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Research paper

Gamma-band qEEG biomarkers as trait indicators in depression

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ABSTRACT

Background: Identifying trait biomarkers that reflect vulnerability to major depressive disorder (MDD), independent of acute symptom fluctuations, is critical for advancing early detection and personalized treatment. Quantitative electroencephalography (qEEG) offers a non-invasive, cost-effective method for assessing neural oscillations as potential trait markers.

Objective: To determine whether resting-state qEEG band power differs at baseline between recurrent and non-recurrent MDD patients and healthy controls (HCs), and whether these differences remain stable over repeated measurements.

Methods: Eighty-five outpatients with MDD (59 recurrent, 26 non-recurrent) and 67 HCs underwent three qEEG recordings: baseline (T0), mid-treatment (T1), and follow-up (T2) within approximately thirty months. One-way ANOVA, controlling for age and gender, compared baseline absolute qEEG power across groups. Bands showing significant differences were further examined using repeated-measures ANCOVA, adjusting for demographic and clinical covariates. Pearson correlations assessed associations between qEEG power and concurrent depression and anxiety severity.

Results: At baseline, absolute gamma power was significantly lower in both recurrent and non-recurrent MDD groups than in HCs across widespread regions. Other frequency bands showed no consistent group differences. Across repeated measures, gamma power remained stable with the most robust stability observed in midline-posterior regions. No significant correlations were found between gamma power and depression or anxiety severity.

Conclusions: The persistence of reduced gamma activity across sessions supports its candidacy as a trait biomarker for MDD, with limited region-specific state sensitivity. qEEG-based markers hold promises for enhancing diagnostic precision and guiding individualized interventions.

1. Introduction

The distinction between "trait markers" and "state markers" in psychiatry reflects a fundamental question regarding the classification of biological and psychological indicators of mental disorders, including Major Depressive Disorder (MDD). This conceptual differentiation was first introduced in the 1970s within the field of biological psychiatry, particularly in biomarker research for schizophrenia and depression. With the advancement of methods such as electroencephalography (EEG), hormonal assays, and neuroimaging, the trait-versus-state framework has become increasingly defined (Gruzelier et al., 2002).

In principle trait markers refer to stable, enduring biological or psychological characteristics that indicate vulnerability to psychopathology, whereas state markers reflect transient changes that occur during acute illness and typically resolve after recovery (Lema et al., 2018). Among biological indicators, several hormonal and neurodevelopmental markers such as brain-derived neurotrophic factor (BDNF) (Correia et al., 2023) and adrenocorticotropic hormone (ACTH) (Choi et al., 2018) have been reported to exhibit both trait- and state-like properties for depression. Similarly, although inflammatory markers such as IL-6, CRP, and TNF-α are often described as state-dependent (Paganin and Signorini, 2024), some evidence suggests they may also function as trait markers (Mandal et al., 2023). Anatomical findings such as reduced hippocampal volume, observed even during remission, have been proposed as potential trait markers due to their relative stability and only partial reversibility (Bremner et al., 2000). Genetic variants such as the 5-HTTLPR serotonin transporter polymorphism have also been suggested as trait-related factors (Fratelli et al., 2020).

Despite these findings, there remains a pressing need for biomarkers that are cost-effective, easily measurable, and suitable for routine

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clinical practice. In this regard, quantitative EEG (qEEG) presents a promising non-invasive modality. Several qEEG-based markers have been studied in the context of trait-versus-state characteristics in depression. For instance, frontal alpha asymmetry has been proposed as a trait marker because it has been observed in both currently depressed patients and individuals with a history of depression (Henriques and Davidson, 1990). However, replication studies have suggested that such patterns may be specific to certain subtypes of depression (Fitzgerald, 2024). Similarly, P300 amplitude reductions in event-related potentials have been considered potential diagnostic markers for depression (Arıkan et al., 2024), though they have generally been described as state-sensitive in MDD, but stable in conditions such as schizophrenia (Mathalon et al., 2000) and anhedonia (Santopetro et al., 2022).

As these examples illustrate, findings regarding qEEG markers with trait-like properties have been inconsistent. Therefore, establishing the trait validity of any candidate marker is essential. A reliable trait marker should first demonstrate a statistically significant difference between patients and healthy controls. Second, this marker should persist beyond the acute episode during remission and remain stable across repeated measures. To evaluate this, it is important to include both recurrent and non-recurrent patients and assess qEEG activity at multiple time points, spanning both acute and follow-up phases.

Accordingly, the present study aimed to compare baseline qEEG recordings between patients with recurrent and non-recurrent depression and healthy controls, and to examine whether qEEG abnormalities identified at baseline remain stable over time using repeated qEEG measurements during and after the acute treatment phase.

2. Methods

2.1. Participants

This study included patients diagnosed with MDD who were treated at a private psychiatric outpatient clinic over a 14-year period, alongside a sample of healthy controls (HC). All psychiatric evaluations and diagnostic interviews were conducted by the same psychiatrist. Diagnoses were established in accordance with the Diagnostic and Statistical Manual of Mental Disorders, Fourth (DSM-4) or Fifth Edition (DSM-5).

Inclusion criteria for the patient group were: (1) availability of qEEG data obtained at three separate time points, and (2) completion of the 17-item Hamilton Depression Rating Scale (HDRS-17) at each corresponding time point. Exclusion criteria were: (1) a history of comorbid psychiatric or neurological conditions (e.g., epilepsy, organic mental syndromes, intellectual disability, or major medical illnesses); (2) bipolar depression or psychotic features; (3) prior electroconvulsive therapy (ECT); and (4) alcohol or substance use disorders. Notably, comorbid anxiety was not considered an exclusion criterion, given its high prevalence in patients with MDD. Based on these criteria, 85 patients remained for the analysis among 2088 patients with MDD.

2.2. Recurrent vs. non-recurrent depression

The patients included were classified into recurrent or non-recurrent MDD groups based on retrospective chart review and clinical criteria. Recurrent depression was defined by either: (1) patient self-report of one or more past depressive episodes at the initial clinical assessment, or (2) documentation of remission (HDRS <7 for at least two months) followed by a return to a depressive state (HDRS >7) during the treatment period. Based on these criteria, 59 patients were classified as recurrent MDD and 26 as non-recurrent MDD.

2.3. Healthy control group

HC participants were recruited from a common work setting and provided with written informed consent. All were evaluated by the same

Table 1
Descriptives and statistics of clinical and demographic variables between groups.

Variables	Groups	Descriptive			Test
		N	*M*	*SD*	*p*
Age	Recurrent	59	43.07	13.77	0.256
	Non-Recurrent	26	39.46	12.26	
	Healthy Control	67	43.2	11.56	
HDRS-17 (T0)	Recurrent	59	20.5	7.6	0.151
	Non-Recurrent	26	17.7	8.51	
HDRS-17 (T1)	Recurrent	59	3.66	6.32	0.086
	Non-Recurrent	26	1.46	1.72	
HDRS-17 (T2)	Recurrent	59	5.33	6.32	0.005
	Non-Recurrent	26	0.73	1.72	
HARS (T0)	Recurrent	59	26.92	13.6	0.093
	Non-Recurrent	26	21.56	11.4	
HARS (T1)	Recurrent	59	4.92	9.49	0.152
	Non-Recurrent	26	1.66	2.83	
HARS (T2)	Recurrent	59	7.06	11.22	0.024
	Non-Recurrent	26	1.66	2.83	
Medication Load[a]	Recurrent	59	2.13	0.95	0.034
	Non-Recurrent	26	1.65	0.93	
Duration Between T0-T1 qEEG measurement (months)	Recurrent	59	12.2	12.2	0.034
	Non-Recurrent	26	3.61	6.31	
Duration Between T1-T2 qEEG measurement (months)	Recurrent	59	21.29	22.18	0.751
	Non-Recurrent	26	23.73	25.65	
Duration Between T0-T2 qEEG measurement (months)	Recurrent	59	33.94	29.95	0.135
	Non-Recurrent	26	23.73	25.65	
Categorical Variables					
Gender		Female	Male	X^2	*p*
	Recurrent	34	23	6.41	0.040
	Non-Recurrent	11	15		
	Healthy Control	25	42		
		Yes	No		
Comorbid Anxiety	Recurrent	44	15	5.50	0.019
	Non-Recurrent	25	1		
SSRI	Recurrent	48	11	0.22	0.638
	Non-Recurrent	20	6		
SNRI	Recurrent	29	30	1.543	0.214
	Non-Recurrent	9	17		
Atypic Antidepressants	Recurrent	17	42	0.864	0.353
	Non-Recurrent	5	21		
TMS	Recurrent	7	52	0.002	0.996
	Non-Recurrent	3	23		
Anticonvulsant	Recurrent	25	34	5.848	0.016
	Non-Recurrent	4	22		
Anxiolytic	Recurrent	13	46	0.740	0.390
	Non-Recurrent	8	18		

The medication load was calculated as the sum of all treatment attempts lasting at least four weeks between the T0 and T2 periods.
HDRS: Hamilton Depression Rating Scale. HARS: Hamilton Anxiety Rating Scale.

Table 2
Medications prescribed at baseline for MDD patients based on recurrence groups.

Medications	Non-Recurrent	Recurrent
Paroxetine	14	27
Escitalopram	0	6
Mirtazapine	1	6
Venlafaxine	0	5
Fluoxetine	0	1
Duloxetine	3	9
Sertraline	9	6
Lamotrigine	0	12
Amitriptyline	0	2
Trazodone	1	5
Alprazolam	1	2
Lorazepam	7	10
TMS	2	3

TMS: Transcranial Magnetic Stimulation.

psychiatrist to exclude any current or past psychiatric diagnoses. None had a history of psychotropic medication use or significant psychiatric symptoms. A total of 67 HCs included in the analysis.

2.4. Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. Written informed consent was obtained from all participants. The study protocol was reviewed and approved by the local ethics committee.

2.5. Procedure and data collection

At each clinical visit, patients underwent a psychiatric evaluation by the attending psychiatrist. On the same day, HDRS-17 was administered and resting-state qEEG recordings were acquired. Pharmacological treatment was initiated following the baseline assessments. Subsequent qEEG, HDRS-17, HARS measurements were collected during follow-up visits at different time intervals depending on clinical progression. Data were stored securely and transferred to SPSS (Version 29, IBM Corp.) for statistical analysis. The final dataset consisted of 85 patients with MDD and 67 healthy controls. Descriptive statistics of the sample are presented in Table 1. Medications used by both MDD groups were presented in Table 2.

2.6. qEEG acquisition

Baseline qEEG data were obtained prior to the initiation of

Table 3
Baseline qEEG absolute powers significantly different between HCs and both MDD groups.

Variable	F (df)	p	Eta Squared	ANOVA			ANCOVA	
				Recurrent-Non Recurrent	Healthy-Non-Recurrent	Healthy-Recurrent	Age	Gender
T6 Gamma	(21.250, 2)	0.000	0.208	0.949	0.000	0.000	0.874	0.507
T6 Gamma 1	(12.220, 2)	0.000	0.131	0.947	0.000	0.000	0.859	0.524
T6 Gamma 2	(27.191, 2)	0.000	0.251	0.873	0.000	0.000	0.870	0.729
T5 Gamma	(12.177, 2)	0.000	0.131	0.826	0.000	0.000	0.624	0.146
T5 Gamma 2	(15.496, 2)	0.000	0.161	0.819	0.000	0.000	0.690	0.182
T4 Gamma	(14.160, 2)	0.000	0.149	0.995	0.002	0.000	0.423	0.984
T4 Gamma 2	(17.029, 2)	0.000	0.174	0.976	0.001	0.000	0.316	0.889
T3 Gamma	(16.024, 2)	0.000	0.165	0.708	0.000	0.000	0.817	0.434
T3 Gamma 1	(10.059, 2)	0.000	0.11	0.618	0.000	0.002	0.753	0.588
T3 Gamma 2	(19.096, 2)	0.000	0.191	0.728	0.000	0.000	0.853	0.415
Pz Gamma	(21.090, 2)	0.000	0.207	0.900	0.000	0.000	0.996	0.245
Pz Gamma 1	(12.361, 2)	0.000	0.132	0.833	0.000	0.000	0.915	0.236
Pz Gamma 2	(24.812, 2)	0.000	0.234	0.923	0.000	0.000	0.945	0.396
P3 Gamma	(16.684, 2)	0.000	0.171	0.972	0.000	0.000	0.894	0.204
P3 Gamma 1	(8.574, 2)	0.000	0.096	0.960	0.003	0.001	0.977	0.247
P3 Gamma 2	(20.256, 2)	0.000	0.2	0.936	0.000	0.000	0.935	0.279
P4 Gamma	(22.257, 2)	0.000	0.216	0.988	0.000	0.000	0.981	0.405
P4 Gamma 1	(13.239, 2)	0.000	0.14	0.983	0.000	0.000	0.907	0.374
P4 Gamma 2	(26.796, 2)	0.000	0.249	0.974	0.000	0.000	0.915	0.650
O1 Gamma	(16.886, 2)	0.000	0.173	0.911	0.000	0.000	0.343	0.689
O1 Gamma 1	(9.322, 2)	0.000	0.103	0.823	0.000	0.002	0.374	0.777
O1 Gamma 2	(20.877, 2)	0.000	0.205	0.855	0.000	0.000	0.491	0.881
O2 Gamma	(20.024, 2)	0.000	0.198	0.837	0.000	0.000	0.951	0.727
O2 Gamma 1	(12.034, 2)	0.000	0.129	0.781	0.000	0.000	0.868	0.753
O2 Gamma 2	(23.326, 2)	0.000	0.224	0.868	0.000	0.000	0.725	0.924
Fz Gamma	(17.768, 2)	0.000	0.18	0.914	0.000	0.000	0.251	0.186
Fz Gamma 1	(8.734, 2)	0.000	0.097	0.877	0.002	0.002	0.193	0.206
Fz Gamma 2	(22.741, 2)	0.000	0.219	0.872	0.000	0.000	0.249	0.288
FP1 Gamma 2	(8.242, 2)	0.000	0.092	0.892	0.007	0.001	0.196	0.002
F7 Gamma	(4.126, 2)	0.000	0.108	0.995	0.004	0.001	0.853	0.003
F7 Gamma 2	(11.197, 2)	0.000	0.121	1.000	0.003	0.001	0.879	0.012
F4 Gamma	(11.646, 2)	0.000	0.126	0.642	0.000	0.001	0.338	0.053
F4 Gamma 2	(12.470, 2)	0.000	0.133	0.634	0.000	0.000	0.454	0.055
F3 Gamma 2	(8.908, 2)	0.000	0.099	0.995	0.003	0.005	0.285	0.027
Cz Gamma	(19.028, 2)	0.000	0.19	0.992	0.000	0.000	0.592	0.083
Cz Gamma 1	(10.770, 2)	0.000	0.117	0.987	0.001	0.000	0.501	0.081
Cz Gamma 2	(22.527, 2)	0.000	0.218	0.970	0.000	0.000	0.650	0.171
C4 Gamma	(12.162, 2)	0.000	0.131	0.997	0.001	0.000	0.575	0.266
C4 Gamma 1	(6.642, 2)	0.002	0.076	0.994	0.011	0.005	0.524	0.285
C4 Gamma 2	(12.952, 2)	0.000	0.138	0.989	0.000	0.000	0.604	0.375
C3 Gamma	(12.098, 2)	0.000	0.13	0.701	0.000	0.000	0.963	0.065
C3 Gamma 2	(12.986, 2)	0.000	0.138	0.658	0.000	0.000	0.974	0.098

Gamma: 30–40 Hz. Gamma 1: 30–35 Hz. Gamma 2: 35–40 Hz.

treatment. All recordings were conducted during midday hours in a quiet, temperature-controlled, and dimly lit room. EEG signals were collected using a 19-channel electro-cap positioned according to the International 10–20 system, covering the following electrode sites: FP1, F7, T3, T5, F3, C3, P3, O1, Fz, Cz, Pz, F4, C4, P4, O2, FP2, F8, T4, and T6. Conductive gel was applied at all sites to ensure optimal signal acquisition. The ground electrode was placed at FPz, and bilateral mastoid electrodes served as references. Electrode impedances were maintained below 5 kΩ.

Recordings were performed using the Neuron-Spectrum-4/P system (Neurosoft Inc.). During each session, participants were seated comfortably and instructed to remain still with their eyes closed. The protocol included 3 min of resting-state recording (eyes closed), followed by 30 s of eyes-open recording, and a subsequent 3.5 min of eyes-closed resting-state data acquisition. The sampling rate was set at 500 Hz.

2.7. qEEG analysis

The raw qEEG recordings were stored in European Data Format (EDF). Artifacts, such as muscle movements, were removed using NeuroGuide software 33 (NeuroGuide Deluxe v3.8.2; Applied Neuroscience, Inc.). The software's automated artifact rejection tool was used with a 1.5 standard deviation threshold for eye movement and drowsiness artifacts. Samples containing artifacts were discarded, ensuring that at least three minutes of artifact-free, closed-eye data were retained for each participant. Absolute power was computed for the following frequency bands: delta (1–4 Hz), theta (4–7 Hz), alpha (8–12 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta (12–25 Hz), beta1 (12–15 Hz), beta2 (15–18 Hz), beta3 (18–25 Hz), high beta (25–30 Hz), gamma (30–40 Hz), gamma 1 (30–35 Hz), gamma 2 (35–40 Hz).

2.8. Statistical analysis

2.8.1. QEEG log transformation

All statistical analyses were conducted using IBM SPSS Statistics version 29. Descriptive statistics were computed for demographic and clinical variables. Normality of EEG data was assessed using the Shapiro-Wilk test. The absolute power was log-transformed to achieve normality. Some qEEG variables had values between 0 and 1 which would produce negative values when transformed. Therefore, 1 was added to all qEEG results before log-transformation was applied. The normality of the distribution of data was determined based on log-transformation results.

2.8.2. Comparison of clinical and demographic variables

Clinical variables, i.e., HDRS scores, HARS scores, duration between T0-T1-T2 period (months), medication load were compared with recurrent and non-recurrent MDD with independent sample test. The medication load was calculated as the sum of all treatment attempts lasting at least four weeks for pharmacotherapy or at least 20 sessions for TMS between the T0 and T2 periods. HCs were included in age and gender comparison. Differences in categorical variables (e.g., gender, comorbid anxiety, SSRI, SNRI, atypical antidepressant, anticonvulsant, anxiolytic medication and TMS treatments) were examined with chi-square test. The threshold for statistical significance was 0.05.

2.8.3. Statistical analysis for trait marker

To identify candidate trait markers, a two-step analytic strategy was employed:

1. Group-level comparison (T0 Baseline):
   One-way ANOVA was used to compare baseline (T0) absolute qEEG power values across three groups: recurrent MDD, non-recurrent MDD, and healthy controls. Bonferroni correction was applied to correct for multiple comparisons. For 19 electrodes and 6 main and 7 sub-frequency bands, totaling 247 comparisons, Bonferroni-corrected significance threshold was set at $p < .00020$. Post-hoc comparisons were conducted using Bonferroni test (Table S1). Among them, the qEEG electrode-band pairs that significantly differed between both patient groups and HCs were adjusted for age and gender and selected as trait marker candidates (Table 3).
   One-way ANOVA was used to compare baseline (T0) absolute qEEG power values across three groups: recurrent MDD, non-recurrent MDD, and healthy controls. Bonferroni correction was applied to correct for multiple comparisons. For 19 electrodes and 6 main and 7 sub-frequency bands, totaling 247 comparisons, Bonferroni-corrected significance threshold was set at $p < .00020$. Post-hoc comparisons were conducted using Bonferroni test (Table S1). Among them, the qEEG electrode-band pairs that significantly differed between both patient groups and HCs were adjusted for age and gender and selected as trait marker candidates (Table 3).
2. Stability overtime (Within-Group Analysis):
   Repeated measures ANOVA were performed to evaluate the temporal stability of each candidate qEEG marker across three time points (T0, T1, T2). Time was treated as a within-subjects factor, and recurrence status (recurrent vs. non-recurrent) was entered as a between-subjects factor. Covariates included age, gender, baseline HDRS scores, medication load, the time interval between qEEG recordings, comorbid anxiety, and anticonvulsant use. Sphericity was tested using Mauchly's test; if violated, Greenhouse-Geisser corrections were applied. Effect sizes were reported using partial eta-squared (η^2).
3. Correlation analysis:
   Additionally, Pearson's correlation analyses were conducted to examine associations between qEEG band power and HDRS-17 and HARS scores at each time point, in order to evaluate state-related variability.

A significant threshold of $p < .05$ was applied throughout. qEEG absolute powers in certain electrode-band pairs that differed from controls and remained stable across time and symptom severity were interpreted as supporting trait-like characteristics.

3. Results

3.1. Clinical results

The results of clinical and demographic variables can be reached from Table 1. A total of 152 participants were included: 59 with recurrent major depressive disorder (MDD), 26 with non-recurrent MDD, and 67 healthy controls. The three groups did not significantly differ in terms of age ($p = .256$).

Depression severity, as measured by HDRS-17 and baseline anxiety severity, as measured by HARS, at baseline (T0) and during earlier treatment phase (T1) did not statistically differ between MDD groups ($p = .151$). However, a significant difference emerged at follow-up assessments. At T2, the recurrent group showed significantly higher HDRS scores (M = 5.33, SD = 6.32) compared to the non-recurrent group (M = 0.73, SD = 1.72), indicating greater residual depressive symptoms over time ($p = .005$). Similarly, the recurrent group again had significantly elevated anxiety levels (M = 7.06, SD = 11.22) relative to the non-recurrent group (M = 1.66, SD = 2.83) at T2 ($p = .024$).

The mean interval between qEEG assessments T0 and T1 was significantly longer ($p = .034$) in the recurrent group (M = 12.20 months, SD = 12.20) than in the non-recurrent group (M = 3.61 months, SD = 6.31), although the total follow-up duration (T0–T2) did not significantly differ ($p = .135$).

Medication load was also higher (p = .034) in recurrent group (M = 2.13, SD = 0.95) than in the non-recurrent group (M = 1.65, SD = 0.93).

For categorical variables, a significant gender distribution difference

Table 4
Repeated measures ANOVA result for qEEG Gamma (30–40 Hz), Gamma 1 (30–35 Hz), and Gamma 2 (35–40 Hz) characteristics over three measurements across recurrent and non-recurrent MDD groups.

Time Point	Group	Mean	SD	N	Effect	F	df	*p*-value*	Partial η^2
C3 Gamma									
1st EEG	Non-recurrent	0.699	0.423	26	Time	2.236	2, 74	0.111	0.029
1st EEG	Recurrent	0.828	0.663	57	Time * Age	1.010	2, 74	0.367	0.013
2nd EEG	Non-recurrent	0.962	0.789	26	Time * Gender	1.924	2, 74	0.150	0.025
2nd EEG	Recurrent	0.919	0.801	57	Time * HDRS	0.042	2, 74	0.958	0.001
3rd EEG	Non-recurrent	1.028	0.495	26	Time * Medication Load	0.863	2, 74	0.424	0.012
3rd EEG	Recurrent	1.129	0.752	57	Time * Duration T0-T1	1.676	2, 74	0.191	0.022
					Time * Duration T1-T2	1.683	2, 74	0.189	0.022
					Time * Duration T0-T2	1.726	2, 74	0.182	0.023
					Time * Comorbid Anxiety	0.308	2, 74	0.735	0.004
					Time * Anticonvulsant	3.065	2, 74	0.050	0.040
					Time * Recurrence	1.390	2, 74	0.252	0.018
C4-Gamma									
1st EEG	Non-recurrent	0.755	0.527	26	Time	2.628	2164	0.076	0.034
1st EEG	Recurrent	0.771	0.603	57	Time * Age	1.387	2164	0.253	0.018
2nd EEG	Non-recurrent	0.873	0.6	26	Time * Gender	1.425	2164	0.244	0.019
2nd EEG	Recurrent	0.872	0.652	57	Time * HDRS	0.566	2164	0.569	0.008
3rd EEG	Non-recurrent	1.027	0.521	26	Time * Medication Load	1.266	2164	0.285	0.017
3rd EEG	Recurrent	1.087	0.648	57	Time * Duration T0-T1	1.770	2164	0.174	0.023
					Time * Duration T1-T2	1.768	2164	0.176	0.023
					Time * Duration T0-T2	1.854	2164	0.162	0.024
					Time * Comorbid Anxiety	0.113	2164	0.893	0.002
					Time * Anticonvulsant	2.114	2164	0.124	0.028
					Time * Recurrence	0.534	2164	0.588	0.007
F7-Gamma									
1st EEG	Non-recurrent	0.902	0.634	26	Time	1.347	2164	0.263	0.018
1st EEG	Recurrent	0.974	0.75	57	Time * Age	0.309	2164	0.735	0.004
2nd EEG	Non-recurrent	0.913	0.623	26	Time * Gender	1.017	2164	0.364	0.014
2nd EEG	Recurrent	1.11	0.877	57	Time * HDRS	0.607	2164	0.546	0.008
3rd EEG	Non-recurrent	1.113	0.667	26	Time * Medication Load	1.210	2164	0.301	0.016
3rd EEG	Recurrent	1.245	0.864	57	Time * Duration T0-T1	0.848	2164	0.430	0.011
					Time * Duration T1-T2	0.887	2164	0.414	0.012
					Time * Duration T0-T2	0.933	2164	0.396	0.012
					Time * Comorbid Anxiety	0.394	2164	0.675	0.005
					Time * Anticonvulsant	1.418	2164	0.245	0.019
					Time * Recurrence	0.051	2164	0.950	0.001
	O1-Gamma								
1st EEG	Non-recurrent	0.686	0.383	26	Time	2.406	2164	0.094	0.031
1st EEG	Recurrent	0.709	0.437	57	Time * Age	5.050	2164	0.008	0.064
2nd EEG	Non-recurrent	0.753	0.472	26	Time * Gender	0.356	2164	0.701	0.005
2nd EEG	Recurrent	0.793	0.667	57	Time * HDRS	0.028	2164	0.973	0.000
3rd EEG	Non-recurrent	0.858	0.334	26	Time * Medication Load	0.599	2164	0.550	0.008
3rd EEG	Recurrent	0.98	0.559	57	Time * Duration T0-T1	0.423	2164	0.656	0.006
					Time * Duration T1-T2	0.479	2164	0.620	0.006
					Time * Duration T0-T2	0.458	2164	0.633	0.006
					Time * Comorbid Anxiety	0.359	2164	0.699	0.005
					Time * Anticonvulsant	1.152	2164	0.319	0.015
					Time * Recurrence	1.085	2164	0.340	0.014
	O2-Gamma								
1st EEG	Non-recurrent	0.628	0.39	26	Time	2.734	1.838,164	0.073	0.036
1st EEG	Recurrent	0.745	0.544	57	Time * Age	3.344	1.838,164	0.042	0.043
2nd EEG	Non-recurrent	0.747	0.47	26	Time * Gender	0.561	1.838,164	0.572	0.008
2nd EEG	Recurrent	0.772	0.501	57	Time * HDRS	0.079	1.838,164	0.924	0.001
3rd EEG	Non-recurrent	0.821	0.278	26	Time * Medication Load	1.545	1.838,164	0.217	0.020
3rd EEG	Recurrent	0.962	0.518	57	Time * Duration T0-T1	0.684	1.838,164	0.495	0.009
					Time * Duration T1-T2	0.685	1.838,164	0.506	0.009
					Time * Duration T0-T2	0.755	1.838,164	0.472	0.010
					Time * Comorbid Anxiety	0.372	1.838,164	0.672	0.005
					Time * Anticonvulsant	1.469	1.838,164	0.233	0.019
					Time * Recurrence	0.651	1.838,164	0.523	0.009
	P3-Gamma								
1st EEG	Non-recurrent	0.626	0.361	26	Time	2.629	2164	0.076	0.034
1st EEG	Recurrent	0.701	0.481	57	Time * Age	1.469	2164	0.233	0.019
2nd EEG	Non-recurrent	0.764	0.529	26	Time * Gender	1.571	2164	0.212	0.021
2nd EEG	Recurrent	0.739	0.56	57	Time * HDRS	0.204	2164	0.815	0.003

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Table 4 (*continued*)

Time Point	Group	Mean	SD	N	Effect	F	df	*p*-value*	Partial η^2
3rd EEG	Non-recurrent	0.825	0.274	26	Time * Medication Load	1.676	2164	0.191	0.022
3rd EEG	Recurrent	0.893	0.5	57	Time * Duration T0-T1	1.316	2164	0.271	0.017
					Time * Duration T1-T2	1.358	2164	0.260	0.018
					Time * Duration T0-T2	1.384	2164	0.254	0.018
					Time * Comorbid Anxiety	0.126	2164	0.882	0.002
					Time * Anticonvulsant	4.370	2164	0.015	0.056
					Time * Recurrence	1.265	2164	0.285	0.017
T3-Gamma									
1st EEG	Non-recurrent	0.679	0.418	26	Time	1.218	2164	0.299	0.016
1st EEG	Recurrent	0.878	0.698	57	Time * Age	0.360	2164	0.698	0.005
2nd EEG	Non-recurrent	1.004	0.836	26	Time * Gender	2.291	2164	0.108	0.030
2nd EEG	Recurrent	0.975	0.851	57	Time * HDRS	0.105	2164	0.901	0.001
3rd EEG	Non-recurrent	1.024	0.591	26	Time * Medication Load	1.520	2164	0.222	0.020
3rd EEG	Recurrent	1.178	0.719	57	Time * Duration T0-T1	1.463	2164	0.235	0.019
					Time * Duration T1-T2	1.461	2164	0.236	0.019
					Time * Duration T0-T2	1.519	2164	0.222	0.020
					Time * Comorbid Anxiety	0.194	2164	0.823	0.003
					Time * Anticonvulsant	3.544	2164	0.034	0.046
					Time * Recurrence	1.171	2164	0.313	0.016
T4-Gamma									
1st EEG	Non-recurrent	0.762	0.604	26	Time	1.361	2164	0.259	0.018
1st EEG	Recurrent	0.818	0.673	57	Time * Age	0.049	2164	0.952	0.001
2nd EEG	Non-recurrent	0.974	0.644	26	Time * Gender	0.003	2164	0.997	0.000
2nd EEG	Recurrent	0.921	0.719	57	Time * HDRS	1.098	2164	0.336	0.015
3rd EEG	Non-recurrent	0.984	0.519	26	Time * Medication Load	1.335	2164	0.266	0.018
3rd EEG	Recurrent	1.181	0.731	57	Time * Duration T0-T1	1.225	2164	0.297	0.016
					Time * Duration T1-T2	1.261	2164	0.286	0.017
					Time * Duration T0-T2	1.313	2164	0.272	0.017
					Time * Comorbid Anxiety	0.817	2164	0.444	0.011
					Time * Anticonvulsant	1.682	2164	0.190	0.022
					Time * Recurrence	0.941	2164	0.393	0.013
C4-Gamma 1									
1st EEG	Non-recurrent	0.5659	0.3841	26	Time	2.084	2164	0.128	0.027
1st EEG	Recurrent	0.5916	0.4539	57	Time * Age	1.009	2164	0.367	0.013
2nd EEG	Non-recurrent	0.6302	0.4237	26	Time * Gender	1.061	2164	0.349	0.014
2nd EEG	Recurrent	0.6694	0.4888	57	Time * HDRS	0.455	2164	0.635	0.006
3rd EEG	Non-recurrent	0.7219	0.3864	26	Time * Medication Load	1.324	2164	0.269	0.018
3rd EEG	Recurrent	0.7829	0.4855	57	Time * Duration T0-T1	1.256	2164	0.288	0.017
					Time * Duration T1-T2	1.253	2164	0.289	0.017
					Time * Duration T0-T2	1.311	2164	0.272	0.017
					Time * Comorbid Anxiety	0.117	2164	0.889	0.002
					Time * Anticonvulsant	2.361	2164	0.102	0.031
					Time * Recurrence	0.252	2164	0.778	0.003
P3-Gamma 1									
1st EEG	Non-recurrent	0.46	0.295	26	Time	2.215	2164	0.113	0.029
1st EEG	Recurrent	0.532	0.347	57	Time * Age	1.168	2164	0.314	0.016
2nd EEG	Non-recurrent	0.537	0.36	26	Time * Gender	1.006	2164	0.368	0.013
2nd EEG	Recurrent	0.563	0.419	57	Time * HDRS	0.143	2164	0.867	0.002
3rd EEG	Non-recurrent	0.569	0.218	26	Time * Medication Load	1.956	2164	0.145	0.026
3rd EEG	Recurrent	0.631	0.303	57	Time * Duration T0-T1	0.746	2164	0.476	0.010
					Time * Duration T1-T2	0.785	2164	0.458	0.010
					Time * Duration T0-T2	0.780	2164	0.460	0.010
					Time * Comorbid Anxiety	0.123	2164	0.884	0.002
					Time * Anticonvulsant	5.042	2164	0.008	0.064
					Time * Recurrence	0.660	2164	0.518	0.009
T3-Gamma 1									
1st EEG	Non-recurrent	0.473	0.267	26	Time	1.028	2164	0.360	0.014
1st EEG	Recurrent	0.663	0.531	57	Time * Age	0.201	2164	0.818	0.003
2nd EEG	Non-recurrent	0.713	0.628	26	Time * Gender	1.651	2164	0.197	0.022
2nd EEG	Recurrent	0.739	0.701	57	Time * HDRS	0.099	2164	0.906	0.001
3rd EEG	Non-recurrent	0.683	0.472	26	Time * Medication Load	2.480	2164	0.087	0.032
3rd EEG	Recurrent	0.792	0.575	57	Time * Duration T0-T1	0.737	2164	0.480	0.010
					Time * Duration T1-T2	0.754	2164	0.472	0.010
					Time * Duration T0-T2	0.771	2164	0.464	0.010
					Time * Comorbid Anxiety	0.178	2164	0.837	0.002
					Time * Anticonvulsant	4.544	2164	0.014	0.058
					Time * Recurrence	0.944	2164	0.392	0.013

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Table 4 (*continued*)

Time Point	Group	Mean	SD	N	Effect	F	df	*p*-value*	Partial η^2
O1-Gamma 1									
1st EEG	Non-recurrent	0.508	0.263	26	Time	1.484	1.793,164	0.231	0.020
1st EEG	Recurrent	0.597	0.419	57	Time * Age	3.900	1.793,164	0.027	0.050
2nd EEG	Non-recurrent	0.577	0.346	26	Time * Gender	0.186	1.793,164	0.807	0.003
2nd EEG	Recurrent	0.581	0.402	57	Time * HDRS	0.117	1.793,164	0.890	0.002
3rd EEG	Non-recurrent	0.628	0.353	26	Time * Medication Load	0.393	1.793,164	0.653	0.005
3rd EEG	Recurrent	0.675	0.458	57	Time * Duration T0-T1	0.359	1.793,164	0.676	0.005
					Time * Duration T1-T2	0.412	1.793,164	0.641	0.006
					Time * Duration T0-T2	0.366	1.793,164	0.671	0.005
					Time * Comorbid Anxiety	0.383	1.793,164	0.682	0.005
					Time * Anticonvulsant	1.000	1.793,164	0.363	0.013
					Time * Recurrence	0.706	1.793,164	0.409	0.009
O2-Gamma-1									
1st EEG	Non-recurrent	0.46	0.295	26	Time	1.964	1.755,164	0.150	0.026
1st EEG	Recurrent	0.567	0.403	57	Time * Age	2.250	1.755,164	0.116	0.030
2nd EEG	Non-recurrent	0.517	0.307	26	Time * Gender	0.216	1.755,164	0.806	0.003
2nd EEG	Recurrent	0.576	0.352	57	Time * HDRS	0.013	1.755,164	0.987	0.000
3rd EEG	Non-recurrent	0.561	0.229	26	Time * Medication Load	1.391	1.755,164	0.252	0.018
3rd EEG	Recurrent	0.682	0.36	57	Time * Duration T0-T1	0.405	1.755,164	0.641	0.005
					Time * Duration T1-T2	0.407	1.755,164	0.640	0.005
					Time * Duration T0-T2	0.453	1.755,164	0.611	0.006
					Time * Comorbid Anxiety	0.334	1.755,164	0.688	0.004
					Time * Anticonvulsant	1.445	1.755,164	0.240	0.019
					Time * Recurrence	0.265	1.755,164	0.739	0.004
FP1 Gamma 2									
1st EEG	Non-recurrent	0.412	0.358	26	Time	2.204	2148	0.114	0.029
1st EEG	Recurrent	0.479	0.502	59	Time * Age	1.721	2148	0.183	0.023
2nd EEG	Non-recurrent	0.465	0.419	26	Time * Gender	0.61	2148	0.537	0.008
2nd EEG	Recurrent	0.649	0.79	59	Time * HDRS	0.76	2148	0.469	0.01
3rd EEG	Non-recurrent	0.567	0.359	26	Time * Medication Load	1.002	2148	0.369	0.013
3rd EEG	Recurrent	0.812	0.785	59	Time * Duration T0–T1	0.716	2148	0.4	0.01
					Time * Duration T1–T2	0.666	2148	0.515	0.009
					Time * Duration T0–T2	0.744	2148	0.471	0.01
					Time * Comorbid Anxiety	0.225	2148	0.799	0.003
					Time * Anticonvulsant	0.293	2148	0.747	0.004
					Time * Recurrence	0.049	2148	0.952	0.001
F3-Gamma 2									
1st EEG	Non-recurrent	0.411	0.358	26	Time	2.793	2164	0.064	0.036
1st EEG	Recurrent	0.458	0.471	57	Time * Age	1.630	2164	0.199	0.022
2nd EEG	Non-recurrent	0.464	0.418	26	Time * Gender	0.248	2164	0.781	0.003
2nd EEG	Recurrent	0.63	0.792	57	Time * HDRS	0.356	2164	0.701	0.005
3rd EEG	Non-recurrent	0.566	0.359	26	Time * Medication Load	0.898	2164	0.409	0.012
3rd EEG	Recurrent	0.805	0.601	57	Time * Duration T0-T1	1.517	2164	0.224	0.020
					Time * Duration T1-T2	1.483	2164	0.230	0.020
					Time * Duration T0-T2	1.578	2164	0.210	0.021
					Time * Comorbid Anxiety	0.688	2164	0.504	0.009
					Time * Anticonvulsant	1.709	2164	0.185	0.023
					Time * Recurrence	0.838	2164	0.435	0.011
F7 – Gamma 2									
1st EEG	Non-recurrent	0.541	0.515	26	Time	1.230	2164	0.295	0.016
1st EEG	Recurrent	0.653	0.613	57	Time * Age	0.293	2164	0.747	0.004
2nd EEG	Non-recurrent	0.541	0.556	26	Time * Gender	0.773	2164	0.464	0.010
2nd EEG	Recurrent	0.723	0.742	57	Time * HDRS	0.177	2164	0.838	0.002
3rd EEG	Non-recurrent	0.715	0.585	26	Time * Medication Load	1.184	2164	0.308	0.016
3rd EEG	Recurrent	0.869	0.704	57	Time * Duration T0-T1	1.224	2164	0.297	0.016
					Time * Duration T1-T2	1.263	2164	0.286	0.017
					Time * Duration T0-T2	1.324	2164	0.269	0.018
					Time * Comorbid Anxiety	0.621	2164	0.539	0.008
					Time * Anticonvulsant	1.336	2164	0.266	0.018
					Time * Recurrence	0.011	2164	0.989	0.000
C3-Gamma 2									
1st EEG	Non-recurrent	0.573	0.661	26	Time	1.667	2148	0.192	0.022
1st EEG	Recurrent	0.5	0.67	57	Time * Age	0.367	2148	0.694	0.005
2nd EEG	Non-recurrent	0.573	0.661	26	Time * Gender	2.200	2148	0.114	0.029
2nd EEG	Recurrent	0.5	0.67	57	Time * HDRS	0.040	2148	0.961	0.001
3rd EEG	Non-recurrent	0.601	0.407	26	Time * Medication Load	0.664	2148	0.516	0.009
3rd EEG	Recurrent	0.685	0.637	57	Time * Duration T0-T1	1.978	2148	0.142	0.026

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Table 4 (*continued*)

Time Point	Group	Mean	SD	N	Effect	F	df	*p*-value*	Partial η^2
					Time * Duration T1-T2	1.979	2148	0.142	0.026
					Time * Duration T0-T2	2.040	2148	0.134	0.027
					Time * Comorbid Anxiety	0.593	2148	0.554	0.008
					Time * Anticonvulsant	2.444	2148	0.090	0.032
					Time * Recurrence	1.846	2148	0.161	0.024
C4-Gamma 2									
1st EEG	Non-recurrent	0.366	0.378	26	Time	2.426	2148	0.092	0.032
1st EEG	Recurrent	0.413	0.556	57	Time * Age	0.975	2148	0.380	0.013
2nd EEG	Non-recurrent	0.489	0.468	26	Time * Gender	1.680	2148	0.190	0.022
2nd EEG	Recurrent	0.447	0.506	57	Time * HDRS	0.526	2148	0.592	0.007
3rd EEG	Non-recurrent	0.596	0.434	26	Time * Medication Load	1.380	2148	0.255	0.018
3rd EEG	Recurrent	0.639	0.571	57	Time * Duration T0-T1	1.673	2148	0.191	0.022
					Time * Duration T1-T2	1.696	2148	0.187	0.022
					Time * Duration T0-T2	1.763	2148	0.175	0.023
					Time * Comorbid Anxiety	0.135	2148	0.873	0.002
					Time * Anticonvulsant	1.861	2148	0.159	0.025
					Time * Recurrence	0.807	2148	0.448	0.011
P3-Gamma 2									
1st EEG	Non-recurrent	0.277	0.228	26	Time	1.917	2148	0.151	0.025
1st EEG	Recurrent	0.315	0.384	57	Time * Age	0.569	2148	0.567	0.008
2nd EEG	Non-recurrent	0.419	0.419	26	Time * Gender	1.745	2148	0.178	0.023
2nd EEG	Recurrent	0.353	0.414	57	Time * HDRS	0.178	2148	0.837	0.002
3rd EEG	Non-recurrent	0.428	0.194	26	Time * Medication Load	1.620	2148	0.201	0.021
3rd EEG	Recurrent	0.492	0.368	57	Time * Duration T0-T1	1.478	2148	0.231	0.020
					Time * Duration T1-T2	1.527	2148	0.221	0.020
					Time * Duration T0-T2	1.566	2148	0.212	0.021
					Time * Comorbid Anxiety	0.204	2148	0.816	0.003
					Time * Anticonvulsant	3.114	2148	0.047	0.040
					Time * Recurrence	1.982	2148	0.141	0.026
P4-Gamma 2									
1st EEG	Non-recurrent	0.272	0.236	26	Time	2.677	2148	0.072	0.035
1st EEG	Recurrent	0.289	0.316	57	Time * Age	1.332	2148	0.267	0.018
2nd EEG	Non-recurrent	0.381	0.338	26	Time * Gender	1.485	2148	0.230	0.020
2nd EEG	Recurrent	0.333	0.339	57	Time * HDRS	0.330	2148	0.720	0.004
3rd EEG	Non-recurrent	0.439	0.227	26	Time * Medication Load	2.293	2148	0.105	0.030
3rd EEG	Recurrent	0.482	0.324	57	Time * Duration T0-T1	1.437	2148	0.241	0.019
					Time * Duration T1-T2	1.472	2148	0.233	0.019
					Time * Duration T0-T2	1.553	2148	0.215	0.021
					Time * Comorbid Anxiety	0.043	2148	0.958	0.001
					Time * Anticonvulsant	2.596	2148	0.078	0.034
					Time * Recurrence	1.471	2148	0.233	0.019
T3-Gamma 2									
1st EEG	Non-recurrent	0.345	0.316	26	Time	1.059	2148	0.349	0.014
1st EEG	Recurrent	0.457	0.568	57	Time * Age	0.083	2148	0.920	0.001
2nd EEG	Non-recurrent	0.643	0.699	26	Time * Gender	2.637	2148	0.075	0.034
2nd EEG	Recurrent	0.565	0.753	57	Time * HDRS	0.136	2148	0.873	0.002
3rd EEG	Non-recurrent	0.639	0.473	26	Time * Medication Load	0.976	2148	0.379	0.013
3rd EEG	Recurrent	0.759	0.675	57	Time * Duration T0–T1	1.785	2148	0.171	0.024
					Time * Duration T1–T2	1.761	2148	0.175	0.023
					Time * Duration T0–T2	1.836	2148	0.163	0.024
					Time * Comorbid Anxiety	0.074	2148	0.929	0.001
					Time * Anticonvulsant	2.514	2148	0.084	0.033
					Time * Recurrence	1.258	2148	0.287	0.017
T4 Gamma 2									
1st EEG	Non-recurrent	0.434	0.515	26	Time	1.364	2148	0.259	0.018
1st EEG	Recurrent	0.456	0.577	59	Time * Age	0.154	2148	0.857	0.002
2nd EEG	Non-recurrent	0.559	0.505	26	Time * Gender	0.069	2148	0.933	0.001
2nd EEG	Recurrent	0.555	0.62	59	Time * HDRS	0.959	2148	0.386	0.013
3rd EEG	Non-recurrent	0.581	0.391	26	Time * Medication Load	1.772	2148	0.174	0.023
3rd EEG	Recurrent	0.771	0.665	59	Time * Duration T0–T1	1.406	2148	0.248	0.019
					Time * Duration T1–T2	1.48	2148	0.231	0.020
					Time * Duration T0–T2	1.513	2148	0.224	0.020
					Time * Comorbid Anxiety	0.718	2148	0.490	0.010
					Time * Anticonvulsant	2.04	2148	0.134	0.027
					Time * Recurrence	0.736	2148	0.481	0.010
T5 Gamma 2									

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Table 4 (*continued*)

Time Point	Group	Mean	SD	N	Effect	F	df	*p*-value*	Partial η^2
1st EEG	Non-recurrent	0.280	0.237	26	Time	1.956	2148	0.145	0.026
1st EEG	Recurrent	0.384	0.472	59	Time * Age	0.388	2148	0.679	0.005
2nd EEG	Non-recurrent	0.420	0.461	26	Time * Gender	0.43	2148	0.651	0.006
2nd EEG	Recurrent	0.410	0.470	59	Time * HDRS	0.139	2148	0.871	0.002
3rd EEG	Non-recurrent	0.447	0.229	26	Time * Medication Load	2.146	2148	0.121	0.028
3rd EEG	Recurrent	0.543	0.486	59	Time * Duration T0–T1	2.256	2148	0.109	0.030
					Time * Duration T1–T2	2.218	2148	0.112	0.029
					Time * Duration T0–T2	2.355	2148	0.099	0.031
					Time * Comorbid Anxiety	0.192	2148	0.825	0.003
					Time * Anticonvulsant	1.658	2148	0.194	0.022
					Time * Recurrence	1.512	2148	0.224	0.020

was also observed across groups ($\chi^2 = 6.41$, $p = .040$), with a higher proportion of males in the non-recurrent MDD group and healthy controls. Comorbid anxiety was more prevalent in the non-recurrent group (74.6 %) compared to the non-recurrent group (96.2 %), and this difference was statistically significant ($\chi^2 = 5.50$, $p = .019$).

No significant differences were observed for SSRI use ($\chi^2 = 0.22$, $p = .638$), SNRI use ($\chi^2 = 1.54$, $p = .214$), atypical antidepressant use ($\chi^2 = 0.86$, $p = .353$), TMS treatment ($\chi^2 = 0.002$, $p = .996$), or anxiolytic use ($\chi^2 = 0.74$, $p = .390$). In contrast, anticonvulsant use was significantly higher in the recurrent group compared to the non-recurrent group, $\chi^2(1) = 5.85$, $p = .016$ (Table 1).

3.2. Baseline qEEG comparison among HCs, recurrent MDD, and non-recurrent MDD

A one-way ANOVA was conducted to assess group differences in baseline resting-state absolute qEEG power among recurrent MDD patients, non-recurrent MDD patients, and healthy controls. To be a candidate trait marker, pairwise comparison must show significant differences between both HC-recurrent MDD and HC-non-recurrent MDD, but both depressive groups should not differ between each other.

Among 19 electrodes, 6 main frequency bands and 7 sub-frequency bands, group differences were specifically observed in gamma-related frequency bands (gamma, gamma1, gamma2), while no consistent differences emerged across delta, theta, alpha, or beta bands (Table S1).

As depicted in Table 3, baseline qEEG analyses revealed robust group effects for gamma-band absolute power across multiple electrode sites (all $ps < 0.001$; $\eta^2 = 0.076–0.251$). Post-hoc tests indicated that these differences were consistently driven by significantly lower gamma power in both recurrent and non-recurrent MDD groups compared with healthy controls (all $ps \leq 0.005$), whereas no significant differences emerged between the two MDD subgroups (all $ps > 0.60$). These effects were observed across the full gamma range (30–40 Hz) as well as the sub-bands gamma1 (30–35 Hz) and gamma2 (35–40 Hz), with the largest effect sizes ($\eta^2 = 0.140–0.251$) at posterior (T3, T4, T5, T6, P3, P4, O1, O2) and midline (Pz, Cz, Fz) sites.

ANCOVA controlling for age and gender demonstrated that the main effects of group remained significant for all identified sites (Table 3). Neither age nor gender were significant covariates for most electrodes (all $ps > 0.05$), except for isolated findings: gender effects at FP1 gamma-2 ($p = .002$), F7 gamma ($p = .003$) and gamma-2 ($p = .012$), and F3 gamma-2 ($p = .027$).

Overall, these results indicate that reduced gamma-band activity, particularly in temporo-parietal and occipital regions, differentiates both recurrent and non-recurrent MDD patients from healthy individuals, independent of demographic covariates.

3.3. Repeated Measure ANOVA comparison between MDD groups

Repeated measures ANOVAs were performed to assess longitudinal changes in absolute gamma (30–40 Hz), gamma 1 (30–35 Hz), and gamma 2 (35–40 Hz) power across three qEEG recordings in recurrent and non-recurrent MDD patients, controlling for age, gender, baseline HDRS scores, medication load, time intervals between recordings, comorbid anxiety, and anticonvulsant use (Table 4). After excluding electrodes that showed a significant main effect of time in the repeated measures ANOVA (Cz, F4, Fz, P4, Pz, T5, and T6 for broad gamma; Cz, P4, Pz, and T6 for gamma1; and F4, Fz, Cz, Pz, and T6 for gamma2), subsequent results on the remaining sites were reported to focus on temporally stable qEEG measures.

3.3.1. Results for qEEG Gamma (30–40 Hz) absolute power

Across most electrodes, no significant main effects of time were observed for broad gamma power after controlling for age, gender, baseline HDRS, medication load, time intervals between recordings, comorbid anxiety, and anticonvulsant use. Significant time × anticonvulsant interactions were found at C3-gamma ($F(2,74) = 3.07$, $p = .050$), P3-gamma ($F(2,164) = 4.37$, $p = .015$), and T3-gamma ($F(2,164) = 3.54$, $p = .034$). Age significantly moderate changes at O1-gamma ($F(2,164) = 5.05$, $p = .008$) and O2-gamma ($F(1.84,164) = 3.34$, $p = .042$). No time × recurrence effects were detected (Table 4).

3.3.2. Results for qEEG Gamma-1 (30–35 Hz) absolute power

Gamma-1 power also demonstrated temporal stability across most sites. Significant time × anticonvulsant interactions emerged at P3-Gamma-1 ($F(2,164) = 5.04$, $p = .008$) and T3-Gamma-1 ($F(2,164) = 4.54$, $p = .014$). Age significantly moderated O1-gamma1 $F(1.79,164) = 3.90$, $p = .027$). No significant time × recurrence interactions were observed (Table 4).

3.3.3. Results for qEEG Gamma-2 (35–40 Hz) absolute power

Gamma-2 power showed no significant main effects of time across electrodes. Anticonvulsant use moderated changes at P3-Gamma-2 ($F(2,148) = 3.11$, $p = .047$). No other significant covariate interactions, including time × recurrence, were found (Table 4).

3.4. Correlation analysis

Correlation analyses examined the relationship between absolute gamma, gamma1, and gamma2 power and concurrent HDRS-17 and HARS scores at the same visit, to assess their association with current depressive and anxiety symptom severity. Across most electrodes and frequency bands, no significant correlations were observed with either HDRS-17 or HARS scores. No significant correlations were observed between gamma power and HDRS, HARS scores at the first point across all regions, suggesting that initial gamma power was not reflective of concurrent symptom severity. Only for FP1 Gamma 2, same-visit correlation analyses revealed a significant positive association at the second point with HDRS ($r = 0.337$, $p < .01$) and with HARS ($r = 0.289$, $p < .05$) (Table 5).

4. Discussion

Across analyses, reduced gamma activity emerged as a consistent

Table 5
Pearson correlations between HDRS, HARS total scores and qEEG absolute power.

Variables	Time	HDRS			HARS		
		First	Second	Third	First	Second	Third
HDRS	First	1.000	−0.203	0.052	0.779**	−0.032	0.151
	Second	−0.203	1.000	0.390**	−0.052	0.722**	0.071
	Third	0.052	0.390**	1.000	0.235*	0.422**	0.938**
HARS	First	0.779**	−0.052	0.235*	1.000	0.005	0.364**
	Second	−0.032	0.722**	0.422**	0.005	1.000	0.099
	Third	0.151	0.071	0.938**	0.364**	0.099	1.000
C3 Gamma	First	0.050	−0.006	−0.017	0.029	−0.144	−0.056
	Second	0.053	0.121	−0.021	0.104	0.043	−0.111
	Third	0.005	0.111	0.078	−0.041	−0.012	−0.058
C3 Gamma-2	First	0.098	0.013	−0.040	0.050	−0.122	−0.099
	Second	0.059	0.086	−0.073	0.094	0.017	−0.145
	Third	0.014	0.094	0.027	−0.051	−0.037	−0.104
C4 Gamma	First	−0.055	−0.016	−0.047	−0.068	−0.132	−0.091
	Second	0.000	0.108	0.045	0.014	0.081	−0.050
	Third	−0.023	0.170	0.085	−0.106	0.084	−0.127
C4 Gamma-2	First	−0.014	−0.002	−0.060	−0.048	−0.111	−0.123
	Second	−0.011	0.084	−0.011	−0.008	0.049	−0.099
	Third	−0.001	0.155	0.026	−0.103	0.071	−0.175
F7 Gamma	First	0.130	0.018	−0.051	0.082	−0.112	−0.039
	Second	0.223*	0.142	0.039	0.229*	0.043	0.008
	Third	0.115	0.152	0.047	0.090	0.004	−0.037
F7 Gamma-2	First	0.159	0.024	−0.066	0.086	−0.103	−0.079
	Second	0.197	0.114	−0.054	0.158	0.011	−0.094
	Third	0.118	0.130	−0.004	0.083	−0.015	−0.088
O1 Gamma	First	−0.042	−0.002	−0.082	−0.123	−0.161	−0.131
	Second	−0.035	0.131	−0.006	−0.074	0.003	−0.158
	Third	−0.119	0.134	0.047	−0.189	−0.030	−0.131
O1 Gamma 1	First	−0.069	−0.026	−0.069	−0.142	−0.167	−0.111
	Second	−0.031	0.150	0.035	−0.064	0.021	−0.134
	Third	−0.122	0.134	0.079	−0.166	−0.011	−0.097
O2 Gamma	First	−0.001	0.012	−0.085	−0.064	−0.127	−0.106
	Second	−0.037	0.123	−0.006	−0.079	−0.001	−0.158
	Third	−0.075	0.155	0.123	−0.153	−0.003	−0.071
O2 Gamma-1	First	−0.024	−0.014	−0.077	−0.081	−0.135	−0.085
	Second	−0.039	0.143	0.038	−0.082	0.024	−0.136
	Third	−0.078	0.170	0.184	−0.130	0.028	−0.014
P3 Gamma	First	−0.035	−0.017	−0.046	−0.048	−0.158	−0.082
	Second	−0.027	0.125	−0.037	0.004	0.028	−0.146
	Third	−0.064	0.182	0.094	−0.078	0.035	−0.111
P3 Gamma-1	First	−0.054	−0.034	−0.022	−0.047	−0.159	−0.049
	Second	−0.023	0.139	−0.002	0.019	0.048	−0.123
	Third	−0.063	0.198	0.170	−0.041	0.068	−0.036
P3 Gamma-2	First	0.021	0.007	−0.067	−0.026	−0.136	−0.125
	Second	−0.016	0.087	−0.079	−0.012	0.014	−0.164
	Third	−0.055	0.173	0.040	−0.116	0.029	−0.181
T3 Gamma	First	0.013	0.035	−0.006	−0.029	−0.034	−0.038
	Second	0.035	0.088	−0.075	0.092	0.002	−0.126
	Third	−0.013	0.247*	0.037	0.019	0.002	−0.087
T3 Gamma-1	First	0.008	0.028	0.031	−0.009	−0.026	0.005
	Second	0.062	0.061	−0.056	0.114	−0.004	−0.097
	Third	−0.002	0.224*	0.057	0.023	−0.003	−0.081
T4 Gamma	First	−0.115	−0.073	−0.048	−0.107	−0.132	−0.069
	Second	0.005	0.109	0.007	0.068	0.047	−0.053
	Third	0.009	0.171	0.044	−0.023	0.012	−0.138
T4 Gamma-2	First	−0.095	−0.049	−0.080	−0.128	−0.129	−0.120
	Second	−0.032	0.108	−0.026	0.029	0.038	−0.088
	Third	0.015	0.164	0.013	−0.023	−0.002	−0.170
F3 Gamma-2	First	0.113	−0.025	−0.066	0.038	−0.120	−0.103
	Second	0.081	0.152	0.011	0.058	0.091	−0.146
	Third	0.114	0.106	0.100	0.073	−0.002	−0.024
F8 Gamma-2	First	−0.069	−0.012	−0.049	−0.092	−0.057	−0.073
	Second	0.057	0.084	0.009	0.054	0.057	−0.043
	Third	0.111	0.173	0.032	0.061	0.023	−0.083
P4 Gamma-2	First	0.016	0.028	−0.080	−0.028	−0.093	−0.129
	Second	−0.032	0.124	−0.043	−0.040	0.042	−0.142
	Third	−0.045	0.201	0.060	−0.141	0.074	−0.195
T3 Gamma-2	First	0.051	0.038	−0.061	−0.022	−0.054	−0.103
	Second	0.012	0.072	−0.110	0.050	−0.004	−0.166
	Third	−0.008	0.261*	0.034	0.028	0.023	−0.083
T5 Gamma-2	First	0.018	−0.023	−0.065	−0.026	−0.163	−0.099
	Second	−0.025	0.101	−0.063	0.038	0.019	−0.135
	Third	−0.043	0.104	0.003	0.005	−0.021	−0.152
FP1 Gamma-2	First	0.118	−0.017	−0.077	0.034	−0.121	−0.087

(*continued on next page*)

Table 5 (*continued*)

Variables	Time	HDRS			HARS		
		First	Second	Third	First	Second	Third
	Second	0.053	0.337**	0.136	0.035	0.289*	−0.144
	Third	0.149	0.294**	0.193	0.167	0.195	0.058

HDRS: Hamilton Depression Rating Scale. HARS: Hamilton Anxiety Rating Scale.
Bold values represent the QEEG power correlated with HDRS or HARS scores measured at the same visit.
** $p < .01$.
* $p < .05$ level.

feature in both recurrent and non-recurrent MDD compared to healthy controls, remaining stable over time despite variations in baseline symptom severity, medication load, comorbid anxiety, and other demographic factors. The most robust trait-like patterns were observed in posterior–parietal (P3, P4, Pz) and occipital (O1, O2) regions, as well as central midline (Cz) sites, even after any clinical or demographic covariate. Frontal sites such as FP1, F3, and F7 demonstrated gamma abnormalities but were partly influenced by gender, while certain parietal and temporal electrodes (e.g., P3, T3) were moderated by anticonvulsant use. Sites exhibiting significant temporal change (e.g., Cz, F4, Fz, P4, Pz, T5/T6 for broad gamma; Cz, P4, Pz, T6 for gamma1; F4, Fz, Cz, Pz, T6 for gamma2) were excluded from advanced stability analyses, reflecting their state sensitivity. These patterns suggest that while posterior and central gamma deficits are the most reliable candidates for trait markers, some frontal and lateralized sites may retain diagnostic relevance but require adjustment for specific clinical confounders.

Gamma oscillations are well-established mediators of cortical integration and large-scale network coordination, underpinning cognitive functions such as working memory and attention (Nir et al., 2007; Tiesinga et al., 2004), functions frequently disrupted in depression. The prominent involvement of posterior-parietal and midline cortical areas in these oscillations aligns closely with default mode network (DMN) dysfunction, a hallmark of major depressive disorder (Chou et al., 2023). Supporting this link, Liu et al. (2022) demonstrated that modulating gamma activity with 40 Hz rTMS increased gamma power in the left parietotemporal region, accompanied by enhanced local and long-range functional connectivity among DMN nodes, which was paralleled by improvements in cognitive performance (Liu et al., 2022). These findings suggest that the gamma deficits observed in our study may represent electrophysiological signatures of DMN dysfunction, characterized by reduced functional connectivity independent of illness duration, treatment status, symptom severity (Tozzi et al., 2021).

Decreased gamma activity also aligns with the neuroinflammation theory of depression. Emerging evidence indicates that reduced gamma power may be influenced by oxidative stress and neuroinflammatory processes (Palmisano et al., 2024), linking it to the pathophysiology of both neurodegenerative and neuropsychiatric disorders, including depression (Guan et al., 2022; Kann et al., 2011; Palmisano et al., 2024). Animal model studies have shown that inducing 40 Hz gamma rhythms may exert neuroprotective effects, reducing amyloid-β levels by 40–60 % and enhancing microglia-mediated clearance(Iaccarino et al., 2016). These findings support the view that the persistent gamma reductions observed in our electrophysiological data may reflect underlying oxidative stress and neuroinflammatory activity. Given that genetic susceptibility to chronic inflammation has also been proposed as a trait marker of depression (Mandal et al., 2023; Mikhalitskaya et al., 2023); reduced gamma activity could also accompany and reinforce such trait-level biological signatures.

Although some studies have shown that gamma activity can change following treatment (Fitzgerald and Watson, 2018), determining whether gamma represents a state or trait marker requires whole-brain, multi-band evaluations. In the present study, we systematically examined all gamma sub-bands across the full cortical surface. As noted previously, gamma activity—particularly around 40 Hz—has been linked to cortical activation and integrative processing in both humans and animals (Iaccarino et al., 2016; Liu et al., 2022). By subdividing the gamma band into gamma-1 (30–35 Hz) and gamma-2 (35–40 Hz), we observed that the gamma-2 band is more prominent as a trait marker candidate compared to gamma-1.

4.1. Strengths and limitations

A key strength of this study is the combined cross-sectional and longitudinal design, allowing simultaneous assessment of between-group differences and within-subject stability. The use of both recurrent and non-recurrent MDD groups further addresses the possibility that recurrence status could influence trait validity. In addition, strict artifact rejection and adjustment for multiple clinical covariates increase confidence in the robustness of the findings.

However, some limitations warrant consideration. First, although the study spans three time points, the intervals between assessments were variable, particularly between T0 and T1, which may introduce heterogeneity in longitudinal effects. Second, medication regimens were not standardized, and although medication load and class (e.g., anticonvulsant use) were statistically controlled, unmeasured pharmacodynamic effects cannot be fully excluded. Third, healthy controls were not followed longitudinally, which limits conclusions about the absolute temporal stability of gamma measures outside the patient population.

5. Conclusion

The current findings support the view that reduced resting-state gamma-band activity, particularly at sites showing both cross-sectional group differences and longitudinal stability, may serve as a candidate trait marker for MDD. Such markers have potential utility for early identification of at-risk individuals, prognostic stratification, and guiding personalized treatment approaches (Lema et al., 2018). Future research should aim to replicate these findings in high-risk individuals, such as first-degree relatives of patients or medication-free samples, extend analyses to functional connectivity in the gamma range, and explore whether these markers predict treatment response or relapse risk over longer follow-up periods.

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CRediT authorship contribution statement

Mehmet Kemal Arıkan: Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Reyhan İlhan:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Conceptualization.

Author's contribution

Author 1 designed the research and wrote the protocol. Author 1 and author 2 conducted literature searches and provided full-text articles. Author 1conducted the statistical analysis. Author 1 and author 2 wrote the first draft of the manuscript and all authors contributed to and have approved the final revised version of the manuscript.

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