Original Manuscript

Predictive Value of qEEG in Manic Switch of Depressed Patients

Clinical EEG and Neuroscience
1–11

DOI: 10.1177/15500594231190278
journals.sagepub.com/home/eeg
Sage

Mehmet Kemal Arıkan[1], Reyhan İlhan[1], Mahmut Taha Özulucan[1], Muhammed Taha Esmeray[1], and Mehmet Güven Günver[2]

Abstract

Backgrounds: More than half of the patients with bipolar disorder (BD) had depressive episodes at the onset of BD. Despite some suggested clinical predictors, there are no certain criteria for predicting which unipolar depression patient switch to manic episodes during the treatment course. Electrophysiological markers can address this issue.

Methods: Pretreatment quantitative electroencephalography (qEEG) records of patients diagnosed with major depressive disorder (MDD) or BD at the first visit were included in the study. Patients with MDD were also grouped with manic switch (MS) or MDD based on the diagnosis of later visits. The qEEG spectral power was analyzed across 3 groups, that is, MS, MDD, and BD.

Results: Compared to patients whose diagnosis did not change, patients with MS had accelerated high-frequency activities predominantly in the left hemisphere (central-parietal-occipital regions). In contrast, they showed increased slow wave activity predominantly in the right hemisphere (parietal-occipital regions).

Conclusion: It can be concluded that searching for electrophysiological markers, which have distinct advantages of repeatability, noninvasiveness, and cost-effectiveness, can facilitate the prediction of the MS.

Keywords

bipolar disorder, major depressive disorder, manic switch, quantitative electroencephalography, preventive medicine, psychiatry

Received February 4, 2023; revised July 6, 2023; accepted July 10, 2023.

Introduction

Bipolar disorder (BD), previously known as manic-depressive disorder, is presented as mood swings changing from a manic episode to a depressive episode or vice versa. The pathophysiology of BD is complex, and the loss of years due to disability constitutes a significant burden.[1]

The lifetime prevalence of BD is 1.02%, higher in Western countries.[2] The apparent sign of the typical BD is a manic or hypomanic mood characterized by a marked period of abnormal and persistently elevated mood, increased goal activity, flight of ideas, psychomotor agitation, and inflated self-esteem. In contrast, the depressive episode shows itself on the opposite end, namely, depressed mood, indecisiveness, recurrent thoughts, and feelings of worthlessness.[3] In addition, the onset of BD often begins with a depressive episode which lasts longer than the manic episode.[4]

Clinical Factors

Despite bipolar depressive episodes being like unipolar depressive episodes, that is, the same diagnostic criteria in DSM-V, studies provide some clinical differences in symptoms, course, and family history that can differentiate bipolar depression from unipolar depression, such as irritable moods during antidepressant treatment, frequent suicide attempts, atypical depressive symptoms,[5] psychotic and melancholic symptoms,[6] diurnal mood variation in depressive episodes,[7] early age of onset,[8] and more frequent family history of BD.[9]

Brain Structural and Functional Difference

Given that depression and mania have reverse symptomatology, patients with BD and major depressive disorder (MDD) are expected to manifest distinct brain morphology and activity, especially in primary brain regions of emotion regulation,[10] psychomotor activity,[11] decision-making, risk evaluation,[12] self-representation,[13] and most importantly brain circuitry of thought processes, that is, anterior cingulate, dorsolateral prefrontal cortex, orbitofrontal cortex, and amygdala.[3,14] Neuroimaging techniques such as magnetic resonance imaging (MRI), functional MRI (fMRI), quantitative electroencephalography (qEEG), event-related potentials (ERP), and

[1]Kemal Arıkan Psychiatry Clinic, Istanbul, Turkey
[2]Department of Biostatistics, Istanbul University, Istanbul, Turkey

Corresponding Author:
Kemal Arıkan, Kemal Arıkan Psychiatry Clinic, Halaskargazi Street, No.103, Gün Apartments, Flat 4B, Osmanbey, Istanbul 34371, Turkey.
Email: mkarikan46@gmail.com

standardized low-resolution brain electromagnetic tomography (sLORETA) are utilized for comparing morphological and functional differences between MDD and BD.

MRI and fMRI

A large MRI study meta-analysis comparing BD, MDD, and healthy controls (HCs) found that patients with MDD and BD had decreased gray matter volumes (GMW) in the medial prefrontal cortex (MPFC), anterior cingulate cortex, and bilateral insula compared to controls. However, only patients with MDD had reduced GMW in the right dorsolateral prefrontal cortex and left hippocampus compared to HCs.[15] A comprehensive review of fMRI also found functional commonalities in the bilateral insula, MPFC, and the left cerebellum for BD and MDD. In contrast, distinct activity is observed in limbic and occipital regions.[16]

Quantitative EEG

Unlike other neuroimaging techniques, qEEG is preferred since it is more affordable, user-friendly, convenient for routine use, and has a high temporal resolution. On the other hand, it necessitates large samples due to a poor signal-noise ratio.[17]

The qEEG studies report that patients with MDD have a more randomized structure than healthy controls.[18] In contrast, patients with BD had reduced alpha frequency synchronization at frontocentral and centroparietal connections.[19] In addition, a comparative study provided different findings in that both patients with MDD and BD differed in functional networks in high beta band compared to HCs at the global level.[20] At the nodal level, patients with BD had altered functional networks in high beta at the right precuneus, left cingulate, and left superior frontal area, while patients with MDD only differed at the right precuneus.[20]

Finally, another resting-state study reported these diagnostic groups did not differ in absolute power and frontal asymmetry. Yet compared to patients with MDD, patients with BD have increased central, temporal theta, and parietotemporal coherence. The groups also differed in right theta cordance.[21]

Event-Related Potential

Event-related potential (ERP) studies also shed light on the difference between bipolar and unipolar depression. Several pieces of evidence reveal patients with BD had less gamma power than patients with HCs[22] and MDD[23] during auditory evoked potential tasks. During emotional tasks, patients with BD also manifested greater gamma power in the left posterior temporal, anterior medial parietal, and right temporal-parietal regions compared to the MDD,[24] but both groups had reduced frontal gamma activity compared to HCs.[25] In addition, more alpha-beta activities in the frontal, parietal, and occipital regions were seen in BD, while increased gamma activity in bilateral temporal areas is observed in MDD.[25]

Machine Learning Techniques

A machine learning study tested MRI data and found that patients with BD had reduced GMW than MDD in the following regions; right hippocampus, amygdala, parahippocampus, fusiform gyrus, insula, Rolandic-frontal operculum, and cerebellum.[26]

As for qEEG data, a study identified patients with BD and MDD by machine learning approach. The extracted features differentiating the patients were mainly in the frontal and parietal cortex.[27]

Discrimination of Manic and Depressive Episodes

Aside from the classification of MDD and BD, qEEG can also be utilized in differentiating manic and depressive episodes of patients with BD. An early study stated that manic episodes were characterized by decreased alpha power in left frontotemporal electrodes, whereas unipolar depression is presented with reduced alpha power in right frontotemporal electrodes.[28] Another study concluded that patients with BD show less prefrontal and temporal theta activities in manic episode than in depressive episodes.[3] Also, apparent prefrontal and parietal beta-2 and beta-3 b and activities were seen in manic episodes.[3] As for patients with euthymic BD, an increase in delta, theta, alpha, and beta activities is observed and not affected by the duration of illness and medication use.[29] However, another study associates euthymic medication-free patients with reduced alpha activity.[30]

Regarding ERP studies of manic and depressive episodes, it has been seen that patients with manic BD have reduced gamma coherence,[31] especially in the right frontotemporal area.[32] In contrast, euthymic patients altered gamma coherence in the bilateral frontotemporal area compared to controls.[33]

The First Manic Switch

High rates of depressive episodes, which subtly differ from unipolar depressive episodes, complicate accurate diagnosis, and appropriate treatment plans.[34] A meta-analysis shows that 15% of patients diagnosed with unipolar depression may have unrecognized BD.[2] Longitudinal studies observing patients with major depression for more than 5 years report that approximately 5% to 10% of the patients showed the first manic episodes after depressive episodes.[35] However, the diagnosis of depressive patients can change after many long years.[36]

The risk factors of MS in BD are crucial for appropriate diagnosis and treatment plans. The most frequent triggers for a manic episode as antidepressant treatment, mostly tricyclic antidepressants, transcranial magnetic stimulation (TMS) and deep brain stimulation, seasonal changes, hormonal imbalance, use of energy drinks acetyl-L-carnitine, biological rhythm changes such as sleep deprivation and fasting, whereas stressful life events were found to be contradictory factors for a manic episode.[37] The neurobiological underpinnings of the MS are

reported as altered catecholamine levels resulting in abnormal monoaminergic activity, upregulation of neuroplastic and neurotrophic factors, hypothalamic-pituitary-adrenal axis hyperactivity, and increased locus coeruleus firing rate at rapid eye movement period with sleep deprivation.[38]

Although some potential clinical risk factors of the manic shift are proposed in the literature, there are no criteria for predicting which unipolar depression patients switch to manic episodes during treatment. The present retrospective study aims to explore any electrophysiological markers that can differentiate depressive patients that would switch into manic episodes from both patients with BD and MDD whose diagnosis did not change over treatment.

Methods

The study was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonization/ Good Clinical Practice Guidelines. All participants gave written informed consent, and the local ethics committee approved the study.

Subjects

The present study screened electronic records of patients consulted at a private psychiatry clinic between 2012 and 2021. We have enrolled 114 patients among 2448 patients diagnosed with MDD or BD based on the following criteria:

1. Aged between 18 and 65 years,
2. Made at least 2 visits,
3. qEEG recording at the first visit,
4. For patients with MDD, Hamilton Depression Rating Scale-17 (HDRS-17)[39] at both visits,
5. For patients with BD, Young Mania Rating Scale (YMRS)[40] at both visits, and
6. For patients with MS, HDSR-17 at the first visit and YMRS scale at the next visit.

Totally, 47 patients with BD with manic episodes, 14 patients with MDD who switched to manic episodes at later visits, and 53 patients with MDD with no manic/hypomanic episodes were determined retrospectively from the psychiatry clinic database.

The same professional psychiatrist diagnosed all the participants at the first visit. The diagnosis of MDD and BD was made according to the DSM-V.[41] Patients with organic or neurological disorders such as epilepsy, head injury, dementia, and mental retardation were excluded from the analysis. Also, psychiatric comorbidities, including personality disorders, were excluded. For bipolar samples, patients only with manic episodes were included. Mixed episodes are excluded.

The patients with MDD whose diagnosis changed into BD at the subsequent visits were categorized as the MS, the rest of the patients whose diagnosis remained same were categorized as MDD or BD. The duration between the 2 visits was approximately 5 weeks. The diagnostic groups include patients with both first episode and recurrent MDD and BD. The duration of the disorders was approximately 8 years. Some patients were drug free, yet the diagnostic groups were homogenous for drug use. Besides, the groups were homogenous for alcohol, cigarette, and substance use. Patients were no more than social drinkers and none of them was diagnosed with an addiction to alcohol, cigarette, and substance, and caffeine. Information for the period between two visits, duration of illness, proportion of drug use, alcohol, cigarette, and substance use was summarized in Table 1. The details regarding medication use and doses are indicated in Table 2.

Clinical Measures

In addition to the semistructured psychiatric interview and appropriate diagnoses made according to DSM-V, the severity of depressive and manic symptoms was evaluated through HDRS-17 or YMRS.

HDRS was developed by Hamilton to measure depression severity.[39] In the semistructured interview, the clinician questions the symptoms of depression experienced in the last week. Although there are various versions, the 17-point version was used in the study. The highest score is 53, indicating severe depression with 29 and above, moderate depression in the 16 to 28 area, mild depression from 8 to 15, and no clinical depression from 0 to 7.[42]

YMRS was developed by Young et al[40] to assess the severity of manic symptoms. The scale consists of 11 items. In a semistructured clinical interview, the clinician questions the past 48h status of the patient. The total YMRS score varies between 0 and 60. YMRS scores are categorized as follows: remission (0-12), minimal symptoms (13-19), mild symptoms (20-25), moderate symptoms (26-37), and severe symptoms (38-60).[40]

qEEG Recording Procedure

A 19-channel (FP1, F7, T3, T5, F3, C3, P3, O1, Fz, Cz, Pz, F4, C4, P4, O2, FP2, F8, T4, and T6) electro-cap was used to record resting-state qEEG recordings. The Ag-AgCl disc electrodes were used for reference and placed on earlobes using EEG paste and ear clips. FPz position was selected for ground electrodes. To decrease impedance, the electroconductive gel was injected onto the scalp through blunt-type dispensing fill needles. All impedances were kept below <5 kohm.

Recordings were obtained in a silent, well-ventilated room with dim light. All the patients were informed about the qEEG process before the recordings. Patients were required to sit still awake and closed-eyed state minimum eye blinks. Approximately 7 min recordings were acquired in resting-state condition (3 min background recording, 30 s open-eyes condition, and 3.30 min closed-eyed condition).

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

Demographics	Diagnostic groups		*N*	*M*	*SD*	*P**
Gender	MS	Female	10	N/A	N/A	.107[a]
		Male	4			
		Total	14			
	MDD	Female	28			
		Male	25			
		Total	53			
	BD	Female	19			
		Male	28			
		Total	47			
	Total	Female	57			
		Male	57			
Age	MS		14	37.28	11.09	.965[b]
	MDD		53	38.39	13.02	
	BD		47	39.55	15.73	
	Total		114	38.73	13.91	
HDRS-17 baseline	MS		14	26.33	13.11	.458[c]
	MDD		53	22.41	9.70	
	BD		47	1.74	10.10	
	Total		114	30.19	11.40	
HDRS-17 second visit	MS		14	4.69	6.04	.308[b]
	MDD		53	2.61	4.12	
	BD		47	1.75	2.21	
	Total		114	3.66	5.24	
YMRS baseline (for BD group only)	MS		1	6.00	N/A	N/A
	MDD		4	1.00	2.00	
	BD		47	13.53	8.69	
	Total		52[d]	12.42	11.00	
YMRS second visit (for MS and BD group)	MS		14	9.35	5.07	.001[c]
	MDD		4	4.50	5.15	
	BD		47	4.15	5.07	
	Total		65			
Duration of illness (years)	MS		14	6.50	3.41	.634[b]
	MDD		53	8.45	9.19	
	BD		47	9.11	9.17	
	Total		114	8.65	8.92	
Duration between 2 visits (weeks)	MS		14	4.21	2.48	.097[b]
	MDD		53	6.38	6.30	
	BD		47	5.24	7.44	
	Total		114	5.64	6.47	
Drug free	MS	Yes	1	N/A	N/A	.213[a]
		No	3			
	MDD	Yes	14			
		No	22			
	BD	Yes	7			
		No	28			
	Missing		39			

(continued)

Table 1. (continued)

Demographics	Diagnostic groups		*N*	*M*	*SD*	*P**
	Total		75			
Smoking	MS	Yes	9	N/A	N/A	.164[a]
		No	4			
	MDD	Yes	33			
		No	19			
	BD	Yes	20			
		No	23			
	Missing		6			
	Total		108			
Alcohol	MS	Yes	5	N/A	N/A	.882[a]
		No	8			
	MDD	Yes	24			
		No	28			
	BD	Yes	19			
		No	24			
	Missing		6			
	Total		108			
Substance	MS	Yes	2	N/A	N/A	.172[a]
		No	11			
	MDD	Yes	2			
		No	50			
	BD	Yes	6			
		No	37			
	Missing		6			
	Total		108			

[a]Pearson chi-square test result.
[b]Independent sample Kruskall-Wallis test result.
[c]Mann-Whitney U test result.
[d]The baseline YMRS scores of MS and MDD patients are missing as they were diagnosed with unipolar depression at the first visit.
* $P < .001$.
Abbreviations: BD, bipolar disorder; HDRS-17, Hamilton Depression Rating Scale-17; MDD, major depressive disorder; MS, manic switch; N/A, not available; YMRS, Young Mania Rating Scale.

The qEEG recordings were obtained via the Neuron-Spectrum 4/P device.[43] EEG data were sampled at 500 Hz; the signals were band-passed filtered at 0.15 to 70 Hz and notch filtered at 50 Hz. The data were recorded at European Data Format and transferred to Neuroguide Deluxe program[44] for artifact elimination and power spectra analysis. All the recorded qEEG data were inspected to eliminate muscle, eyeblink, and electrode popping artifacts. Artifacts were manually eliminated offline by a specialist trained by a neurologist at a neuropsychiatry clinic. At least 3 min artifact-free data were analyzed. Fast Fourier transformation was applied. Data were averaged across the recording epochs (2 s) for each electrode. Average absolute power was calculated for each of the following bands: delta (1-4 Hz), theta (4-7 Hz), alpha (8-12 Hz), alpha-1 (8-10 Hz), alpha-2 (10-12 Hz), beta (12-25 Hz), beta-1 (12-15 Hz), beta-2 (15-18 Hz), beta-3 (18-25 Hz), high beta (25-30 Hz), gamma (30-50 Hz), gamma-1 (30-35 Hz), gamma-2 (35-40 Hz), and high gamma (40-50 Hz).

Statistical Analysis

All the statistical analyses were conducted in SPSS (version 25). The statistical tests were performed between 3 groups, namely, MS, MDD, and BD. The normality was checked for all continuous variables, that is, age, HDRS-17, and YMRS at both visits, duration between 2 visits, duration of illness, and qEEG absolute powers. The distribution was not normal for these variables. The chi-square test was selected to check the distribution of categorical variables, that is, gender, drug use, cigarette, alcohol, and substance use differences across 3 groups. For clinical scales, depression severity was controlled between MDD and MS groups at the first visit, while YMRS scores were checked at the second visit between BD and MS groups; for these analyses, the Mann-Whitney U test was used. The significance level was set at <0.05 for these analyses. qEEG absolute powers were analyzed via the nonparametric Kruskal-Wallis test. It was an exploratory analysis. Bonferroni correction was applied to Kruskal-Wallis to cancel

Table 2. Medication and Dose Information.

Medications	N	Dose (mg)	
		Minimum	Maximum
Antidepressants			
Paroxetine	57	10	100
Fluoxetine	8	20	40
Duloxetine	11	30	60
Venlafaxine	3	150	150
Citalopram	2	20	20
Escitalopram	9	100	100
Trazodone	3	50	50
Mood Stabilizers			
Lamotrigine	18	100	500
Lithium	26	300	900
Valproic acid	5	500	100
Antipsychotics			
Olanzapine	12	3	20
Risperidone	9	1	8
Aripiprazole	21	5	15
Quetiapine	7	13	200
Benzodiazepines			
Lorazepam	8	0.5	5
Anticholinergic agents			
Biperiden	16	2	2

out the irrelevant results due to multiple comparisons. Therefore, the significance level was set at <0.0166. Finally, the pairwise Kruskal-Wallis post hoc test was applied to the significant electrode-EEG band pairs. The significance level was set at <0.05 for the post hoc analyses.

Results

Continuous Variables

Independent sample Kruskal-Wallis test showed that the groups did not differ in age ($P = .965$), HDRS-17 at the second visit ($P = .308$), duration of illness ($P = .634$), duration between 2 visits ($P = .097$) (Table 1).

Categorical Variables

Pearson chi-square test indicated that the groups were homogenous for gender ($P = .107$), drug-free state ($P = .213$), smoking ($P = .164$), alcohol use ($P = .882$), and substance use ($P = .172$) (Table 1).

Depressive Symptoms at First Visit

Mann-Whitney U test showed that the severity of depressive symptoms at first did not differ between MDD and MS ($P = .458$). The BD group was not included in this analysis since this group was in manic episodes. (Table 1).

Manic Symptoms at Second Visit

Mann-Whitney U test showed that the severity of manic symptoms at the second visit differed between treated BD group and patients switched to manic episode MS ($P = .001$). The MDD group was not included in this analysis since they were in depressive episodes (Table 1).

qEEG Absolute Power Analysis Between Groups

During qEEG recordings, patients with MDD and MS were in depressive episodes, while patients with BD were in manic episodes. Kruskal-Wallis test with Bonferroni correction showed group differences for 17-electrode band pairs ($P < .0166$) (Table 3). In addition, Kruskal-Wallis pairwise comparison indicated the difference between groups ($P < .05$) (Table 4). These results can be grouped into four categories.

(a) MS group had higher absolute power than only the MDD group (MS > MDD): Cz Gamma and Cz Gamma-2 (Table 4).
(b) Both MS and BD groups had higher absolute power than the MDD group (MS > MDD, BD > MDD): Cz Gamma-1, P4 Delta, O1 Delta, O1 High Beta, O2 High Beta, T5 Delta, T6 Delta (Table 4).
(c) MS group had higher absolute power than both MDD and BD groups (MS > MDD, MS > BDD): Pz Gamma, P3 Gamma-2, O1 Gamma, O1 Gamma-1, O1 Gamma-2, T5 Gamma-2 (Table 4).
(d) MS group had higher absolute power than BD, which in turn had higher power than MDD groups (MS > BD > MDD): O2 Delta and O2 Theta (Table 4).

Discussion

The present study investigated differential electrophysiological markers of depressed patients who switched to manic episodes and patients whose diagnoses did not change. We found that patients with MS had accelerated high-frequency activities predominantly in the left posterior hemisphere (ie, central-parietal-occipital regions). In contrast, they showed increased slow wave activity predominantly in the right posterior hemisphere (ie, parietal-occipital regions).

In the literature, qEEG-based studies generally use task-based paradigms.[22–25,30–33] For instance, Velasques et al used a prosaccade attention task for patients with manic BD and HCs. They observed that patients with BD have reduced gamma coherence compared to controls.[31] Özerdem et al[32] investigated patients with manic BD during the visual oddball paradigm. They found that patients with mania also have impaired gamma coherence but only in the right frontotemporal area,[32] which is reduced compared to HCs.

Further, recent studies find meaningful results on the other qEEG measures such as synchronization,[19] functional cortical networks,[18,20] cordance,[21] and coherence,[21] or they report

Table 3. The qEEG Absolute Powers of Patients Differed Among Diagnostic Groups.

qEEG bands (absolute power)	Diagnosis ($N = 114$)	Kruskal-Wallis (P)
Cz Gamma	MS	.010
	MDD	
	BD	
Cz Gamma-1	MS	.012
	MDD	
	BD	
Cz Gamma-2	MS	.012
	MDD	
	BD	
P3 Gamma-2	MS	.006
	MDD	
	BD	
P4 Delta	MS	.004
	MDD	
	BD	
Pz Gamma	MS	.014
	MDD	
	BD	
O1 Delta	MS	.004
	MDD	
	BD	
O1 High Beta	MS	.009
	MDD	
	BD	
O1 Gamma	MS	.001
	MDD	
	BD	
O1 Gamma-1	MS	.002
	MDD	
	BD	
O1 Gamma-2	MS	.001
	MDD	
	BD	
O2 Delta	MS	.001
	MDD	
	BD	
O2 Theta	MS	.001
	MDD	
	BD	
O2 High Beta	MS	.007
	MDD	
	BD	
T5 Delta	MS	.003
	MDD	
	BD	
T5 Gamma-2	MS	.007
	MDD	
	BD	
T6 Delta	MS	.001
	MDD	
	BD	

Abbreviations: BD, bipolar disorder; MDD, major depressive disorder; MS, manic switch; qEEG, quantitative electroencephalography.

qEEG activity discrimination based on machine learning techniques.[26,27] These studies revealed that both patients with MDD and BD had abnormalities in functional cortical networks; however, they show comparable distinctions which machine learning techniques can detect.

As for absolute power in resting-state qEEG, an earlier review reported that patients with BD with psychosis had higher theta and delta[45] and decreased alpha powers at bilateral central regions compared to HCs.[46] Besides, this abnormality is also seen in euthymic bipolar patients in that they had higher delta, theta, alpha, and beta activity in the visuospatial area than HCs, irrespective of medication status.[29]

Between episodic switches, patients with BD also show functional distinct activity. An earlier longitudinal study indicates that patients with BD show opposite asymmetric electrophysiological patterns depending on mood state.[47] Also, another early study revealed left occipital alpha dominance.[28] In our study, no findings were found for alpha frequency; however, the abovementioned findings are the results of comparison with HCs, not MDDs. Secondly, these studies investigated patients who were already diagnosed with BD. Regarding switching from hypomania to mania, one resting-state qEEG study longitudinally followed patients with bipolar II to switch into bipolar I and found elevated left alpha asymmetry as a predictor of switching hypomania to mania.[48] Another qEEG study compared patients with BD in depressive or manic episodes longitudinally and cross-sectionally.[3] Our results coincide with this study[3] in that patients with BD in manic episodes have more high-frequency activities at parietal regions than patients with MDD.

One interesting finding is that the patients with MS had increased fast activity, primarily in gamma bands. Previous studies revealed that the qEEG gamma band could differentiate patients with BD and MDD in tasked-based paradigms. A review of qEEG gamma oscillations on mood disorders[49] states that gamma oscillations differentiate MDD from HCs, discriminate BD from MDD, and even distinguish bipolar depression from unipolar depression. However, these studies found gamma activity differences between these diagnostic groups through evoked potentials tasks rather than resting-state qEEG.[49] It should be noted that resting-state or task-based gamma may signal distinct conclusions.

As for MDD, our nonswitching depression group showed the least gamma power in the overall cortex. In line with our result, an sLORETA study revealed that resting-state gamma power was reduced in patients with MDD, particularly in anterior cingulate regions,[50] and increased after recovery with TMS treatment.[51] It could be noted that gamma power is more likely to be a state marker for MDD, while for BD, studies report contrary results.[49] Future studies could target the gamma power change in BD and MDD after recovery. In our present research, both the MS group in depressive episodes and the BD group in manic episodes have more gamma power in central, parietal,

Table 4. Post Hoc Test Results Among Three Groups; Patients With MDD, BD, and MS.

			Kruskal-Wallis pairwise (*P**)		
qEEG bands (absolute power)	Diagnosis ($N = 114$)	*Median (IQR)*	MS-MDD	MDD-BD	BD-MS
				MS > MDD	
Cz Gamma	**MS**	0.53 (0.37-0.70)	0.017	0.120	0.511
	MDD	0.35 (0.29-0.48)			
	BD	0.45 (0.31-0.58)			
Cz Gamma-2	**MS**	0.13 (0.06-0.24)	0.004	0.100	0.080
	MDD	0.06 (0.04-0.09)			
	BD	0.07 (0.05-0.10)			
				MS > MDD, BD > MDD	
Cz Gamma-1	**MS**	0.45 (0.32-0.55)	0.009	0.030	0.256
	MDD	0.31 (0.25-0.41)			
	BD	0.40 (0.29-0.54)			
P4 Delta	**MS**	3.35 (2.87-4.02)	0.002	0.028	0.111
	MDD	2.76 (2.58-3.10)			
	BD	3.05 (2.60-3.38)			
O1 Delta	**MS**	3.10 (2.79-3.71)	0.016	0.004	0.641
	MDD	2.78 (2.44-3.03)			
	BD	3.01 (2.78-3.57)			
O1 High Beta	**MS**	0.91 (0.76-1.20)	0.006	0.030	0.200
	MDD	0.70 (0.51-0.87)			
	BD	0.81 (0.60-0.96)			
O2 High Beta	**MS**	0.97 (0.71-1.38)	0.006	0.023	0.216
	MDD	0.68 (0.57-0.85)			
	BD	0.81 (0.65-1.08)			
T5 Delta	**MS**	3.15 (2.78-4.20)	0.001	0.045	0.060
	MDD	2.55 (2.25-2.95)			
	BD	2.73 (2.37-3.35)			
T6 Delta	**MS**	3.24 (3.28-3.78)	0.008	0.001	0.612
	MDD	2.54 (2.22-2.89)			
	BD	2.96 (2.41-3.32)			
				MS > MDD, MS > BD	
Pz Gamma	**MS**	0.51 (0.35-0.83)	0.004	0.186	0.048
	MDD	0.35 (0.27-0.43)			
	BD	0.38 (0.28-0.50)			
P3 Gamma-2	**MS**	0.18 (0.06-0.30)	0.002	0.293	0.015
	MDD	0.05 (0.04-0.09)			
	BD	0.07 (0.05-0.09)			
O1 Gamma	**MS**	0.63 (0.49-0.94)	0.000*	0.071	0.020
	MDD	0.34 (0.27-0.50)			
	BD	0.40 (0.31-0.58)			
O1 Gamma-1	**MS**	0.49 (0.40-0.80)	0.001	0.083	0.027
	MDD	0.30 (0.23-0.42)			
	BD	0.34 (0.26-0.52)			
O1 Gamma-2	**MS**	0.19 (0.10-0.32)	0.000*	0.096	0.007
	MDD	0.06 (0.05-0.11)			
	BD	0.08 (0.05-0.13)			
T5 Gamma-2	**MS**	0.13 (0.67-0.18)	0.002	0.269	0.018
	MDD	0.06 (0.04-0.09)			
	BD	0.06 (0.04-0.12)			
				MS > BD > MDD	
O2 Delta	**MS**	3.54 (3.17-3.97)	0.000*	0.018	0.042
	MDD	2.83 (2.49-3.12)			
	BD	3.14 (2.61-3.57)			

(continued)

Table 4. (continued)

qEEG bands (absolute power)	Diagnosis ($N = 114$)	*Median (IQR)*	Kruskal-Wallis pairwise (P*)		
			MS-MDD	MDD-BD	BD-MS
O2 Theta	**MS**	3.21 (2.80-3.78)	0.000*	0.035	0.028
	MDD	2.40 (1.98-2.82)			
	BD	2.70 (2.27-3.11)			

* $P < .001$.

Abbreviations: BD, bipolar disorder; IQR, interquartile range; MDD, major depressive disorder; MS, manic switch; qEEG, quantitative electroencephalography.

and occipital regions than MDD. Given that previous studies report that gamma power may not be a state marker for BD,[49] our result implies that gamma power can be a trait marker of bipolarity even before the first manic episode.

One of the limitations of our study is the need for a control group. Previous MRI, fMRI, EEG, and ERP studies indicate that patients with BD and MDD differ from each other and HCs.[15,20,22,25,29,31] Nevertheless, it should be noted that this comparative study does not focus on differentiating BD-MDD from HCs but rather on distinguishing depressive patients who will switch to their first manic episode within MDD populations. Therefore, "nonswitching MDD patients" as a control group is more appropriate than "the healthy control" group as in other studies of clinical predictors of patients with BD.[8,9]

Another point is the small sample size of the MS group, yet the rate of patients with MDD who switched to the manic episode is already low, so the rate of the MS in our study is concordant with reported rates.[35] Nevertheless, the results should be interpreted as preliminary for clinical relevance as the sample size is modest. Another limitation of our study is that some patients were not drug free; some used alcohol, some were smokers, and some used substances that may confound the resting state of brain activity. However, the proportion of medication, alcohol, cigarette, and substance use is the same across groups. Thus, the difference between groups in qEEG activity can be reliable. Finally, we could not compare the results with drug-free patients. Hence, we cannot be sure that antidepressants triggered the MS or the MS occured in the typical course of the disease. On the other hand, the treatment of the patients with MDD is the same in the MS group. Therefore, it could be argued that a distinct electrophysiological characteristic is present in patients with MS not explained by antidepressant use only. Moreover, although it has been classified differently before, antidepressant treatment-related mania has been considered an episode of BD in DSM-V.[41] Therefore, the exact reason of manic switch could be negligible in the present research.

Treatment-related MS constitutes an ethical debate in psychiatry. Our findings prove that routine electrophysiological measurement can facilitate the prediction of the MS, hence having an ethical significance. Quantitative electroencephalography is an objective, affordable, and convenient neuroimaging method for routine use in psychiatry. To prevent malpractice in BD, we suggest that qEEG be considered for psychiatric patients.

Historically our study is the first to use resting-state qEEG in predicting the first MS. Our results imply that it might be possible to concentrate on preventing BD just before the outbreaks happen. Since psychiatry is relatively limited in preventive medicine, this electrophysiological pattern should be considered seriously. Whether the electrophysiological marker found in this study will normalize with treatment is the topic of future research.

Author Contributions

MKA and Rİ designed the research and wrote the protocol. Rİ, MTÖ, and MTE conducted literature searches and provided summaries of previous research studies, and wrote the first draft of the manuscript. MGG conducted the statistical analysis. All authors contributed to and have approved the final manuscript.

Declaration of Conflicting Interests

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

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Reyhan İlhan https://orcid.org/0000-0002-2117-8276
Muhammed Taha Esmeray https://orcid.org/0000-0002-8271-9662
Mehmet Kemal Arıkan https://orcid.org/0000-0003-1500-6555
Mehmet Güven Günver https://orcid.org/0000-0002-4628-8391

References

1. Miller JN, Black DW. Bipolar disorder and suicide: a review. *Curr Psychiatry Rep*. 2020;22(2):6. doi:10.1007/s11920-020-1130-0
2. Moreira ALR, Van Meter A, Genzlinger J, Youngstrom EA. Review and meta-analysis of epidemiologic studies of adult bipolar disorder. *J Clin Psychiatry*. 2017;78(9):e1259–e1269. doi:10.4088/JCP.16r11165
3. Painold A, Faber PL, Milz P, et al. Brain electrical source imaging in manic and depressive episodes of bipolar disorder. *Bipolar Disord*. 2014;16(7):690–702. doi:10.1111/bdi.12198
4. Carvalho AF, Firth J, Vieta E. Bipolar disorder. *N Engl J Med*. 2020;383(1):58–66. doi:10.1056/NEJMra1906193

5. Hirschfeld RM. Differential diagnosis of bipolar disorder and major depressive disorder. *J Affect Disord*. 2014;169(Suppl 1): S12–S16. doi:10.1016/S0165-0327(14)70004-7
6. Mitchell PB, Malhi GS. Bipolar depression: phenomenological overview and clinical characteristics. *Bipolar Disord.* 2004; 6(6):530–539. doi:10.1111/j.1399-5618.2004.00137.x
7. Forty L, Smith D, Jones L, et al. Clinical differences between bipolar and unipolar depression. *Br J Psychiatry*. 2008;192(5): 388–389. doi:10.1192/bjp.bp.107.045294
8. Inoue T, Inagaki Y, Kimura T, Shirakawa O. Prevalence and predictors of bipolar disorders in patients with a major depressive episode: the Japanese epidemiological trial with latest measure of bipolar disorder (JET-LMBP). *J Affect Disord.* 2015;174: 535–541. doi:10.1016/j.jad.2014.12.023
9. Calabrese JR, Muzina DJ, Kemp DE, et al. Predictors of bipolar disorder risk among patients currently treated for major depression. *MedGenMed*. 2006;8(3):38.
10. Ochsner KN, Silvers JA, Buhle JT. Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. *Ann N Y Acad Sci*. 2012;1251(1): E1–E24. doi:10.1111/j.1749-6632.2012.06751.x
11. Ford J, Dierks T, Fisher D, et al. Neurophysiological studies of auditory verbal hallucinations. *Schizophr Bull.* 2012;38(4):715–723. doi:10.1093/schbul/sbs009
12. Wallis JD. Orbitofrontal cortex and its contribution to decision-making. *Annu Rev Neurosci*. 2007;30(1):31–56. doi:10.1146/annurev.neuro.30.051606.094334
13. Moran J, Kelley W, Heatherton T. What can the organization of the brain's default mode network tell us about self-knowledge? *Front Hum Neurosci.* 2013;7. doi:10.3389/fnhum.2013.00391
14. Ghaznavi S, Deckersbach T. Rumination in bipolar disorder: evidence for an unquiet mind. *Biol Mood Anxiety Disord*. 2012;2(1):2. doi:10.1186/2045-5380-2-2
15. Wise T, Radua J, Via E, et al. Common and distinct patterns of grey-matter volume alteration in major depression and bipolar disorder: evidence from voxel-based meta-analysis. *Mol Psychiatry*. 2017;22(10):1455–1463. doi:10.1038/mp.2016.72
16. Gong J, Wang J, Qiu S, et al. Common and distinct patterns of intrinsic brain activity alterations in major depression and bipolar disorder: voxel-based meta-analysis. *Transl Psychiatry*. 2020;10(1):353. doi:10.1038/s41398-020-01036-5
17. Yasin S, Hussain SA, Aslan S, Raza I, Muzammel M, Othmani A. EEG based major depressive disorder and bipolar disorder detection using neural networks: a review. *Comput Methods Programs Biomed*. 2021;202:106007. doi:10.1016/j.cmpb.2021.106007
18. Hasanzadeh F, Mohebbi M, Rostami R. Graph theory analysis of directed functional brain networks in major depressive disorder based on EEG signal. *J Neural Eng*. 2020;17(2):026010. doi:10.1088/1741-2552/ab7613
19. Kim DJ, Bolbecker AR, Howell J, et al. Disturbed resting state EEG synchronization in bipolar disorder: a graph-theoretic analysis. *Neuroimage Clin*. 2013;2:414–423. doi:10.1016/j.nicl.2013.03.007
20. Kim S, Baek JH, Shim SH, et al. Alteration of cortical functional networks in mood disorders with resting-state electroencephalography. *Sci Rep*. 2022;12(1):5920. doi:10.1038/s41598-022-10038-w
21. Tas C, Cebi M, Tan O, Hızlı-Sayar G, Tarhan N, Brown EC. EEG power, cordance and coherence differences between unipolar and bipolar depression. *J Affect Disord.* 2015;172:184–190. doi:10.1016/j.jad.2014.10.001
22. Oda Y, Onitsuka T, Tsuchimoto R, et al. Gamma band neural synchronization deficits for auditory steady state responses in bipolar disorder patients. *PLoS One*. 2012;7(7):e39955. doi:10.1371/journal.pone.0039955
23. Isomura S, Onitsuka T, Tsuchimoto R, et al. Differentiation between major depressive disorder and bipolar disorder by auditory steady-state responses. *J Affect Disord.* 2016;190:800–806. doi:10.1016/j.jad.2015.11.034
24. Liu TY, Hsieh JC, Chen YS, Tu PC, Su TP, Chen LF. Different patterns of abnormal gamma oscillatory activity in unipolar and bipolar disorder patients during an implicit emotion task. *Neuropsychologia*. 2012;50(7):1514–1520. doi:10.1016/j.neuropsychologia.2012.03.004
25. Lee PS, Chen YS, Hsieh JC, Su TP, Chen LF. Distinct neuronal oscillatory responses between patients with bipolar and unipolar disorders: a magnetoencephalographic study. *J Affect Disord.* 2010;123(1):270–275. doi:10.1016/j.jad.2009.08.020
26. Vai B, Parenti L, Bollettini I, et al. Predicting differential diagnosis between bipolar and unipolar depression with multiple kernel learning on multimodal structural neuroimaging. *Eur Neuropsychopharmacol.* 2020;34:28–38. doi:10.1016/j.euroneuro.2020.03.008
27. Ravan M, Noroozi A, Sanchez MM, et al. Discriminating between bipolar and major depressive disorder using a machine learning approach and resting-state EEG data. *Clin Neurophysiol*. 2023;146:30–39. doi:10.1016/j.clinph.2022.11.014
28. Kano K, Nakamura M, Matsuoka T, Iida H, Nakajima T. The topographical features of EEGs in patients with affective disorders. *Electroencephalogr Clin Neurophysiol.* 1992;83(2):124–129. doi:10.1016/0013-4694(92)90025-D
29. El-Badri SM, Ashton CH, Moore PB, Marsh VR, Ferrier IN. Electrophysiological and cognitive function in young euthymic patients with bipolar affective disorder. *Bipolar Disord*. 2001;3(2):79–87. doi:10.1034/j.1399-5618.2001.030206.x
30. Başar E, Güntekin B, Atagün I, Turp Gölbaşı B, Tülay E, Özerdem A. Brain's alpha activity is highly reduced in euthymic bipolar disorder patients. *Cogn Neurodyn*. 2012;6(1):11–20. doi:10.1007/s11571-011-9172-y
31. Velasques B, Bittencourt J, Diniz C, et al. Changes in saccadic eye movement (SEM) and quantitative EEG parameter in bipolar patients. *J Affect Disord*. 2013;145(3):378–385. doi:10.1016/j.jad.2012.04.049
32. Özerdem A, Güntekin B, Saatçi E, Tunca Z, Başar E. Disturbance in long distance gamma coherence in bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34(6):861–865. doi:10.1016/j.pnpbp.2010.04.001
33. Özerdem A, Güntekin B, Atagün I, Turp B, Başar E. Reduced long distance gamma (28-48 Hz) coherence in euthymic patients with bipolar disorder. *J Affect Disord*. 2011;132(3):325–332. doi:10.1016/j.jad.2011.02.028
34. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. *Lancet.* 2016;387(10027):1561–1572. doi:10.1016/S0140-6736(15)00241-X
35. O'Donovan C, Alda M. Depression preceding diagnosis of bipolar disorder. *Front Psychiatry*. 2020;11:500. doi:10.3389/fpsyt.2020.00500
36. Angst J, Sellaro R, Stassen HH, Gamma A. Diagnostic conversion from depression to bipolar disorders: results of a long-term prospective study of hospital admissions. *J Affect Disord.* 2005;84(2-3):149–157. doi:10.1016/S0165-0327(03)00195-2
37. Rodrigues Cordeiro C, Côrte-Real BR, Saraiva R, Frey BN, Kapczinski F, de Azevedo Cardoso T. Triggers for acute mood episodes in bipolar disorder: a systematic review. *J Psychiatr Res*. 2023;161:237–260. doi:10.1016/j.jpsychires.2023.03.008

38. Salvadore G, Quiroz JA, Machado-Vieira R, Henter ID, Manji HK, Zarate CA. The neurobiology of the switch process in bipolar disorder: a review. *J Clin Psychiatry*. 2010;71(11):1488–1501. doi:10.4088/JCP.09r05259gre
39. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960;23(1):56–62. doi:10.1136/jnnp.23.1.56
40. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry.* 1978;133(5):429–435. doi:10.1192/bjp.133.5.429
41. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013.
42. Williams JBW. A structured interview guide for the Hamilton Depression Rating Scale. *Arch Gen Psychiatry*. 1988;45(8):742. doi:10.1001/archpsyc.1988.01800320058007
43. Neurosoft. NEURON-SPECTRUM-4/P: 21-channel clinical diagnostic EEG system. 2023. https://neurosoft.com/en/catalog/eeg/neuron-spectrum-1-4p
44. Applied Neuroscience Inc. NeuroGuide^{TM}. 2022. https://appliedneuroscience.com/product/neuroguide/
45. Degabriele R, Lagopoulos J. A review of EEG and ERP studies in bipolar disorder. *Acta Neuropsychiatr.* 2009;21(2):58–66. doi:10.1111/j.1601-5215.2009.00359.x
46. Clementz BA, Sponheim SR, Iacono WG, Beiser M. Resting EEG in first-episode schizophrenia patients, bipolar psychosis patients, and their first-degree relatives. *Psychophysiology*. 1994;31(5):486–494. doi:10.1111/j.1469-8986.1994.tb01052.x
47. Koek R. Hemispheric asymmetry in depression and mania: a longitudinal QEEG study in bipolar disorder. *J Affect Disord.* 1999;53(2):109–122. doi:10.1016/S0165-0327(98)00171-2
48. Nusslock R, Harmon-Jones E, Alloy LB, Urosevic S, Goldstein K, Abramson LY. Elevated left mid-frontal cortical activity prospectively predicts conversion to bipolar I disorder. *J Abnorm Psychol.* 2012;121(3):592–601. doi:10.1037/a0028973
49. Fitzgerald PJ, Watson BO. Gamma oscillations as a biomarker for major depression: an emerging topic. *Transl Psychiatry*. 2018;8(1):177. doi:10.1038/s41398-018-0239-y
50. Pizzagalli DA, Peccoralo LA, Davidson RJ, Cohen JD. Resting anterior cingulate activity and abnormal responses to errors in subjects with elevated depressive symptoms: a 128-channel EEG study. *Hum Brain Mapp*. 2006;27(3):185–201. doi:10.1002/hbm.20172
51. Noda Y, Zomorrodi R, Saeki T, et al. Resting-state EEG gamma power and theta–gamma coupling enhancement following high-frequency left dorsolateral prefrontal rTMS in patients with depression. *Clin Neurophysiol.* 2017;128(3):424–432. doi:10.1016/j.clinph.2016.12.023