Original Manuscript

Monitoring the Response of Treatment in Major Depressive Disorder with EEG: Could it be an Indicator of Returning to Health in Responders

Clinical EEG and Neuroscience
1–10

DOI: 10.1177/15500594241310949
journals.sagepub.com/home/eeg
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Abstract

Background: Quantitative electroencephalography (qEEG) data can facilitate the monitoring of treatment progress and the evaluation of therapeutic responses in patients with Major Depressive Disorder (MDD). This study aims to compare the qEEG data of MDD patients and healthy controls, both before and after treatment, to assess the effect of treatment response on neural activity. **Methods:** A total of 72 patients, aged 18–60, who had not used any psychopharmacological medication for at least two weeks, were included in the study. Based on a minimum 50% reduction in scores on the Hamilton Depression Rating Scale (HDRS-17) and Hamilton Anxiety Rating Scale (HARS), the patients were divided into two groups: responders (n = 51) and non-responders (n = 21). qEEG data were recorded before and after treatment. **Results:** Responders exhibited a significant shift in cortical activity—particularly in theta, alpha, and high-beta power—toward patterns resembling those observed in the healthy control group (improvement range: 15% to 67%). In contrast, non-responders showed minimal changes in cortical activity (improvement range: 38% to 46%). These findings suggest that while qEEG spectral data reflect marked neural changes in responders, no significant alterations occur in non-responders. **Conclusion:** The use of qEEG spectral analysis to monitor MDD patients provides valuable insights into treatment efficacy. The distinct patterns of cortical activity observed across most brain regions before treatment, compared to healthy individuals, highlight the potential of qEEG to predict treatment outcomes.

Keywords
alpha oscillation, major depressive disorder, quantitative EEG, treatment response

Received July 16, 2024; revised December 3, 2024; accepted December 6, 2024.

Introduction

Major Depressive Disorder (MDD) is a highly prevalent mental health condition, with a lifetime prevalence rate of 10.8% worldwide.[1] It represents a significant public health concern, contributing substantially to disability and workforce loss on a global scale.[2] MDD impairs not only individuals' mental well-being but also their physical health, social relationships, and overall quality of life. Additionally, MDD imposes a heavy economic burden, with estimates indicating an annual global cost exceeding $210 billion.[3] In Europe alone, the economic impact of MDD amounts to approximately €118 billion per year.[4] These figures underscore the importance of effective treatments, which not only improve individual well-being but also reduce the societal and economic burdens of the disorder.

Antidepressant medications are commonly recommended as first-line treatments for MDD.[5,6] However, treatment outcomes are often suboptimal, with only 30% of patients achieving full remission. The remaining 70% either exhibit partial improvement without complete remission (20%) or show no significant response to treatment (50%).[7] Clinical guidelines typically recommend a response evaluation period of 4 to 8 weeks.[8] However, the need to wait several weeks to assess treatment efficacy can be challenging, especially during the acute phase when symptoms are most severe. As approximately 70% of patients may not respond to the initial treatment, additional

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interventions—such as switching medications or adding adjunctive treatments—may further prolong the treatment process.

In psychiatric practice, treatment monitoring involves the systematic evaluation of a patient's response to interventions, including medication and psychotherapy. This process tracks clinical progress, side effects, adherence to treatment, and changes in symptoms over time to ensure the safety and efficacy of the therapeutic plan.[9] Monitoring methods include self-reports, clinical interviews, standardized rating scales, and physiological assessments. However, objective biomarkers that reliably assess treatment outcomes and guide treatment strategies remain limited.[10] There is an urgent need for neurophysiological biomarkers to enhance treatment approaches and develop novel therapies.

Several techniques are available for measuring brain activity in mental health disorders to identify potential neurophysiological biomarkers, including positron emission tomography (PET),[11] functional magnetic resonance imaging (fMRI),[12] functional near-infrared spectroscopy (fNIRS)[13] magnetoencephalography (MEG),[14] and electroencephalography (EEG).[15] Among these, EEG is particularly notable for its accessibility, high temporal resolution, non-invasive application, portability, and cost-effectiveness. These characteristics make EEG especially suitable for monitoring clinically significant changes in disorders like MDD.[16]

In the context of MDD, several qEEG parameters, primarily frequency band analyses, have been explored. Studies comparing individuals with MDD to healthy controls have reported increased alpha band activity, particularly in the frontal and parietal regions, which may reflect introversion and reduced cognitive processing.[17] Similarly, increased theta power in the frontal and limbic regions has been associated with impaired emotional processing and deficits in cognitive control.[18] Furthermore, elevated beta power has been reported in MDD patients, potentially indicating heightened arousal and mental activity compared to healthy individuals.[19]

In addition to absolute power, other qEEG features—such as coherence, entropy, and asymmetry—have been examined to predict treatment response.[20–23] However, these studies have yielded conflicting results. For instance, some studies suggest that treatment non-responders display elevated resting-state theta power,[24] while others report reduced theta power in similar patient populations.[25] These inconsistencies may be attributable to the heterogeneity of MDD symptoms, the presence of comorbid psychiatric conditions, or the inclusion of various depression subtypes across studies.

Given the variability in previous findings, there remains significant potential to further explore qEEG as a tool for understanding the neurophysiological mechanisms underlying MDD and monitoring treatment response. Although studies with similar objectives exist, our study seeks to contribute novel insights by investigating whether the findings align with or extend the results of previous research. Specifically, the aim of this study is to explore the potential of qEEG in monitoring treatment response by comparing the pre-treatment and post-treatment (eighth week) qEEG measurements of MDD patients with those of healthy controls.

Methods

Participants

This retrospective study included patients diagnosed with MDD who were admitted to a private psychiatric clinic between March 2011 and March 2023. All patients were evaluated by the same psychiatrist during their visits. Diagnoses were made based on criteria outlined in either the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*[26] or *DSM-5*[27]

Inclusion criteria were as follows: Age between 18 and 60 years. No use of psychopharmacological agents for at least the previous two weeks. Assessment of anxiety and depression using the Hamilton Depression Rating Scale (HDRS-17) and Hamilton Anxiety Rating Scale (HARS) both before and after treatment. Availability of qEEG data recorded both pre-treatment and post-treatment.

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.

Healthy Controls

The healthy control group consisted of visitors to the same psychiatric clinic, selected after undergoing psychiatric evaluations by the same psychiatrist. These individuals had no psychiatric history and had never used psychotropic medications. Controls with a history of epilepsy, neurological diseases, alcohol, or substance dependence were excluded. Additionally, participants were required to have qEEG recordings within the normal range compared to a normative database provided by the qEEG software. Abnormal qEEGs resulting from artifacts, such as electrode displacement, were excluded.

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).

Data Collection and Filtering

All patients underwent a psychiatric evaluation during their initial visit to the clinic. On the same day, the HDRS-17 was administered, and resting-state qEEG recordings were obtained. Following diagnosis, patients were prescribed antidepressant medication. After approximately eight weeks, clinical assessments were repeated, including HDRS-17 and qEEG measurements. All data were stored securely in a private database and later transferred to SPSS (version 29) for statistical analysis.

Patient files were reviewed retrospectively, and the inclusion and exclusion criteria were applied. Based on the clinical outcomes, patients were classified as responders ($n = 51$) if their HDRS-17 scores decreased by at least 50% and as non-responders ($n = 21$) if they did not achieve this reduction. The final sample included 72 MDD patients (40 females, 32 males) and 57 healthy controls (27 females, 30 males) aged 18–65 (mean = 36.68 ± 13.04 years).

Hamilton Depression Rating Scale (HDRS-17)

The HDRS-17 was developed by Max Hamilton[28] to assess the severity of depression. It consists of a semi-structured interview, during which the clinician evaluates depressive symptoms experienced over the previous week. Scores range from 0 to 53, with higher scores indicating more severe depression. Scores are categorized as follows: 0–7 (no depression), 8–15 (mild depression), 16–28 (moderate depression), and 29+ (severe depression).[29]

Hamilton Anxiety Rating Scale (HARS)

The HARS, developed by Hamilton,[30] measures the severity of anxiety symptoms experienced within the past 72 h. The scale includes 14 items, each scored from 0 to 4. The total score ranges from 0 to 56, with the following categories: 17 or below (mild anxiety), 18–24 (mild to moderate anxiety), 25–30 (moderate to severe anxiety), and 31+ (severe anxiety).[31]

qEEG Recording

All participants underwent EEG recording before initiating treatment. They were asked to abstain from caffeine, nicotine, alcohol, and non-prescribed drugs for at least one hour before the session. Recordings were conducted 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. Electrode impedance was verified to be below 5 kΩ.

Resting-state qEEG was recorded using a NeuronSpectrum-4/P device.[32] Participants sat comfortably with their eyes closed during the recording. The session lasted approximately 7 min, including 3 min of resting-state recording, 30 s of open-eye recording, and 3.5 min of closed-eye recording. The data were sampled at 500 Hz, with a bandpass filter of 0.15–70 Hz and a notch filter at 50 Hz.

qEEG Analysis

The raw EEG 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) Beta (12-25 Hz) High Beta (25-30 Hz) Gamma (30-50 Hz). The raw EEG data were evaluated by a neurologist for the presence of encephalomalacia, isolated epileptiform activity, discharges, and paroxysmal events if the QEEG mapping revealed significant abnormalities, such as atypical delta or theta power or markedly reduced beta power. In cases where such findings were confirmed, the corresponding data were excluded from further analysis.

Group Topographic Mapping. The data files were organized into five groups using NeuroGuide software:

1. Depression-Responder-Pre-Treatment
2. Depression-Responder-Post-Treatment
3. Depression-Non-Responder-Pre-Treatment
4. Depression-Non-Responder-Post-Treatment
5. Healthy Controls

Group averages and topographic brain maps were generated using the NeuroBatch and NeuroStat plugins of the software.[34] For the details group mapping calculation see Supplemental material (see S1)

Statistical Analysis

Statistical analyses for group mappings were conducted using the NeuroStat application (version 24). Independent samples t-tests were performed to compare pre- and post-treatment qEEG data between responders, non-responders, and healthy controls (see S2) In these comparisons, treatment response and diagnosis served as independent variables, while absolute power values of each electrode-band pair were treated as dependent variables. Additional analyses were conducted using SPSS (version 29.0.2.0).

Chi-square tests were used to examine differences in categorical variables (eg, gender). Independent samples t-tests

were employed to compare continuous variables, including HDRS-17 and HARS scores, age, illness duration, and age at onset. A significance threshold of $p < .05$ was applied for all analyses.

Results

Sociodemographic and Clinical Variables

The sociodemographic and clinical characteristics of the participants are presented in Table 1. There were no significant differences in age or gender between the patient groups and healthy controls. Similarly, no significant differences were found between the responder and non-responder groups in terms of baseline age, gender, HDRS-17 scores, HARS scores, age at disease onset, or illness duration. The distribution of treatment modalities is also detailed in Table 1, showing that the patient groups were homogeneous with regard to the type of antidepressant prescribed (SSRIs or SNRIs). Additionally, a small number of patients (n = 7) received only transcranial magnetic stimulation (TMS, FDA-approved protocol for depression with figure 8 coil, placed on left dorsolateral prefrontal cortex, 10 Hz frequency, 120% motor threshold intensity, 3000 pulses in totla), with 5 of them classified as responders.

Table 1. Descriptive Statistics and Group Comparisons on Demographic and Clinical Variables.

Demographics	Diagnostic Groups		*N*	*M*	*SD*	*p*
Gender	Responder	Female	29			.637[a]
		Male	22			
		Total	51			
	Nonresponder	Female	11			
		Male	10			
		Total	21			
	Healthy	Female	27			
		Male	30			
		Total	57			
	Total	Female	67			
		Male	62			
Age	Responder		51	37.92	12.31	.830[b]
	Non-responder		21	37.19	14.78	
	Healthy		57	35.38	13.13	.594[c]
	Total		129	36.68	13.05	
HDRS-17	Responder		51	21.78	8.36	.528[b]
Baseline	Non-responder		21	20.28	10.54	
	Total		72	21.33	9.01	
HARS	Responder		51	27.56	11.78	.787[b]
Baseline	Non-responder		21	26.71	13.07	
	Total		72	27.31	12.09	
HDRS-17	Responder		51	1.92	2.83	<.001[b]
Post-treatment	Non-responder		21	13.42	10.31	
	Total		72	5.27	7.95	
HARS	Responder		51	3.50	4.62	<.001[b]
Post-treatment	Non-responder		21	15.71	11.70	
	Total		72	7.21	9.15	
Duration of illness (years)	Responder		51	7.75	8.05	.177[b]
	Non-responder		21	11.21	9.03	
	Total		72	8.56	8.34	
Age at disease onset	Responder		51	30.54	14.12	.322[b]
	Non-responder		21	26.21	14.49	
	Total		72			
Antidepressant Type	Responder	SSRI	34			.099[d]
		SNRI	11			
	Non-Responder	SSRI	16			
		SNRI	1			
	Total		33			

Note: YBOCS = Yale-Brown Obsessive Compulsive Rating Scale. HDRS = Hamilton Depression Rating Scale. HARS = Hamilton Anxiety Rating Scale.
[a]Pearson Chi-square test result.
[b]Independent Sample t-test.
[c]One-way ANOVA test result.
[d]Fisher's Exact test result.

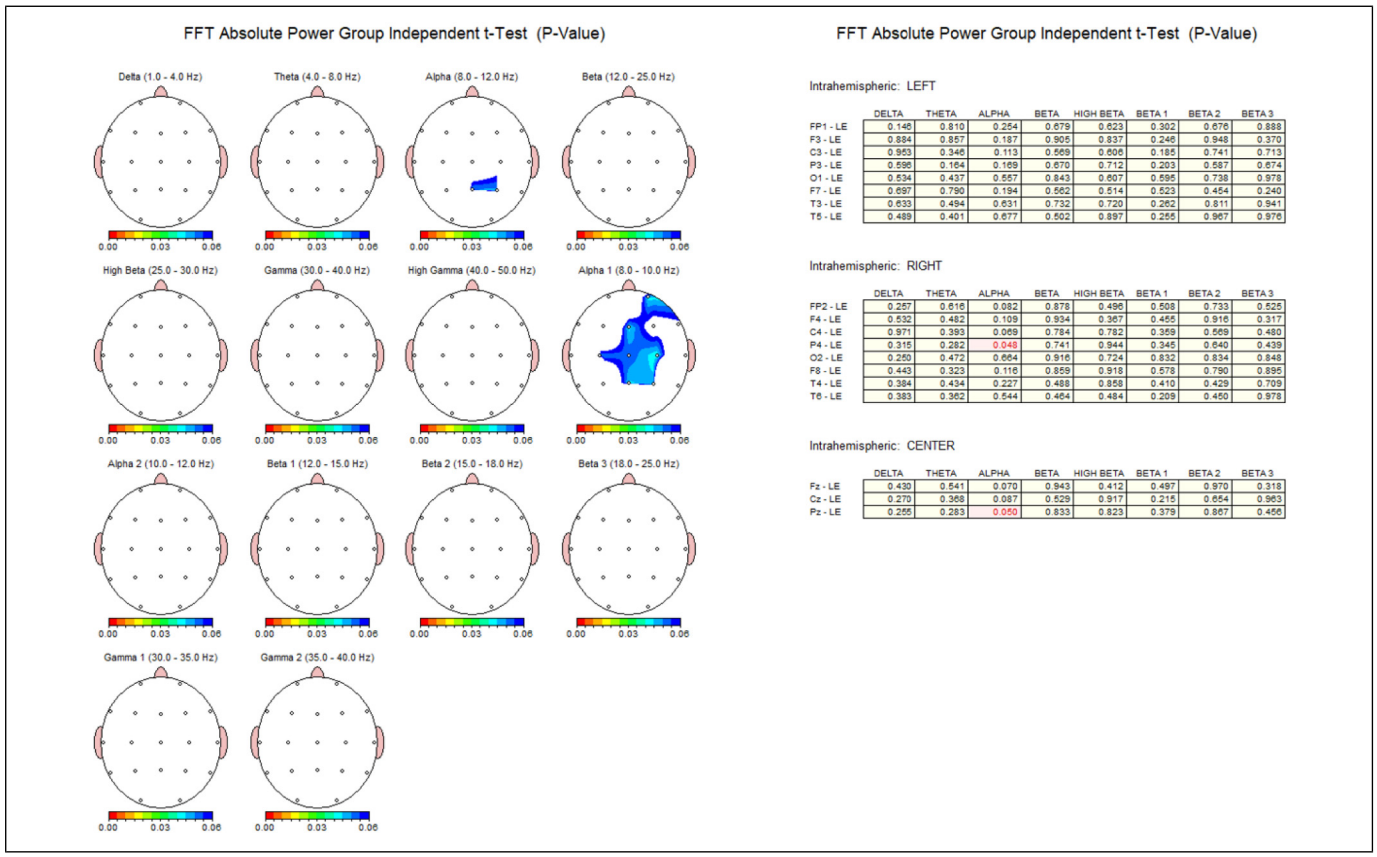

Figure 1. Baseline QEEG differences between treatment responsive and non-responsive MDD patients.
Note: The depicted areas represent the specific electrodes that show significant differences between groups in the relevant frequency band.

As expected, responders demonstrated significantly greater reductions in HDRS-17 and HARS scores after treatment compared to non-responders (Table 1).

Comparison of Responders and Non-Responders

Out of the 72 patients diagnosed with MDD, 51 were classified as responders to antidepressant treatment. The independent samples t-test revealed a few significant differences in qEEG patterns between responders and non-responders (Figure 1). Specifically, responders exhibited significantly higher alpha power compared to non-responders in the right parieto-central region, indicating distinct neurophysiological changes associated with treatment response.

Comparison of MDD Patients and Healthy Controls

The results of the qEEG comparisons between MDD patient groups (responders and non-responders) and healthy controls (HCs) are presented in Figures 2 and 3.

Baseline qEEG Comparison. At baseline, both responders and non-responders displayed significant differences in qEEG activity compared to healthy controls ($p < .001$), as indicated by the red regions in Figures 2A and 3A. These differences highlight the distinct neurophysiological profiles of MDD patients before treatment.

Post-Treatment qEEG Comparison. After treatment, the qEEG activity of the responder group showed normalization, with most brain regions no longer significantly different from those of healthy controls. This normalization is indicated by the blue (non-significant, $p > .05$) and white (n.s.) regions in Figure 2B.

In contrast, the non-responder group did not exhibit substantial normalization of qEEG activity. Many brain regions remained significantly different from those of healthy controls ($p < .01$), as shown in Figure 3A and B.

These findings suggest that while responders experienced meaningful neurophysiological changes associated with their clinical improvement, non-responders continued to exhibit altered brain activity patterns post-treatment.

Discussion

In this study, patients diagnosed with MDD were retrospectively classified into responders and non-responders based on their treatment outcomes, all under the care of the same physician at a single treatment center. The pre- and post-treatment

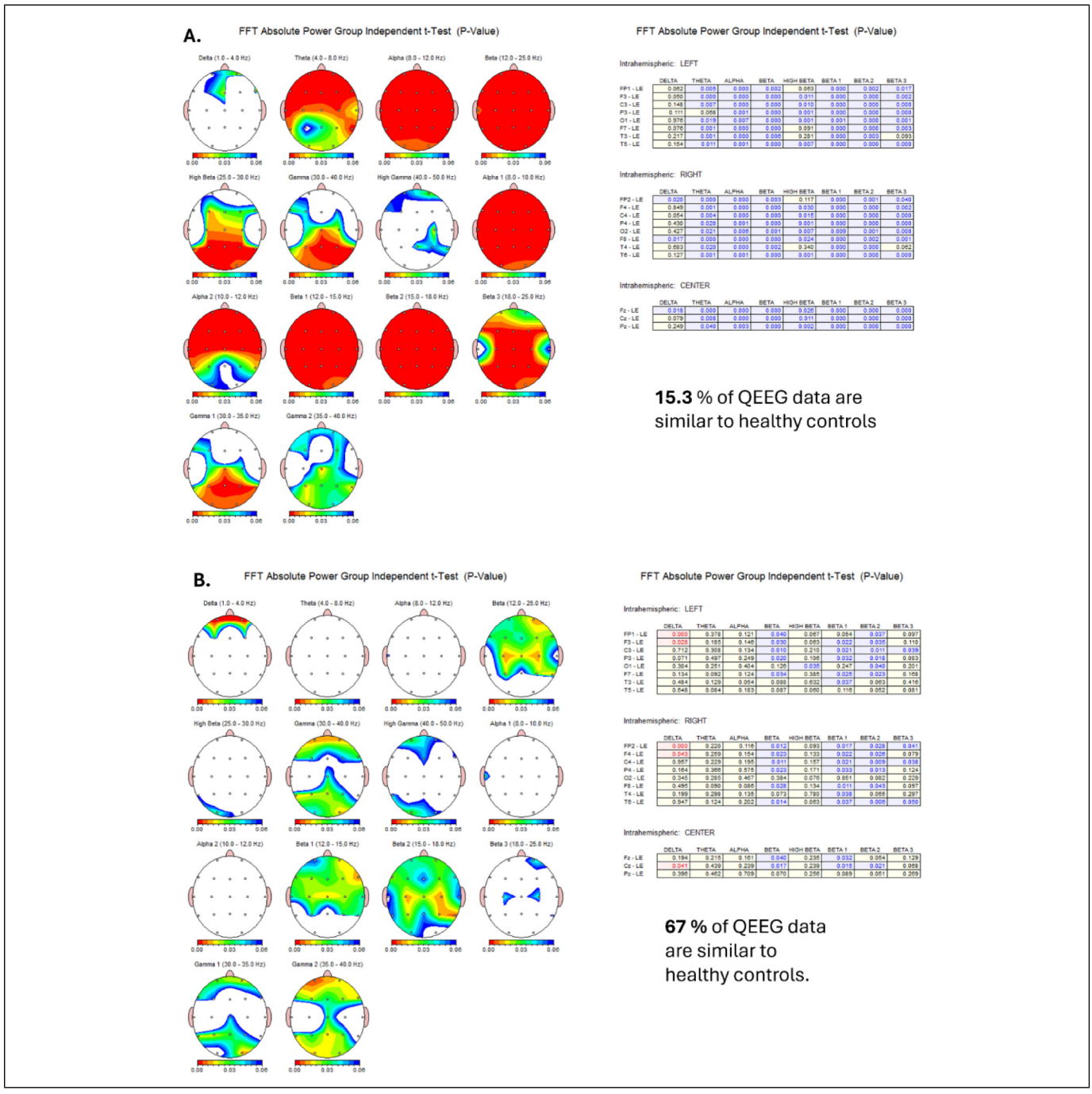

Figure 2. Comparison of QEEG topographic maps between treatment responsive MDD patients and HCs before (A) and after (B) treatment.

qEEG spectral data of these patients were compared with those of healthy controls to identify neurophysiological changes related to treatment. The primary objective was to assess the potential of qEEG spectral data for monitoring treatment response in patients with MDD.

Comparison of baseline qEEGs of MDD patients showed that treatment responders had higher right parieto-central alpha power than non-responders. However, the most notable finding of this study is that patients who responded to treatment exhibited significant changes in theta, alpha, and high beta absolute power across almost all brain regions, achieving patterns like those of healthy controls (similarity change: from 15% to 67%). In contrast, non-responders showed no meaningful changes in cortical activity (similarity change: from 38% to 46%). These results suggest that qEEG spectral data reflect significant neurophysiological changes in treatment-responsive patients, while non-responsive patients maintain brain activity patterns. In addition

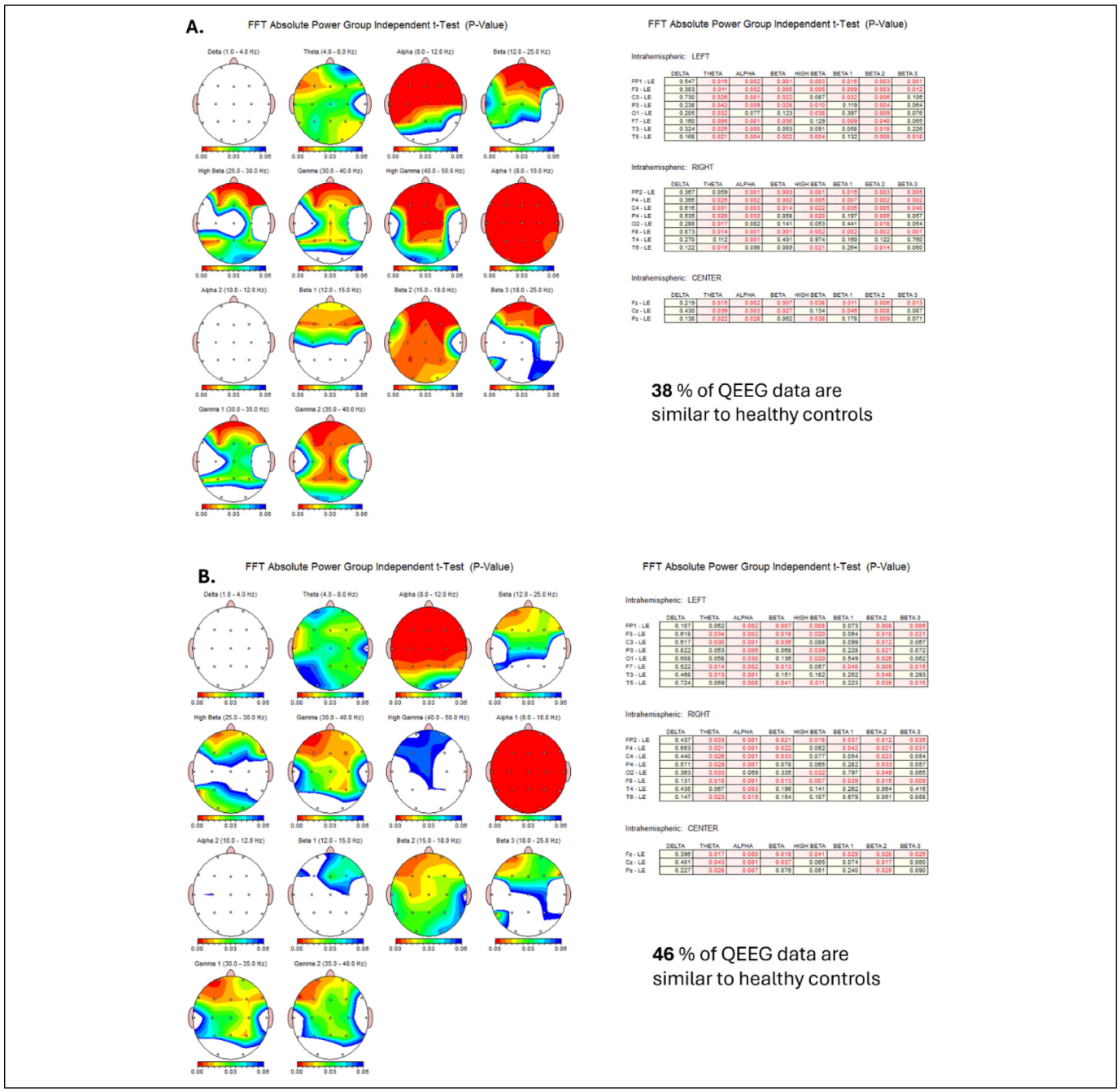

Figure 3. Comparison of QEEG topographic maps between treatment non- responsive MDD patients and HCs before (A) and after (B) treatment.

Normalization of Theta, Alpha and High Beta

Theta waves are primarily associated with the hippocampus and are linked to memory processing and emotional regulation.[35] The reduction in excessive theta activity observed in responders may reflect improved emotional regulation and enhanced prefrontal cortex function through treatment.

Excessive alpha waves have been linked to depression and anxiety, potentially due to imbalances in thalamo-cortical loops.[35] The normalization of alpha activity in responders could indicate that pharmacological interventions modulated thalamo-cortical interactions,[36] contributing to the observed therapeutic effects.

Elevated beta activity is often associated with anxiety, insomnia, and stress, reflecting heightened cortical arousal.[37] The reduction in high beta power among responders may suggest that antidepressants, with their anxiolytic effects, alleviated anxiety by stabilizing cortical overactivity.

Comparison with Previous Studies

Previous research has highlighted the biomarker potential of EEG parameters such as event-related potentials (ERPs), frequency band changes, and sleep patterns. However, their application in routine clinical practice remains limited.[38,39] Consistent with the current study's findings, research indicates that higher pre-treatment alpha power predicts better treatment outcomes.

For example, Ulrich et al[40] found that responders exhibited a dominant alpha frequency 1.5 Hz higher than non-responders at baseline, with further increases during treatment with amitriptyline or pirlindole.[38–41] However, non-responders showed no significant changes in alpha frequency.

Knott et al[39] reported that MDD patients who responded to imipramine had higher pre-treatment alpha power and lower theta power than non-responders. At post-treatment, responders exhibited increased theta power, particularly in anterior regions, while non-responders did not show such changes. These findings align with the results of this study, although differences in other frequency bands (alpha, beta, delta) were not significant in previous research, potentially due to smaller sample sizes and shorter study durations.

Similarly, Bruder et al[41] found that responders to fluoxetine had higher pre-treatment alpha and theta power compared to non-responders and healthy controls, suggesting a link between pre-treatment neural activity at alpha frequency and treatment outcomes. However, inconsistencies in prior studies may stem from small sample sizes, heterogeneity in gender distribution, and inadequate assessment of psychiatric comorbidities. For example, Knott et al[42] observed that male MDD patients experienced widespread reductions in alpha power and increases in theta/delta power after six weeks of paroxetine treatment, with these changes corresponding to reduced depression severity. However, this study did not include a healthy control group, nor were patients stratified by treatment response, limiting the generalizability of its findings. On the other hand, machine learning algorithms applied to the large sample resting state qEEG data profoundly presented that higher baseline alpha power in including right parietal region could be the neurobiological marker of response to sertraline treatment compared to placebo.[43]

Limitations

The retrospective design of the present study presents certain limitations. The relatively small sample size, especially among non-responders, may reflect the tendency of treatment-resistant patients to discontinue psychiatric follow-ups. For EEG recording, although some EEG recordings of the participants were also visually inspected by a neurologist, other EEGs were analyzed using automated calculations. Additionally, the use of the Neurostat program for group comparisons did not incorporate Bonferroni corrections, which may increase the number of significant electrode-band pairs. Another limitation is the lack of a structured diagnostic tool, such as SCID, to comprehensively assess comorbid psychiatric conditions beyond anxiety. This may have introduced variability in the findings.

Conclusion

The results of this study support the potential utility of qEEG spectral analysis for the clinical monitoring of MDD patients. The observed pre-treatment differences between patients and healthy controls across nearly all brain regions suggest that qEEG may also have predictive value for treatment outcomes. However, further research is needed to confirm these findings and establish qEEG as a routine tool in psychiatric practice. Future studies should aim to address the limitations of the current study by including larger sample sizes, accounting for gender differences, and employing structured diagnostic tools to assess comorbidities.

Acknowledgements

None declared.

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).

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).

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

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