PSYCHOLOGICAL MEDICINE

QEEG Coherence Changes after a Single Dose of Aripiprazole as a Predictor of Short Term Response to Treatment in Schizophrenia

Gautam Sharma

ABSTRACT

Objective: **The study aimed to investigate the correlation between qEEG coherence changes after a single dose of Aripiprazole in various bands and short-term treatment response in patients with schizophrenia.**

Methodology: **Sample consisted of 32 patients with schizophrenia who were drug naïve or drug free for the last 4 weeks. The qEEG data was collected using Neurofax EEG-1100. The baseline data was collected at rest before starting aripiprazole and second qEEG recorded after 4 to 5 hours of administering a single dose of Aripiprazole. The power spectral analysis was calculated with Fast Fourier Transform (FFT), followed by the Fischer's Z transformation. The Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) were administered at the intake and after 4 weeks on aripiprazole and correlation were performed with qEEG coherence changes.**

Results: **No significant correlation between PANSS and BPRS scores with qEEG coherence changes in the interhemisphere, there was significant negative correlation between PANSS Total and PANSS Negative scores with F3-C3 in delta band ($p < 0.05$) (2 -tailed) in left intrahemisphere. In the right intrahemisphere qEEG coherence, there was a significant negative correlation between PANSS total with FT10-C4 in delta band, FT10-P4 and FT10-CP4 in the theta band ($p < 0.05$) (2 -tailed), PANSS Positive scores and FT10-C4 in delta band ($p < 0.01$) (2 -tailed), FT10-P4 in delta band, FT10-P4 theta band, FP2-T10 theta band ($p < 0.05$) (2 -tailed). A positive correlation was found between PANSS Negative scores with qEEG coherence in FT10-P4, F8-T10 in beta 3 band.**

Conclusion: **A good predictor of short-term outcome after a single dose of aripiprazole, in patients with schizophrenia, receiving aripiprazole therapy is intrahemisphere and not interhemisphere qEEG coherence changes. This is shown particularly in the left hemisphere in delta band and in right intrahemisphere in delta, theta band and beta 3 band. This study supports the theory that dysconnectivity between cortical areas rectifies with antipsychotics.**

KEY WORDS

qEEG, coherence, schizophrenia, aripiprazole, Pharmaco-EEG

INTRODUCTION

Schizophrenia has been known to be a devastating illness with a poor prognosis since antiquity (Sawa and Snyder, 2002). However, despite the implementation of a scientific nosology, the conceptualization of schizophrenia is an issue not easily amenable to empirical resolution. There is little basis for regarding the operational definition in the present classificatory systems (ICD-10, DSM-V) as the true construct of schizophrenia (Andreasen, 1982; Meehl, 1989; Tsuang *et al*., 2000; First *et al*., 2004; Kahn *et al*., 2015). Moreover, in psychiatry, selecting an antipsychotic for schizophrenia is more of an art than a science, which is based on the clinical experience and preference. Early intervention with appropriate antipsychotic to alleviate the symptoms is of utmost importance to negate the ill effects of hyperactive dopaminergic, catecholamines and hypothalamic-pituitary-adrenal activation to the brain structures.

Efforts to identify the underlying disturbances in schizophrenia are currently focused on three general lines of inquiry: 1) examination of the mechanism of action of the drugs that alleviate the symptoms of schizophrenia, 2) examination of neuro-anatomical and neuro-physiological abnormalities in the schizophrenia patients, and 3) examination of candidate genes that confer susceptibility to schizophrenia (Sawa and Snyder, 2002).

In 1929, Hans Berger, a psychiatrist in Jena, began a series of reports that are accepted as the first systematic description of human EEG. The quantitative EEG, with its inherent advantages over conventional EEG is a promising tool that can be utilized in psychopharmacology for understanding and developing novel medications for schizophrenia and differentiate schizophrenia spectrum disorders (Zaytseva *et al*., 2018) from other psychotic disorders (Howells *et al*., 2018).

Quantitative EEG studies of schizophrenia use various parameters like relative power, absolute power, and interhemispheric and intrahemispheric coherence, mean frequency, and symmetry. Evidence from various neuroanatomical theories implicate multiple brain areas rather than a single abnormal area. This multiplicity of affected areas suggests a disease of disconnections between important cerebral regions that usually work in concert to regulate cognition and behavior (Weinberger and Berman, 1988; Egan and Weinberger, 1997), with this evidence it would be relevant to focus on qEEG coherence that studies connections between cortical regions. These changes can be seen in a much faster time interval with qEEG which is independent of patient or doctor's

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Department of Psychiatry, Dr. RML Hospital & PGIMER
New Delhi 110001, India
Correspondence to: Gautam Sharma
(e-mail: gautamsharma@dr.com)

Table 1: Comparison of PANSS and BPRS scores

	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 score	38.94	9.19	14.38	6.54	17.095	.000*

* $p < 0.01$

Table 2: Group Difference of Interhemispheric Coherence-

Channel pair	Pre Drug		Post Drug		t	p
	Mean	SD	Mean	SD		
FT7-FT8 Delta	.17	.14	.34	.45	-2.199	.035
C3-C4 Delta	.28	.26	.38	.31	-2.258	.031
P3-P4 Delta	.31	.28	.47	.39	-2.389	.023
TP8-01 Delta	.20	.19	.37	.32	-3.017	.005
O1-O2 Delta Band	.46	.30	.70	.50	-3.855	.001**
TP8-01 Theta	.20	.14	.31	.23	-2.304	.028
O1-O2 Theta Band	.75	.41	.84	.54	-2.040	.05*
Fp1-Fp2 Alpha2	.92	.70	.85	.48	2.011	.053
F7-F8 Alpha2 Band	.59	.45	.47	.45	2.650	.013*
FT9-FT10 Beta2 Band	.22	.21	.33	.28	-2.848	.008**
O1-O2 Beta2 Band	.70	.46	.85	.61	-3.047	.005**
O1-O2 Beta3	.69	.46	.81	.59	-2.359	.025
Fp1-Fp2 Gamma1	.55	.34	.69	.55	-2.457	.020*
Fp1-Fp2 Gamma2	.55	.34	.68	.54	-2.329	.027*

** $p < 0.01$ (2-tailed) * $p < 0.05$ (2-tailed)

Table 3: Group difference of left intrahemispheric coherence-

Channel pair	Pre Drug		Post Drug		t	p
	Mean	SD	Mean	SD		
F3-C3 Delta Band	.41	.33	.49	.28	-2.072	.047
FT9-T7 Delta Band	.29	.28	.41	.35	-2.063	.048
FT9-C3 Theta Band	.13	.13	.24	.26	-2.230	.033*
F7-T9 Alpha2 Band	.39	.39	.24	.24	2.539	.016
F7-O1 Alpha2 Band	.26	.24	.16	.14	2.610	.014*
FP1-P3 Beta1 Band	.17	.19	.13	.11	2.618	.014*
FT9-T7 Beta3 Band	.25	.23	.38	.31	-2.393	.023*
F7-T7 Gamma1 Band	.42	.31	.66	.51	-2.837	.008**
FT9-T7 Gamma1 Band	.38	.41	.63	.56	-2.359	.025*
F7-T7 Gamma2 Band	.44	.37	.66	.51	-2.690	.011*

** $p < 0.01$ (2-tailed) * $p < 0.05$ (2-tailed)

evaluation and is dependent on the patient's physiological response to the drug.

Coherence measures the synchronicity of short distance and long-distance cortical fibres at different leads (Nuwer, 1988). Hence, coherence analysis of the electroencephalogram (EEG) is considered an indicator of functional connections between different cortical regions. Coherence is normalized by the power of a given frequency band and it is independent of the amplitude of the oscillations of the two signals. This property makes coherence analysis a relatively unbiased method when comparing groups of subjects particularly in treatment (Roberts *et al*., 2016; Li *et al*., 2017). A coherence decrease between two regions presumably indicates a decrease in their functional connections.

Changes in qEEG coherence indicate that neuronal circuitry is affected by schizophrenia and antipsychotics can certainly impact these changes (MacCrimmon *et al*., 2012). Studies of coherence in patients with schizophrenia have reported contrasting results. One study (Merrin *et al*., 1989) compared coherence in drug naive patients with schizophrenia. Other studies compared coherence post medication (Nagase, 1996; Mann, 1997) and found increased mean coherence as compared to control subjects, mainly in low frequency in left dorsolateral prefrontal cortex (FP1-F7 and F7-F3). However, there are also reports of decreased frontal coherence in the delta and alpha band as compared to normal controls (Tauscher *et al*., 1998). Norman *et al*. (1997) studied EEG coherence patterns in patients with schizophrenia during mathematical task and reported left frontal-temporal connectivity to have a negative relationship to reality distortion. Recent studies have shown low absolute coherence in schizophrenia in C3-C4 and T3-T4 in the alpha band as compared to normal and relative coherence in P3-P4 in the alpha band (Yeum and Kang, 2018)

The study by Merrin *et al*. (1989), in patients with schizophrenia, affective disorder, and normal controls during resting and task condition found higher interhemisphere and intrahemisphere coherence in the theta band and slight increase in interhemispheric alpha coherence in schizophrenia. After treatment, a significant increase of theta power was present, but there was no significant change in coherence. Similarly, study between schizophrenia and normal, high coherence was seen in all bands in the interhemisphere during photic stimulation (Wada *et al*., 1994).

Quantitative EEG studies can be interpreted according to a model suggesting that the connections between left frontal and temporal lobes are disrupted in schizophrenia, which are in line with results suggested by a regional cerebral blood flow study during verbal tasks (Frith *et al*., 1995).

It has been suggested that during maturation process, a defect in reorganization of human brain function takes place resulting in reduction of redundant cortical synaptic connections (Sawa and Snyder, 2002). This defect during maturation process may underlie the causes of schizophrenia, which may emerge during adolescence. Hence, schizophrenia is considered a neurodevelopmental and neurodegenerative disorder leading to abnormality of brain connections. This pathophysiologic theory has been supported by various studies using structural and function neuroimaging (Niznikiewicz, 2003).

During task qEEG, patients with schizophrenia had higher interhemispheric and intrahemispheric coherence in the theta band and tended to have a higher intrahemispheric alpha coherence. The pharmacological treatment was associated with clinical improvement and increases in spectral power; however, there was no changes in coherence values (Merrin, 1989). Increased anterior coherence also has often been reported. Coherence measures may contribute to distinguishing other psychiatric disorders from schizophrenia. Patients with predominantly negative symptoms had lower frontal interhemispheric coherence (Gerez and Tello, 1995).

Disconnection theories of schizophrenia have suggested a disintegration of neuronal system (Di Lorenzo *et al*., 2015). In a study by Knott *et al*. (2002) patients with schizophrenia reported interhemispheric and intrahemispheric coherence following single dose of clozapine. There was a trend of increased delta at prefrontal site pairs whereas reduction of theta interhemispheric at central and parietal site pairs. Intrahemispheric theta coherence was increased at Fp1-F3 and Fp2-F4 with decreased at the C4-P4 site.

Table 4: Pearson's Correlation between PANSS /BPRS and Interhemisphere coherence between electrodes (N = 32)

	FT7-FT8 Delta	C3-C4 Delta	P3-P4 Delta	Tp8-O1 Delta	O1-O2 Delta	TP8-O1 Theta	O1-O2 Theta	Fp1-Fp2 Alpha 2	F7-F8 Alpha2-	FT10 Beta 2	O1-O2 Beta 2	O1-O2 Beta 3	Fp1-Fp2 Gamma1	Fp1-2 Fp2 Gamma
PAN-T	-.220	-.261	-.054	-.062	-.193	-.068	-.167	.150	-.012	-.041	-.080	-.010	-.065	-.130
PAN-P	-.305	-.184	-.138	-.268	-.088	-.232	-.046	.051	-.142	.089	.034	.036	-.168	-.164
PAN-N	-.200	-.311	-.113	-.049	-.098	-.104	-.150	.263	.191	.003	-.121	-.042	.033	-.092
PAN-G	-.074	-.100	.044	.061	-.208	.050	-.137	.030	-.102	-.058	-.070	.011	-.066	-.081
BPRS	.022	.018	-.011	-.055	-.276	-.049	-.091	.032	.054	-.145	-.009	.087	-.117	-.172

** Correlation is significant at the 0.01 level (2-tailed)

* Correlation is significant at the 0.05 level (2-tailed).

PAN-T: Difference in total PANSS score, PAN-P: Difference in PANSS Positive scores; PAN-N: Difference in Negative scores; PAN-G: Difference in PANSS General Scores.

Table 5: Pearson's Correlation between PANSS /BPRS and coherence between electrodes in Left Intrahemisphere (N = 32)

	F3-C3 Delta	FT9-T7 Delta	FT9-C3 Theta	F7-T9 Alpha2	F7-O1 Alpha2	FP1-P3 Beta1	FT9-T7 Beta3	F7-T7 Gamma1	FT9-T7 Gamma1	F7-T7 Gamma2
PAN-T	-.406*	-.067	-.258	-.058	-.227	.315	.290	.100	.259	.055
PAN-P	-.257	-.252	-.259	.005	-.146	.260	.305	.042	.224	-.013
PAN-N	-.422*	-.124	-.078	-.182	-.090	.273	.293	.146	.314	.132
PAN-G	-.270	.043	-.233	.019	-.322	.234	.137	.095	.108	.034
BPRS	.004	-.143	-.274	-.255	-.195	.009	.038	.029	.088	-.022

** Correlation is significant at the 0.01 level (2-tailed)

* Correlation is significant at the 0.05 level (2-tailed).

PAN-T: Difference in total PANSS score, PAN-P: Difference in PANSS Positive scores; PAN-N: Difference in Negative scores; PAN-G: Difference in PANSS General Scores.

METHODOLOGY

The study population consisted of 38 patients diagnosed with a clinical diagnosis of Schizophrenia as per the ICD-10 DCR (WHO, 1993) taken up by the purposive sampling method, if they met the inclusion and exclusion criteria. The study was approved by the Institutional Review Board of Central Institute of Psychiatry, Kanke, Ranchi, and all subjects gave written informed consent. The age group was between 18-50 years male, right handed, admitted as voluntary patients. They were drug naïve or drug free status from any oral antipsychotic medication for last 4 weeks or any depot antipsychotics in the last 3 months or did not receive ECT in the last 6 months. Patients were excluded with a co-morbid diagnosis of mental retardation, organic mental syndrome, brief reactive psychosis, history of alcohol or drug dependence in the last 6 months, or had clinically significant hepatic, renal, metabolic or neurological disorder. Patients unwilling or unable to comply with the study protocol were excluded too.

The following tools were used- Neurofax EEG-1100 for qEEG data, Diagnostic Criteria for Research (DCR), ICD-10 (WHO, 1993), Sidedness Bias Schedule (SBS) (Mandal *et al*., 1992), The Positive and Negative Syndrome Scale (PANSS) (Kay *et al*., 1987), Brief Psychiatric Rating Scale-Anchored (BPRS-A) (Woerner *et al*, 1988), and Matlab software V.6.5 for qEEG data processing.

The first qEEG was recorded followed by a dose of aripiprazole (15 mg Tablet) to all the patients and the second qEEG was recorded after 4 to 5 hrs. Continuous resting EEG of each subject was recorded for approximately 15 minutes with eyes closed. This was done to ensure enough artifact free EEG signals for processing. Later, the data was processed to remove artifacts during offline. Analogue to digital (AD) conversion was by 16 bits, the time constant (TC) was 0.03Hz and hi-cut frequency was set at 300Hz. An average of 3 minutes of data was collected from each recording for further analysis using Matlab v 6.5.

Computations involved nine frequency bands of coherence in various bands: delta (1-4 Hz), theta (5-8 Hz), alpha 1 (9-10 Hz), alpha 2 (11-12 Hz), beta 1(13 -18 Hz) beta 2 (19-20 Hz) beta 3 (21-30 Hz) gamma 1 (30-100 Hz) gamma 2 (30-130 Hz). Welch averaged periodogram was used in the Fourier transformation for spectral analysis. For further statistical analysis of coherence data, Fischer's Z transformation was used, as the data were not normally distributed. The data was computed using standardized software- Matlab.

Drug therapy was continued with aripiprazole 15 mg /day given once daily until a re-evaluation was done after 2 weeks. Patients with a reduction in 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 elevated to 30 mg once daily after two weeks.

The paired t-test was calculated for coherence between the predrug and post drug qEEG. Following this, Pearson's correlation coefficient was calculated between the difference of PANSS / BPRS scores and difference of qEEG coherence. Statistical analysis was done using Statistical Package for Social Sciences (SPSS for Windows version 11.0).

RESULTS

The study group initially consisted of 38 male patients diagnosed as schizophrenia, (n = 38) as per the ICD-10 Diagnostic Criteria for Research, however, six patients were dropped from the study as they refused to comply for the second qEEG recording. Thus, further analyses were done for the remaining 32 patients. Age of the patients ranged from 19 to 37 years, with a mean age of 29.44years (SD ± 4.89).

The study group consisted of 32 male patients diagnosed as schizophrenia (n = 32) as per the ICD-10 Diagnostic Criteria for Research, of whom 17 were diagnosed as paranoid schizophrenia and 15 were having undifferentiated schizophrenia. Onset of the illness was insidious in 29 patients (90.6%), two (6.3%) had an acute onset and one (3.1%) had abrupt onset. Illness duration ranged from 0.2-9 years, with a mean of 3.58years (SD ± 2.55). The age of onset of illness ranged from 19-35 years, with mean age of onset of 26.13 ± 5.59 years. The study sample consisted of 13 drug naïve (8 paranoid, 5 undifferentiated) and 19 drug free (9 paranoid and 10 undifferentiated) with mean drug free duration of 7.16 ± 3.1 months (range 3-24 months).

All the patients were drug free at the time of enrolment. Following the first qEEG, all patients received 15mg of aripiprazole. After two weeks, 12 (37.5%) patients received 30 mg of aripiprazole, while the rest, i.e., 20 (62.5%) patients continued on the same dose.

The mean PANSS and BPRS score at baseline and after 4 weeks on Aripiprazole is shown in Table 1.

After single dose, there was significant ($p < 0.05$) increase in coherence between FT10-C4, FT10-P4, F8-T8 and F8-T10 in delta band.

Table 6: Pearson's Correlation between PANSS /BPRS and coherence between electrodes in Right Intrahemisphere (N = 32)

	PAN-T	PAN-P	PAN-N	PAN-G	BPRS
FT10-C4 Delta	-.422*	-.468**	-.320	-.246	-.177
FT10-P4 Delta	-.301	-.371*	-.211	-.190	-.221
F8-T8 Delta	-.253	-.260	-.243	-.165	.048
F8-T10 Delta	-.231	-.183	-.127	-.198	-.246
FT10-C4 Theta	-.219	-.220	-.123	-.162	.035
FT10-P4 Theta	-.354*	-.402*	-.204	-.254	-.277
FP2-T10 Theta	-.328	-.362*	-.154	-.256	-.261
F8-T8 Theta	-.153	-.326	-.254	.020	.124
F8-T10 Theta	-.130	-.251	-.209	-.013	.096
FT10-CP4 Theta	-.369*	-.258	-.299	-.267	-.074
FT10-P4 Theta	-.171	-.201	-.253	-.041	.078
FT10-T8 Theta	-.006	-.174	.054	.012	.011
FT10-C4 Alpha1	-.141	-.038	.021	-.313	-.141
FP2-P6 Apha2	.065	.113	.128	.018	.070
FT10-C4 Beta1	-.066	-.050	.091	-.102	-.200
FT10-P4 Beta1	-.053	-.116	-.042	.055	.062
F4-T8 Beta1	.035	-.168	-.092	.200	.220
F8-T8 Beta1	.042	.007	-.033	.120	.213
FT10-T8 Beta1	.013	-.079	.133	-.022	-.186
FT10-P4 Beta2	-.048	-.109	.031	-.039	-.091
FP2-T10 Beta2	.117	.140	.122	.127	.181
F4-T8 Beta2	.178	.014	.076	.278	.272
F8-T8 Beta2	.018	-.006	.101	.020	-.132
F8-T10 Beta2	.134	-.043	.175	.135	-.175
FT10-T8 Beta2	.171	.091	.250	.111	-.030
FT10-P4 Beta 3	.261	.032	.406*	.204	.151
FP2-T10 Beta 3	.232	.107	.244	.259	.217
F8-T8 Beta 3	.213	-.025	.088	.339	.312
F8-T10 Beta 3	.277	.104	.363*	.231	.049
FT10-CP4 Beta 3	.185	.285	.158	.141	.137
FT10-P6 Beta 3	.244	.099	.304	.189	-.050
FT10-T8 Beta 3	.234	.132	.176	.262	.307

** Correlation is significant at the 0.01 level (2-tailed)

* Correlation is significant at the 0.05 level (2-tailed).

PAN-T: Difference in total PANSS score, PAN-P: Difference in PANSS Positive scores; PAN-N: Difference in Negative scores; PAN-G: Difference in PANSS General Scores.

Coherence increased in theta band between FT10-C4, FT10-P4, FP2-T10, F8-T8, F8-T10, FT10-CP4, and FT10-T8. Coherence increased in alpha 1 band between FT10-C4. Decreased coherence in alpha 2 in FP2_P6. Significant increase in coherence in beta 1 in FT10-C4, FT10-P4, F4-T8, F8-T8, and FT10-T8. Significant increase in coherence in beta 2 in FT10-P4, FP2-T10, F4-T8, F8-T8, F8-T10, and FT10-T8. Significant increase in coherence in beta 3 in FT10-P4, FP2-T10, F4-T8, F8-T8, F8-T10, FT10-CP4, FT10-P6, and FT10-T8. There was significant increase in coherence in gamma 1 band in F8-T10, FT10-P6, and FT10-T8 ($p < 0.05$) (Table 2).

DISCUSSION

This study explores the single dose effect on the qEEG coherence as a predictor of response to treatment. Aripiprazole produces a statistically significant ($p < 0.01$) improvement from the baseline in PANSS, PANSS-positive, PANSS- negative, PANSS- general scores. Thus, this study found that aripiprazole 15mg/day and 30mg/day were an effective treatment for patients with schizophrenia. This study also suggests that a dopamine D2 partial agonist aripiprazole can exhibit clinically meaningful and sustained improvement in schizophrenia symptoms, with efficacy sustained throughout the four-week duration of the study.

In this study, decrease delta was seen in the midline (FPz, Fz, FCz, Cz, CPz, Pz, Oz) after a single dose of aripiprazole. In earlier studies, the delta band was noted to be increased in all regions in patients with schizophrenia (Begic *et al*., 2000). From imaging studies in patients with schizophrenia, there is decreased metabolism in the frontal and temporal region (Weinberger and Berman, 1988), suggesting that delta band is inversely correlated to metabolism. The decrease in delta may be an indicator of increased metabolism in this region, suggesting normalization. A decrease in the frontal delta activity is a crucial factor that explains the hypofrontality hypothesis (Andreasen *et al*., 1992; Gur and Gur, 1995). In the left intrahemisphere, there was a significant negative correlation between PANSS total and PANSS Negative scores with F3-C3 in delta band ($p < 0.05$) (2-tailed). In the right intrahemisphere qEEG coherence, there was significant negative correlation between PANSS total with FT10-C4 in delta band, PANSS Positive scores and FT10-C4 in Delta band ($p < 0.01$) (2 -tailed), FT10-P4 delta band, after a single dose of aripiprazole suggesting that antipsychotics help in increasing metabolism and supports the hypofrontality theory.

In regards to theta band, earlier studies had shown high responders to clozapine to have relationship between right anterior-medial temporal (T4) and central (C4) electrodes paired with prefrontal electrodes, left central (C3), temporal (T3) and parietal (P3) electrodes (Lacroix, 1995). In this study too, there was a significant negative correlation between PANSS total with FT10-P4, FT10-CP4, FP2-T10 ($p < 0.05$) (2-tailed) in the right intrahemisphere in the theta band after a single dose of aripiprazole. Further, hippocampus generate theta rhythm and from this result, it may suggest that fronto-temporal lobe and hippocampus have a connection that alters with antipsychotics, and this observation is in concordance with the earlier observation of implicating hippocampal and frontal-temporal regions in schizophrenia (Harrison, 2004).

Decreased alpha coherence in intrahemisphere and intra hemisphere in patients with schizophrenia is known (Merrin and Floyd, 1996), and its relationship to negative symptoms (John *et al*, 2002). In this study there was significant decrease in alpha 2 band coherence in F7-F8, F7-O1 and FP2-P6, however there was no significant correlation to PANSS and BPRS score after single dose of aripiprazole.

Tauscher *et al*. (1998) reported decreased beta 1 coherence in patients with schizophrenia as compared to normal subjects, particularly significant between intrahemisphere prefrontal region with frontal (Fp1-F3) and the fronto-temporal region (F8-T4). In this study, there was no significant difference in this region. However, there was a significant decrease in the beta range in the left prefrontal and parental region (Fp1-P3). On the right side, beta increased after a single dose of aripiprazole between the frontal and temporal region, frontal and central region and parietal region (FT10-C4, FT-P4, F4-T8, F8-T8, FT10-T8). This suggests that change in the beta range could indicate the efficacy of this drug as there was a significant positive correlation between PANSS Negative scores with qEEG coherence in FT10-P4, F8-T10 in beta 3 band. It is known from earlier studies that high beta waves have a relationship to arousal and paranoia, which is a key feature of schizophrenia (Zaytseva *et al*., 2018).

There are few studies that have explored the single dose effect and qEEG changes (Galderisi, 2002). However, there is only one study (Knott *et al*., 2002) that has addressed this issue regarding the correlation of PANSS and the qEEG coherence after a single dose as a predictor of outcome using clozapine. They reported changes in intrahemispheric coherence with chronic treatment at 6 weeks, but no correlation between interhemispheric and intrahemispheric coherence changes to outcome. This study outcome could not be compared due to various methodological issues.

The study suggests dysconnectivity between various regions and limbic system, particularly in the right hemisphere in fronto-temporal and temporo-parietal connection that are implicated in schizophrenia (Yeum and Kang, 2018; MacCrimmon *et al*., 2012; Kahn *et al*., 2015; Yildiz *et al*., 2012) that alleviate with aripiprazole.

Generalization of the data is a limiting factor as the duration of study was short, sample consisted of only males, the surface qEEG recording is not true representation of the deep structures involved in schizophrenia, diurnal variation effect on qEEG recording was not considered and single dose qEEG effect would not reflect the full effect of the drug as it would not have attained its peak concentration in the brain. It is proposed that the similarity and difference in the coherence

in various bands may be due to the subgroup in the group of schizophrenia, and the duration of illness effect (neurotoxicity theory). The difference in the inter and intrahemisphere coherence change could be related to neuroanatomical distinction as few nerve fibers entering a hemisphere arise from the contralateral hemisphere, whereas major nerve fibers entering the grey matter of the cerebral cortex derive from other cortical areas within the same hemisphere (Nunez, 2006).

Further, researchers may focus on the qEEG profile of different clusters of symptoms in schizophrenia and help explain the electrophysiological correlates of the psychopathology. It is essential to have qEEG profiles of all efficacious antipsychotics, with focus on the effects of a single dose, after peak concentration, after short and long intervals of treatment, especially with the association with outcomes. In fact, a database of all potential drugs would greatly add to the existing knowledge of electrophysiology and drug action.

CONCLUSION

In conclusion, schizophrenia has been considered a disorder of connections between various regions of the brain. The antipsychotics that alleviate the symptoms are presumed to improve the connections between these regions. The intrahemispheric qEEG change after a single dose of aripiprazole in patients with schizophrenia was a good predictor of short-term outcome, particularly in the left hemisphere in delta band, right intrahemisphere in theta band and beta band. The qEEG interhemisphere coherence is not a good predictor of an outcome. Aripiprazole has proved to be an efficacious drug for the treatment of schizophrenia. This study is in line with previous work done using MRI, fMRI, PET, and SPECT and qEEG implicating the prefrontal, frontal, temporal, parietal, and supports the theory of dysconnectivity between cortical areas particularly in the rights hemisphere in fronto-temporal and temporo-parietal connection, that stabilize with antipsychotics.

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