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State-Dependent qEEG Biomarkers in Depression

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Abstract

Backgrounds: Identifying state biomarkers in major depressive disorder (MDD) is critical for understanding neurobiological underpinnings of disorder. Quantitative electroencephalography (qEEG) has emerged as a promising tool for distinguishing stable versus dynamic neural alterations associated with MDD.

Methods: This study included 70 patients diagnosed with MDD and 98 healthy controls (HC). Resting-state qEEG recordings were obtained at three time points: baseline(T0), early treatment(T1), and late treatment(T2). Patients were categorized as responders(≥50%HDRS-21) or non-responders. Changes in absolute band power across delta, theta, alpha, beta, and gamma frequencies were compared with HCs. Associations between qEEG activity with HDRS and HARS scores at each time point were calculated.

Results: Responders showed longitudinal reductions in delta power with normalization toward HCs. Gamma activity increased marginally over time. Non-responders exhibited stable and elevated delta and alpha power that persisted across sessions. Decreased fronto-central delta and increased left fronto-central gamma power were also associated with improvement in depression and anxiety.

Conclusion: MDD Responders demonstrated state-dependent electrophysiological normalization, while non-responders show stable pattern with unchanged depressive state. These findings highlight the utility of qEEG state-markers in monitoring clinical improvement in depression.

Keywords

major depressive disorder, EEG, state marker, alpha, delta

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Introduction

The investigation of biomarkers in mental health problems is driven by finding objective criteria that can provide information about diagnosis, prognosis, and treatment options.[1] Among mental disorders depression exhibits variability in symptomatology which underscores the need for objective biomarkers that can guide real-time clinical decision-making.

One of the core challenges in this research area is distinguishing between trait markers, which reflect stable neurobiological predispositions, and state markers, which are dynamic, fluctuate with clinical symptoms and often normalize following effective treatment.[2]

State-dependent biomarkers are important for monitoring treatment and predicting relapses and to understand the progression of illness.[3] In recent years, quantitative electroencephalography (qEEG) has emerged as a promising tool for detecting such biomarkers due to its non-invasiveness, high temporal resolution, and accessibility.[4-6]

Several studies with qEEG have demonstrated that abnormalities in patients diagnosed with major depressive disorder (MDD) can normalize in parallel with clinical improvement, suggesting a state-dependent profile. For instance, elevated alpha power over frontal regions has been shown to decrease following successful antidepressant treatment[7] while prefrontal gamma oscillations may increase with symptom remission.[8] These findings imply that specific electroencephalogram (EEG) characteristics not only monitor the presence of depressive symptoms but may also mirror neurophysiological mechanisms underpinning recovery.

Despite these promising leads, the field still lacks consensus on which qEEG markers are reliably state-dependent versus

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trait-related. Moreover, many prior studies have been cross-sectional or have not incorporated healthy control comparisons, limiting their ability to distinguish normalization from random fluctuation. Longitudinal designs, particularly those involving multiple timepoints and responder/non-responder subgroup analyses, could be better suited to observe state markers.

This study addresses this gap by examining qEEG changes at three time points—baseline (T0), early treatment (T1), and late treatment (T2)—in a cohort of MDD patients who responded and did not respond to treatment. By comparing these changes with a healthy control group, we aim to identify electrophysiological features that dynamically reflect clinical improvement and thus serve as state-dependent markers of depression. We hypothesize that MDD patients who respond to treatment will exhibit changes over time in specific qEEG frequency bands, and that these changes will normalize towards the healthy control group. However, given the varying reports in the literature, this study retains its exploratory nature in terms of identifying which specific frequency bands will normalize with treatment.

Methods

Participants

This study included patients diagnosed with MDD who were admitted to a private psychiatric clinic over a 14-year period, as well as healthy controls (HCs). All patients were evaluated by the same psychiatrist during their visits. Diagnoses were made based on criteria outlined in Diagnostic and Statistical Manual of Mental Health Disorders fourth edition (DSM-4-TR)[9] or DSM-5.[10] The number of patients remaining after applying the following inclusion and exclusion criteria is shown in the flowchart (Figure 1). The final sample included 70 MDD patients.

Inclusion criteria were as follows: Severity assessment of depression using the Hamilton Depression Rating Scale (HDRS-21)[11] and severity assessment of anxiety using Hamilton Anxiety Rating Scale (HARS)[12] both before and after treatment. Availability of qEEG data recorded at T0, T1, T2.

Exclusion Criteria were as follows: (1) Patients with comorbid conditions, such as epilepsy, organic mental disorders, intellectual disabilities, neurological diseases, or other medical illnesses. Patients with bipolar or psychotic depression were also excluded. However, anxiety was not considered an exclusion criterion due to its high comorbidity with MDD. (2) Patients who had undergone electroconvulsive therapy (ECT). (3) Individuals with alcohol or substance dependence.

Treatment Procedure. Medication choice was based on clinical judgment, considering symptom profile, prior treatment history, and tolerability. For participants who did not respond to the initial antidepressant within 8 to 12 weeks, a second qEEG recording was obtained after switching to or augmenting an alternative pharmacological treatment (Table A1), mostly Selective Serotonin Reuptake Inhibitors or Selective Norepinephrine Reuptake Inhibitors are used as they are the frequently choiced strategy.[13] To check whether the dose of antidepressants differed between groups, all antidepressant doses were converted into fluoxetine-equivalent doses based on established dose equivalency tables.[14]

Healthy Controls. The healthy control group consisted of individuals recruited from a shared workplace environment, all of whom provided informed consent prior to participation. Psychiatric evaluations were conducted by the same psychiatrist to ensure consistency in diagnostic assessment. None of the participants had a history of psychiatric disorders, had ever used psychotropic medication, or exhibited any current psychiatric symptoms at the time of assessment. Additionally, all participants underwent qEEG recordings as part of the study protocol. A total of 98 participants were included as HCs.

Responder Versus Non-Responder Groups. All patients underwent a psychiatric evaluation during their visits to the clinic. On the same day, HDRS-21 was administered, and resting-state qEEG recordings were obtained. Following diagnosis, patients were prescribed antidepressant medication (Table A1). After approximately 4-12 weeks, clinical assessments were repeated, including HDRS and HARS. At later visits, the second and third qEEG recordings of these patients were recorded along with HDRS and Hamilton Anxiety Rating Scale (HARS)[12] scales.

Based on the clinical outcomes, patients were classified as responders (n = 54) if their HDRS scores decreased by at least 50% and as non-responders (n = 16) if they did not achieve this reduction.

Ethical Approval

The study adhered to the principles outlined in the Declaration of Helsinki and the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) guidelines. Written informed consent was obtained from all participants, and the study was approved by the local ethics committee (Approval No: 61351342/May 2023-20).

qEEG Recording

All participants underwent qEEG recording before initiating treatment. Recordings were conducted at midday in a quiet, dimly lit, air-conditioned room. A 19-channel electro-cap was applied in accordance with the 10–20 International System (electrode locations: FP1, F7, T3, T5, F3, C3, P3, O1, FZ, CZ, PZ, F4, C4, P4, O2, FP2, F8, T4, T6). Transparent electro-gel was injected into the electrodes to improve conductivity. The ground electrode was placed at FPz, with mastoid electrodes on both earlobes serving as reference electrodes(A1-A2). Electrode impedance was verified to be below 5 kΩ. qEEG recording and analysis was performed according to the committee report on

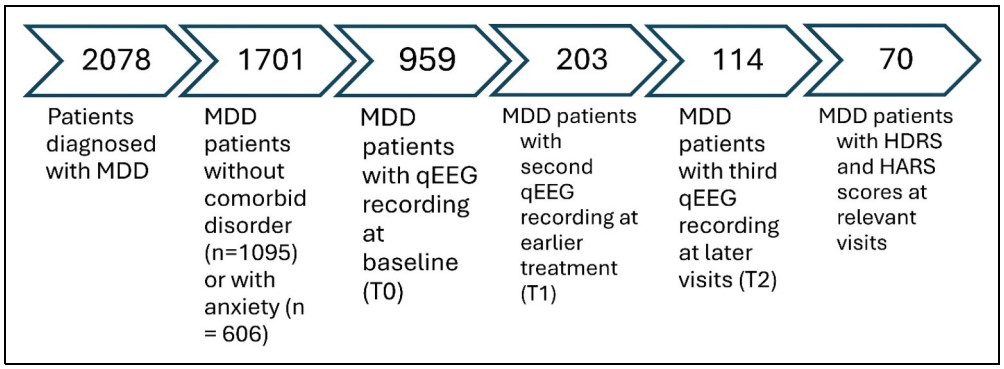

Figure 1. The Number of MDD Patients Included in the Analysis After Applying Inclusion and Exclusion Criteria.

publication guidelines and the recommendations for studies using qEEG.[15]

Resting-state qEEG was recorded using a Neuron-Spectrum-4/P device.[16] Participants sat comfortably with their eyes closed during the recording. The session lasted approximately 7 min, including 3 min of closed-eye resting-state recording, 30 s of open-eye recording, and 3.5 min of closed-eye recording. A total of 6-min eyes-closed EEG was analyzed for artifact rejection. The data were sampled at 500 Hz, with a bandpass filter of 0.15–70 Hz and a notch filter at 50 Hz.

qEEG Artifact Rejection. The raw qEEG recordings were stored in European Data Format (EDF). Artifacts, such as muscle movements, were removed using NeuroGuide software[17] (NeuroGuide Deluxe v3.8.2; Applied Neuroscience, Inc.). The software's automated Z-scored artifact rejection tool was used for drowsiness, eye movements, and muscle movements. The high-sensitivity settings with a 1.5 standard deviation threshold for the amplitude multiplier were selected. Because artifact amplitudes are generally much higher than those of normal EEG waves, a 1.5 SD threshold is in fact more conservative for artifact removal. A Z-Score of 1.5 standard deviations means that if at least one second of successive instantaneous Z-Scores is equal to or less than 1.5 standard deviations, a selection is made. The neurologist visually examined the EEG data using the software interface that both highlights automatically detected artifacts and provides access to the raw EEG traces. The automatic artifact free selections were then visually examined. Samples containing artifacts were discarded, ensuring that at least three minutes of artifact-free, closed-eye data were retained for each participant.

qEEG Spectral Analysis. The Fast Fourier Transformation parameters are epoch = 2 s at a sample rate of 128 sample/sec = 256 digital time points and a frequency range from 0.5 to 40 Hz at a resolution of 0.5 Hz using a cosine taper window. Each 2 s FFT is 101 rows (frequencies 0 to 50 Hz)×19 columns (electrode locations) = 1919 element cross-spectral matrix for each subject. The FFT mean, variance, standard deviation, sum of squares, and squared sum of the real (cosine) and imaginary (sine) coefficients of the cross-spectral matrix is computed across the sliding average of edited EEG for all 19 leads for the total number of 101 frequencies and 1919 log transformed elements for each subject at 0.5 Hz resolution. More details of spectral analysis can be found in manual of the program.[18(pp272-275)]

Data were averaged across the recording epochs for each electrode, and the absolute power was computed for the following frequency bands: Delta (1-4 Hz), Theta (4-7 Hz), Alpha (8-12 Hz), Beta (12-25 Hz), High Beta (25-30 Hz), Gamma (30-50 Hz).

Statistical Analysis

All statistical analyses were conducted using SPSS (Version 29). Prior to analysis, absolute qEEG power values were log-transformed to approximate normality. A constant of 1 was added to all values before transformation to avoid negative values. Normality of log-transformed data was assessed using the Shapiro–Wilk test, and homogeneity of variances was evaluated via Levene's test. Since these assumptions were met, parametric tests were applied.

To test which groups had changed in qEEG over time, groups at three time points were separately analyzed. A repeated measure ANOVA was used for this analysis. Then, the significantly changed electrode band pairs were compared with the records of HCs that were recorded at one time. An independent sample T-test was used for the analysis. At third step, the t scores obtained from t-test were used to construct line graphics. The t scores which become close to 0 were interpreted as MDD group and HCs were similar for the absolute power of that electrode band pair. Additionally, Pearson's correlation analyses were conducted to examine associations between qEEG band power and HDRS and HARS scores at each time point, to evaluate state-related variability. Assumptions of linearity and normality for correlation analyses were checked and confirmed. The threshold for statistical significance was 0.05.

Effect sizes were reported using partial eta squared (η^2) for repeated-measures ANOVAs and Cohen's d for t-tests. Exact *P*-values and degrees of freedom are reported for all significant and non-significant tests to enhance transparency. Post-hoc

power was calculated for t-test and observed power was reported for within-subject ANOVA to assess the likelihood of detecting effects, particularly in the smaller non-responder group. Where power was low, results are interpreted with caution.

Clinical Variables. Clinical variables, i.e, HDRS scores, HARS scores, antidepressant dose, duration of disease(years), were compared between responder and non-responders with independent sample test. HCs were included in age and gender comparison. Differences in categorical variables (eg, gender, comorbid anxiety, medication other than antidepressant use) were examined with chi-square test. The threshold for statistical significance was 0.05.

Results

Demographic and Clinical Variables

As shown in Table 1, no significant differences were observed between responders and non-responders in age $t(68) = 0.82$, $P = .416$, illness duration $t(68) = 0.91$, $P = .367$, antidepressant dosage $t(68) = 1.25$, $P = .215$, or in the intervals between EEG assessments T0–T1: $P = .660$; T1–T2: $P = .107$; T0–T2: $P = .281$. Therefore, these variables were not included as covariates in subsequent analyses.

Baseline HDRS and HARS scores were comparable between groups (HDRS: $P = .703$; HARS: $P = .498$). In contrast, at follow-up timepoints, responders showed significant reductions in both measures (HDRS T1 and T2: $P < .001$; HARS T1: $P = .027$, T2: $P = .026$), confirming clinical improvement. Notably, all responders showed at least a 50% reduction in both HDRS and HARS scores.

Categorical variables such as gender ($\chi^2 = 5.21$, $P = .061$) and comorbid anxiety ($\chi^2 = 3.31$, $P = .068$) showed no significant group differences.

qEEG Findings

Delta Band. Significant longitudinal reductions in delta power were found at the following sites in responders: C3 ($F(2106) = 4.14$, $P = .025$, $\eta^2 = 0.057$), F3 ($F = 6.39$, $P = .009$, $\eta^2 = 0.124$), F4 ($F = 3.61$, $P = .040$, $\eta^2 = 0.074$), FP1 ($F = 7.295$, $P = .004$, $\eta^2 = 0.131$), FP2 ($F = 7.06$, $P = .004$, $\eta^2 = 0.131$), O2 ($F = 3.58$, $P = .032$, $\eta^2 = 0.050$), Cz ($F = 4.80$, $P = .015$, $\eta^2 = 0.093$), Fz ($F = 8.13$, $P = .003$, $\eta^2 = 0.119$), and P3 ($F = 5.61$, $P = .009$, $\eta^2 = 0.088$) (Table 2). Post-hoc comparisons with healthy controls showed that responder delta activity converged toward control values over time (eg, FP1 T0: $t(150) = 3.43$, $P < .001$, $d = 0.65$; T2: $t(150) = 0.68$, $P = .248$), indicating normalization (Table 2) (Figure 2)(Figure S1). In contrast, non-responders exhibited no significant delta changes across time (all $F < 1.6$, $P > .10$), and comparisons with healthy controls remained significant (eg, FP2 T2: $t(112) = 2.66$, $P = .016$, $d = 0.99$), suggesting a persistent abnormal pattern (Table 2) (Figure 3) (Figure S2).

Theta Band. Compared to HCs, patients had increased theta activity at baseline. However, none of the response groups show changes in theta activity over time. Therefore, they were excluded from subsequent analysis.

Alpha Band. Significant longitudinal reductions in alpha power were found at the following sites in responders: F3 ($F(2106) = 4.76$, $P = .014$, $\eta^2 = 0.082$), FP1 ($F = 6.21$, $P = .004$, $\eta^2 = 0.121$), FP2 ($F = 4.00$, $P = .024$, $\eta^2 = 0.121$), F7 ($F = 4.08$, $P = .022$, $\eta^2 = 0.073$), and Cz ($F = 3.10$, $P = .050$, $\eta^2 = 0.057$)(Table 2)(Figure 2)(Figure S1)

However, most alpha values remained above healthy control levels at T2 (eg, FP1: $t(150) = 2.22$, $P = .014$, $d = 0.376$), except for Cz (T2: $t(150) = 0.01$, $P = .498$). Non-responders showed no significant alpha change across time or normalization ($P > .05$) (Table 2) (Figure 3)(Figure S2).

Beta Band. Significant beta activity changes were found in responders at F7 ($F(2106) = 3.55$, $P = .034$, $\eta^2 = 0.071$) and Fz ($F = 3.89$, $P = .031$, $\eta^2 = 0.080$), with a gradual reduction observed across visits (Table 2) (Figure 2). On the other hand, T0 beta power in non-responders is similar compared to the HCs in these regions which showed no significant changes with treatment (Table 2) (Figure 3).

High Beta Band. None of the response groups show changes in high beta activity over time. Therefore, they were not included in further analysis.

Gamma Band. Baseline gamma power for each MDD response groups did not differ from HCs. However, responders showed significant increases in gamma power over time at: T6 ($F(2106) = 4.23$, $P = .019$, $\eta^2 = .086$), Cz ($F = 3.46$, $P = .044$, $\eta^2 = .071$), T4 ($F = 3.44$, $P = .045$), and F3 ($F = 3.63$, $P = .034$) (Figure 2). There is no gamma activity difference at T0 between non-responder and HC groups in these regions (Figure 3). No significant gamma changes were found across time for non-responders (Table 2).

Correlation Analysis

The correlations between QEEG absolute power and concurrent HDRS and HARS total scores evaluated at the same visit were focused on checking whether they are linked to current depressive and anxiety state. Significant positive correlations were observed between qEEG absolute power and HDRS and HARS scores for FP2-Delta ($r = .254$, $P < .01$); F3 Delta ($r = .298$, $P < .01$), F3 Gamma ($r = -.252$, $P < .01$) at second measurement, for FP1 Delta ($r = .273$, $P < .01$) at third measurement. While midline fronto-central delta shows correlation with only depressive symptomatology, midline central gamma showed negative correlation only with current anxiety state (Table 3).

Table 1. Descriptives and Statistics of Clinical and Demographic Variables Between Groups.

Variable	Groups	Descriptive			Test
		N	M	SD	*P*
Age	Responder	54	41.87	13.05	.416
	Non-Responder	16	37.18	13.51	
	Healthy Control	98	42.13	14.46	
Duration of Disease (years)	Responder	54	12.02	9.79	.367
	Non-Responder	16	9.07	11.9	
Antidepressant dose (fluoxetine equivalence)	Responder	54	40.08	16.63	.215
	Non-Responder	16	33.32	16.64	
HDRS (Baseline)	Responder	54	21.27	7.41	.703
	Non-Responder	16	22.12	8.97	
HDRS (Response)	Responder	54	2.7	2.75	<.001
	Non-Responder	16	20.5	10.85	
HDRS (Monitoring)	Responder	54	2.78	5.28	.027
	Non-Responder	16	9.5	9.91	
HARS (Baseline)	Responder	54	26.77	12.23	.498
	Non-Responder	16	24.43	11.4	
HARS (Response)	Responder	54	3.34	3.79	<.001
	Non-Responder	16	20.93	14.95	
HARS (Monitoring)	Responder	54	3.96	7.87	.026
	Non-Responder	16	10.78	15.5	
Duration Between T0-T1 qEEG measurement (months)	Responder	54	3.51	8.35	.660
	Non-Responder	16	4.75	13.69	
Duration Between T1-T2 qEEG measurement (months)	Responder	54	10.29	8.35	.107
	Non-Responder	16	4.00	13.69	
Duration Between T0-T2 qEEG measurement (months)	Responder	54	14.2	14.54	.281
	Non-Responder	16	8.93	15.03	
Categorical Variables					
Gender		Female	Male	X^2	*P*
	Responder	31	23	5.21	.061
	Non-Responder	8	8		
	Healthy Control	39	59		
		Yes	No		
Comorbid Anxiety	Responder	40	14	3.31	.068
	Non-Responder	8	8		

Discussion

This study aimed to identify state dependent electrophysiological characteristics of MDD patients who were classified as responders and non-responders to antidepressant treatment, and to determine which markers should be further investigated in future research and clinical evaluation. The findings suggest that qEEG is not only useful in diagnosing depression but also serves as an affordable and reproducible tool for monitoring patients and distinguishing responders from non-responders.

Delta Activity

A significant longitudinal reduction in delta power across frontocentral regions was observed in responders. Over time, these changes converged toward levels seen in HCs, as demonstrated by non-significant t-test comparisons at endpoint. This normalization indicates that increased delta power in depression may represent a state-dependent marker in treatment responders, sensitive to treatment-related changes. Conversely, non-responders exhibited persistently elevated delta activity with no significant change across sessions. As depression remained unchanged, so did delta activity which strengthens the argument that the delta activity as state marker of depression. These findings are partially consistent with prior studies. While delta power decreased by a successful TMS treatment in depression,[19] other studies reported increased delta power with antidepressant treatment.[20] Consequently, changes in delta activity have been associated with enhanced cognitive control, suppression of attentional distraction, and improvements in depressive symptoms.[21] Finally, the correlation analysis between changed qEEG markers showed that prefrontal delta activity is positively correlated with severity of depression and anxiety.

Theta Activity

As the increased theta activity in MDD patients did not change with treatment they were not included in the further analysis for state markers. On the other hand, it could be argued that the

Table 2. Statistically Significant Differences in qEEG Absolute Power Across Time Based on Groups.

			Descriptive			t test (with HC)					ANOVA within subject				
QEEG Variables	Measurement	Groups	N	M	SD	t	df	*P*	Cohen's d	Post-hocPower	F	df	*P*	Partial Eta Square	Observed power
FP1 Delta	First EEG	Responder	54	3.401	0.776	3.428	150	.000	0.647	0.967	7.295	2106	.004	0.131	0.908
		Non-Responder	16	3.312	1.019	1.4	112	.18	0.625	0.633	1.566	2,30	.117	0.204	0.256
		Healthy Control	98	3.037	0.502										
	Second EEG	Responder	54	3.171	0.522	1.361	150	.088	0.231	0.272					
		Non-Responder	16	3.242	1.002	1.447	112	.151	0.390	0.300					
		Healthy Control	98	3.037	0.502										
	Third EEG	Responder	54	3.035	0.377	0.681	150	.248	0.115	0.104					
		Non-Responder	16	3.784	0.54	4.369	112	.001	1.178	0.991					
		Healthy Control	98	3.037	0.502										
FP2 Delta	First EEG	Responder	54	3.419	0.771	4.21	150	0	0.713	0.987	7.056	2106	.004	0.136	0.95
		Non-Responder	16	3.497	0.397	2.149	112	.001	0.890	0.905	0.319	2,30	.727	0.028	0.053
		Healthy Control	98	3.031	0.44										
	Second EEG	Responder	54	3.111	0.51	1.134	150	.26	0.198	0.213					
		Non-Responder	16	3.634	0.457	3.171	112	.003	1.044	0.970					
		Healthy Control	98	3.031	0.44										
	Third EEG	Responder	54	3.066	0.392	1.05	150	.296	0.176	0.178					
		Non-Responder	16	3.606	0.645	2.663	112	.016	0.994	0.955					
		Healthy Control	98	3.031	0.44										
F3 Delta	First EEG	Responder	54	2.998	0.568	1.834	150	.034	0.311	0.445	6.392	2106	.009	0.124	0.871
		Non-Responder	16	3.336	0.623	3.178	112	.003	1.089	0.980	0.596	2,30	.499	0.051	0.343
		Healthy Control	98	2.836	0.449										
	Second EEG	Responder	54	2.835	0.389	−0.113	150	.455	−0.019	0.051					
		Non-Responder	16	3.215	0.38	2.914	112	.002	0.786	0.824					
		Healthy Control	98	2.836	0.449										
	Third EEG	Responder	54	2.697	0.362	−1.575	150	.059	−0.267	0.347					
		Non-Responder	16	3.184	0.375	2.371	112	.01	0.639	0.652					
		Healthy Control	98	2.836	0.449										
F4 Delta	First EEG	Responder	54	2.962	0.522	3.09	150	.001	0.524	0.866	3.612	2106	.04	0.074	0.707
		Non-Responder	16	3.207	0.398	3.87	112	.001	1.295	0.997	0.115	2,30	.846	0.01	0.064
		Healthy Control	98	2.731	0.346										
	Second EEG	Responder	54	2.803	0.422	0.831	150	.204	0.141	0.131					
		Non-Responder	16	3.269	0.569	3.012	112	.008	1.109	0.983					
		Healthy Control	98	2.731	0.346										
	Third EEG	Responder	54	2.766	0.378	0.631	150	.265	0.107	0.096					
		Non-Responder	16	3.189	0.689	2.501	112	.023	1.029	0.966					
		Healthy Control	98	2.731	0.346										
F7 Delta	First EEG	Responder	54	3.025	0.7	2.523	150	.006	0.428	0.708	3.35	2106	.045	0.069	0.62
		Non-Responder	16	3.199	0.47	2.856	112	.003	0.770	0.808	0.257	2,30	.703	0.023	0.057
		Healthy Control	98	2.77	0.53										
	Second EEG	Responder	54	2.86	0.487	0.82	150	.207	0.139	0.129					
		Non-Responder	16	3.208	0.46	2.885	112	.002	0.778	0.816					

(continued)

Table 2. Continued.

QEEG Variables	Measurement	Groups	Descriptive N	M	SD	t test (with HC) t	df	P	Cohen's d	Post-hocPower	ANOVA within subject F	df	P	Partial Eta Square	Observed power
		Healthy Control	98	2.77	0.53										
	Third EEG	Responder	54	2.747	0.505	0.073	150	.471	0.012	0.051					
		Non-Responder	16	3.305	0.713	3.038	112	.001	0.819	0.854					
		Healthy Control	98	2.77	0.53										
F8 Delta	First EEG	Responder	54	2.95	0.674	2.806	150	.003	0.516	0.856	4.238	2106	.025	0.113	0.695
		Non-Responder	16	3.16	0.571	3.554	112	.001	0.956	0.940	0.166	2,30	.816	0.039	0.058
		Healthy Control	98	2.628	0.496										
	Second EEG	Responder	54	2.724	0.459	0.924	150	.179	0.151	0.144					
		Non-Responder	16	3.22	0.653	3.338	112	.001	0.900	0.911					
		Healthy Control	98	2.628	0.496										
	Third EEG	Responder	54	2.701	0.48	1.083	150	.14	0.184	0.190					
		Non-Responder	16	3.104	0.669	2.407	112	.014	0.845	0.874					
		Healthy Control	98	2.628	0.496										
Fz Delta	First EEG	Responder	54	3.127	0.686	3.133	150	.001	0.617	0.951	8.127	2106	.003	0.119	0.928
		Non-Responder	16	3.245	0.316	2.894	112	.005	0.780	0.818	0.783	2,30	.434	0.055	0.187
		Healthy Control	98	2.786	0.394										
	Second EEG	Responder	54	2.853	0.345	1.157	150	.124	0.196	0.210					
		Non-Responder	16	3.33	0.388	3.925	112	.001	1.058	0.973					
		Healthy Control	98	2.786	0.394										
	Third EEG	Responder	54	2.772	0.476	0.116	150	.454	0.020	0.052					
		Non-Responder	16	3.214	0.386	3.216	112	.002	0.867	0.890					
		Healthy Control	98	2.786	0.394										
C3 Delta	First EEG	Responder	54	2.849	0.528	1.693	150	.046	0.287	0.391	4.142	2106	.025	0.057	0.602
		Non-Responder	16	3.052	0.366	2.483	112	.007	0.669	0.692	0.394	2,30	.647	0.002	0.054
		Healthy Control	98	2.7	0.428										
	Second EEG	Responder	54	2.66	0.371	−0.485	150	.314	−0.082	0.077					
		Non-Responder	16	3.146	0.58	2.436	112	.008	0.657	0.676					
		Healthy Control	98	2.7	0.428										
	Third EEG	Responder	54	2.641	0.442	−0.455	150	.325	−0.077	0.074					
		Non-Responder	16	3.001	0.413	2.69	112	.004	0.725	0.760					
		Healthy Control	98	2.7	0.428										
Cz Delta	First EEG	Responder	54	2.921	0.458	1.283	150	.101	0.217	0.247	4.803	2106	.015	0.093	0.837
		Non-Responder	16	3.287	0.494	3.076	112	.003	0.829	0.862	0.567	2,30	.52	0.05	0.172
		Healthy Control	98	2.833	0.386										
	Second EEG	Responder	54	2.864	0.394	0.155	150	.438	0.026	0.053					
		Non-Responder	16	3.256	0.569	2.37	112	.02	0.639	0.652					
		Healthy Control	98	2.833	0.386										
	Third EEG	Responder	54	2.711	0.336	−1.928	150	.034	−0.313	0.449					
		Non-Responder	16	3.162	0.352	1.947	112	.054	0.525	0.488					
		Healthy Control	98	2.833	0.386										
P3 Delta	First EEG	Responder	54	2.76	0.5	1.41	150	.162	0.248	0.307	5.61	2106	.009	0.088	0.814

(continued)

Table 2. Continued.

QEEG Variables	Measurement	Groups	Descriptive			t test (with HC)					ANOVA within subject				
			N	M	SD	t	df	*P*	Cohen's d	Post-hocPower	F	df	*P*	Partial Eta Square	Observed power
		Non-Responder	16	2.939	0.38	1.813	112	.073	0.489	0.435	0.904	2,30	.39	0.07	0.23
		Healthy Control	98	2.627	0.451										
	Second EEG	Responder	54	2.651	0.439	0.217	150	.829	0.036	0.055					
		Non-Responder	16	2.954	0.426	1.961	112	.052	0.529	0.494					
		Healthy Control	98	2.627	0.451										
	Third EEG	Responder	54	2.488	0.389	−1.633	150	.105	−0.265	0.342					
		Non-Responder	16	3.184	0.767	2.34	112	.032	0.877	0.897					
		Healthy Control	98	2.627	0.451										
O2 Delta	First EEG	Responder	54	2.705	0.541	2.156	150	.034	0.390	0.627	3.583	2106	.032	0.05	0.54
		Non-Responder	16	3.178	0.62	4.169	112	0	1.124	0.985	0.905	2,30	.419	0.142	0.461
		Healthy Control	98	2.534	0.441										
	Second EEG	Responder	54	2.65	0.481	1.422	150	.158	0.246	0.302					
		Non-Responder	16	3.073	0.431	3.223	112	.001	0.869	0.892					
		Healthy Control	98	2.534	0.441										
	Third EEG	Responder	54	2.487	0.465	0.01	150	.992	0.002	0.050					
		Non-Responder	16	2.934	0.487	1.709	112	.09	0.461	0.395					
		Healthy Control	98	2.534	0.441										
FP1 Alpha	First EEG	Responder	54	2.731	0.781	3.771	150	0	0.696	0.983	6.212	2106	.004	0.121	0.037
		Non-Responder	16	2.844	0.989	2.879	112	.005	0.776	0.814	0.026	2,30	.921	0.002	0.061
		Healthy Control	98	2.262	0.57										
	Second EEG	Responder	54	2.59	0.746	2.546	150	.006	0.467	0.782					
		Non-Responder	16	2.875	1.044	2.206	112	.042	0.841	0.871					
		Healthy Control	98	2.262	0.57										
	Third EEG	Responder	54	2.507	0.696	2.221	150	.014	0.376	0.597					
		Non-Responder	16	2.877	0.741	3.292	112	.001	0.888	0.904					
		Healthy Control	98	2.262	0.57										
FP2 Alpha	First EEG	Responder	54	2.723	0.757	8.328	150	0	0.693	0.982	4.001	2106	.024	0.121	0.755
		Non-Responder	16	3.028	0.573	3.881	112	0	1.046	0.970	2.048	2,30	.169	0.002	0.279
		Healthy Control	98	2.266	0.572										
	Second EEG	Responder	54	2.605	0.775	4.251	150	0	0.479	0.802					
		Non-Responder	16	3.072	0.64	4.055	112	0	1.093	0.980					
		Healthy Control	98	2.266	0.572										
	Third EEG	Responder	54	2.543	0.707	3.82	150	0	0.436	0.724					
		Non-Responder	16	2.869	0.751	3.146	112	.001	0.848	0.877					
		Healthy Control	98	2.266	0.572										
F3 Alpha	First EEG	Responder	54	2.853	0.803	3.536	150	.001	0.599	0.940	4.762	2106	.014	0.082	0.78
		Non-Responder	16	3.141	0.731	3.442	112	0	0.928	0.927	1.136	2,30	.33	0.038	0.139
		Healthy Control	98	2.435	0.586										
	Second EEG	Responder	54	2.745	0.761	2.582	150	.011	0.438	0.728					
		Non-Responder	16	3.203	0.803	3.56	112	0	0.960	0.942					
		Healthy Control	98	2.435	0.586										

(continued)

Table 2. Continued.

QEEG Variables	Measurement	Groups	Descriptive			t test (with HC)					ANOVA within subject				
			N	M	SD	t	df	*P*	Cohen's d	Post-hocPower	F	df	*P*	Partial Eta Square	Observed power
	Third EEG	Responder	54	2.667	0.76	2.084	150	.039	0.353	0.544					
		Non-Responder	16	3.018	0.784	2.987	112	.002	0.805	0.842					
		Healthy Control	98	2.435	0.586										
F7 Alpha	First EEG	Responder	54	2.421	0.792	3.165	150	.001	0.602	0.942	4.082	2106	.022	0.073	0.724
		Non-Responder	16	2.564	0.749	2.756	112	.003	0.743	0.780	0.453	2,30	.596	0.018	0.9
		Healthy Control	98	2.031	0.518										
	Second EEG	Responder	54	2.325	0.721	2.452	150	.008	0.456	0.763					
		Non-Responder	16	2.609	0.811	3.064	112	.003	0.826	0.859					
		Healthy Control	98	2.031	0.518										
	Third EEG	Responder	54	2.242	0.721	1.946	150	.027	0.359	0.558					
		Non-Responder	16	2.498	0.802	2.637	112	.005	0.711	0.743					
		Healthy Control	98	2.031	0.518										
Cz Alpha	First EEG	Responder	54	3.102	0.84	2.974	150	.002	0.541	0.887	3.102	2106	.05	0.057	0.599
		Non-Responder	16	3.426	0.763	3.416	112	.001	0.921	0.923	0.559	2,30	.528	0.012	0.077
		Healthy Control	98	2.698	0.655										
	Second EEG	Responder	54	3	0.82	0.251	150	.401	0.396	0.642					
		Non-Responder	16	3.474	0.793	3.446	112	0	0.929	0.927					
		Healthy Control	98	2.698	0.655										
	Third EEG	Responder	54	2.946	0.812	0.006	150	.498	0.347	0.530					
		Non-Responder	16	3.323	0.703	3.153	112	.002	0.850	0.878					
		Healthy Control	98	2.698	0.655										
F7 Beta	First EEG	Responder	54	2.309	0.481	5.356	150	0	0.908	1.000	3.552	2106	.034	0.071	0.711
		Non-Responder	16	2.093	0.453	0.906	112	.183	0.244	0.146	0.434	2,30	.562	0.032	0.123
		Healthy Control	98	1.925	0.374										
	Second EEG	Responder	54	2.234	0.575	3.362	150	.001	0.637	0.962					
		Non-Responder	16	2.051	0.552	0.851	112	.198	0.230	0.135					
		Healthy Control	98	1.925	0.374										
	Third EEG	Responder	54	2.137	0.474	2.902	150	.002	0.492	0.822					
		Non-Responder	16	2.161	0.606	1.559	112	.061	0.420	0.340					
		Healthy Control	98	1.925	0.374										
Fz Beta	First EEG	Responder	54	2.468	0.427	4.073	150	0	0.715	0.987	3.898	2106	.031	0.08	0.785
		Non-Responder	16	2.397	0.348	1.216	112	.082	0.473	0.413	0.216	2,30	.734	0.019	0.513
		Healthy Control	98	2.186	0.365										
	Second EEG	Responder	54	2.413	0.435	3.062	150	.003	0.546	0.892					
		Non-Responder	16	2.372	0.398	1.216	112	.226	0.328	0.226					
		Healthy Control	98	2.186	0.365										
	Third EEG	Responder	54	2.36	0.465	2.298	150	.024	0.416	0.684					
		Non-Responder	16	2.414	0.405	1.572	112	.119	0.424	0.344					
		Healthy Control	98	2.186	0.365										
F3 Gamma	First EEG	Responder	54	0.874	0.542	1.407	150	.161	0.239	0.288	3.635	2106	.034	0.075	0.319
		Non-Responder	16	0.592	0.307	−1.762	112	.081	−0.475	0.416	1.436	2,30	.257	0.115	0.24

(continued)

Table 2. Continued.

			Descriptive			t test (with HC)					ANOVA within subject				
QEEG Variables	Measurement	Groups	N	M	SD	t	df	*P*	Cohen's d	Post-hocPower	F	df	*P*	Partial Eta Square	Observed power
		Healthy Control	98	0.794	0.479										
	Second EEG	Responder	54	0.97	0.63	2.156	150	.033	0.365	0.572					
		Non-Responder	16	0.609	0.421	−1.144	112	.255	−0.309	0.206					
		Healthy Control	98	0.794	0.479										
	Third EEG	Responder	54	1.119	0.68	3.001	150	.003	0.509	0.847					
		Non-Responder	16	0.825	0.903	−0.2	112	.842	−0.054	0.054					
		Healthy Control	98	0.794	0.479										
Cz Gamma	First EEG	Responder	54	0.724	0.409	0.025	150	.98	0.004	0.050	3.461	2106	.044	0.071	0.339
		Non-Responder	16	0.59	0.33	−1.765	112	.08	−0.476	0.417	0.7	2,30	.443	0.06	0.2
		Healthy Control	98	0.761	0.399										
	Second EEG	Responder	54	0.789	0.436	0.777	150	.439	0.139	0.128					
		Non-Responder	16	0.591	0.383	−1.25	112	.214	−0.337	0.236					
		Healthy Control	98	0.761	0.399										
	Third EEG	Responder	54	0.897	0.477	1.564	150	.121	0.276	0.367					
		Non-Responder	16	0.649	0.484	−1.02	112	.31	−0.275	0.173					
		Healthy Control	98	0.761	0.399										
P4 Gamma	First EEG	Responder	54	0.669	0.408	−0.176	150	.861	−0.030	0.054	3.444	2106	.037	0.071	0.299
		Non-Responder	16	0.609	0.358	−1.258	112	.211	−0.339	0.239	0.576	2,30	.509	0.05	0.075
		Healthy Control	98	0.718	0.445										
	Second EEG	Responder	54	0.742	0.426	0.549	150	.584	0.092	0.084					
		Non-Responder	16	0.591	0.382	−1.161	112	.248	−0.313	0.210					
		Healthy Control	98	0.718	0.445										
	Third EEG	Responder	54	0.8	0.387	1.024	150	.308	0.165	0.162					
		Non-Responder	16	0.642	0.471	−1.009	112	.315	−0.272	0.170					
		Healthy Control	98	0.718	0.445										
T4 Gamma	First EEG	Responder	54	0.791	0.631	−0.171	150	.865	−0.029	0.053	3.438	2106	.045	0.071	0.468
		Non-Responder	16	0.496	0.363	−3.492	112	.001	−0.625	0.633	1.652	2,30	.221	0.131	0.274
		Healthy Control	98	0.821	0.608										
	Second EEG	Responder	54	0.947	0.654	1.095	150	.276	0.188	0.197					
		Non-Responder	16	0.618	0.455	−1.517	112	.132	−0.409	0.324					
		Healthy Control	98	0.821	0.608										
	Third EEG	Responder	54	1.032	0.67	1.509	150	.134	0.259	0.331					
		Non-Responder	16	0.734	0.739	−1.176	112	.242	−0.317	0.214					
		Healthy Control	98	0.821	0.608										
T6 Gamma	First EEG	Responder	54	0.686	0.423	−0.613	150	.541	−0.098	0.089	4.225	2106	.019	0.086	0.473
		Non-Responder	16	0.669	0.446	−1.188	112	.237	−0.320	0.218	0.125	2,30	.808	0.011	0.117
		Healthy Control	98	0.752	0.526										
	Second EEG	Responder	54	0.77	0.468	0.335	150	.738	0.055	0.062					
		Non-Responder	16	0.683	0.527	−0.877	112	.382	−0.236	0.140					
		Healthy Control	98	0.752	0.526										
	Third EEG	Responder	54	0.827	0.438	0.693	150	.49	0.110	0.099					
		Non-Responder	16	0.648	0.464	−1.244	112	.216	−0.335	0.234					
		Healthy Control	98	0.752	0.526										

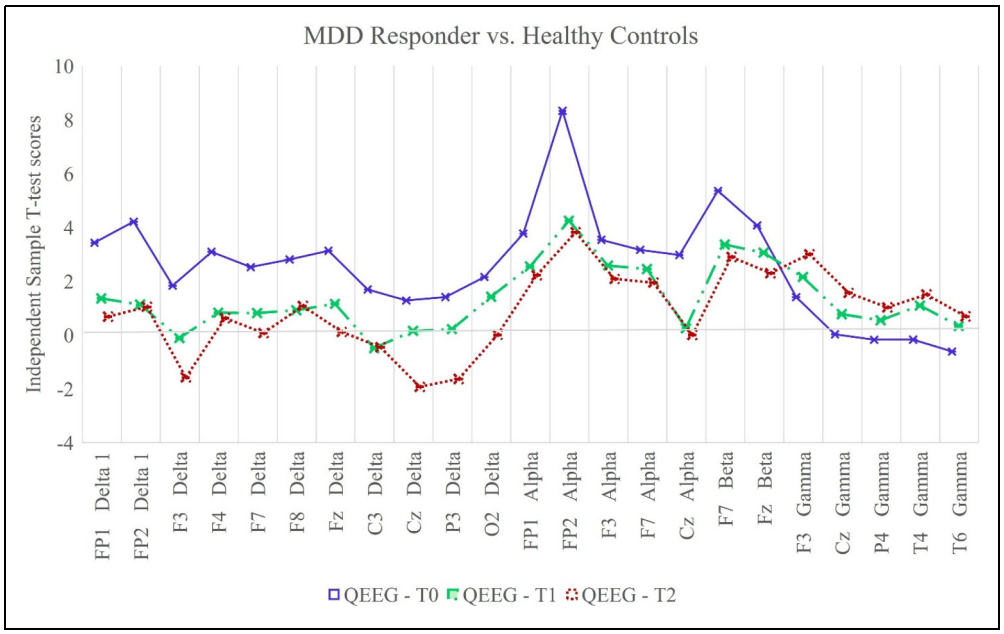

Figure 2. QEEG Absolute Power Difference Between MDD Responders and Healthy Controls Across Time. *Note.* T test scores approaching to 0 represent no difference between MDD responders and HCs in the related qEEG absolute power. Positive t scores represent MDD group had increased qEEG activity, negative t scores represent MDD group had decreased qEEG activity compared to HCs. MDD, Major Depressive Disorder. HC = Healthy Controls.

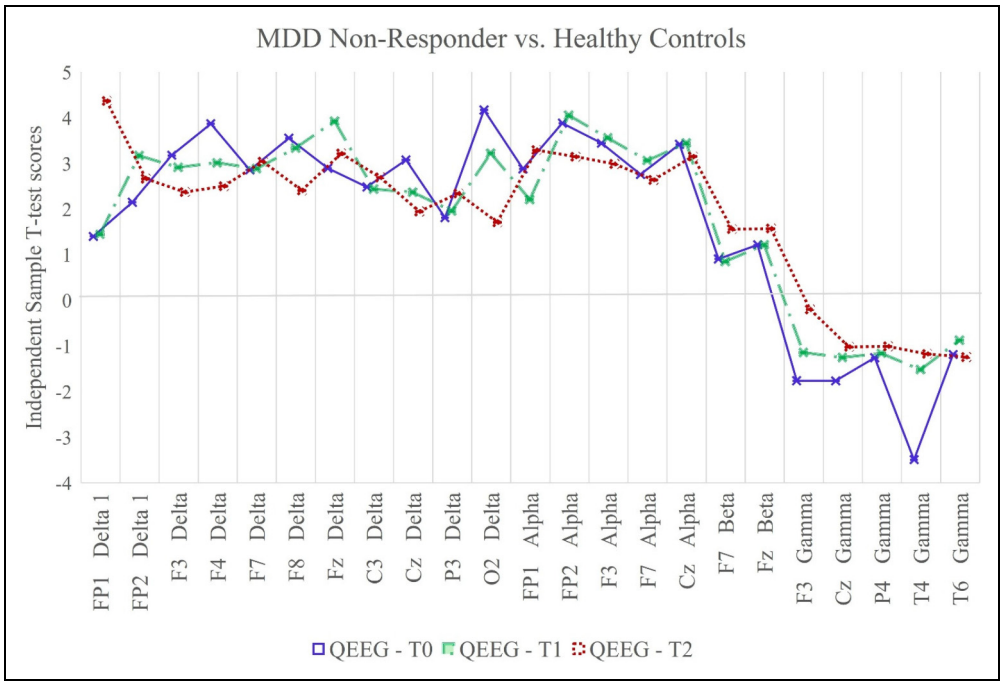

Figure 3. QEEG Absolute Power Difference Between MDD Non-Responders and Healthy Controls Across Time. *Note.* T test scores diverging from 0 represent there is difference between MDD responders and HCs in the related qEEG absolute power. Positive t scores represent MDD group had increased qEEG activity, negative t scores represent MDD group had decreased qEEG activity compared to HCs. MDD, Major Depressive Disorder. HC = Healthy Controls.

theta activity could be a candidate for trait markers. In the literature, it was reported that patients with MDD had elevated theta activity, associated with treatment non-response but not with remission.[22] However, further conditions are needed such as recurrence status, high risk population to certainly claim that theta activity could be a trait marker in depression.

Table 3. Pearson Correlations QEEG Variables, HDRS-21 and HARS Scores among Depressed Patients (N = 70).

Variables Tested	HDRS (T0)	HDRS (T1)	HDRS (T2)	HARS (T0)	HARS (T1)	HARS (T2)
HDRS (T0)	1.000	0.374**	0.223	**0.773****	0.379**	0.281**
HDRS (T1)	0.374**	1.000	0.438**	0.141	**0.896****	0.377**
HDRS (T2)	0.223	0.438**	1.000	0.268**	0.518**	**0.932****
HARS (T0)	**0.773****	0.141	0.268**	1.000	0.289**	0.376**
HARS (T1)	0.379**	**0.896****	0.518**	0.289**	1.000	0.549**
HARS (T2)	0.281**	0.377**	**0.932****	0.376**	0.549**	1.000
FP1 Delta (T0)	0.111	−0.090	0.150	0.131	−0.035	0.150
FP1 Delta (T1)	0.044	0.063	0.164	−0.013	0.071	0.187
FP1 Delta (T2)	0.249**	0.493**	**0.273****	0.157	0.519**	**0.348****
FP2 Delta (T0)	0.167	0.021	0.159	0.161	0.052	0.162
FP2 Delta (T1)	0.183	**0.254****	0.157	0.117	**0.275****	0.176
FP2 Delta (T2)	0.157	0.377**	0.240	0.086	0.421**	**0.286****
F3 Delta (T0)	0.048	0.096	0.132	0.028	0.146	0.076
F3 Delta (T1)	0.083	**0.298****	0.211	0.030	**0.333****	0.207
F3 Delta (T2)	0.130	0.419**	0.115	−0.002	0.413**	0.123
F4 Delta (T0)	0.170	0.107	0.119	0.093	0.129	0.089
F4 Delta (T1)	−0.018	0.206	0.055	−0.073	0.151	0.038
F4 Delta (T2)	0.056	0.344**	0.010	0.002	0.336**	0.012
F7 Delta (T0)	0.049	−0.012	0.060	−0.007	0.069	0.056
F7 Delta (T1)	0.009	0.183	0.202	0.019	**0.286****	0.247**
F7 Delta (T2)	0.311**	0.395**	**0.249****	0.223	0.513**	**0.278****
F8 Delta (T0)	0.083	0.052	0.176	−0.041	0.114	0.140
F8 Delta (T1)	0.055	0.197	0.181	−0.030	0.233	0.179
F8 Delta (T2)	−0.034	0.217	0.011	0.027	0.232	0.040
Fz Delta (T0)	0.051	0.028	0.123	0.028	0.031	0.061
Fz Delta (T1)	0.044	**0.285****	0.131	−0.043	0.249	0.124
Fz Delta (T2)	0.091	0.275**	0.102	0.001	0.283**	0.112
C3 Delta (T0)	0.088	0.013	0.022	−0.038	0.003	−0.003
C3 Delta (T1)	−0.071	0.206	0.168	−0.096	0.244	0.209
C3 Delta (T2)	0.031	0.296**	0.033	−0.079	0.249	−0.028
Cz Delta (T0)	0.222	0.209	0.038	0.129	0.164	0.005
Cz Delta (T1)	0.020	**0.259****	0.095	−0.033	0.232	0.122
Cz Delta (T2)	0.185	0.408**	0.043	−0.001	0.363**	0.021
P3 Delta (T0)	0.089	−0.045	−0.058	0.025	−0.031	−0.087
P3 Delta (T1)	−0.116	0.168	0.159	−0.075	0.172	0.197
P3 Delta (T2)	0.118	0.528**	0.084	−0.091	0.466**	0.032
O2 Delta (T0)	−0.016	0.094	−0.064	−0.092	0.046	−0.125
O2 Delta (T1)	−0.023	0.164	0.090	−0.063	0.097	0.073
O2 Delta (T2)	0.054	0.243**	−0.064	−0.076	0.165	−0.111
FP1 Alpha (T0)	−0.045	−0.041	0.007	0.088	−0.026	0.006
FP1 Alpha (T1)	−0.115	0.025	0.061	0.028	0.063	0.051
FP1 Alpha (T2)	−0.069	0.142	0.163	0.036	0.181	0.158
FP2 Alpha (T0)	−0.020	0.063	0.005	0.132	0.097	0.010
FP2 Alpha (T1)	−0.078	0.106	0.036	0.045	0.156	0.026
FP2 Alpha (T2)	−0.048	0.141	0.145	0.059	0.206	0.136
F3 Alpha (T0)	−0.089	0.011	−0.015	0.046	0.007	−0.024
F3 Alpha (T1)	−0.126	0.057	0.039	−0.013	0.098	0.034
F3 Alpha (T2)	−0.089	0.089	0.154	0.034	0.123	0.137
F7 Alpha (T0)	−0.105	−0.053	0.003	0.034	−0.021	0.007
F7 Alpha (T1)	−0.166	−0.006	0.047	−0.023	0.057	0.060
F7 Alpha (T2)	−0.068	0.063	0.145	0.011	0.115	0.150
Cz Alpha (T0)	−0.086	0.030	−0.033	0.055	0.005	−0.047
Cz Alpha (T1)	−0.111	0.089	0.044	−0.001	0.113	0.041
Cz Alpha (T2)	−0.081	0.134	0.162	0.034	0.154	0.141
F7 Beta (T0)	0.091	−0.214	0.057	0.194	−0.178	0.041
F7 Beta (T1)	0.027	−0.172	0.081	0.162	−0.103	0.130
F7 Beta (T2)	0.085	−0.021	0.016	0.119	−0.036	0.030

(continued)

Table 3. Continued.

Variables Tested	HDRS (T0)	HDRS (T1)	HDRS (T2)	HARS (T0)	HARS (T1)	HARS (T2)
Fz Beta (T0)	0.006	−0.141	−0.085	0.153	−0.197	−0.084
Fz Beta (T1)	−0.025	−0.124	−0.090	0.101	−0.117	−0.057
Fz Beta (T2)	0.017	0.017	0.023	0.120	0.013	0.027
F3 Gamma (T0)	0.062	−0.224	−0.164	0.115	−0.270**	−0.165
F3 Gamma (T1)	−0.159	**−0.252****	−0.202	−0.021	**−0.283****	−0.153
F3 Gamma (T2)	−0.058	−0.155	−0.147	0.043	−0.145	−0.105
Cz Gamma (T0)	0.037	−0.180	−0.209	0.089	−0.229	−0.214
Cz Gamma (T1)	−0.196	−0.234	−0.226	−0.058	**−0.277****	−0.176
Cz Gamma (T2)	−0.134	−0.210	−0.222	−0.015	−0.229	−0.171
P4 Gamma (T0)	0.049	−0.114	−0.181	0.061	−0.161	−0.186
P4 Gamma (T1)	−0.119	−0.179	−0.212	−0.011	−0.216	−0.151
P4 Gamma (T2)	−0.057	−0.172	−0.192	0.007	−0.155	−0.140
T4 Gamma (T0)	−0.051	−0.205	−0.158	0.004	−0.264**	−0.163
T4 Gamma (T1)	−0.110	−0.206	−0.039	0.033	−0.200	0.029
T4 Gamma (T2)	0.032	−0.109	−0.076	0.087	−0.075	−0.023
T6 Gamma (T0)	0.024	−0.075	−0.187	0.023	−0.128	−0.191
T6 Gamma (T1)	−0.092	−0.125	−0.204	−0.031	−0.183	−0.153
T6 Gamma (T2)	−0.018	−0.150	−0.175	0.008	−0.158	−0.137

Note. HDRS-21: Hamilton Depression Rating Scale. HARS: Hamilton Anxiety Rating Scale. Bold values represent the QEEG power or clinical scales are correlated with HDRS-21 or HARS scores measured at the same visit.

** $P < .01$.

* $P < .05$ level.

Alpha Activity

Although alpha band power was elevated in patients with depression compared to healthy controls, treatment response was associated with only partial normalization. Specifically, alpha power decreased among treatment responders but remained statistically higher than in healthy controls across most electrodes—except at the Cz site, where full normalization was observed. In contrast, non-responders exhibited no significant change in alpha activity. Moreover, alpha power did not correlate with depression or anxiety severity as measured by HDRS and HARS scales. Taken together, these findings suggest that alpha band activity may not represent a robust state-dependent neural marker of depression. Rather, its limited sensitivity to symptom changes and persistent elevation in most regions even after clinical improvement indicate that it may reflect both state and trait-like neurophysiological characteristic. In the literature, the findings also confirm this conclusion. For instance, a study examining EEG alpha power and asymmetry in depressed patients undergoing fluoxetine treatment, compared the responders and non-responding with HCs. The results showed the stability of occipital alpha power and the authors interpreted them as state independent features of MDD.[23] On the other hand, another study found decreased relative alpha power in responders with 8 weeks of escitalopram treatment.[24]

Beta Activity

Regarding fast band activity, beta power reductions in responders were observed at F7 and Fz. Given the association of increased beta activity with heightened arousal and anxiety, the observed reduction may indicate relief of psychomotor agitation or affective tension, supporting its role as a state marker. Beta activity in non-responders remained stable and within normal limits, suggesting it may not play a central pathophysiological role in treatment-nonresponse.

Gamma Activity

Despite no baseline differences from HCs, an increase in gamma activity over time was found in responders (T4, T6, Cz, F3) while it remained unchanged in non-responders. Besides, the increased gamma activity is negatively correlated with the severity of depression and anxiety meaning that the observed increase in gamma activity with treatment is related with clinical improvement in F3 and Cz regions. These gamma changes likely represent state-dependent neural dynamics previously associated with cognitive-affective restoration.[8] It could be argued that increased gamma in responders might be related to enhanced cognitive functioning or attentional capacity.[25]

Our previous research demonstrated that brain mapping analyses could be useful in tracking treatment response.[4] However, the present study differs by incorporating a larger number of qEEG recordings and applying repeated measures analysis to distinguish between trait and state-dependent electrophysiological markers, along with correlation with improvement with HDRS and HARS. Indeed, responders showed improvement in both depression and anxiety domains. Our correlation analyses showed that delta and gamma power changes

were associated with both HDRS and HARS, suggesting overlapping neural mechanisms, which can be solved by SSRIs and SNRIs as prescribed for anxiety beyond depression.[26]

Our results indicate that in responders, qEEG changes occur dynamically throughout treatment, whereas in non-responders, these changes remain static. This suggests that electrophysiological markers are state-dependent in responders and trait-dependent in non-responders. While our primary aim was not diagnostic classification, the observed state-dependent EEG changes in responders suggest potential utility in treatment monitoring. Although some abnormal qEEG patterns were observed in both MDD groups compared to HCs, to establish diagnostic utility, comparisons across multiple psychiatric disorders would be necessary. However, the persistence of certain EEG patterns, particularly in non-responders, may serve prognostic purposes by identifying individuals less likely to benefit from conventional treatment.

Limitations

Given the exploration nature of this study, corrections for multiple comparisons were not applied. While the sample size of the non-responder group was relatively small, power analyses were conducted post hoc to estimate the reliability of non-significant findings. Although this study focused on absolute power, alternative EEG analytic methods including Current Source Density, which provides improved localization and may reduce widespread drug effects may offer complementary insights into spatial and temporal neural dynamics. Future studies should increase the sample size and consider replication using source-localized approaches. A further limitation is the use of fluoxetine-equivalents for dose standardization. Although only 2 patients (3.7%) in the responder group and none in the non-responder group received fluoxetine, its long half-life differs from other SSRIs/SNRIs. We nevertheless used fluoxetine as the reference because it is the most widely adopted standard for dose conversion in second-generation antidepressants[14] Besides, the healthy control group underwent only a single qEEG assessment, which limited our ability to compare longitudinal stability between patients and controls. Finally, although comorbid anxiety was not excluded due to its high prevalence in MDD, it may still have influenced the electrophysiological patterns observed. Correlation of QEEG variables with both HDRS and HARS scores suggests that some of the observed state markers could be specific for depression with comorbid anxiety. Future studies with stratified diagnostic subgroups may help isolate the contributions of specific comorbidities.

Conclusion

In conclusion, this study provides novel evidence that treatment response in major depressive disorder is associated with distinct qEEG dynamics over time. Responders exhibited normalization trends in delta, alpha, beta, and gamma band activity, indicating these oscillatory changes may be state-dependent markers of clinical improvement. In contrast, non-responders demonstrated stable qEEG patterns, particularly in delta and alpha bands, suggesting electrophysiological signatures of treatment resistance.

These findings reinforce the potential utility of qEEG not only for diagnostic support but also for longitudinal treatment monitoring and prognostic prediction. qEEG is a clinically practical and accessible tool. In addition to numerical values, it provides topographic brain maps that compare individual EEG data with age- and sex-adjusted normative databases. This allows clinicians to identify abnormal patterns and monitor their normalization over time, offering a convenient way to track treatment-related changes and state marker dynamics in routine practice. However, clinical integration requires further standardization. Future research should aim to replicate and extend these findings in larger and pharmacologically homogeneous cohorts.

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Ethical Statement

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Uskudar University (61351342/MAY 2023-20).

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Data Availability Statement

The data that support the findings of this study are not publicly available. However, the data are available on request from the corresponding author (M.K.A).

Supplemental Material

Supplemental material for this article is available online.

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Appendix

Table A1. Medications Prescribed at First and Later Visits Based on Response Groups.

	Medication on first visit			Medication in later visit		
Groups	Medications	N	Percent	Medications	N	Percent
Non-responder	Paroxetine	6	37.5	Paroxetine	6	37.5
	Venlafaxine	2	12.5	Venlafaxine	0	0.0
	Duloxetine	1	6.3	Duloxetine	4	25.0
	Sertraline	3	18.8	Sertraline	3	18.8
	TMS	4	25.0	TMS	3	18.8
	Total	16	100.0	Total	16	100.0
Responder	Paroxetine	29	53.7	Paroxetine	28	51.9
	Citalopram	3	5.6	Citalopram	3	5.6
	Venlafaxine	4	7.4	Venlafaxine	4	7.4
	Fluoxetine	2	3.7	Fluoxetine	2	3.7
	Duloxetine	7	13.0	Duloxetine	6	11.1
	Sertraline	6	11.1	Sertraline	5	9.3
	TMS	3	5.6	TMS	3	5.6
	Lamotrigine	0	0	Lamotrigine	3	5.6
	Total	54	100.0	Total	54	100.0

Note. Patients who received TMS included as they also received pharmacological treatment in parallel.