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Theta-cordance as a biomarker of treatment response to intermittent theta burst stimulation in patients with treatment-resistant depression

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ABSTRACT

Objective: To test whether baseline or treatment-related changes in prefrontal theta cordance are associated with clinical outcome after intermittent theta burst stimulation (iTBS) for major depressive disorder (MDD).
Methods: Retrospective analysis of 30 inpatients receiving 10 sessions of left-sided iTBS over 2 weeks. Resting-state 19-channel EEG was processed to compute theta cordance (plus delta/alpha/beta) in predefined cortical clusters pre/post the iTBS treatment period. Depression was rated pre/post with the Hamilton Depression Rating Scale (HAM-D) and the Major Depression Inventory (MDI); correlations linked baseline values and change scores to symptom improvement.
Results: Baseline prefrontal theta cordance was not associated with outcome. Change scores were region-specific: responders showed greater occipital decreases (OC $p = 0.036$; MLOC $p = 0.009$) and a trend toward left-frontal increases (MLFC $p = 0.072$); exploratory alpha and delta effects also emerged.
Conclusions: Theta cordance may predict and track symptom improvement following iTBS, indicating state-dependent neurophysiology.
Significance: Theta cordance may serve as a dynamic, region-specific EEG marker to monitor and personalize iTBS; prospective validation is warranted.

1. Introduction

Major depressive disorder (MDD) represents a common psychiatric disorder associated with considerable burden for affected individuals, their families and societies across the globe (Chen et al., 2025; Proudman et al., 2021). Although several classes of antidepressant drugs are available and have been shown to be superior to placebo treatment (Cipriani et al., 2018), the rate of nonresponse to pharmacological treatments is high, with an estimated number of 30% of patients failing to benefit from adequate trials of at least two antidepressants (McIntyre et al., 2023).

Transcranial magnetic stimulation (TMS) as a non-invasive and safe neuromodulation technique represents a potential alternative to standard antidepressant treatments, using strong and fluctuating magnetic fields to induce electric currents in the human brain (Barker et al., 1985; Rossini et al., 2015). The first FDA-approved TMS protocol in the treatment of MDD, introduced in 2008, involved high-frequency (10 Hz) stimulation over the left dorsolateral prefrontal cortex (dlPFC)—a target based on neuroimaging and lesion studies implicating this region in affect regulation (Cotovio et al., 2023). Clinical trials and *meta*-analyses have demonstrated that this protocol is associated with response rates of ~ 30–50% and remission rates of ~ 20–35%, offering a viable alternative for pharmacoresistant patients (Berlim et al., 2014; Blumberger et al., 2018; Lefaucheur et al., 2020). More recently, intermittent theta burst stimulation (iTBS), which applies 50 Hz pulse triplets repeated at 200 ms intervals, was shown to be non-inferior to standard 10 Hz rTMS in a large multicenter trial (Blumberger et al., 2018). Hence, iTBS delivering 600 pulses per session (session duration: 192 s) to the left dlPFC received FDA approval in 2018 (Cotovio et al., 2023). The shorter duration together with comparable efficacy have facilitated the widespread clinical adoption of iTBS as a first-line neuromodulatory intervention in depression, with proven efficacy (Kishi et al., 2024).

Despite these advantages, interindividual variability in response to antidepressant treatment attempts remains a key challenge, also in iTBS,

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with significant proportions of patients failing to achieve meaningful symptom reduction. Given the long duration of both pharmacotherapy and TMS treatment trials, there is growing interest in identifying predictors and biomarkers of treatment response. Current research efforts regarding rTMS treatment effects explore diverse predictive modalities, including clinical and demographic factors, structural and functional neuroimaging as well as electrophysiological measures based on electroencephalography (EEG) such as quantitative EEG (qEEG) measures (Chu et al., 2025; Gonterman, 2023; Kar, 2019).

Among EEG-based metrics, theta cordance has emerged as a particularly promising biomarker of antidepressant medication response (Srivastava et al., 2024). Originally developed as an indicator of regional brain perfusion (Leuchter et al., 1999, 1994), cordance is a qEEG metric that combines information from both absolute and relative spectral power for a given frequency band, most commonly theta (4–8 Hz). Early reductions in theta cordance, observed over the prefrontal cortex, have repeatedly been shown to be predictive of ensuing treatment response for several classes of antidepressant drugs (Bares et al., 2010, 2008; Cook et al., 1999; Leuchter et al., 2009).

In rTMS treatment studies, early decreases in (prefrontal) theta cordance (typically assessed from baseline to week 1) have been validated as potential biomarkers of subsequent treatment response, reflecting neurophysiological changes associated with clinical improvement (Bailey et al., 2019; Bares et al., 2015; Hunter et al., 2018). In parallel, baseline levels of (pre-)frontal cordance in different frequency bands have been investigated as predictive markers of subsequent clinical outcome, aiming to identify responders and non-responders prior to treatment initiation (Arns et al., 2012; Ebrahimzadeh et al., 2023; Erguzel et al., 2015; Hasanzadeh et al., 2019). While many of the published models demonstrated substantial predictive accuracy, they varied considerably in terms of predictor selection, analytical approach, and operational definitions of prefrontal cordance, reflecting differences in EEG preprocessing pipelines and electrode montages. For example, Arns et al. (2012) found significantly lower baseline levels of prefrontal beta and delta cordance in non-responders compared to responders. Bares et al. (2015) were able to show that responders to rTMS treatment showed higher baseline levels of prefrontal theta cordance as well as larger decreases in prefrontal theta cordance after one week of rTMS treatment.

Building on this work, the present study investigates prefrontal theta cordance as both a predictive and correlative biomarker of clinical response to iTBS in MDD. Specifically, we assessed whether baseline cordance values and treatment-induced changes were associated with symptom improvement, based on pre- and post-treatment qEEG data. This study was conducted as a retrospective, naturalistic observational analysis of open-label iTBS treatment in routine inpatient care.

Given that this is the first iTBS trial to examine associations between prefrontal theta cordance and treatment response in patients with MDD, we adopted a conservative statistical approach and tested our hypotheses using two-sided tests.

We specifically hypothesized that (1) baseline levels of prefrontal theta cordance would be significantly associated with clinical outcome following iTBS, and (2) treatment-related changes in cordance would similarly correlate with symptom improvement. In order to assess the specificity of these associations, we additionally explored theta cordance values in non-prefrontal electrode clusters (regional specificity) as well as the other EEG frequency bands (frequency specificity).

2. Methods

2.1. Study design and ethical approval

Data for the present retrospective analysis was collected in the course of routine clinical care at the Bezirksklinikum Woellershof, Germany from May 2023 to July 2024 in cooperation with the Department of Psychiatry and Psychotherapy of the University of Regensburg, Germany, located at the medbo Bezirksklinikum Regensburg. The study was approved by the ethics committee of the University of Regensburg (Approval ID: 22–2958-104) and was conducted in accordance with the Declaration of Helsinki. All data were pseudonymized prior to statistical analysis.

2.2. Sample and clinical setting

The sample consisted of 30 inpatients diagnosed with unipolar MDD who underwent ten sessions of iTBS treatment over two weeks. Inclusion criteria comprised a current depressive episode and insufficient response to at least one prior monotherapy with either antidepressant medication or psychotherapy.

Exclusion criteria included pregnancy, neurological comorbidities, and the presence of any TMS-related contraindications such as ferromagnetic implants or a history of epileptic seizures. All patients received iTBS as part of their regular inpatient treatment within a naturalistic setting.

2.3. iTBS treatment protocol

For iTBS treatment delivery, a MagVenture MagPro X100 stimulator and a figure-of-eight coil (MCF-B65) was used. Motor threshold was determined via electromyographic registration of the right abductor pollicis brevis (APB) using a C-B60 coil and a Neurowerk system (Sigma Medizin-Technik). All magnetic stimulations were conducted with biphasic pulses with default current direction settings.

For motor hotspot determination the coil was systematically positioned over patients' left motor cortex and adjusted until the strongest and most reliable responses in the right APB were observed. Subsequently, the resting motor threshold (RMT) was defined as the minimum intensity (in % of maximum stimulator output, MSO) required to elicit a motor-evoked potential of > 0.05 mV in at least 5 out of 10 trials in the right APB identified via electromyography (EMG). The treatment target for iTBS was located over the left dlPFC, approximated using the EEG 10–20 electrode position F3 (Herwig et al., 2003). For consistent coil placement across sessions, patients wore individualized treatment caps with stimulation targets marked at F3, supplemented by nasion-to-cap and midline measurements.

The iTBS protocol followed standard parameters (Huang et al., 2005): 600 pulses delivered in triplet bursts at 50 Hz, repeated every 200 ms (5 Hz), in a total of 20 trains. Initially treatment intensity was targeted to reach between 100% and 120% of RMT depending on patient tolerability. However, due to individual tolerability limitations and a predefined maximum output limit of 60% of maximum stimulator output (MSO) applied in our clinical setting in order to prevent significant drops in pulse amplitude for the second and third pulse of the TBS bursts seen at higher intensities (Gutiérrez-Muto et al., 2020), stimulation intensity had to be adjusted downward in several patients. As a result, the mean of the finally achieved intensity was 87.6% RMT (SD = 13.3%), with stimulation intensities ranging from 66.7% to 127.7% RMT. Each session lasted approximately 3 min. Patients received one session per weekday across two weeks (10 sessions total).

2.4. Clinical outcome measures

Depressive symptoms were assessed immediately before the first and after the final iTBS treatment session (week 2) using both self-report and clinician-administered instruments.

As primary clinical outcome, depressive severity was rated by trained clinicians using the 17-item Hamilton Depression Rating Scale (HAM-D-17) (Hamilton, 1960). The total score was derived by summing the 17 core items.

As an additional clinical outcome, patients completed the Major Depression Inventory (MDI) (Olsen et al., 2003), a validated 10-item questionnaire. Items 8 to 10 include two alternative sub-items each; in

line with standard procedures, the higher of the two was used for scoring. Total scores were calculated by summing responses across all items.

For both instruments, change in depressive symptoms was calculated as the difference between baseline and post-treatment scores (ΔScore = Pre – Post), such that higher values indicate greater clinical improvement.

2.5. EEG acquisition and preprocessing

Directly before and after rTMS treatment, five minutes of resting state qEEG were recorded. Patients were instructed to sit upright in a relaxed position, keep their eyes closed, and minimize movement, facial tension, and blinking throughout the measurements. QEEG was recorded by means of a Nihon Kohden Neurofax EEG-1200 system (Nihon Kohden Corporation, Tokyo, Japan) together with an electrode cap with 19 passive electrodes (Ag/AgCl) placed according to the 10–20 system. Data was recorded at a sampling rate of 200 Hz with electrodes A1 and A2 as online references. Moreover, an online low-pass filter with a cut-off at 70 Hz as well as an online bandstop filter at 50 Hz were applied. Impedances were kept below 10 kΩ for the entire recording.

Raw EEG data were preprocessed in Matlab (R2024b; Mathworks, USA) using the Fieldtrip toolbox (Oostenveld et al., 2011) and a custom-written semi automatic pipeline. The data was bandpass filtered from 1 – 45 Hz and bandstop filtered from 49 – 51 Hz using a 4th order Butterworth filter. Hereafter, noisy sensors were identified for later interpolation, and anomalous signal components (2 s epochs) were rejected via visual inspection. In order to identify and eliminate horizontal and vertical eye movements, an independent component analysis (ICA, fastICA, https://research.ics.aalto.fi/ica/fastica/index.shtml) was performed. Identified noisy sensors were interpolated via weighted neighbors, thereby the mean signal of neighboring electrodes was used for replacement. Neighboring sensors were defined by a triangulation of 2D sensor position projection. Data was re-referenced to the average of all sensors. As a final step, the data underwent visual inspection for validation, and residual artifacts, if present, were removed.

2.6. Cordance calculation and regional analysis

Cordance was calculated in Matlab (R2024b; Mathworks, USA) following the algorithm described by Leuchter et al. (1999). Bipolar signals were formed between one target channel and its nearest neighboring channels. Using these bipolar signals, absolute and relative power spectra were calculated in the Delta (0.5 – 4 Hz), Theta (4 – 8 Hz) Alpha (8 – 12 Hz) and Beta (12 – 20 Hz) frequency bands. This procedure was repeated for each sensor. Obtained power spectra values underwent square-root transformation, z-score normalization across channels and were added up to receive single cordance values per electrode and frequency band of interest.

Cordance values for the four frequency bands (delta, theta, alpha, beta) were averaged across predefined regional electrode clusters for our employed electrode montage (see Fig. A1 in the Appendix). The prefrontal cluster was defined as Fp1, Fp2, and Fz, based on prior qEEG work using similar montages (Bares et al., 2015). In addition, we implemented a set of lateralized frontal and posterior clusters, adapted from Hunter et al. (2018). As our 19-channel EEG montage did not include electrode FPz, these clusters were modified accordingly. The final cluster definitions were as follows: (1) prefrontal (PFC) – Fp1, Fp2, Fz; (2) midline-left frontal (MLFC) – Fp1, F3, F7, Fz; (3) midline-right frontal (MRFC) – Fp2, F4, F8, Fz; (4) central (CC) – Fz, C3, C4, Cz, Pz; (5) occipital (OC) – O1, O2, P3, P4, Pz; (6) midline-left occipital (MLOC): T7, P3, O1, Pz; (7) midline-right occipital (MROC): T8, P4, O2, Pz.

For each cluster, cordance values were averaged per time point. Change scores were calculated as the difference between post- and pre-treatment values (ΔCordance = Post – Pre). The prefrontal and lateralized frontal clusters were used in hypothesis-driven analyses; posterior clusters were included to assess regional specificity.

2.7. Statistical and graphical analyses

All statistical analyses were conducted using R (version 4.3.2) and RStudio (version 2023.23.1, Build 402). Descriptive statistics were calculated for demographic and clinical variables. Pre- to post-treatment changes in depression severity (HAM-D and MDI total scores) were analyzed using paired-sample t-tests. A significance threshold of $p \leq 0.05$ was applied, and Cohen's d was computed as a measure of effect size.

To assess potential predictors of treatment response, we compared patients classified as responders vs. non-responders according to the Hamilton Depression Rating Scale (HAM-D). Response was defined as a $\geq$ 50% reduction in HAM-D total score from pre- to post-treatment. Group comparisons included demographic variables (e.g., age, sex) and baseline clinical scores (HAM-D, MDI) and are reported in Table 1. A corresponding analysis based on the MDI definition of response was conducted analogously and is reported in Appendix B.

To evaluate potential confounding effects of treatment dose, we additionally calculated bivariate Pearson correlations between the average stimulation intensity and both clinical outcome measures (HAM-D and MDI change scores) as well as theta cordance change scores for each of the regional clusters.

To test our primary hypotheses, we first analysed whether changes in prefrontal theta cordance occurred using paired samples t-tests (comparison of baseline and post-treatment cordance values for each of the regional clusters). After that, we applied bivariate Pearson correlation analyses addressing the two main research questions:

1. Whether baseline levels of prefrontal theta cordance were significantly associated with clinical response to iTBS (i.e., change scores in HAM-D and MDI);
2. Whether treatment-related changes in prefrontal theta cordance (ΔCordance = post – pre) were significantly correlated with symptom improvement.

In addition, for both research questions exploratory correlation

Table 1
Sample descriptives and baseline comparisons for non-responders (n = 16) and responders (n = 14) to iTBS treatment, based on HAM-D ratings.

	Non-responder (n = 16)	Responder (n = 14)	p-value
Age	47.1 (15.1)	51.4 (14.1)	p = 0.42
Gender			p = 0.98
Female n (%)	8 (50.0)	6 (42.9)	
Male n (%)	8 (50.0)	8 (57.1)	
Diagnosis			p = 0.69
First Depr. Episode, F32 n (%)	5 (31.3)	3 (21.4)	
Recurr. Depr. Disorder, F33 n (%)	11 (68.7)	11 (78.6)	
Comorbidity			all p >
Anxiety Disorder n (%)	3 (18.8)	2 (14.3)	0.33
OCD n (%)	2 (12.5)	0 (0.0)	
Personality Disorder n (%)	4 (25.0)	1 (7.1)	
Other n (%)	2 (12.5)	1 (7.1)	
HAM-D_BL *M (SD)*	22.3 (8.4)	22.8 (9.4)	p = 0.89
MDI_BL *M (SD)*	33.1 (11.0)	28.6 (10.2)	p = 0.25
Medication			all p >
SSRI n (%)	10 (62.5)	7 (50.0)	0.37
SNRI n (%)	2 (12.5)	4 (28.6)	
TCA n (%)	6 (37.5)	8 (57.1)	
NDRI n (%)	3 (18.8)	1 (7.1)	
AP n (%)	4 (25.0)	2 (14.3)	
BZD n (%)	1 (6.3)	0 (0.0)	
INT – %RMT *M (SD)*	88.4 (16.9)	86.8 (7.8)	p = 0.74

analyses were performed for theta cordance values in non-prefrontal electrode clusters to assess the regional specificity of observed associations. Likewise, in order to examine frequency specificity, we extended the primary correlation analyses beyond theta to include delta (0.5–4 Hz), alpha (8–12 Hz), and beta (12–20 Hz) bands. Correlation coefficients were interpreted using conventional thresholds ($r < .10$ = negligible; 0.10–.29 = small; 0.30–.49 = moderate; ≥.50 = large). No correction for multiple comparisons was applied due to the exploratory nature of these analyses.

For complementary categorical analyses, we visualized the topographic distribution of theta cordance changes (ΔCordance) in iTBS responders and non-responders, again defined by the ≥ 50% HAM-D criterion. Topoplots for the MDI-based responder definition are reported in Appendix B. Topographic maps were generated using the R package eegUtils (version 0.8.0) to visualize spatial distributions of theta cordance. Electrode positions were based on standardized channel coordinates from the eegkit::eegcoord dataset. Topographic maps were computed using the topoplot() function with biharmonic spline interpolation with high spatial resolution (grid_res = 1000) to allow for fine-grained interpolation of the scalp field. Color gradients were symmetrically scaled around zero and based on z-transformed cordance values to ensure comparability across groups and time points. Separate maps were created for treatment responders and non-responders, highlighting baseline levels of theta cordance as well as changes in cordance following treatment (i.e., ΔCordance).

To assess regional specificity, we additionally compared baseline theta cordance as well as treatment-induced theta cordance changes between responders and non-responders using independent samples *t*-tests for each electrode cluster. These comparisons served to validate and contextualize correlational findings regarding frontal theta cordance and treatment response.

3. Results

3.1. Sample characteristics and overall treatment effect

The final sample comprised 30 inpatients with major depressive disorder (MDD) who completed the full iTBS treatment course and had complete qEEG and clinical data. The mean age was 49.1 years (SD = 14.6), and 16 patients (53.3%) were female. At baseline, patients showed moderate to severe depression, with a mean HAM-D score of 22.5 (SD = 8.7) and MDI score of 31.0 (SD = 10.7).

To evaluate the overall clinical effect of the iTBS intervention, we conducted paired-samples t-tests comparing pre- and post-treatment scores. Results revealed a significant reduction in depressive symptoms as measured by both the HAM-D ($t(29) = 6.62, p < 0.001, d = 1.21$) and the MDI ($t(29) = 6.53, p < 0.001, d = 1.19$). This indicates a statistically and clinically meaningful treatment effect in the overall sample.

Based on the HAM-D response criterion (≥50% reduction), 14 patients (46.7%) were classified as responders and 16 (53.3%) as non-responders. Table 1 presents demographic and baseline clinical characteristics stratified by HAM-D response status. No significant between-group differences were observed in age, sex, diagnostic status, baseline symptom severity, medication regimen as well as stimulation intensity (all $p > 0.24$). The corresponding MDI-based responder analysis could be reported in Table A1 in Appendix B.

3.2. Association between cordance and clinical outcome

We first examined whether theta cordance changed following iTBS treatment by comparing baseline and post-treatment values across predefined electrode clusters. Paired-samples t-tests revealed no significant differences in any cluster (all $p > 0.15$).

Next, we tested whether baseline theta cordance in predefined frontal clusters (PFC, MRFC, MLFC) predicted clinical response to iTBS (Hypothesis 1). No significant associations were observed for either HAM-D or MDI outcomes (*all* $p > 0.13$ and $p > 0.39$, respectively; see Table 2).

Exploratory analyses indicated that higher baseline theta cordance in the occipital cluster (OC) was significantly associated with greater HAM-D improvement ($r = 0.41, p = 0.026$). For none of the other frequency bands significant associations were found between baseline cordance values and clinical improvement on either outcome scale (see Table 2).

We next examined whether treatment-related changes in theta cordance (Δ = post – pre) correlated with symptom improvement. In the MLFC cluster, positive trends were observed (HAM-D: $r = 0.34$, $p = 0.062$; MDI: $r = 0.32, p = 0.080$). Reductions in occipital theta cordance were significantly associated with clinical improvement (HAM-D: $r = –.36, p = 0.048$; MDI: $r = –.46, p = 0.011$). Fig. 1 shows scatterplots of the associations between occipital (OC cluster) theta cordance and HAM-D improvement, for baseline values (panel A) and within-subject change scores (panel B). Visual inspection suggests that the observed associations are not attributable to single influential data points.

For alpha cordance changes, similar effects were observed: negative correlations emerged in the OC and MROC clusters (HAM-D: $r = –.50$ and –.51, both $p < 0.01$). For delta cordance, a significant positive association with HAM-D improvement was found in the MRFC cluster ($r = 0.37$, $p = 0.044$). No other frequency-band or region combinations showed consistent or statistically significant correlations with symptom change (all $p > 0.10$). Full results are reported in Table 3.

Control analyses revealed only weak-to-negligible and statistically non-significant associations between average treatment intensity (% RMT) and both clinical symptom improvement (all $p > 0.35$) and iTBS-induced changes in theta cordance across regional clusters (all $p > 0.35$).

3.3. Topographical distribution of theta cordance at baseline and following treatment

Topographic maps of theta cordance before iTBS treatment (panels A and B) and iTBS-induced changes in theta cordance (panels C and D) are shown in Fig. 2. Maps are stratified by HAMD-defined treatment response, with responders depicted in panels A and C, and non-responders in panels B and D.

Beyond visualization, we also tested for group differences in theta cordance values between responders and non-responders, to evaluate the specificity of observed associations. First, we conducted independent samples *t*-tests for each electrode cluster to compare baseline theta cordance values between responders and non-responders. No statistically significant group differences emerged (all $p > 0.07$). The largest numerical difference was observed in the MLOC cluster ($t(27.9) = –1.88$, $p = 0.070$), where responders showed higher baseline values than non-responders (see panels A and B, Fig. 2).

As a first step regarding the overall topographic change analysis, we examined whether theta cordance changed following iTBS treatment by comparing baseline and post-treatment values across the predefined electrode clusters. Paired-samples t-tests revealed no significant overall differences in any cluster (all $p > 0.15$).

As a next step, we conducted a series of independent samples *t*-tests to assess eventual differences between responders and non-responders regarding changes in theta cordance (ΔCordance) across electrode clusters. Significant group differences emerged in the OC and MLOC clusters, with responders showing a reduction in theta cordance and non-responders exhibiting an increase (OC: $t(27.8) = 2.21$, $p = 0.036$; MLOC: $t(27.3) = 2.80, p = 0.009$). A statistical trend was observed in the MLFC cluster ($t(26.7) = 1.87$, $p = 0.072$), with greater cordance increases among responders. No significant group differences were observed in other regions (all $p > 0.29$; see also panels C and D, Fig. 2).

4. Discussion

This study examined the potential of theta cordance as an EEG-based

Table 2
Pearson correlations between baseline cordance and symptom improvement by electrode cluster and frequency band (n = 30).

	Delta Cordance		Theta Cordance		Alpha Cordance		Beta Cordance	
Electrode cluster	ΔHAM-D *r*	ΔMDI *r*	ΔHAM-D *r*	ΔMDI *r*	ΔHAM-D *r*	ΔMDI *r*	ΔHAM-D *r*	ΔMDI *r*
PFC	0.17	0.22	–0.17	–0.01	–0.22	0.14	–0.11	0.24
MRFC	0.10	0.08	–0.28	–0.08	–0.22	0.03	0.04	0.29
MLFC	0.29	0.17	–0.27	–0.16	–0.22	0.09	–0.07	0.12
CC	0.14	0.23	–0.04	–0.04	–0.27	0.05	–0.15	–0.12
OC	–0.10	–0.02	**0.41***	0.17	0.26	0.16	–0.16	–0.21
MROC	–0.15	0.04	0.22	0.17	0.16	0.12	–0.24	–0.15
MLOC	–0.03	–0.11	0.33†	0.09	0.21	0.00	0.09	–0.05

Notes.
† $p < 0.10$,
* $p < 0.05$ (uncorrected, two-tailed),

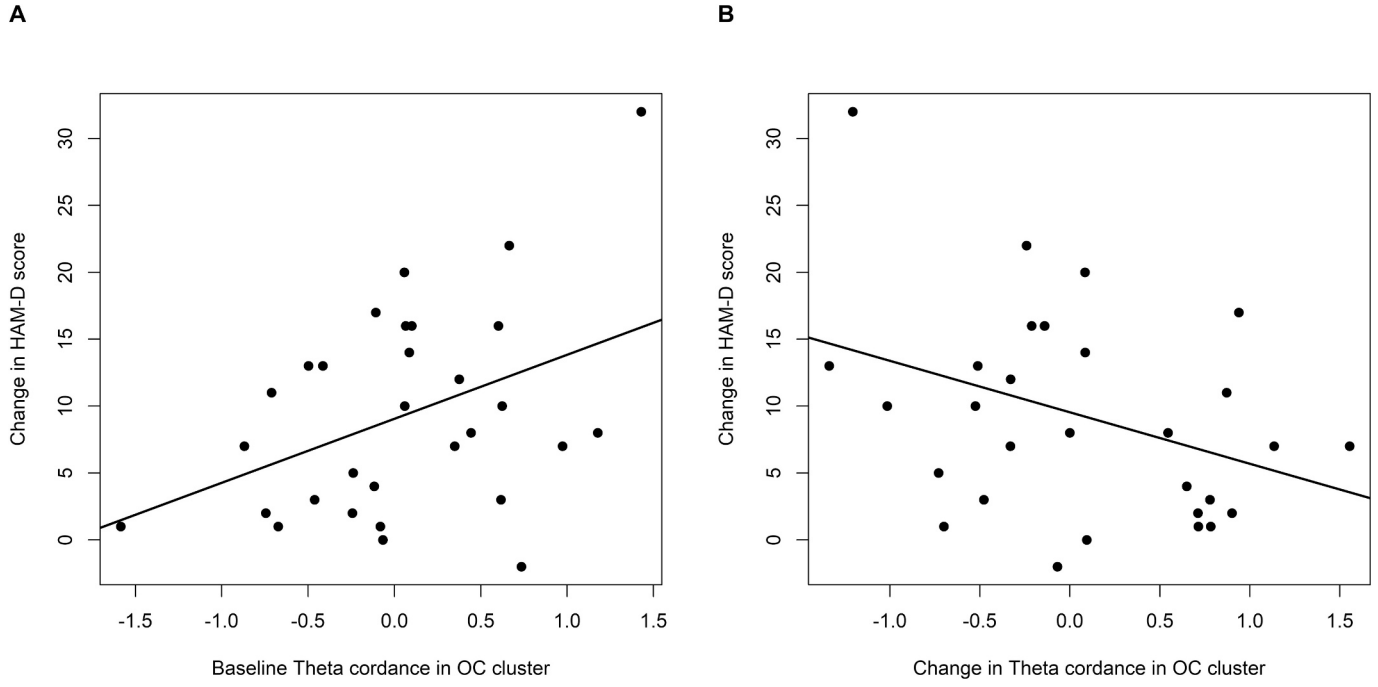

Fig. 1. Relationships between occipital theta cordance and antidepressant response to iTBS. (A) Baseline theta cordance in the occipital (OC) cluster versus HAM-D improvement. (B) Change in occipital theta cordance versus HAM-D improvement. Each point represents an individual patient; solid lines show linear regression fits.

Table 3
Pearson correlations between changes in cordance and symptom improvement by electrode cluster and frequency band (n = 30).

	Delta ΔCordance		Theta ΔCordance		Alpha ΔCordance		Beta ΔCordance	
Electrode cluster	ΔHAM-D *r*	ΔMDI *r*	ΔHAM-D *r*	ΔMDI *r*	ΔHAM-D *r*	ΔMDI *r*	ΔHAM-D *r*	ΔMDI *r*
PFC	–0.10	–0.08	0.34†	0.23	0.19	–0.12	0.02	–0.11
MRFC	**0.37***	–0.10	0.15	0.14	0.11	0.15	–0.30	–0.17
MLFC	–0.28	0.06	0.34†	0.32†	0.23	–0.08	0.10	0.10
CC	–0.17	–0.12	0.18	–0.08	0.06	0.20	0.00	–0.08
OC	–0.09	–0.11	**–0.36***	**–0.46***	**–0.50****	–0.15	0.09	–0.10
MROC	0.06	–0.27	–0.09	–0.26	**–0.51****	–0.01	0.23	0.10
MLOC	–0.13	0.12	–0.35†	–0.23	–0.10	–0.15	–0.05	–0.19

Notes.
† $p < 0.10$,
* $p < 0.05$ (uncorrected, two-tailed),
** $p < 0.01$ (uncorrected, two-tailed).

predictor or biomarker of clinical response to intermittent theta burst stimulation (iTBS) in patients with major depressive disorder (MDD). Two main hypotheses guided our analysis: (1) that baseline levels of prefrontal theta cordance would predict subsequent symptom improvement, and (2) that treatment-related changes in theta cordance would be associated with clinical outcome.

To further contextualize these analyses, we explored the spatial specificity of effects by examining additional electrode clusters beyond the prefrontal cortex. Moreover, to assess frequency specificity, we extended all correlation analyses to include delta, alpha, and beta bands

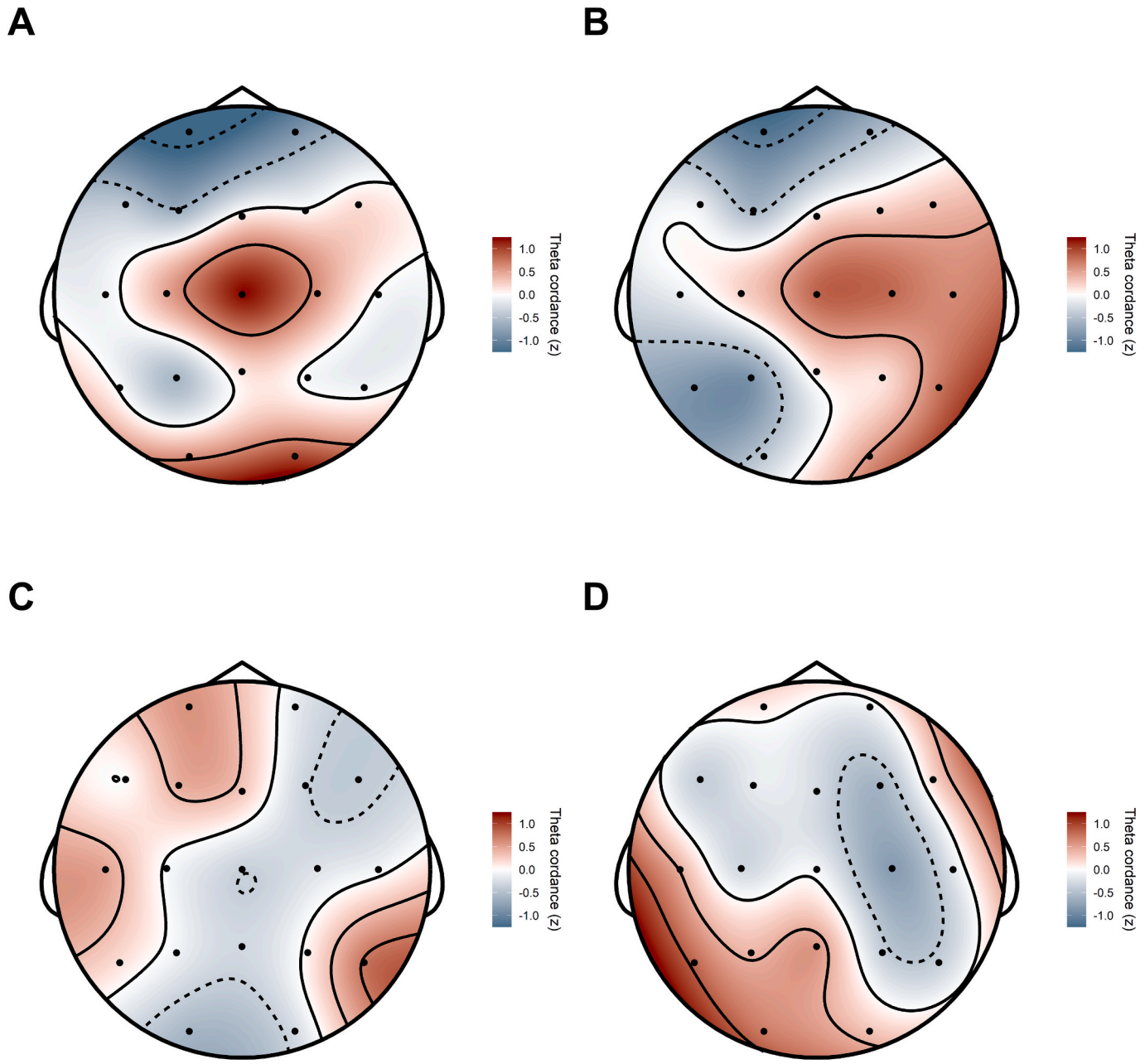

Fig. 2. Topographic maps illustrating baseline levels of theta cordance (panels A and B) as well as iTBS-induced changes in theta cordance (panels C and D) for responders (panels A and C) and non-responders (panels B and D) to iTBS treatment; elevations are coded in red, decreases in blue. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in an exploratory manner. Finally, we complemented our correlational results with inferential group comparisons (responders vs. non-responders) and topographic analyses to identify spatial patterns of cordance change across the scalp.

4.1. Hypothesis 1: Prefrontal theta cordance as a predictor of clinical improvement

We did not observe clear evidence in support of the first hypothesis. Only weak (values of $|r|$ between 0.17 and 0.28) and statistically insignificant associations were found between baseline theta cordance in any of the predefined prefrontal clusters (PFC, MRFC, MLFC) and clinical outcome, as measured by either the clinician-rated HAM-D or the self-report MDI. Contrary to this, we found unexpected and modest associations between baseline theta cordance and clinical improvement in (left) occipital electrode clusters.

Our null findings in the prefrontal electrode clusters are consistent with previous studies in pharmacotherapy (e.g. Baskaran et al., 2018) and rTMS (e.g. Arns et al., 2012), which likewise failed to establish pretreatment theta cordance as a reliable predictor of treatment response. Notably, Arns et al. (2012) reported predictive effects only for delta and beta—but not theta—cordance in their large naturalistic rTMS sample, despite theta being commonly regarded as the most neurobiologically interpretable and clinically promising frequency band. In contrast, Bares et al. (2015) found significantly higher baseline prefrontal theta cordance in responders compared to non-responders, along with stronger cordance reductions after one week of treatment. Several methodological differences may account for these discrepancies. For instance, Bares et al. (2015) applied right-sided inhibitory (1 Hz) rTMS, whereas we employed excitatory iTBS over the left DLPFC. Moreover,

while Bares et al. (2015) assessed early changes after one week of stimulation, our study used a pre/post design over two weeks. Compared to Arns et al. (2012), who applied 10 Hz rTMS over a longer period (~4 weeks), our shorter iTBS course may have captured different neurophysiological dynamics. Finally, differences in EEG preprocessing, cluster definitions, or sample characteristics (e.g., inpatient vs. outpatient populations) could also contribute to divergent findings.

Taken together, our present results add further evidence supporting the potential role of baseline theta cordance as a predictor of treatment effects in TMS treatment. However, given the inconsistencies in size and anatomical position of these associations between studies, results may vary as a function of employed TMS treatment protocol and/ or targeted patient population. The importance of these methodological aspects should be further investigated by future studies of theta cordance in the TMS field.

4.2. Hypothesis 2: Prefrontal theta cordance changes as correlates of clinical improvement

Regarding hypothesis 2, our correlational analyses provided only partial support. Changes in theta cordance from pre- to post-treatment showed regionally specific associations with symptom improvement. Most notably, reductions in occipital cordance were significantly associated with improvements in both HAM-D and MDI. In addition, we observed a medium-sized positive (though non-significant) trend for cordance increases in the left frontal cluster (MLFC). These findings suggest that treatment-induced modulations of theta activity in specific cortical regions may be functionally relevant for symptom change.

To further characterize the spatial pattern of cordance modulation, we conducted direct group comparisons of theta cordance change scores between responders and non-responders. Significant differences emerged in the occipital (OC) and left occipitotemporal (MLOC) clusters, where responders exhibited post-treatment reductions, while non-responders showed increases (OC: $p = 0.036$; MLOC: $p = 0.009$). A trend towards statistical significance was also observed in the midline-left frontal (MLFC) cluster ($p = 0.072$), with responders showing greater theta cordance increases.

In contrast, no significant group differences were found in baseline theta cordance across any electrode cluster (all $p > 0.07$), suggesting that the observed associations with clinical response are more likely driven by treatment-related modulations than by static pre-existing differences. This pattern strengthens the interpretation of cordance change as a state-sensitive and dynamic correlate of antidepressant effects. Topographic plots were used to visually illustrate these change patterns across the scalp. While not inferential in nature, they provided consistent spatial support: responders showed frontal theta increases and posterior reductions, whereas non-responders displayed minimal frontal changes and posterior increases. These topographical differences align with the statistically identified clusters and lend further support to the interpretation of region-specific markers of clinical response.

Exploratory analyses of other frequency bands revealed additional region-specific associations. In particular, reductions in alpha cordance in the occipital (OC) and right occipitotemporal (MROC) clusters were significantly associated with symptom improvement. Similarly, increases in delta cordance in the midline-right frontal cluster (MRFC) correlated with HAM-D reduction. Beta cordance did not show consistent associations. These results suggest that different frequency bands may capture distinct facets of treatment-related neuroplasticity.

Notably, our findings diverge from those of earlier rTMS studies. Both Bailey et al. (2019) and Bares et al. (2015) reported decreases in prefrontal theta cordance among responders, whereas we observed increases. Similarly, Hunter et al. (2018) found that early reductions in central (but not frontal) theta cordance predicted treatment response, whereas we found no central effects. These discrepancies may reflect differences in stimulation protocol (1 Hz or 10 Hz rTMS vs. iTBS), lateralization (right vs. left DLPFC), timing of assessment (e.g., early change after 1 week vs. endpoint change after 2 weeks), or sample characteristics. It is also possible that excitatory patterned protocols like iTBS engage distinct neurophysiological mechanisms compared to conventional rTMS. In contrast, our finding of posterior theta reductions aligns with broader assumptions about the normalization of default mode network hyperconnectivity, which has been linked to depressive rumination and shown to decrease following effective treatment (e.g. Liston et al., 2014; Sheline et al., 2010).

Taken together, these findings suggest that changes in theta and alpha cordance may index functionally relevant neurophysiological adaptations to iTBS. However, the divergence in directionality and regional effects compared to prior studies underscores the need for protocol-specific biomarker models and prospective validation in larger samples.

4.3. Methodological considerations and limitations

Several limitations of the present study warrant consideration. First, the sample size was modest ($N = 30$), which may have limited the power to detect small-to-moderate effects—particularly for the correlational and subgroup analyses. A sensitivity analysis for our employed correlational analyses showed, that at a sample size of $n = 30$ (with $\alpha = 0.05$ and $1\text{-}\beta = 0.80$), our study design was sensitive to identify significant correlations only at a size of $|r| \sim 0.36$ or larger. While our within-subject design and multimodal outcome assessment enhances internal validity, replication in larger samples is needed to confirm the observed patterns. Future prospective studies employing larger sample sizes with adequate statistical power may also benefit from mixed-effects modeling approaches.

Second, although cordance has been proposed as a clinically relevant EEG marker, its neurophysiological underpinnings remain incompletely understood. The exact mechanisms linking cordance changes to symptom improvement—whether via modulation of cerebral perfusion, connectivity, or neurochemical systems—are still under investigation. Accordingly, interpretations of frequency-specific or region-specific effects should be considered exploratory. In line with this thought, future studies also should try to include a more complete set of EEG metrics in larger patient samples in order to validate cordance metrics as indicators of prospectively established antidepressant effects of iTBS treatment. This might well include measures derived of the gamma frequency band, which has been related to brain functions such as mood regulation and other executive brain functions (see Fitzgerald & Watson, 2018).

Third, due to the absence of a sham control group, our findings cannot disentangle specific iTBS-induced effects from potential unspecific influences, such as placebo response or time-related changes under ongoing pharmacotherapy and in-patient treatment. However, the distinct spatial patterns and their associations with symptom trajectories strengthen the argument for physiologically meaningful treatment effects.

Fourth, our EEG data were collected at rest (eyes closed), limiting interpretability with regard to task-related functional engagement. Future studies may combine resting-state and task-based EEG to better capture dynamic changes in neural processing.

Finally, we did not correct for multiple comparisons in our exploratory correlation analyses. While this decision was based on the hypothesis-generating nature of the study, it increases the risk of false-positive findings and emphasizes the need for cautious interpretation and independent replication.

4.4. Conclusions and outlook

In this naturalistic EEG study of iTBS treatment in patients with major depression, we investigated both baseline predictors and treatment-related changes in theta cordance as potential biomarkers of clinical response. Our results found a predictive value of baseline occipital theta cordance and also revealed regionally specific associations

between cordance changes and symptom improvement—most notably in occipital and left frontal regions. Exploratory analyses further suggested that alpha and delta cordance may also reflect frequency-specific facets of neurophysiological adaptation to iTBS. These findings underscore the relevance of dynamic, spatially resolved EEG markers in capturing individual trajectories of treatment response. At the same time, inconsistencies with prior studies highlight the need for protocol-specific validation and larger-scale prospective trials to establish robust, generalizable EEG biomarkers for clinical application.

Data availability

The data that support the findings of this study are available from the corresponding author, AR, upon reasonable request.

CRediT authorship contribution statement

Andreas Reissmann: Conceptualization, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Maximilian Rupprecht:** Writing – original draft, Writing – review & editing. **Berthold Langguth:** Conceptualization, Supervision, Writing – review & editing. **Johanna Rischer:** Data curation, Formal analysis, Writing – review & editing. **Stefan Schoisswohl:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2026.2111710.

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