Neuropsychiatr Invest. 2022;60(4):85-90

Original Article
10.5152/NeuropsychiatricInvest.2022.22014

Regional Absolute Power Quantitative EEG After Single Dose of Aripiprazole in Patients with Schizophrenia

Gautam Sharma[1], **Shipra Singh**[2]

[1]*Department of Psychiatry, Dr. Ram Manohar Lohia Hospital & ABVIMS, New Delhi, India*

[2]*Department of Psychiatry, Institute of Mental Health, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences (PGIMS), Rohtak, India*

ABSTRACT

Objective: The aim of this study is to investigate the relationship between regional absolute power quantitative electroencephalogram (EEG) after a single dose of aripiprazole and short-term treatment response in patients with schizophrenia as a predictor.

Methods: The study analyzed the regional absolute power quantitative EEG in 32 patients with schizophrenia who were either drug naive or off-medication for last 4 weeks. The quantitative EEG was undertaken at intake and after 4 to 5 hours of a single dose of aripiprazole. Welch-averaged periodogram was used in the Fourier transformation for spectral analysis. After fast Fourier transform of quantitative EEG data, the mean absolute power in delta, theta, alpha, beta, and gamma band in 13 regions was analyzed and correlated with Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale-Anchored (BPRS-A) scores.

Results: Regional absolute power spectral analysis after single dose of aripiprazole showed significant decrease in delta, theta, alpha 1, alpha 2, beta 1 in midline region, alpha 2 band in right occipital region and gamma 2 in prefrontal region. Further analysis with PANSS and BPRS-A showed no significant correlation; however, aripiprazole proved to be an efficacious drug for schizophrenia.

Conclusion: This result suggests that the regional absolute power after a single dose attenuates but does not correlate to predict a clinical response. This study kindles the idea for further studies in selected quantitative EEG channels, to predict a clinical response to psychotropic drugs during the early phase of illness and to understand the etiology of schizophrenia and further development of novel drugs.

Keywords: qEEG, schizophrenia, aripiprazole, antipsychotic, pharmaco-EEG

Corresponding author:
Shipra Singh

E-mail:
ssomvanshi27@gmail.com

Received: June 26, 2022
Accepted: October 10, 2022
Publication Date: November 10, 2022

INTRODUCTION

Schizophrenia is a complex disease regarding etiology, clinical manifestation, course, treatment response, and outcome.[1,2] The poor understanding of the pathophysiology of schizophrenia led to various treatment methods based on trial and error. Since the introduction of chlorpromazine in 1952,

Cite this article as: Sharma G, Singh S. Regional absolute power quantitative EEG after single dose of aripiprazole in patients with schizophrenia. *Neuropsychiatr Invest.* 2022;60(4):85-90.

antipsychotics have been the mainstay in the treatment of schizophrenia. It is relevant to identify the responders from non-responders to an antipsychotic so as to decrease the duration of untreated psychosis by selecting appropriate antipsychotics at an early stage.[2,3] This has significant clinical implications, such as understanding long-term drug side effects, reducing illness burden and hospitalization cost, and improved prognosis. Identifying biological markers to predict treatment response as in personalized medicine intervention will result in overall better outcome in schizophrenia.[4,5]

In the recent past, quantitative EEG (qEEG)-based biomarkers have been studied to differentiate neurological[6] and psychiatric disorders[7-11] with high sensitivity and specificity,[12] and exploring biomarkers was envisioned for the Diagnostic and Statistical Manual of Mental Disorders (DSM), fifth edition (DSM-5) too.[13] Quantitative EEG is easily available, noninvasive, and independent of patient's or doctor's evaluation and depends on the patient's physiological response, with good temporal resolution making it a reliable tool in selecting appropriate antipsychotic for patients with schizophrenia. A comprehensive understanding of qEEG in schizophrenia could provide insight into pathophysiological changes[14] and of the neural mechanism's underlying response to antipsychotic treatment for further development of novel medication.[15,16] There have been few studies that have explored the qEEG changes after a single dose of antipsychotics and predicting the response in patients with schizophrenia.

It is known that patients with schizophrenia show higher absolute power activation in delta, theta, and beta bands with decreased alpha band[17,18] as compared to normal control[7,19-21]; however, studies have also shown no difference in the alpha band.[22] An earlier study by Harris et al[17] has shown difference in the first episode and chronic schizophrenia with regard to the mean peak frequency in the delta band. Antipsychotics modify qEEG, and drug response could bring normalization.[23] A study has differentiated responders based on the absolute power increase in theta2, alpha1, and symptoms. In most pharmaco-EEG studies, there are confusing results related to a single dose of antipsychotics. A study by Galderisi et al[24] compared the qEEG profile of drug-naive patients and that of 29 patients with schizophrenia after a single dose (at 6 hours) of haloperidol, as a predictor of short-term response. The responders showed fewer slower and faster activities than the non-responders. The responder group exhibited a significant decrease of delta, a significant increase of fast theta, and a significant increase of slow alpha and beta2. The non-responders exhibited a significant decrease of delta and an increase of beta2 but also showed a significant decrease of slow alpha; thus, responders and non-responders could be predicted with an accuracy of 89.3%.[24] Mucci et al[15] found responders to have an increase in fast theta and slow alpha, whereas non-responders showed a decrease in slow alpha. Both groups showed a significant decrease in delta and increase in beta2. Saletu et al[25] showed a decrease in delta and theta over the left temporal region after a single dose of 50 mg of amisulpride, which further decreased with a dose on day 42 over the frontal and left parietal and right temporo-occipital regions, with an increase in beta, whereas alpha did not exhibit any change. After a single dose of clozapine, Knott et al[26] showed an increase in delta posteriorly (P3, P4, Pz, O1, O2, and Oz) and in alpha and beta anteriorly (Fp1, Fp2, Fpz, F3, F4, C3, and C4) with decreased alpha power in the occipital region (O1, O2, and Oz) in responders as compared to non-responders. Nagase et al[27] reported a decrease in theta power in medicated patients after 6 months of treatment with antipsychotics.

Other studies that explored qEEG after varied intervals (hours after single dose to weeks on regular medication) of antipsychotic treatment found different qEEG pictures.[28] One study, using conventional EEG in patients with schizophrenia, found increased alpha activity only in responders to haloperidol as compared to non-responders.[29] Lacroix et al[30] found no relationship between qEEG changes in the amplitude of any frequency band and clinical response; however, there was a significant relation between reduction in alpha and theta band coherence and a favorable response to the drug. Moore et al[31] studied the group effect of haloperidol and remoxipride and found that responders showed an increase in alpha activity as compared to non-responders at 6 weeks. Fluperlapine, an atypical antipsychotic which was withdrawn due to it causing agranulocytosis, showed an increase in delta, theta, and beta activity with decreased alpha band; in another study, haloperidol showed a decrease in delta, theta, and fast beta with increased alpha in P3, P4, O1, and O2 to Cz.[32] Another study showed that clozapine induced marked increases in slow-wave activity and decreased alpha activity, while risperidone, quetiapine, olanzapine, aripiprazole, amisulpride, paliperidone, ziprasidone, and haloperidol showed an increase in alpha activity over the occipital area.[20] A study using depot injection of haloperidol decanoate in patients with schizophrenia showed an increase in the absolute alpha power in the first week in the left hemisphere. Increase in slow alpha after medication was significantly correlated with a favorable clinical response.[33] Small et al[34] described an increase of alpha activity after a single dose of clozapine (25 mg) in patients with treatment-resistant schizophrenia.

The present study focuses on the changes in high-resolution qEEG measures of spectral power in patients with schizophrenia with a single dose of Aripiprazole, and to assess whether such changes could predict the clinical outcome after four weeks of Aripiprazole. Aripiprazole is the first non-D2 receptor antagonist and represents a novel treatment developed for patients with schizophrenia. The efficacy of aripiprazole is primarily due to the parent drug and, to a lesser extent, its major metabolite, dehydro-aripiprazole. Aripiprazole is effective against both positive and negative symptoms.[35] However, just as there is a lot that is unknown about this drug, there is a lot that is yet to be discovered regarding the etiopathological understanding of schizophrenia. This study aims to assess the qEEG changes following aripiprazole intake in patients with schizophrenia. Finding a biological predictor is not a simple task using qEEG as it is known that several factors impact an outcome in any given patient.

METHODS

Participants

The patients attending the psychiatry outpatient department, who were diagnosed with schizophrenia as per the International Classification of Diseases (ICD-10) Classification of Mental and Behavioral Disorders, were screened. Based on the inclusion and exclusion criteria, those fulfilling the criteria were recruited in the study. Purposive sampling method was utilized. The study was based on the mandatory dissertation work of postgraduate course in psychiatry and was approved by the Institutional Ethics Committee of the Central Institute of Psychiatry, Ranchi, India. Written informed consent was obtained from all participants and their caregivers. Participants who were between 18 and 50 years of age, right-handed, and started on tablet aripiprazole 15 mg by the treating clinicians were included. They had to be either drug naïve or drug free from any oral antipsychotic medications for the last 4 weeks or any depot antipsychotics in the last 3 months or should not have

received electroconvulsive therapy in the last 6 months. Patients who had a comorbid diagnosis of mental retardation, organic brain disorders, a brief reactive psychosis, a history of alcohol or drug dependence in the last 6 months, or a clinically significant hepatic, renal, metabolic, or neurological disorder or who were unable to comply with the study protocol were excluded. Thirty-eight patients were initially enrolled. However, 6 patients were lost to follow-up assessment.

Assessment Tools

The following tools were used in the study:

1. Neurofax EEG-1100: It was used for qEEG data.

2. MATLAB software V.6.5 for qEEG data processing.

3. ICD-10 Diagnostic Criteria for Research: It lays down internationally agreed diagnostic criteria specifically designed for use when conducting research on mental and behavioral disorders. The contents are derivative of the Tenth Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10).[36]

4. Sidedness Bias Schedule: It was used to assess the handedness or hand preference in participants.[37]

5. Positive and Negative Syndrome Scale (PANSS): It is a 30-item symptom rating scale that was designed to measure the core positive and negative symptoms of schizophrenia and related psychopathology (e.g., anxiety and depression) during the past 7 days, as reported by hospital staff, family, or other collateral informants. Each of the items making up the positive and negative scales correlated very strongly with the scale total ($P < .001$) and the mean item total correlations of 0.62 and 0.70, respectively. The alpha coefficients ranged from 0.64 to 0.84.[38]

6. Brief Psychiatric Rating Scale-Anchored (BPRS-A): Brief Psychiatric Rating Scale is a widely used inventory used for the assessment of psychopathology, particularly in the context of outcome evaluation in psychopharmacological trials. Brief Psychiatric Rating Scale-Anchored is a modification of BPRS, consisting primarily of adding exclusionary statements which attempt to facilitate clear definition and restrict overgeneralizations.[39]

Procedure

Participants, included in the study, were first prepared for the procedure. Patients' hair was washed thoroughly with a soap containing no glycerin and then allowed to dry properly. All subjects were asked not to smoke or take caffeine during the 3 hours preceding the recording. Recording was done in a reclining position in a light-attenuated and soundproof room. The subjects were asked to remain relaxed and to minimize motor movements during the recording. The insulated room was air-conditioned to avoid sweating. The other electronic gadgets like mobile phones, telephones, and other instruments known to cause artefacts in the room were switched off.

EEG data were acquired from 64 channels through Nihon Kohden Neurofax electroencephalograph EEG-1100K. Data were sampled at 1000 Hz/per channel and stored in ASCII format for offline analysis. Ag–AgCl electrodes were applied on scalp according to international 10/10 system using a linked ear reference. The sites were FP2, AF8, F8, FT8, T8, FP1, AF7, F7, FT7, T7, Fz, F2, F4, F6, F1, F3, F5, FCz, FC2, FC4, FC6, FC1, FC3, FC5, Cz, C2, C4, C6, C1, C3, C5, CPz, CP2, CP4, CP6, TP8, CP1, CP3, CP5, TP7, PZ, F10, F9, AF2, AF4, AF3, Oz, O2, O1, P6, P3, P7, P8, P2, P5, P1, T2, and T1. Skin resistance at each site was kept below 5 KΩ. Eye movement potentials were recorded using 2 electrodes placed 1-cm lateral to the outer canthus of each eye.

The first qEEG was recorded at baseline, that is, before the intake of aripiprazole (15 mg) by the patient, and the second qEEG was recorded after 4-5 hours of taking the aripiprazole. This gap was decided based on the time duration required for aripiprazole to reach its peak plasma concentration, that is, 3-5 hours. Continuous resting EEG of each subject was recorded for approximately 15 minutes with eyes closed. This was done to ensure enough artefact-free EEG signal for processing. Later, the data were processed to remove artefacts offline. Analog to digital conversion was 16 bits, the time constant was 0.03 Hz, and the high-cut frequency was set at 300 Hz. An average of 3 minutes of data was collected from each recording for further analysis using MATLAB v 6.5.

Computations involved 9 frequency bands of spectral power in various bands: delta (1-4 Hz), theta (5-8 Hz), alpha1 (9-10 Hz), alpha2 (11-12 Hz), beta1(13 -18 Hz), beta2 (19-20 Hz), beta3 (21-30 Hz), gamma1 (30-100 Hz), and gamma2 (30-130 Hz). Welch-averaged periodogram was used in the Fourier transformation for spectral analysis. The data were computed using standardized software MATLAB.

To improve the understanding of regional changes in the absolute power, the average of the power scores of channels was calculated. Thus, 13 regions were identified for power spectral analysis: (1) right prefrontal—FP2, AF4, and AF8; (2) right frontal—F2, FC2, F4, FC4, F6, FC6, F8, and F10; (3) right temporal—FT8, T8, TP8, FT10, T10, and T2; (4) right central—C2, C4, and C6; (5) right parietal—CP2, P2, CP4, P4, CP6, P6, and P8; (6) right occipital—O2; (7) midline—FPz, AFz, Fz, FCz, Cz, CPz, Pz, and Oz; (8) left prefrontal—FP1,AF3, and AF7; (9) left frontal—F1, FC1, F3, FC3, F5, FC5, F7, and F9; (10) left temporal—FT7, T7, TP7, FT9, T9, and T1; (11) left central—C1, C3, and C5; (12) left parietal—CP1, P1, CP3, P3, CP5, P5, and P7; and (13) left occipital—O1. The data of channels included were averaging for each region and were log transformed.

Drug therapy was continued with aripiprazole 15 mg once daily while waiting for a reevaluation, which was done after 2 weeks. Patients with a reduction in the PANSS total score >25% were continued on the same dose of aripiprazole, while those with a reduction in PANSS total score of <25% had the daily dose raised to 30 mg once daily after 2 weeks. The study protocol mentioned that in the event of any occurrence of side effects of aripiprazole (extrapyramidal symptoms

Table 1. Illness-Related Characteristics of the Participants

Variable	Study Group (n = 32)		
	Mean	Standard Deviation	Range
Age of onset (years)	26.13	5.59	19-35
Duration of illness (years)	3.58	2.55	0.2-9.0
Drug-free duration (months)	7.16	3.1	3-24

Table 2. Comparison of PANSS and BPRS-A Scores at Baseline and at 1 Month using Paired *t*-Test

	Baseline (n = 32)		1 month (n = 32)			
	Mean	SD	Mean	SD	*t*	*P*
Total PANSS	103.37	21.81	56.03	11.70	14.182	.000*
PANSS—positive symptoms	27.94	5.51	14.66	4.597	17.829	.000*
PANSS—negative symptoms	27.03	9.02	14.75	4.597	9.304	.000*
PANSS—general symptoms	48.31	11.26	26.53	5.346	12.439	.000*
Total BPRS-A score	38.94	9.19	14.38	6.54	17.095	.000*

$P < .01$.
BPRS-A, Brief Psychiatric Rating Scale-Anchored; PANSS, Positive and Negative Syndrome Scale

like akathisia, etc.) during the 1-month study period, the drug given for its management, if interferes with qEEG (e.g., benzodiazepines), would be excluded from the study. Patients were assessed at baseline, prior to initiation of aripiprazole on PANSS and BPRS-A, which was done again after continuation of 1 month of treatment.

Statistical Analysis

Statistical analysis was done using Statistical Package for Social Sciences version 11.0 (SPSS Inc., Chicago, IL, USA). Paired *t*-test was calculated between the pre-drug and post-drug regional absolute power in qEEG. Following this, Pearson's correlation coefficient was calculated between the difference of PANSS/BPRS-A scores and difference of regional absolute power qEEG.

RESULTS

The study group initially consisted of 38 male patients diagnosed as schizophrenia; however, 6 patients were dropped from the study as they refused to conform to the second qEEG recording. Thus, further analyses were done for the rest of 32 patients. The age of the patients ranged from 19-37 years, with a mean age of 29.44 years (SD ±4.89). All of them were right-handed. About 50.1% were diagnosed as paranoid schizophrenia and rest as undifferentiated schizophrenia; and majority had insidious onset (90.6%).

Table 3. Group Difference of Absolute Power Pre- and Post-drug Administration Using Paired *t*-Test

	Pre-drug		Post-drug			
Region	Mean	SD	Mean	SD	*t*	*P*
Midline delta band	85.60	2.38	42.82	2.07	3.65	.001**
Midline theta band	169.52	2.47	92.44	2.12	3.685	.001**
Midline alpha 1	169.52	2.47	92.44	2.12	3.231	.003*
Right occipital alpha 2	503.36	3.73	435.72	3.77	5.162	.000**
Midline alpha 2	258.48	2.50	111.14	2.45	4.224	.000**
Midline beta 1	72.69	2.46	42.90	2.39	2.538	.017*
Right prefrontal gamma 2	20.42	2.51	2.81	1.55	11.952	.000**

Regions and corresponding channels for absolute power: midline FPz, AFz, Fz, FCz, Cz, CPz, Pz, Oz, right occipital O2, prefrontal FP2, AF4, and AF8.
*Significant at the level <.05 (2-tailed).
**Significant at the level <.01 (2-tailed).

Illness-related characteristics are demonstrated in Table 1. The mean of the subscales and of total scores of PANSS and scores of BPRS-A at baseline and at 1 month is shown in Table 2, and the difference in the aforementioned scores is statistically significant.

All the patients were drug free at the time of enrolment. Following the first qEEG, all patients received 15 mg of aripiprazole. After 2 weeks, 12 (37.5%) patients received 30 mg of aripiprazole, while the rest, i.e., 20 (62.5%) patients, continued on the same dose. None of the study participants exhibited any side effects of aripiprazole during the study period.

Regional absolute power spectral analysis showed a significant ($P < .05$) decrease in delta, theta alpha1, alpha2, and beta1 band in the midline region, alpha2 in the right occipital region, and gamma2 in the right prefrontal region. There was no significant change in other bands in any of the 13 given regions (Table 3). The regional absolute power in various bands did not have any significant correlation with assessment measure scores (i.e., PANSS total, PANSS positive, PANSS negative, PANSS general psychopathology, and BPRS-A scores), as shown in Table 4.

DISCUSSION

The study reports that there was a significant reduction in PANSS and BPRS-A scores at 4 weeks after taking aripiprazole, as documented in earlier studies.[40,41] Hence, it can be inferred that the sample consisted of responders to aripiprazole. A single-dose aripiprazole modified the regional qEEG power spectrum as a decrease in delta, theta, alpha1, alpha2, and beta1 in the midline region, alpha2 band in the right occipital region, and gamma2 in the prefrontal region. The results can be compared with earlier studies with atypical antipsychotic after a single dose. Hyun et al[20] found a decrease in alpha in the occipital region with clozapine. Saletu et al[25] showed a decrease in delta and theta as seen in their study; however, an increase in beta, with no change in alpha activity after a single dose of amisulpride over the frontal and left parietal and right temporo-occipital regions unlike in this study has been reported. Begic et al[7] reported a decrease in delta power in the sulpiride, haloperidol, and fluphenazine-treated group in the central, temporal, and occipital regions (C3, C4, T3, T4, O1, and O2 regions), as seen in the study.

Mucci et al[15] reported that both responders and non-responders show a decrease in delta and an increase in beta2 after a single dose of haloperidol and clopentixol; however, responders showed an increase in fast theta and slow alpha, whereas non-responders showed a decrease in slow alpha which was not seen in this study. After a single dose of haloperidol or clopentixol, Galderisi et al[24] reported an increase in alpha1 in responders, which is also not seen in this study. In a study by Knott et al.[26] after a single dose of

Table 4. Pearson's Correlation Between PANSS/BPRS-A and Absolute Power in Various Regions

	Midline Delta	Midline Theta	Midline Alpha 1	Right Occipital Alpha 2	Midline Alpha 2	Midline Beta 1	Right Prefrontal Gamma 2
PANSS—total	–0.014	0.076	–0.054	–0.084	0.009	0.075	–0.043
PANSS—positive	0.045	0.091	–0.043	–0.144	0.038	0.094	–0.023
PANSS—negative	0.047	0.167	0.078	0.005	0.072	0.080	–0.050
PANSS—general psychopathology	–0.032	0.042	–0.121	–0.112	–0.051	0.055	–0.026
BPRS-A	0.020	0.129	0.007	–0.106	0.050	0.097	–0.024

BPRS-A, Brief Psychiatric Rating Scale-Anchored; PANSS, Positive and Negative Syndrome Scale; PANSS—general psychopathology, difference in PANSS general psychopathology scores; PANSS—negative, difference in negative scores; PANSS—positive, difference in PANSS positive scores; PANSS—total, difference in total PANSS score.

clozapine, patients showed an increase in delta posteriorly (P3, P4, Pz, O1, O2, and Oz) and in alpha and beta anteriorly (Fp1, Fp2, Fpz, F3, F4, C3, and C4) with decreased alpha power occipital (O1, O2, and Oz); however, alpha2 was decreased in the right occipital area in this study. Begic et al[7] reported decreased beta2 power with all 3 drugs—sulpiride, haloperidol, and fluphenazine. Knott et al[26] reported a decrease in beta power in the posterior region after a single dose of clozapine; compared to this study, it was seen that low beta decreased in the midline region. This suggests that aripiprazole and clozapine may have a similar EEG profile that could be explored further. The results can be mentioned in context to schizophrenia patients that they have higher regional absolute power that attenuated after a single dose of aripiprazole. The results are not in sync with numerous earlier studies, probably because of the difference in various parameters (e.g. qEEG variables, antipsychotic class, illness chronicity, duration of the second qEEG after initiating medication) used in those studies. Gross et al[42] examined the relation of symptom clusters of schizophrenia with absolute powers of main frequency bands in qEEG and found significant positive correlations between the beta and psychomotor poverty. Trends toward positive correlations were observed between delta and PANSS-negative subscale and psychomotor poverty. On the other hand, Ozaki et al[43] found that when patients taking different types of antipsychotics were compared with drug-free patients, no significant change was observed in any spectrum power for the aripiprazole or blonanserin groups; however those taking risperidone had a significant increase in alpha and beta power. Additionally, assessment of negative symptoms in combination with power in the delta, theta, beta1, and beta2 bands may be helpful in predicting transition to psychosis in at-risk individuals.[44] This study did not show correlations between PANSS/BPRS-A scores with a change in averaged absolute power after a single dose of aripiprazole.

The study reports that aripiprazole is an effective antipsychotic for patients with schizophrenia. A single dose of aripiprazole attenuated the qEEG power spectrum in various regions, as a decrease in delta, theta, alpha1, alpha2, and beta1 in the midline region, alpha2 band in the right occipital region, and gamma 2 in the prefrontal region; however, it did not show a significance correlation when compared to PANSS and BPRS-A scored to predict the outcome.

This study had several limitations, as participants were only males and subtle diurnal variations in qEEG recording were not controlled; recording of qEEG done after a single dose would not reflect the full effect of drug as it might not have attained its peak concentration in the brain tissues because of first-pass metabolism and blood–brain barrier. The absolute power of the given channels of qEEG was averaged as per region rather than individual channels, hence making it difficult to compare with earlier studies. The duration of the study was short, and a longer follow-up might be a better indicator of the outcome. Patients in the present study had shown a significant clinical improvement; hence, the study could not explore the non-responders. In addition, patients who were abstinent from alcohol or other substances from the last 6 months were included in the study, not considering the long-term or the relatively permanent damage or changes in the brain caused by these substances.

Future research needs to focus on the individual channel qEEG profile of different clusters of symptoms in schizophrenia and help explain the electrophysiological correlates of psychopathology. There is also a need to study the qEEG profile in subtypes of schizophrenia to find the qEEG characteristics specific to the disorders and response to antipsychotics.

Ethics Committee Approval: Ethics Committee approval was received from the Ethics Committee of Central Institute of Psychiatry, affiliated with Ranchi University in 2005. Approval number is not available as it was undertaken as a postgraduate MD thesis project, for which individual letters were not provided.

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – G.S., S.S.; Design – G.S. S.S.; Supervision – G.S.; Funding – None; Materials – G.S.; Data collection and/or processing – G.S., S.S.; Analysis and /or interpretation – G.S., S.S.; Literature review – G.S., S.S.; Writing – G.S., S.S.; Critical review – S.S.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Tsuang MT, Stone WS, Faraone SV. Towards the prevention of schizophrenia. *Biol Psychiatry*. 2000;48(5):349-356. [CrossRef]
2. Lally J, MacCabe JH. Antipsychotic medication in schizophrenia: a review. *Br Med Bull*. 2015;114(1):169-179. [CrossRef]
3. Smith RC, Leucht S, Davis JM. Maximizing response to first-line antipsychotics in schizophrenia: a review focused on finding from meta-analysis. *Psychopharmacol (Berl)*. 2019;236(2):545-559. [CrossRef]
4. Lydiard RB, Laird LK. Prediction of response to antipsychotics. *J Clin Psychopharmacol*. 1988;8(1):3-13. [CrossRef]

5. Weickert CS, Weickert TW, Pillai A, Buckley PF. Biomarkers in schizophrenia: a brief conceptual consideration. *Dis Markers*. 2013;35(1):3-9. [CrossRef]
6. Chaturvedi M, Hatz F, Gschwandtner U, et al. Quantitative EEG (QEEG) measures differentiate Parkinson's disease (PD) patients from healthy controls (HC). *Front Aging Neurosci*. 2017;9:3. [CrossRef]
7. Begić D, Popović-Knapić V, Grubišin J, et al. Quantitative electroenc ephalography in schizophrenia and depression. *Psychiatr Danub*. 2011;23(4):355-362.
8. Ogrim G, Kropotov J, Hestad K. The quantitative EEG theta/beta ratio in attention deficit/hyperactivity disorder and normal controls: sensitivity, specificity, and behavioral correlates. *Psychiatry Res*. 2012;198(3):482-488. [CrossRef]
9. Kim JW, Lee YS, Han DH, Min KJ, Lee J, Lee K. Diagnostic utility of quantitative EEG in un-medicated schizophrenia. *Neurosci Lett*. 2015;589:126-131. [CrossRef]
10. Newson JJ, Thiagarajan TC. EEG frequency bands in psychiatric disorders: a review of resting state studies. *Front Hum Neurosci*. 2018;12:521. [CrossRef]
11. Howells FM, Temmingh HS, Hsieh JH, van Dijen AV, Baldwin DS, Stein DJ. Electroencephalographic delta/alpha frequency activity differentiates psychotic disorders: a study of schizophrenia, bipolar disorder and methamphetamine-induced psychotic disorder. *Transl Psychiatry*. 2018;8(1):75. [CrossRef]
12. Thatcher RW. Validity and reliability of quantitative electroencephal ography (qEEG). *J Neurother*. 2010;33722(727):122-152.
13. Kupfer DJ, Regier DA. Neuroscience, clinical evidence, and the future of psychiatric classification in DSM-5. *Am J Psychiatry*. 2011;168(7):672-674. [CrossRef]
14. Baradits M, Kakuszi B, Bálint S, et al. Alterations in resting-state gamma activity in patients with schizophrenia: a high-density EEG study. *Eur Arch Psychiatry Clin Neurosci*. 2019;269(4):429-437. [CrossRef]
15. Mucci A, Volpe U, Merlotti E, Bucci P, Galderisi S. Pharmaco-EEG in psychiatry. *Clin EEG Neurosci*. 2006;37(2):81-98. [CrossRef]
16. Siekmeier PJ, VanMaanen DP. Development of antipsychotic medications with novel mechanisms of action based on computational modeling of hippocampal neuropathology. *PLoS One*. 2013;8(3):e58607. [CrossRef]
17. Harris A, Melkonian D, Williams L, Gordon E. Dynamic spectral analysis findings in first episode and chronic schizophrenia. *Int J Neurosci*. 2006;116(3):223-246. [CrossRef]
18. Goldstein MR, Peterson MJ, Sanguinetti JL, Tononi G, Ferrarelli F. Topographic deficits in alpha-range resting EEG activity and steady state visual evoked responses in schizophrenia. *Schizophr Res*. 2015;168(1-2):145-152. [CrossRef]
19. Saletu B, Küfferle B, Anderer P, Grünberger J, Steinberger K. EEG-brain mapping in schizophrenics with predominantly positive and negative symptoms. Comparative studies with remoxipride/haloperidol. *Eur Neuropsychopharmacol*. 1990;1(1):27-36. [CrossRef]
20. Hyun J, Baik MJ, Kang UG. Effects of psychotropic drugs on quantitative EEG among patients with schizophrenia-spectrum disorders. *Clin Psychopharmacol Neurosci*. 2011;9(2):78-85. [CrossRef]
21. Maccrimmon D, Brunet D, Criollo M, Galin H, Lawson JS. Clozapine augments delta, theta, and right frontal EEG alpha power in schizophrenic patients. *ISRN Psychiatry*. 2012;2012:596486. [CrossRef]
22. Yeum TS, Kang UG. Reduction in alpha peak frequency and coherence on quantitative electroencephalography in patients with schizophrenia. *J Korean Med Sci*. 2018;33(26):e179. [CrossRef]
23. Galderisi S, Mucci A, Mignone ML, Maj M, Kemali D. CEEG mapping in drug-free schizophrenics. Differences from healthy subjects and changes induced by haloperidol treatment. *Schizophr Res*. 1991;6(1):15-23. [CrossRef]
24. Galderisi S, Maj M, Mucci A, Bucci P, Kemali D. QEEG alpha 1 changes after a single dose of high-potency neuroleptics as a predictor of short-term response to treatment in schizophrenic patients. *Biol Psychiatry*. 1994;35(6):367-374. [CrossRef]
25. Saletu B, Küfferle B, Grünberger J, Földes P, Topitz A, Anderer P. Clinical, EEG mapping and psychometric studies in negative schizophrenia: comparative trials with amisulpride and fluphenazine. *Neuropsychobiology*. 1994;29(3):125-135. [CrossRef]
26. Knott V, Labelle A, Jones B, Mahoney C. Quantitative EEG in schizophrenia and in response to acute and chronic clozapine treatment. *Schizophr Res*. 2001;50(1-2):41-53. [CrossRef]
27. Nagase Y, Okubo Y, Toru M. Electroencephalography in schizophrenic patients: comparison between neuroleptic-naive state and after treatment. *Biol Psychiatry*. 1996;40(6):452-456. [CrossRef]
28. Harris A, Gordon E, Anderson J, Ritchie G, McLachlan C, Meares R. Change in quantified electroencephalography (QEEG) with medication and altered clinical state in the same subjects with schizophrenia. *Schizophr Res*. 1997;23(1):87-89. [CrossRef]
29. Czobor P, Volavka J. Pretreatment EEG predicts short-term response to haloperidol treatment. *Biol Psychiatry*. 1991;30(9):927-942. [CrossRef]
30. Lacroix D, Chaput Y, Rodriguez JP, et al. Quantified EEG changes associated with a positive clinical response to clozapine in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 1995;19(5):861-876. [CrossRef]
31. Moore DP. On an engaging patient with paranoid schizophrenia. *Am J Psychiatry*. 1997;154(8):1178.
32. Saletu B, Küfferle B, Grünberger J, Anderer P. Quantitative EEG, SPEM, and psychometric studies in schizophrenics before and during differential neuroleptic therapy. *Pharmacopsychiatry*. 1986;19(6):434-437. [CrossRef]
33. Schellenberg R, Schwarz A, Knorr W, Haufe C. EEG-brain mapping. A method to optimize therapy in schizophrenics using absolute power and center frequency values. *Schizophr Res*. 1992;8(1):21-29. [CrossRef]
34. Small JG, Milstein V, Small IF, Miller MJ, Kellams JJ, Corsaro CJ. Computerized EEG profiles of haloperidol, chlorpromazine, clozapine and placebo in treatment resistant schizophrenia. *Clin Electroencephalogr*. 1987;18(3):124-135.
35. Kane JM, Carson WH, Saha AR, et al. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry*. 2002;63(9):763-771. [CrossRef]
36. AC01696967 A, editor. *The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research*. Geneva: World Health Organization; 1993.
37. Mandal MK, Pandey G, Singh SK, Asthana HS. Hand preference in India. *Int J Psychol*. 1992;27(6):433-442. [CrossRef]
38. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261-276. [CrossRef]
39. Woerner MG, Mannuzza S, Kane JM. Anchoring the BPRS: an aid to improved reliability. *Psychopharmacol Bull*. 1988;24(1):112-117.
40. Kumar P B S, Pandey RS, Thirthalli J, Kumar P T S, Kumar C N. A comparative study of short term efficacy of aripiprazole and risperidone in schizophrenia. *Curr Neuropharmacol*. 2017;15(8):1073-1084. [CrossRef]
41. Ribeiro ELA, de Mendonça Lima T, Vieira MEB, Storpirtis S, Aguiar PM. Efficacy and safety of aripiprazole for the treatment of schizophrenia: an overview of systematic reviews. *Eur J Clin Pharmacol*. 2018;74(10):1215-1233. [CrossRef]
42. Gross A, Joutsiniemi SL, Rimon R, Appelberg B. Correlation of symptom clusters of schizophrenia with absolute powers of main frequency bands in quantitative EEG. *Behav Brain Funct*. 2006;2(1):23. [CrossRef]
43. Ozaki T, Toyomaki A, Hashimoto N, Kusumi I. Quantitative resting state electroencephalography in patients with schizophrenia spectrum disorders treated with strict monotherapy using atypical antipsychotics. *Clin Psychopharmacol Neurosci*. 2021;19(2):313-322. [CrossRef]
44. Zimmermann R, Gschwandtner U, Wilhelm FH, Pflueger MO, Riecher-Rössler A, Fuhr P. EEG spectral power and negative symptoms in at-risk individuals predict transition to psychosis. *Schizophr Res*. 2010;123(2-3):208-216. [CrossRef]