8	64.0- 98.8	57.9- 88.5

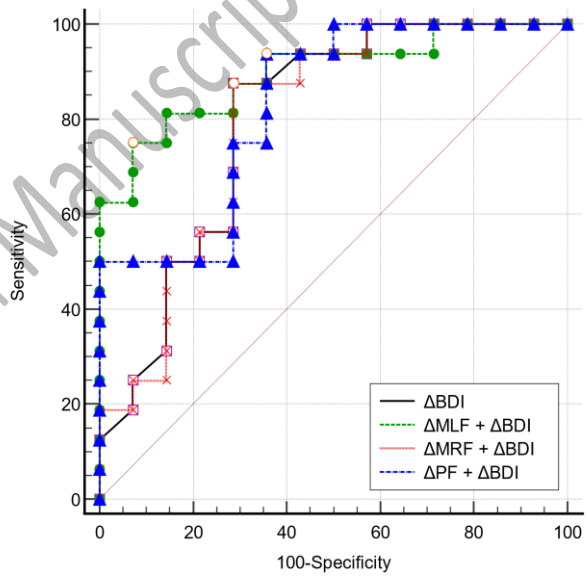
Note. ΔBDI = change in Beck Depression Inventory (BDI) score from baseline to week 1; ΔPF = change in prefrontal cordance (PF) from baseline to week 1; ΔMRF = change in midline right frontal (MRF) cordance from baseline to week 1; ΔMLF = change in midline left frontal (MLF) cordance from baseline to week 1. Combined predictors are denoted as follows: ΔBDI+ΔPF (combination of BDI and PF changes), ΔBDI+ΔMRF (combination of BDI and MRF changes), and ΔBDI+ΔMLF (combination of BDI and MLF changes)

Figure 1 *Receiver operating characteristic (ROC) curves for individual predictors (ΔBDI, ΔPF, ΔMRF, and ΔMLF)*



Note. ΔBDI = change in Beck Depression Inventory (BDI) score from baseline to week 1; ΔPF = change in prefrontal cordance (PF) from baseline to week 1; ΔMRF = change in midline right frontal (MRF) cordance from baseline to week 1; ΔMLF = change in midline left frontal (MLF) cordance from baseline to week 1.

Figure 2 *Receiver operating characteristic (ROC) curves for combined predictor models (ΔBDI+ΔPF, ΔBDI+ΔMRF, and ΔBDI+ΔMLF) predicting response status*



Note. Combined predictors are denoted as follows: ΔBDI+ΔPF (combination of BDI and PF changes), ΔBDI+ΔMRF (combination of BDI and MRF changes), and ΔBDI+ΔMLF (combination of BDI and MLF changes), all measured from baseline to week 1.

Pairwise Comparison of AUC Values Between Individual and Combined Predictor Models

Pairwise comparisons of AUCs for response revealed that combined models of ΔBDI+ΔPF, ΔBDI+ΔMLF, and ΔBDI+ΔMRF performed better than ΔBDI alone (Table 4). Table 4 shows that in comparing individual predictors in predicting response to tDCS, ΔBDI, ΔMLF, and ΔPF have no significant difference. These three predictors all differed significantly from ΔMRF, indicating that ΔMRF lacks sufficient predictive accuracy for tDCS response in patients with MDD. As shown in Table 4, pairwise comparisons of AUCs revealed that none of the combined models (ΔBDI+ΔPF, ΔBDI+ΔMRF, ΔBDI+ΔMLF) achieved statistically significantly higher AUC values than ΔBDI alone (all 95% confidence intervals for the difference included zero; ΔBDI+ΔPF: p = .490; ΔBDI+ΔMRF: p = .789; ΔBDI+ΔMLF: p = .093). The comparison for ΔBDI+ΔMLF approached but did not reach conventional statistical significance (p = .093). These results indicate that, in this sample, adding EEG-derived theta cordance measures to symptom change alone did not provide statistically significant incremental predictive value, although the trend for ΔBDI+ΔMLF suggests this combination may merit further investigation in larger samples. No significant differences were observed among the remaining combined models.

Table 4 *Pairwise comparisons of AUC values for week 1 predictors of response status*

Comparison	Difference between areas (95% CI)	*z* statistic	*p*-value (Sig)
Individual Predictors			
ΔBDI vs. ΔMLF	-.219 to .224	.019	p = .98
ΔBDI vs. ΔMRF	.018 to .558	2.090	***p* = .04**
ΔBDI vs. ΔPF	-.217 to .275	.230	p = .82
ΔMLF vs. ΔMRF	.045 to .535	2.321	***p* = .020**
ΔMLF vs. ΔPF	-.215 to .277	.248	p = .80
ΔMRF vs. ΔPF	.047 to .471	2.406	***p* = .02**
Combined vs. Simple			
ΔBDI vs. ΔBDI+ΔMLF	-.024 to .224	1.683	p = .09
ΔBDI vs. ΔBDI+ΔMRF	-.014 to .018	.267	p = .79
ΔBDI vs. ΔBDI+ΔPF	-.062 to .129	.689	p = .49
ΔBDI+ΔMRF vs. ΔBDI+ΔMLF	-.023 to .229	1.602	p = .11
ΔBDI+ΔMLF vs. ΔBDI+ΔPF	-.060 to .194	1.031	p = .30
ΔBDI+ΔMRF vs. ΔBDI+ΔPF	-.058 to .130	.742	p = .46

Note. ΔBDI = change in Beck Depression Inventory (BDI) score from baseline to week 1; ΔPF = change in prefrontal cordance (PF) from baseline to week 1; ΔMRF = change in midline right frontal (MRF) cordance from baseline to week 1; ΔMLF = change in midline left frontal (MLF) cordance from baseline to week 1. Combined predictors are denoted as follows: ΔBDI+ΔPF (combination of BDI and PF changes), ΔBDI+ΔMRF (combination of BDI and MRF changes), and ΔBDI+ΔMLF (combination of BDI and MLF changes). A 95% confidence interval containing zero signifies no statistically significant difference between the two AUCs at α = .05.

Discussion

Summary of Main Findings

This proof-of-concept study aimed to explore whether early alterations in prefrontal theta cordance are linked to early clinical improvement observed during tDCS in a homogeneous cohort of female patients with TRD. The goal was to identify potential electrophysiological correlates, not to establish validated predictors. The study found that reductions in theta cordance, particularly in the MLF region, were strongly associated with the classification of early response defined at the same time point. This suggests theta cordance may be a correlative electrophysiological marker that is worth further investigation. However, as shown in Table 4, pairwise comparisons revealed that none of the combined models (including ΔBDI+ΔMLF) achieved statistically significantly higher AUC values than ΔBDI alone (all $p > .05$). The comparison for ΔBDI+ΔMLF approached statistical significance but ultimately fell short of the conventional threshold ($p = .093$). Therefore, while the numerical AUC for the combined model was higher, this study did not find statistically significant incremental predictive value from adding theta cordance measures to symptom change alone in this sample. The area under the curve, an essential metric for assessing predictive measurements, demonstrated consistent values across the three brain regions and BDI scores, indicating the potential reliability of theta cordance measurements for predicting treatment response. This exploratory integration of clinical features and prefrontal neural markers highlights a potential pathway for future research aimed at predicting treatment response in depression (Brunoni et al., 2016). If validated, such an approach could eventually be suitable for patients with TRD, but substantial further research is required.

Neurophysiological Interpretation

The theta cordance changes observed in this study may be interpreted within complementary neurophysiological frameworks. Theta cordance has been associated with regional cerebral perfusion and metabolic activity (Leuchter et al., 2009, 2017) and may function as an indirect index of cortical physiological state. The reductions in prefrontal theta cordance following the electrical intervention are consistent with the neuromodulatory aftereffects of stimulation in a region commonly targeted to enhance cortical excitability in depression (Boggio et al., 2008; Shiozawa et al., 2014). Modulation of cortical excitability may influence regional oscillatory dynamics and metabolic demand, as reflected in cordance measures. From a network perspective to the brain function, decreased theta cordance may also indicate a

reduction in maladaptive theta synchrony within prefrontal–limbic circuits, potentially reflecting improved regulatory control (Bares et al., 2009; Krepel et al., 2018; Leuchter et al., 2009; Mulert et al., 2007).

Comparable patterns of theta cordance change have been linked to treatment response across various therapeutic modalities, including rTMS, ECT, and pharmacological interventions (Bares et al., 2010, 2015; Leuchter et al., 2021). Although experimental and preclinical models suggest that tDCS can induce changes in cortical excitability and synaptic plasticity, including long-term potentiation (Cooke, 2006; Korai et al., 2021), the present study did not directly assess these mechanisms. Therefore, the observed cordance reductions in our study should be interpreted as electrophysiological correlates of clinical improvement, rather than as direct indicators of the mechanisms of tDCS.

The observed changes of theta cordance in the left prefrontal cortex following tDCS are consistent with the targeted engagement of the DLPFC, which plays an important role in mood regulation. These electrophysiological changes align with the premise that tDCS influences cortical excitability, though our study cannot confirm a direct causal or neuroplastic mechanism.

The alterations in theta cordance likely represent the changes in functional brain connectivity and neural oscillatory dynamics that underpin emotional and cognitive processes affected in depression. Such changes may facilitate the restoration of dysfunctional neural circuits implicated in TRD, thereby correlating with the observed clinical improvements measured by reductions in depressive symptom severity. This coupling of neurophysiological and clinical data supports the potential construct validity of theta cordance as a biomarker that may index treatment-related neural activity changes.

The observed pattern of theta cordance change across frontal regions suggests it may be a coherent electrophysiological signal related to treatment outcome, potentially offering information distinct from clinical scales alone. While this pattern is consistent with mechanisms of tDCS effects involving synaptic plasticity, our data do not directly test these mechanisms.

Comparison with Prior Literature

The pattern of theta cordance reduction in responders is consistent with some prior studies of antidepressants and neuromodulation (Bares et al., 2015; Bares et al., 2010), but contrasts with findings of increased cordance following ECT in late-life depression (Ward et al., 2020).

To our knowledge, this is one of the first studies to examine theta cordance as a correlate of tDCS response in TRD. The results of this preliminary investigation add to our understanding of the possible electrophysiological markers associated with the antidepressant mechanisms of tDCS in treatment-resistant depression. Specifically, the observed changes in theta cordance provide preliminary objective evidence of altered cortical functioning within prefrontal circuits implicated in mood regulation. Future research integrating such electrophysiological markers with clinical measures in larger, controlled trials could, upon validation, contribute to a more detailed understanding of treatment response. This line of investigation may eventually inform the development of more targeted neuromodulation strategies, but it is currently at an early, proof-of-concept stage and is not yet ready to guide clinical practice. Thus, within the constraints of this exploratory study, theta cordance measures provide an early electrophysiological correlate of clinical change in a specific TRD population.

Limitations

Several noteworthy limitations must be taken into account when interpreting the results of this study. (1) Lake of Sham control. The lack of a placebo or control condition restricts our capacity to draw causal inferences and compromises the internal validity of the study. Without appropriate controls, it is difficult to determine whether the observed effects are attributable solely to the intervention or are confounded by other variables. Therefore, sham-controlled randomized trials are a necessary next step to establish efficacy and isolate tDCS-specific effects. (2) Small sample size and overfitting risk. The relatively small sample size, while comparable to other initial proof-of-concept neurophysiological studies, is a key limitation that elevates the risk of statistical overfitting and optimistic bias in our predictive models. Importantly, no independent validation sample was used, and no cross-validation or bootstrapping procedures were applied. Therefore, the reported AUCs and accuracy metrics are almost certainly inflated due to overfitting and the circularity of using Week 1 data to classify Week 1 outcome; they do not represent generalizable predictive performance. Our sample, with 16 responders, is below common recommendations for developing stable multivariate predictive models. Although we employed simple two-predictor models to mitigate overfitting, the lack of internal validation means the high AUC values should be interpreted as demonstrating a strong initial predictive model, not as a finished, clinically usable algorithm. Consequently, the specific coefficients, cut-off values, and AUCs from our logistic regression and ROC analyses must be interpreted with caution and are presented as

preliminary, exploratory findings. (3) Limited generalizability. The study included only young adult female participants (aged 18–40). While this was a deliberate choice to control for sex-based and developmental heterogeneity and focus on a population with a high prevalence of TRD, it severely limits the generalizability of our findings. The predictive performance of theta cordance may differ in males, older adults, individuals outside the studied age range, or those with non-TRD forms of depression. Therefore, prospective external validation in a larger, independent mixed-sex cohort is an essential next step to confirm the reliability and generalizability of these predictive models before any clinical application can be considered (Metz, 1978). Consequently, the results should be interpreted as applicable only to the specific demographic studied. (4) Measurement tool limitations. Regarding measurement tools, the use of cordance as a neurophysiological indicator carries inherent limitations. The physiological basis of cordance is not fully elucidated, and there remains debate about its specificity and sensitivity in predicting antidepressant treatment response (Baskaran et al., 2018). Some studies have failed to replicate early reductions in theta cordance among responders, necessitating cautious interpretation of these results. Therefore, the findings are not generalizable to young adult females with TRD, and caution is warranted when extrapolating them to broader clinical populations. (5) Exploratory design. Most importantly, the exploratory design, lack of a control group, and unvalidated predictive models mean this study cannot support any current clinical application or change in practice. The findings are strictly preliminary and hypothesis-generating.

Conclusions and Future Directions

This proof-of-concept study provides preliminary evidence that in young adult females with TRD, early alterations in theta cordance within the prefrontal, midline left, and midline right frontal regions, combined with initial improvements in depressive symptomatology, are associated with and may hold promise as candidate early indicators of antidepressant treatment response within the first week of therapy. Our exploratory integrative predictive models demonstrated encouraging within-sample accuracy compared to models based solely on early symptom changes, suggesting the potential future incremental value of EEG-derived biomarkers, though this requires rigorous external validation. These findings offer a preliminary contribution to the existing literature by elucidating the role of theta cordance reduction as a neurophysiological correlate of treatment response in a specific demographic of patients with treatment-resistant depression. This study represents an initial exploratory

step in the long-term pursuit of personalized medicine in psychiatry, highlighting a potential pathway for future EEG-informed therapeutic strategies that would require extensive validation. The results have no immediate clinical implications. They offer promising hypotheses and avenues for future research aimed at refining predictive algorithms and testing their utility across diverse clinical settings and populations. Critical next steps include sham-controlled RCTs to establish causality, followed by validation of predictive models in larger, independent, and mixed-sex cohorts. The associations presented here are preliminary and do not support any current clinical application.

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