Original article / *Araştırma*

EEG complexity and frequency in chronic residual schizophrenia

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ABSTRACT

Objective: *Some studies on schizophrenia showed an increased complexity in electroencephalography (EEG) whereas others detected a decreased complexity. Because this discrepancy might be due to the clinical features or complexity measures used, we employed two different complexity measures in a group of schizophrenics similar in illness duration (chronic) and symptom profile (residual).* ***Methods:*** *Right-handed chronic residual schizophrenic patients (10 male, 10 female) and age- and sex-matched 20 healthy controls were included in the study. Eyes-closed resting EEG series were measured through quantitative EEG band activities, the log energy entropy (LEE) values, and the Hurst exponents (HE) of EEG measurements were computed for each electrode site.* ***Results:*** *Significantly higher LEE values in the prefrontal, frontal, temporal and parietal locations were observed in schizophrenic patients compared with controls. HE values were significantly higher on the right frontal area in the schizophrenics. Patient group showed increased prefrontal, frontal and parietal delta activity, prefrontal, left temporal and right parietal theta activity and increased left temporal alpha activity.* ***Discussion:*** *In the present study, we found that chronic residual schizophrenia is associated with decreased complexity and increased smoothness in EEG. In addition, EEG of patients was characterized by obvious slowness at prefrontal and frontotemporal regions, dominantly. An integration of EEG complexity and frequency analysis can be proposed as an innovative tool in schizophrenia research.* ***(Anatolian Journal of Psychiatry 2016; 17(5):385-392)***

Keywords: *schizophrenia, EEG, complexity, frequency*

Kronik rezidüel şizofrenide EEG kompleksitesi ve frekansı

ÖZ

Amaç: *Şizofreni üzerine yapılan çalışmaların bir kısmı elektroensefalografide (EEG) kompleksitenin arttığını, bazı çalışmalar ise azaldığını göstermiştir. Bu çelişki hastalığın klinik özelliklerine veya kullanılan ölçüm yöntemlerine bağlı olabilir. Bunu giderebilmek için biz hastalık süresi ve belirti profili açısından benzer bir şizofreni hasta grubunu seçtik (kronik rezidüel şizofrenisi olanlar) ve iki farklı kompleksite ölçüm yöntemi uyguladık.* ***Yöntem:*** *Sağ elli kronik rezidüel şizofreni hastaları (10 erkek, 10 kadın) ve yaş ve cinsiyet aşısından eşleştirilmiş 20 sağlıklı kontrol çalışmaya alındı. Gözler kapalıyken yapılan çekime dayanarak her elektrot bölgesi için nicel EEG band aktiviteleri, log enerji entropi (LEE) ve Hurst eksponentleri (HE) ölçüldü.* ***Sonuçlar:*** *Prefrontal, frontal, temporal and pariyetal alanlarda LEE değerleri şizofreni hastalarında kontrollerle karşılaştırıldığında anlamlı derecede yüksekti. Şizofreni hastalarında sağ frontal alanda anlamlı derecede yüksek HE değerleri saptandı. Hasta grubunda prefrontal, frontal ve pariyetal delta aktivitesi; prefrontal, sol temporal ve sağ pariyetal teta aktivitesi ve sol temporal alfa aktivitesi yüksekti.* ***Tartışma:*** *Bu çalışmada, kronik rezidüel şizofrenide EEG'nin daha az kompleks ve daha 'düz' olduğunu bulduk. Hastaların EEG'lerinde, baskın olarak prefrontal ve frontotemporal alanlarda yavaşlama gözlemledik. EEG kompleksite ve frekans analizlerinin birlikte kullanımı şizofreni araştırmalarında yeni bir araç olabilir.* ***(Anadolu Psikiyatri Derg 2016; 17(5):385-392)***

Anahtar sözcükler: *Şizofreni, EEG, kompleksite, frekans*

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INTRODUCTION

EEG complexity can be considered as indicator identifying the variability of electrophysiological patterns depending on functional brain activities. Complexity algorithms can estimate the grade of entropy that implies the randomness of a system. Therefore, the computation of entropy can be correlated with the complexity of a system. In other words, orderliness of a bio-physiologic time series like EEG can be quantified by its entropies. The level of EEG complexity was calculated with several entropy approaches.[1,2]

Research on EEG complexity in schizophrenia has produced inconsistent results. Some studies showed decreased complexity while others exhibited increased complexity.[2] Lee et al. called attention to the fact that the studies showing increased complexity have generally been conducted on drug-naïve patients with recent-onset illness that predominantly presented with positive symptoms.[3] On the other hand, the subjects recruited in the studies reporting decreased complexity had somewhat chronic and negative syndrome and had been using antipsychotic drugs for a long time. To overcome the discrepancy, we only enrolled patients having similar characteristics: residual schizophrenics who had been chronically ill for years.

Another factor responsible for the contradictory findings produced by the previous research might be the employment of different complexity measures in different studies. In an attempt to surmount this at least partially, we used two distinct measures of complexity. Logarithmic energy entropy (LEE) was proposed to detect seizures due to its high sensitivity on the degree of EEG complexity. Since LEE is a logarithmic expression; the higher its numeric value, the less random the EEG activity is.

Hurst exponents (HE) estimates the predictability of a time series. HE is based on the asymptotic behavior of the rescaled range of a signal and has been widely used to evaluate the self-similarity and correlation properties of long-range dependence and its degree of fractional time series. We assessed the HE to observe the electrophysiological randomness in schizophrenia.

We thought that comparing EEGs of patients and controls not only in complexity but also in frequency might shed further light on the area. We hypothesized that chronic residual schizophrenia is characterized by decreased complexity and slowness in EEG.

METHODS

Participants

Table 1 shows the characteristics of the patients and the controls. Twenty right-handed outpatients diagnosed with schizophrenia, residual subtype, by two psychiatrists according to the DSM-IV were recruited from Neuropsychiatry Istanbul Hospital. Only patients scoring 4 or higher on the Clinical Global Impression Scale for Severity were included. They were assessed with the Positive and Negative Syndrome Scale.[4] The antipsychotics used were risperidone (five patients), olanzapine (four patients), quetiapine (four patients), amisulpride (two patients), clozapine (two patients), flupenthixol (two patients), chlorpromazine (two patients), aripiprazole (one patient), sulpiride (one patient), trifluoperazine (one patient), ziprasidone (one patient), and pimozide (one patient) (the total number exceeds 20 since some patients used more than one antipsychotic). Some patients had also been taking additional drugs (antidepressants, anticonvulsants etc.) None of the participants were on neuroleptic treatment for at least 2 weeks at the time of measurement of EEG. Age- and gender-matched controls were included. No patient had undergone electroconvulsive treatment within last six months. Seizure disorder, head injury leading to loss of consciousness and substance abuse prior to data collection (subjects were screened) were excluded. Smokers were not excluded. Thirteen patients (65%) and 8 controls (40%) were smokers. The study design was approved by the local ethics committee on research involving human subjects.

Data collection

With a 16-channel Neuroscan Synamps II (Neuroscan Products, Compumedics, Charlotte, NC, USA), silver-silver chloride electrodes were applied to the scalp surface according to the international 10-20 system. EEG series with duration of three minutes were digitized by 12-bit analog-to-digital converter with the sampling frequency of 250 Hz. Raw data were filtered by a notch filter at 50 *Hz*. Impedances were kept less than 5 kΩ. Electro-Oculo-Gram (EOG) signals greater than 50 µVolt peak-to-peak were rejected to eliminate artifacts originated from eye movements. All acquired EEG data were filtered with a low pass, a high pass and notch filter at 0.5 Hz, at 70 Hz and at 50 Hz, respectively in Scan Edit 4.3 software (Compumedics, Inc.).

Empirical multi-channel data were analyzed by using LEE and HE. All applications were performed into MATLAB (The Mathworks, Natick, MA). Fast Fourier Transform (FFT) analysis was applied on EEG signals to obtain spectral powers in those bands of frequency: delta: 0-4 Hz, theta: 5-7 Hz, alpha: 8-12 Hz, beta: 13-22 Hz.

Both LEE and HE were applied to experimental data after a preprocessing consisting of a successful windowing on individual records. For each participant, single trial of 3 minutes was windowed by a window having constant width of 10 seconds. Then, both approaches were applied to 18 non-overlapping small epochs for each participant. Quantitative values obtained for these non-overlapping windowed epochs were averaged for each participant.

Statistics

The Wilcoxon sign rank test was applied to not only average entropies but also average exponents to clarify the differences between patients and controls. Statistics of the test is the p-value.

RESULTS

The PANSS scores and other clinical features of the participants are shown in Table 1.

Table 1. The characteristics of the participants

		Patients	Controls	p
Gender	Female (n)	10	10	>0.05
	Male (n)	10	10	>0.05
Age (range, SD)	Mean±SD	42.1±8.71	41.9±8.49	>0.05
	Range	18-51	18-51	
Age at onset	Mean±SD	20±3.18		
	Range	14-28		
Duration of illness	Mean±SD	21.1±7.22		
	Range	4-30		
Number of hospitalizations	Mean±SD	2.8±1.91		
	Range	0-7		
PANSS		89.70±19.03		
Positive scale		12.40±4.51		
Negative scale		29.65±5.76		
General psychopathology		57.64±11.79		

PANSS: Positive and Negative Syndrome Scale

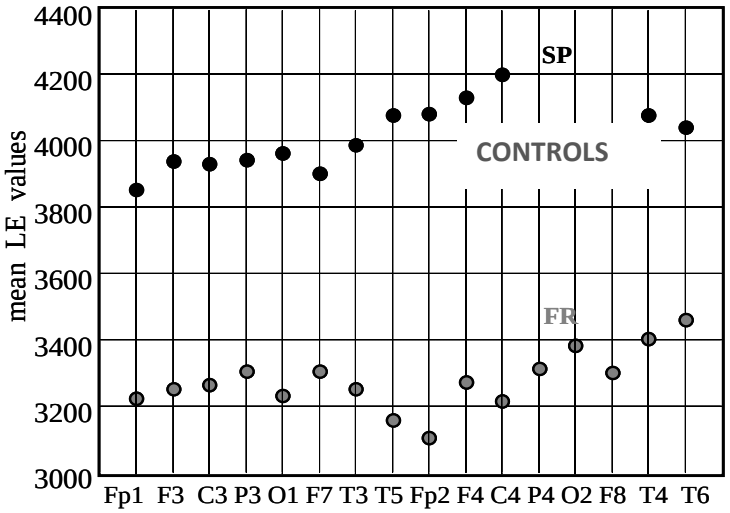


Figure 1. Mean Logarithmic Energy Entropy (LEE) values of the patients with schizophrenia (in blanks filled with black) and the controls (in blanks filled with gray) over electrodes. All the LEE values are higher in the patients than in the controls (significant differences are shown in Table 2).

Higher LEE values, though they did not reach significant levels everywhere, were generated by patients in comparison to controls at all electrode locations (Figure 1). There was a significant difference between the LEE values of patients and controls at Fp1, Fp2, F4, F7, F8, T3, T4, P3 and P4 locations (p<0.01) (Table 2). HE values were higher in the patients than in the controls in all electrode sites; nevertheless, HEE values showed a significant difference only at F4 and F8 locations (p<0.01) (Table 2).

FFT band powers of multiple epochs are seen in Figure 2. Delta activity was significantly higher in patients than in controls at Fp1, Fp2, F3, F4, F7, F8, T3, T5, P3 and P4 (p<0.01) (Table 3). Mean

Table 2. p-values between controls and patients with respect to the HE and the LEE

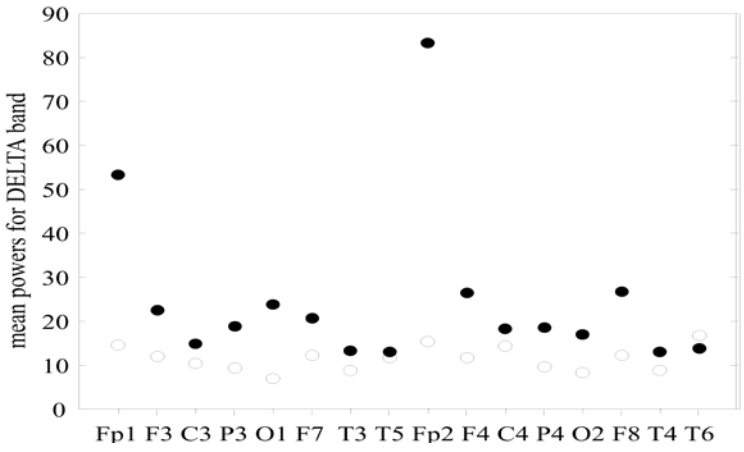
Electrodes	HE values		p-values	p-values
	Patients	Controls	for the HE	for the LE
Fp1	0.5577	0.5602	0.19	<0.01
F3	0.5455	0.5301	0.09	0.03
C3	0.5384	0.5382	0.23	0.26
P3	0.5556	0.5271	0.22	<0.01
O1	0.5400	0.5208	0.05	0.16
F7	0.5429	0.5255	0.12	0.002
T3	0.5542	0.5348	0.21	0.002
T5	0.5518	0.5374	0.52	0.05
Fp2	0.5312	0.5111	0.41	<0.01
F4	0.5549	0.5134	0.002	0.001
C4	0.5474	0.5222	0.18	0.08
P4	0.5601	0.5361	0.79	<0.01
O2	0.5461	0.5275	0.10	0.11
F8	0.5647	0.5328	0.001	0.001
T4	0.5704	0.5326	0.57	0.002
T6	0.5464	0.5257	0.12	0.03

HE: the Hurst exponent, LEE: The logarithmic energy entropy. The values for both the LEE (shown in Figure 1) and HE values are higher in the patients than in the controls in all electrode sites (but not all differences are significant).

Table 3. p-values between controls and patients with respect to particular EEG frequency bands

Electrodes	p-values for DELTA	p-values for THETA	p-values for ALPHA
Fp1	<0.01	<0.01	0.12
F3	<0.01	0.12	0.20
C3	0.02	0.04	0.12
P3	<0.01	<0.01	0.04
O1	0.01	0.01	0.17
F7	<0.01	0.02	0.29
T3	<0.01	<0.01	<0.01
T5	<0.01	<0.01	0.14
Fp2	<0.01	<0.01	0.11
F4	<0.01	0.03	0.12
C4	0.04	0.06	0.14
P4	<0.01	<0.01	0.03
O2	0.01	0.01	0.40
F8	<0.01	0.01	0.06
T4	0.02	0.01	0.02
T6	0.01	0.02	0.25

Since no electrode side showed any significant difference in beta activity between the patients and the controls, the comparisons related beta waves are not shown.



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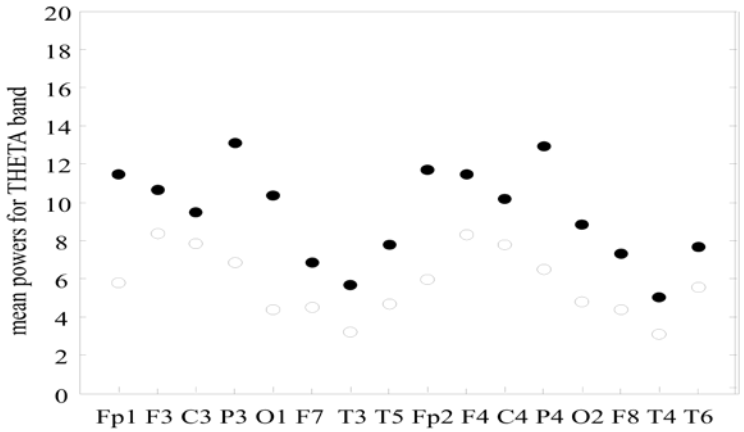

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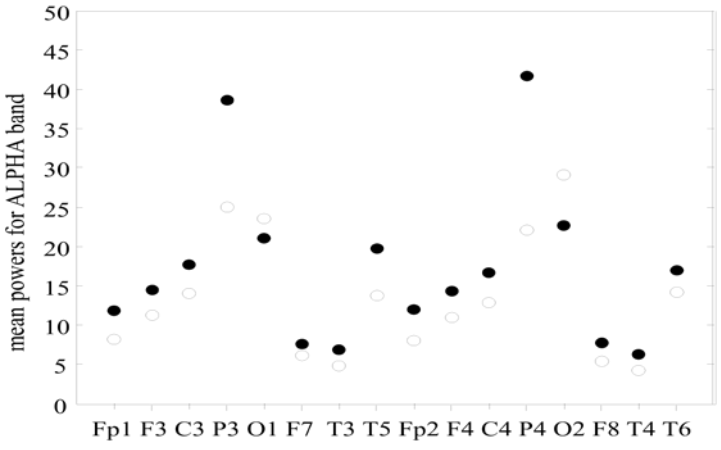

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Figure 2. Mean delta (a), theta (b) and alpha (c) powers of patients (in filled blanks) and controls (circles) over electrodes. Since no electrode side showed any significant difference in beta activity between the patients and the controls, the values related to beta waves are not shown.
Figure 2a shows that mean powers for delta are higher in the patients in all electrode sites except T6.
Figure 2b shows that mean powers for theta are higher in the patients in all electrode sites.
Figure 2c shows that mean powers for alpha are higher in the patients in all electrode sites except O1 and O2.
Whether these differences are significant or not are shown in Table 3.

powers for delta were higher in patients than in controls in all electrode sites except T6; however, right temporal electrodes and occipital electrodes were below the level of significance.

Mean powers for theta were higher in patients than in controls in all electrodes (Figure 2). However, only prefrontal, left temporal and right parietal electrodes reached the level of significance. Patients had significantly higher theta band activity compared with the controls on Fp1, Fp2, P4, T3, and T5 regions ($p<0.01$) (Table 3).

Mean powers for alpha were higher in the patients than in the controls in all electrode sites except O1 and O2 (Figure 2). However, alpha band activity was significantly higher at left temporal site (T3) in schizophrenics ($p<0.01$) (Table 3). Beta activity significantly differed between the patients and the controls in no electrode place.

DISCUSSION

The major finding of our study is that EEGs of chronic residual schizophrenics were of reduced complexity and obvious slowness, predominantly in the prefrontal and frontotemporal regions.

Complexity research lacks consistent findings. Elbert et al.[5] used dimensional complexity and showed increased complexity in schizophrenics on neuroleptic medication whereas the complexity estimated by the same method was reduced in medication-free first-episode patients in other studies.[6-8] Complexity was increased in neuroleptic-naïve patients suffering from the first-episode schizophrenia[9] while it was found either decreased[6,10] or increased[11] in patients on medication. Lee et al. suggested that those controversies might be due to the fact that the studies showing increased complexity in schizophrenia have generally been conducted using drug-naïve patients with recent-onset disease that predominantly presented with positive symptoms.[3] In contrast, subjects enrolled in the studies reporting decreased complexity had somewhat chronic illness with negative symptoms and had been using antipsychotic medications for a long time.

An advantage of our study is that we selected a specific patient group (chronic patients with residual schizophrenia) in contrast to previous research conducted in more or less chronic or medicated patients, which did not differentiate positive or negative symptoms or included schizophrenics having positive symptoms as well as those with negative ones. Thus, we avoided the confounding effect that might be created by completely different clinical features. When we only take into consideration only those studies that recruited patients who had been treated with neuroleptics, our results support some previous researches[10,12-15] while contradicting others.[5,16] Consistently, Raghavendra et al. compared patients with positive symptoms with those with negative symptoms using fractal dimension and found increased complexity in schizophrenic subjects with positive symptoms but decreased complexity in those with negative symptoms.[17]

Our sample was characterized not only by negative symptoms but also by a longer duration of illness and an older age. Our patients had a mean age of 42.1. In other comparable studies, mean age was 33.4,[12] 35.8,[13] and 31.9.[16] The mean duration of illness was 21.1 in our sample while it was 12.9 by Jin et al.[13] and 5.9 by Fernandez et al.[16] Some other authors did not mention about the onset of schizophrenia. The onset was between the ages of 14 and 28 in our sample, denoting a chronic disease. All of our patients had been taking medications since the diagnosis had been made. Therefore, the findings of the present study are consistent with the literature, supporting the view that factors such as aging, disease process and medication might alter the original brain function.[2]

However, it is still difficult to answer which one among these factors of older age, protracted illness and chronic medication is responsible for decreased complexity for several reasons. First, untreated patients though they have chronic schizophrenia are extremely rare in modern societies. Second, it would be unethical to have healthy controls use medication for a long time to observe drug effects. In order to minimize the medication effect as far as possible, we selected our sample among those who had not been using medication for more than two weeks. Takahashi et al. as an attempt to search the effect of antipsychotic medication on EEG, enrolled drug-naïve patients and observed an increased complexity in the frontotemporal areas that returned to the levels seen in normal controls in the frontal and central sites after two to eight weeks, though remained high in the temporal ones.[18] Therefore, it can be concluded that antipsychotic drugs, though they have a role in decreasing complexity, are not the single factor. Continuing or discontinuing medication for weeks or months may not have the same effect on the brain as continuing or discontinuing for years; however, the above-mentioned practical

and ethical concerns make it difficult to produce a satisfactory solution to this problem.

Studies on various neuropsychiatric disorders have shown different patterns of complexity. An increased complexity has been observed in depression, mania and attention deficit and hyperactivity disorder whereas EEG was found to be of low complexity in Alzheimer's disease, obsessive-compulsive disorder, dissociative states, anorexia nervosa, post-traumatic stress disorder and panic disorder.[1,19] It seems that pathology does not impair functioning toward a single direction; instead, different patterns of electrophysiological activity emerge as findings of mental illnesses. Yang and Tsai,[20] in an attempt to solve this dichotomy, suggested that complexity does not denote 'randomness'. Any complex structure must essentially include some remarkable amount of information, and complexity may increment proportionally with the increasing information. As an example, Yang and Tsai[20] gave a Shakespearean text that is both complex and highly informative. By contrast, a text typed aimlessly by a monkey should be referred to as 'random' rather than 'complex' because it conveys no information.

The EEG of our patients was apparently characterized by increased delta and theta activities. A review of 53 studies investigating EEG frequency bands in schizophrenia has shown that the most consistent finding is the predominance of slow rhythms.[21] More recent studies have also confirmed the fact that theta and delta waves increase in schizophrenia, notably in the frontocentral regions.[22,23] A noteworthy finding is that people at risk for psychosis and patients in the first episode of psychosis do not differ from controls in theta and delta frequencies, in contrast to those suffering from chronic psychosis.[22] These EEG changes are not related to antipsychotic use.[21] The preponderance of abnormal oscillations at low frequencies in schizophrenics has been presumed to represent thalamocortical dysrhythmia (thalamic bursting, i.e. abnormal theta and delta oscillations in the thalamus).[21]

Decreased complexity and increased delta and theta power were apparent primarily at prefrontal and frontotemporal regions and secondarily in temporal and parietal lobes. This finding is consistent with previous neuroimaging studies of schizophrenia.[24]

The relationship between psychosis and the electrophysiological markers of brain activity are usually surprising, as exemplified by 'forced normalization' seen in epileptic patients. Inducing seizures through camphor or electroconvulsive treatment result in improvement in psychosis. Forced normalization refers to the opposite of this phenomenon, i.e. the emergence of psychotic symptoms after seizures are controlled and EEG is at least relatively restored to normal.[25] It has been proposed that although cortical discharges disappear, subcortical electrical instability can subsist and might be the source of mental symptoms (through, for instance, kindling).[25] Complexity measures may improve the usefulness of EEG in neuropsychiatry.

The present study has some shortcomings. First, sample size was too small for a topic confused by contradictory results. Recruiting more participants would produce more significant results. Second, employing additional neurocognitive tests and investigating their relationship with EEG complexity would enhance the value of a study measuring the parameters believed to be concerned with the integration of information process and with cognitive flexibility. Third, we did not take smoking status into consideration. Nevertheless, smoking is quite common in schizophrenia and it is a confounding factor in all cognitive studies. Fourth, as discussed above, the effect of long-term antipsychotic use on EEG complexity is yet to be answered due to ethical and practical reasons.

CONCLUSION

We integrate our results to gain an insight into abnormalities in the brains of schizophrenic persons, from a wide range of perspectives such as complexity, smoothness, and frequency. Patients had a decreased complexity and increased smoothness, measured by LEE, and an increase in slow activity, measured by FFT analysis. The right hemisphere was found to be more regular than the left one in schizophrenics. Both complexity and frequency analysis indicated that the abnormalities most often originated in the prefrontal, frontotemporal and parietal regions. Future studies of larger sample sizes that will be conducted on the different subtypes of schizophrenia using different subclasses of antipsychotic medications will shed further light on the area.

Authors' contributions: *O.T.: Evaluating the participants, screening the literatüre, writing the manuscript; S.A.: Finding the subjects, statistics in MATLAB; G.H.S.: Evaluating the participants; D.G.: Statistics.*

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