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ORIGINAL RESEARCH

Electrophysiological Markers Predicting Antipsychotic Treatment Response in Patients with Schizophrenia: A Retrospective Study

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Purpose: This study aimed to provide an objective means of predicting treatment responses in patients with schizophrenia using quantitative electroencephalography (qEEG) as an electrophysiological indicator. We obtained qEEG recordings from patients with schizophrenia and explored them for patterns indicative of treatment responsiveness.

Patients and Methods: The study included 68 patients had been diagnosed with schizophrenia spectrum disorder. After retrospectively gathering demographic information, clinical data such as qEEG, Positive and Negative Syndrome Scale (PANSS), a multiple regression analysis was performed. This analysis employed baseline qEEG findings as independent variables and PANSS score changes as dependent variables to discern causal relationships.

Results: The mean age of the participants was 38.4 years(*SD* =13.73). The mean PANSS score on admission was 92.97, decreasing to 67.41 at discharge. Multiple regression analysis revealed that delta waves in T4 (β=0.346, t=3.165, p=0.002), and high-beta waves in Fp2 (β=0.231, t=2.361, p=0.021) were associated with PANSS changes in absolute power. In addition, the delta waves of O2 (β=0.250, t=3.288, p=0.002); beta waves of T3 (β=−1.463, t=−5.423, p<0.001) and O2 (β=0.551, t=3.366, p=0.001); high beta waves of Fp1 (β=0.307, t=4.026, p<0.001), T3 (β=0.855, t=4.414, p<0.001) and T6 (β=−0.838, t=−4.559, p<0.001) of absolute power using the Z-score were also related to PANSS changes. Pearson's correlation analysis showed that only delta waves at Cz (r= 0.246, p=0.043) in absolute power correlated with changes in the PANSS.

Conclusion: We found that certain qEEG wave patterns in patients with schizophrenia prior to antipsychotic treatment were linked to PANSS changes before and after treatment. Delta waves and beta waves, primarily in the frontal and temporal regions, were found to be significantly associated with changes in PANSS scores. In the future, the qEEG indicators identified in this study could serve as electrophysiological markers for predicting antipsychotic treatment responses in patients with schizophrenia.

Keywords: schizophrenia, treatment response, quantitative electroencephalography, electrophysiological marker, retrospective study

Introduction

Schizophrenia, typically onset in early adulthood, manifests symptoms including delusions, hallucinations, disorganized language, emotional blunting, and cognitive impairment.[1] Without early intervention, it can lead to significant social dysfunction and a chronic course.[2,3] Despite treatment with antipsychotic medications, some patients exhibit poor responsiveness, termed treatment-resistant schizophrenia, which may involve abnormalities beyond the dopamine system, such as the glutamate system.[4–8] The development of atypical antipsychotic drugs in the 1990s expanded treatment options, but the response to antipsychotics varies widely among individuals, with an estimated prevalence of treatment-resistant schizophrenia reaching up to 30%.[9,10]

Various studies have attempted to develop a method for predicting treatment responsiveness in schizophrenia, utilizing techniques such as electroencephalography (EEG), functional magnetic resonance imaging (fMRI), cortisol and inflammatory markers, and genetic markers; however, no method has proven effective.[11–14] EEG is a non-invasive,

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accessible, and cost-effective approach.[11] Quantitative electroencephalography (qEEG), a non-invasive method with excellent temporal resolution, allows the quantitative analysis of electroencephalogram.[15] With its accessibility and low cost, qEEG has gained popularity in clinical, cognitive psychology, and engineering fields.[15] Unlike conventional EEG readings, qEEG analysis employs computer algorithms that enable the detection of abnormal findings not visible in traditional EEG readings.[15] There have been studies investigating neurophysiological markers of schizophrenia using qEEG,[15] but research on predicting treatment responsiveness in schizophrenia has been limited.

Inhibitory GABAergic cell abnormalities in schizophrenia have been identified in numerous studies, and the resulting dissonance between the cortex and thalamus reportedly manifests as abnormalities in specific frequency bands of brainwave patterns.[16] Consistent findings include increased slow waves, decreased alpha waves, and increased beta waves, primarily in the frontal lobe.[17] Increased slow waves in the frontal lobe indicate functional decline, whereas increased beta wave activity in specific regions has been observed in patients with schizophrenia exhibiting hallucinatory symptoms.[15,18] These abnormal quantitative brainwave results are particularly prevalent in the frontal lobes of patients with schizophrenia.[19] The increase in slow waves (delta and theta) in the frontal lobe of patients with schizophrenia is interpreted as reflecting a functional decline in this region. This is further supported by other neuroimaging examinations that have confirmed reduced blood flow, atrophy, and decreased metabolic rates in the frontal lobe.[20,21] Studies have also explored the electrophysiological characteristics of different subtypes of schizophrenia. Developing biomarkers to predict treatment response objectively, quickly, and accurately is of paramount importance. Recent studies on schizophrenia have used EEG to predict treatment responses, suggesting the potential of mismatch negativity (MMN) as a biomarker for improving or preventing the onset of psychosis.[11] Moreover, a recent meta-analysis suggesting the potential of EEG as a biomarker for predicting response to antipsychotics highlighted that changed theta power, reduced beta-band activity, increased alpha activity, and decreased coherence in theta, alpha, and beta-band at pre-treatment resting-state EEG were identified as the most relevant predictors of poor response.[22] Additionally, research using qEEG to predict ECT treatment response in schizophrenia revealed higher assortativity among several brain regions in the beta and theta bands within the response group.[23]

Ideally, biomarkers should be measurable before the disease becomes chronic, aid in disease prevention and cessation, be convenient to measure, and reflect disease prognosis.[24] Electrophysiological markers hold promise as better markers than traditional neuropsychological markers because they can aid an early diagnosis, reflect early stage functional brain damage associated with schizophrenia pathophysiology, and are closely correlated with cognitive impairment.[25] Because of their high temporal resolution, electrophysiological markers can sensitively detect changes over time.[26] Consequently, while predicting treatment response in patients with schizophrenia using qEEG is considered useful, previous studies have primarily focused on clozapine or first-generation antipsychotics, or did not account for medication dosage, which presented limitations.[22] Additionally, many studies lacked information on treatment duration, and previous medication use.[22] Therefore, this study aimed to objectively predict the treatment response of patients with schizophrenia and explore electrophysiological markers to assess treatment effectiveness more quickly and accurately.

Material and Methods

Participants

This study included patients with schizophrenia who received inpatient treatment at the Department of Psychiatry, Catholic University of Daegu Hospital between June 2019 and September 2022. Upon admission, eligible Participants were diagnosed with schizophrenia, schizoaffective disorder, or schizophreniform disorder based on the DSM-5 diagnostic criteria. All participants were Korean. The exclusion criteria were serious physical or neurological conditions that could affect health, a history of substance abuse or withdrawal, a high risk of self-harm requiring immediate intervention, overt suicidal thoughts, brain damage or concussion with loss of consciousness, significant intellectual decline prior to the onset of schizophrenic symptoms, a history of convulsive disease, intellectual disability, organic brain disease, or alcohol or drug dependence. This study was approved by the Institutional Review Board (IRB) of Daegu Catholic University Medical Center (DCUMC IRB approval No. CR-23-063) and was performed in accordance with the

Declaration of Helsinki (World Medical Association: Ethical Principles for Medical Research Involving Human Subjects, 1964). The need for informed consent was waived due to the retrospective nature of the study.

Measures

Sociodemographic data including sex and age were collected. Clinical data consisted of qEEG results, Positive and Negative Syndrome Scale (PANSS) scores, and antipsychotic drug doses converted into chlorpromazine equivalents.

Positive and Negative Syndrome Scale (PANSS)

Kay et al[27] developed the PANSS to assess schizophrenia, enhancing replicability and objectivity while enabling symptom comparison.[27,28] With 30 items rated on a severity scale, it categorizes symptoms into positive, negative, and general psychopathology.[27,28] Widely used, PANSS improves interrater reliability and facilitates comparisons with other mental disorders.[28] In this study, the PANSS was administered by psychiatrists who had been regularly providing clinical care to the study participants after receiving sufficient pre-assessment training.

Chlorpromazine Equivalents

Chlorpromazine was the first antipsychotic drug to introduce pharmacological treatment for schizophrenia.[29] Subsequent antipsychotic drugs have necessitated conversion to chlorpromazine-equivalent doses for dosage comparisons due to differing potencies.[30] Clinical trial limitations, mainly involving chronic patients, have prompted alternative methods such as expert consensus and regression equations for determining dose equivalence.[30] Many studies on treatment-resistant schizophrenia have defined the criteria for chlorpromazine equivalent doses (eg, doses of ≥600 mg without any treatment response).[7]

EEG Recording and Analysis

EEG recordings were conducted using a 44-channel comet plus digital EEG system (Grass Technologies, USA) at Daegu Catholic University Hospital. The electrodes were placed according to the International 10–20 system, with the ear serving as the reference electrode. Gold-plated cup electrodes were used, maintaining impedance below 5 Ω. On the first day of admission, participants underwent qEEG examination, during which they were seated in a quiet room and instructed to keep their eyes closed for the duration of the 4-minute resting EEG measurement, from which skilled researchers manually selected 10-second artifact-free segments. Automatic eyeblink removal was performed using the Neuroguide(version 3.2.8; Applied Neuroscience, Inc., St. Petersburg, FL, USA) and segments similar to the selected artifact-free segments were automatically chosen. This process ensured that a minimum of 60s of selected resting brain waves were used for quantitative analysis. Fast Fourier Transformation was employed to digitize the EEG data and obtain the power spectrum values for several frequency bands, including delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–25 Hz), and high beta (25–30 Hz). The z-scores of the absolute power for these frequency ranges were separately calculated for each of the 19 channels by comparing them with the normal database. The z-score indicated where the data fell within the normal distribution of the control group in the NeuroGuide. The z-scores provided in the NeuroGuide are based on a standard normal distribution with a mean of 0 and variance of 1, and they reflect the comparison results with data matched for age and sex within the database.[31]

Statistical Analysis

Based on the nature of the data, demographic and clinical variables were compared using either a *t*-tests, chi-square test, or Fisher's exact test. To examine the impact of baseline qEEG Measures on the change in PANSS scores before and after admission, we employed a multiple regression analysis and conducted a correlation analysis to ascertain the linear relationship between the two variables. Statistical significance was set at a p value of <0.05. All analyses were performed using the statistical program SPSS (version 25.0; IBM Corp., Armonk, NY, USA). The sample size was determined using G Power version 3.1.9.4. To detect an effect size ($f^2=0.15$) with multiple linear regression, considering an α error of 0.05, a β error of 0.2 (power=80%), and 1 covariate, a sample size of 68 was required.

Results

Demographic Data

The mean age of all participants was 38.4 years (*SD* =13.73), and the mean admission period was 24.56 days. Among the participants, 50 were diagnosed with schizophrenia, multiple episodes, currently in an acute episode; 14 were diagnosed with schizophrenia, first episode, currently in an acute episode; and 4 were diagnosed with schizophreniform disorder. The mean PANSS score was 92.97 at admission and 67.41 at discharge. Participants were prescribed an antipsychotic drug at an equivalent dose of chlorpromazine, with a mean intake of 458.81 mg at hospitalization and 704.67 mg at discharge (Table 1). At the time of discharge, none of the patients were using first-generation antipsychotics. The change in chlorpromazine dosage was included as a covariate in the regression analysis. Additionally, there were 14 patients who used benzodiazepines, with a lorazepam-equivalent dose of 1.44 mg. This was also included as a variable in the regression analysis.

Multiple Regression Analysis

Several EEG frequencies were associated with changes in the PANSS. In terms of absolute power, delta wave in T4 (β=0.346, t=3.165, p=0.002), and high beta wave in Fp2 (β=0.231, t=2.361, p=0.021) were associated with PANSS changes. In terms of absolute power using Z-score, delta wave in O2(β=0.250, t=3.288, p=0.002), beta wave in T3 (β=−1.463, t=−5.423, p<0.001), O2 (β=0.551, t=3.366, p=0.001), high beta wave in Fp1 (β=0.307, t=4.026, p<0.001), T3 (β=0.855, t=4.414, p<0.001), and T6 (β=−0.838, t=−4.559, p<0.001) were associated with PANSS changes. No significant correlations were found between the theta and alpha waves in either absolute or relative power (Table 2).

Pearson Correlation Analysis

In terms of absolute power, delta waves at Cz (r= 0.246, p=0.043) were associated with PANSS changes. In absolute power using the Z-score, a trend was observed in the delta wave at Cz (r= 0.227, p=0.063), C3 (r= 0.223, p=0.067), and C4 (r= 0.227, p=0.058); however, this did not reach statistical significance (Figure 1).

Table 1 Characteristics of the Study Population (N=68)

	N=68
Sex(M/F)	33/35
Age	38.43
Admission date (days)	24.56
PANSS at admission	92.97
PANSS at discharge	67.41
PANSS changes (%)	27.18
GAF at admission	39.49
GAF at discharge	56.54
CGI at admission	5.16
CGI at discharge	3.34
Chlorpromazine equivalent dose at admission (mg)	458.81
Chlorpromazine equivalent dose at discharge (mg)	704.67

Abbreviations: PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning; CGI, Clinical Global Impression.

Table 2 Multiple Regression Analysis in Absolute Power and Z-Score Absolute Power

Power	Frequency band	Lead	Regression Coefficient (β)	t	*P* value
Absolute power	Delta	T4	0.346	3.165	**0.002**
	High Beta	Fp2	0.231	2.361	**0.021**
Z-score Absolute Power	Delta	O2	0.250	3.288	**0.002**
	Beta	T3 O2	−1.463 0.551	−5.423 3.366	**<0.001** **0.001**
	High Beta	Fp1 T3 T6	0.307 0.855 −0.838	4.026 4.414 −4.559	**<0.001**

Note: The p values in bold are statistically significant (p<0.05).

Discussion

Our study included 68 participants diagnosed with schizophrenia or schizophreniform disorder. The mean age was 38.4 years, with a mean admission date of 24.56 days. The PANSS scores showed a significant reduction from 92.97 at admission to 67.41 at discharge, accompanied by an increase in the mean chlorpromazine-equivalent antipsychotic dosage from 458.81 mg to 704.67 mg. Multiple regression analysis identified that delta waves in the T4 region(temporal area) and high beta waves in the Fp2 region(frontal area) were significantly associated with PANSS score changes in absolute power. Additionally, when considering Z-scores for absolute power, delta waves in the O2 region(occipital area),

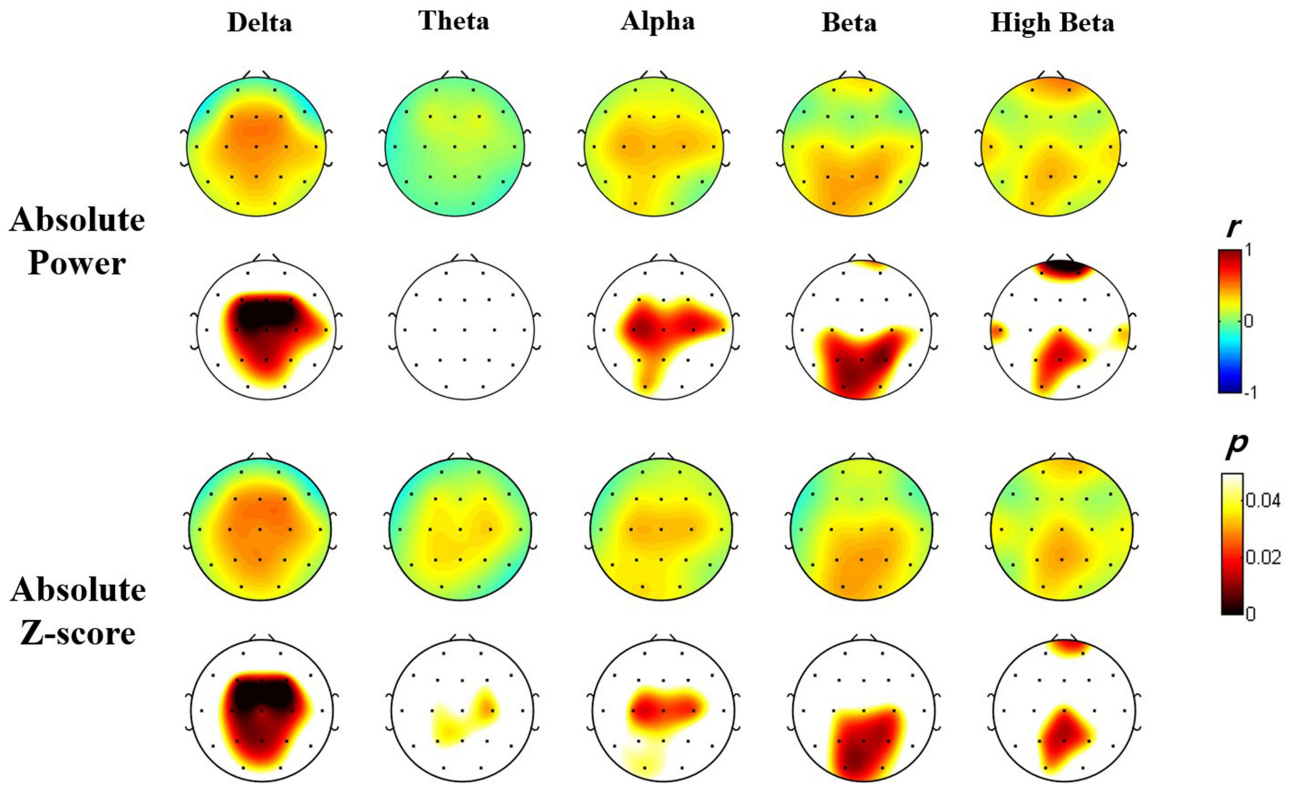

Figure 1 Topographical representation of the statistical results of the Pearson correlation analysis between the change in PANSS scores and EEG analysis.
Notes: Upper topoplots denote Pearson's correlation coefficients (R). Lower topoplots denote statistical significance (P) after applying the Bonferroni correction.
Abbreviations: PANSS, Positive and Negative Syndrome Scale; EEG, electroencephalogram.

beta waves in the T3 and O2 regions(temporal and occipital area), and high beta waves in the Fp1, T3, and T6 regions (frontal and temporal area) were significantly related to PANSS score changes. Pearson correlation analysis further supported these findings, particularly highlighting delta waves at the Cz region(central area) in absolute power. These Results suggest that specific qEEG wave patterns are predictive of antipsychotic treatment response in patients with schizophrenia.

Regarding sociodemographic information, our findings were similar to those of previous studies conducted on individuals with schizophrenia; however, there were some differences. In a study aimed at predicting treatment responsiveness in 111 hospitalized schizophrenia patients receiving atypical antipsychotics, the mean age was 35.6 years in the olanzapine group, 35.04 years in the risperidone group, and 36.21 years in the paliperidone group.[32] The mean PANSS score at admission was 89.59 points, which decreased to 75.36 points at week 4 and 73.59 points at week 8.[32] Another study examining the prescribing patterns of antipsychotic medications in 1032 patients admitted for schizophrenia found that the participants had a mean age of 38.39 years and a mean GAF score of 44.40 at admission.[33]

Multiple regression analysis demonstrated that specific EEG frequencies were associated with changes in the PANSS. Notably, delta wave activity at T4 and high beta wave activity at Fp2 were positively associated with PANSS changes in absolute power, highlighting their potential as significant predictors of treatment response. Additionally, in the relative power analysis using Z-scores, delta wave activity in O2, beta wave activity in T3 and O2, and high beta wave activity in Fp1, T3, and T6 were associated with PANSS changes. Previous studies have primarily focused on monitoring brain wave changes in the frontal cortex, and have concluded that increased delta and theta waves in individuals with schizophrenia reflect functional impairments in this region.[20,21] Research findings regarding delta waves were particularly common. A study that evaluated emotion recognition skills in patients with treatment-resistant schizophrenia before and after clozapine initiation found that emotion recognition deficits were associated with increased delta wave activity in the posterior, frontal-midline, and frontal-temporal regions.[34] Previous studies revealed a significant positive correlation between delta power and negative symptom rating scale scores in the temporal lobe of individuals with schizophrenia.[35] Additionally, it has been reported that the use of clozapine in patients with schizophrenia leads to a significant increase in delta-wave activity in the occipital area.[36]

In a study that classified schizophrenia patients into subgroups and compared differences in brain waves, it was found that the beta2 band (18–22 Hz) was the most distinctive when comparing schizophrenia patients with high cognitive/disorganization symptoms with those without such symptoms.[37] Findings have also indicated increased beta wave activity in the frontal cortex of schizophrenia patients exhibiting hallucinatory symptoms.[15,18] In another study, although the sample size was limited to 23 participants, it was observed that an increase in beta wave activity was associated with a decrease in the level of insight in patients with schizophrenia. This negative correlation was evident in the F3 and C3 regions.[38] These findings from prior research partially support the results of the present study. Meanwhile, the results of the multiple regression analysis showed significant outcomes in several leads from the frontal, temporal, and occipital areas, which is consistent with previous findings.[22] The involvement of most brain regions reflects the dysfunction of both local and long-range brain networks in patients with schizophrenia as recorded by EEG. This aligns with the concept of schizophrenia as a whole-brain disorder related to large-scale network disruptions.[22] Furthermore, it suggests that measurable changes can be observed depending on the treatment responsiveness of patients with schizophrenia.

Although certain associations were observed in the Pearson correlation analysis, specifically concerning the delta wave activity in Cz, C3, and C4, it is important to note that statistical significance was not consistently reached, despite the observation of noticeable trends. In a study of 32 patients with schizophrenia who had not taken medication for over 4 weeks, EEG measurements were taken approximately 4–5 hours after aripiprazole administration.[39] The findings revealed a significant reduction in delta wave activity in the central region, which supports the outcomes of this study; however, further research with larger sample sizes is required to confirm these potential correlations.

This study has several limitations, one of which is the study is the sample size. Although this study yielded valuable insights into predicting treatment-resistant schizophrenia using qEEG measures, the sample size may not fully represent the heterogeneity of individuals with this condition. A larger and more diverse sample size could provide a more comprehensive understanding of the predictive capabilities of qEEG in this context. Second, because schizophrenia exhibits various psychiatric characteristics, a subgroup analysis may have been necessary; however, this was not conducted in the present study. Furthermore, our study did not account for factors such as sex or age in the patients with schizophrenia. Previous

research has indicated that female patients with schizophrenia tend to exhibit higher values of beta waves in the left frontal, temporal, and parietal regions than males, which are associated with elevated PANSS and BPRS scores.[40] Therefore, future studies should consider these factors. Third, when patients were divided into treatment-responsive and treatment-resistant groups based on PANSS changes, there were no significant differences in age or sex; however, there were significant differences in the dosage of antipsychotics used and PANSS scores at admission. To address these problems, we included these variables in the regression analysis.

Conclusion

This study observed significant associations between specific EEG frequencies and changes in PANSS scores, emphasizing the potential value of these EEG patterns as predictors of treatment response in patients with schizophrenia. Although some trends were identified in the Pearson correlation analysis, further research with larger sample sizes is required to confirm these potential correlations. Nonetheless, our study opens new avenues for predicting treatment responsiveness in patients with schizophrenia using qEEG analysis, offering potential guidance for treatment strategies and individualized interventions.

Institutional Review Board Statement

The studies were reviewed and approved by Institutional Review Board (IRB) of Daegu Catholic University Medical Center. All procedures followed the declaration of Helsinki.

Data Sharing Statement

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Disclosure

The authors have no potential conflicts of interest to disclose for this work.

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