Original Article

Abnormalities of Quantitative Electroencephalography in Children with Asperger Disorder Using Spectrogram and Coherence Values

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Objective: To obtain abnormalities in quantitative Electroencephalography (QEEG) and to observe connectivity between electrodes in children with Asperger disorder.
Method: In this study, spectrogram criteria and coherence values are used as a tool for evaluating QEEG in 15 children with Asperger disorder (10 boys and 5 girls aged between 6 to 11 years old) and in 11 control children (7 boys and 4 girls with the same age range).
Results: The evaluation of QEEG using statistical analysis and spectrogram criteria demonstrates that the relaxed eye-opened condition in gamma frequency band (34-44Hz) has the best distinction level of 96.2% using spectrogram. The children with Asperger disorder had significant lower spectrogram criteria values ($p<0.01$) at Fp1 electrode and lower values ($p<0.05$) at Fp2 and T6 electrodes. Coherence values at 171 pairs of EEG electrodes indicate that the connectivity at (T4, P4), (T4, Cz), (T4, C4) electrode pairs and (T4, O1) had significant differences ($p<0.01$) in the two groups in the gamma band.
Conclusions: It is shown that gamma frequency band can discriminate 96.2% of the two groups using the spectrogram criteria. The results demonstrate that there are more abnormalities in the prefrontal and right temporal lobes using spectrogram criteria and there are more abnormalities in the connectivity of right temporal lobe with the other lobes in the gamma frequency band.

Keywords: *Asperger syndrome, Investigative techniques, Quantitative Electroencephalography (QEEG),*

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Asperger's disorder (AD), first described in 1944(1), was not well known in English speaking countries until the paper of Wing in 1981 (2). She used the term Asperger's disorder to heighten awareness about this particular type of autism spectrum disorder(3).
Autistic spectrum disorder (ASD, comprising autism and Asperger disorder) is a highly genetic neurodevelopment disorder affecting approximately 60 per 10,000 persons (4). In the studies conducted since 1987, Fombonne has reported different prevalence estimates ranging from 2.5 to 72.6 per 10,000 with a median rate of 11.3 per 10,000 (5).
AD disorder is characterized by impairments in reciprocal social interaction and communication and a restricted repertoire of interests, behaviors and activities; however, it differs from autism because no clinically significant delay in spoken or receptive language and no cognitive development, self help skills or curiosity about the environment are associated with this disorder(6, 7).
Dawson and colleagues recorded EEG in children with ASD during visual attention and found that abnormality decreased the EEG spectral power (using Fourier analysis) over frontal and temporal areas in the delta, theta and alpha frequency ranges, but normal power in the beta range (8). In contrast, Bashina and coauthors observed a decreased spectral power in alpha/2 bands (7.5-11 Hz), but an increased spectral power in delta, alpha3 (11.5-13 Hz) and beta bands, 'at rest' in children with ASD and AD(9). In addition, an abnormal EEG asymmetry was reported in a few studies. Recently Orekhava et al. have obtained an increase of gamma activity under the controlled condition of visual attention and behavioral stillness (10).Although EEG abnormalities and clinical seizures may play a role in ASDs, the exact frequency of EEG abnormalities in an ASD population that did not have clinical seizures or prior abnormal EEGs is unknown (11).
Spectrogram (magnitude of Short-time Fourier transform, STFT) is very powerful in showing frequency characteristics of signals in the time domain (12, 13). Seventy percent of the maximum value of

spectrogram is used as a threshold to discriminate AD groups against control groups. This criteria (70 percent of maximum of spectrogram here after named spectrogram criteria) was employed in the relaxed eye-opened condition for recording QEEG signal in the frequency bands of delta (0-4 Hz), theta (4-8 Hz), alpha (8-12Hz), beta (12-36 Hz), gamma (36-44 Hz) and the frequency band showed significant differences in the two groups has obtained (gamma band).

Increase in gamma spectral power is seen at Fp1 and Fp2 in children with AD but it can not be used to discriminate the AD from control children; whilst using spectrogram criteria it is decreased at Fp1, Fp2 and T6 and it could discriminate the two groups of children with an excellent precision level (96.2%).

Electroencephalographic coherence analysis constitutes a noninvasive technique for studying corticocortical associations and can be interpreted as the degree of coupling between two signals. Coherence of EEG signals from different brain regions is assumed to index anatomic functional coupling between these signals in the frequency domain (14,15). In this study, the connectivity between 171 $(19\times18/2)$ pairs of EEG electrodes was assessed using magnitude squared coherence (MSC) values. The results indicate that there are abnormalities in the connectivity of temporal lobes with the other lobes.

Studies in very young children are of particular interest for understanding the pathogenesis of AD. The possibility of using functional neuroimaging is limited in investigations of very young children. In contrast, QEEG can be recorded even in infants. Therefore, this method is of potential interest for both exploratory purposes and early differential diagnosis of AD.

Materials and Method

Participants

Fifteen children with AD (10 boys and 5 girls) with the age range of 6 to 11 were studied; all children had verbal IQ scores of higher than 85 (The Wechsler Intelligence Scale for children). Each interview and Diagnosis was conducted by 2 child and adolescent psychiatrists based on DSM-IV-TR criteria (Diagnostic and statistical manual of mental disorders-Text Revision)(16). The clients were recruited from the autism clinic of a University Hospital and the private clinic of one of the authors in Tehran. All the subjects with AD were medication-free for at least two weeks prior to QEEG recording. The control group consisted of 11 age-matched children without past or present neurological disorders (7 boys and 4 girls).

Handedness was measured using the Edinburgh Handedness Inventory (17). This inventory uses a parental questionnaire including 10 questions about preferential hand usage during performance of skilled actions such as throwing a ball, writing with a pencil and eating with a spoon. One left-handed and one ambidextrous subject were in the control group and there was one left-handed in the AD group. The remainders were all right-handed.

An informed consent was obtained after the procedures and purpose of the study were described to the parents of control children and the caregivers or parents of children with AD. An EEG was recorded under special conditions from every one of the children; and a print of the recorded EEG signal was given to every child's parents.

EEG recording

The EEG signals were recorded at the sampling rate of 256 Hz with ESI-128 (NeuroScan Company, US). Electrodes were positioned from the 21 scalp loci according to the international 10–20 system; Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2, A1 and A2 with both earlobes were chosen as common referential electrodes and are shown in Fig. 1 (18). Aid was taken from additional external electrodes in upper and lower eye-lid dye for extraction eye artefact. More than 20 minutes of EEG recording of data was conducted only when the child was awake and seated on a chair in a calm state and in the relaxed eye-opened condition.

The recordings were visually inspected by an expert neurologist in encephalography to reject artefacts. Thus, only EEG data which were free from electrooculographic and movement artefacts and had minimal electromyography (EMG) activity were selected. Then, EEGs were organized in 3 second artefact-free epochs (768 points) that were copied for off-line analysis on a personal computer. An average number of 25.0 ± 10 artefact-free epochs were selected from each electrode for each subject in a relaxed eye-opened condition.

In order to remove the residual EMG activity and the noise due to the electrical main, all the selected epochs were digitally filtered. We used a FIR (finite-duration impulse response) band-pass filter with cut-off frequencies at 0.5 and at 100 Hz and then we processed the data with a notch filter of 50 Hz City electricity interference with Matlab 7.1 (The Mathworks, Inc.).

Since frequency bands in EEG signals are very helpful in understanding brain functioning, in this research signals were divided into five frequency bands.

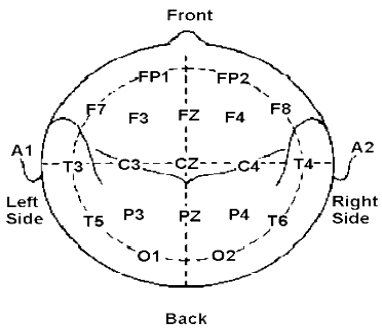

Figure 1. International (10-20) EEG electrodes placement system

Spectrogram

The STFT of a generic signal $x(t)$ is defined as:

$$STFT(t, f) = \int_{-\infty}^{+\infty} x(\tau) w^*(\tau - t) e^{-j2\pi f\tau} d\tau \qquad (1)$$

Where * denotes the complex conjugate and $w(t)$ is a window function that has a short time duration.

The spectrogram of $x(t)$ is the magnitude of STFT. The result of the transform is a two-dimensional map in time-frequency space that provides a measure of how the frequency content of the signal evolves in time. The spectrogram was estimated by dividing the digital time series into several overlapping blocks, each one advancing in time. The blocks were then multiplied by the window function and Fourier was transformed (19, 20).

In this work, the spectrogram criteria are used as a discriminating tool for separating the two groups. The spectrogram criteria were obtained for all the electrodes and were averaged based on all the artifact-free 3 second epochs in the five frequency bands.

Coherence values

Averaged periodogram was calculated over all the 3 second epochs for each recording. A Hamming window with over 50% overlap was used in order to prevent spectral leakage. Auto and cross-power spectra were estimated for the 171 electrode pairs in order to obtain MSC function. For the two signals $\xi(t)$ and $\eta(t)$ with respective auto spectra $P_{\xi\xi}(f)$ and $P_{\eta\eta}(f)$, and cross-spectrum $P_{\xi\eta}(f)$, MSC function was given at each frequency bin by the following equation (21):

$$MSC(f) = \frac{\left|P_{\xi\eta}(f)\right|^2}{P_{\xi\xi}(f) P_{\eta\eta}(f)} \qquad (2)$$

Where MSC function is estimated by the coherence range between 0 and 1.

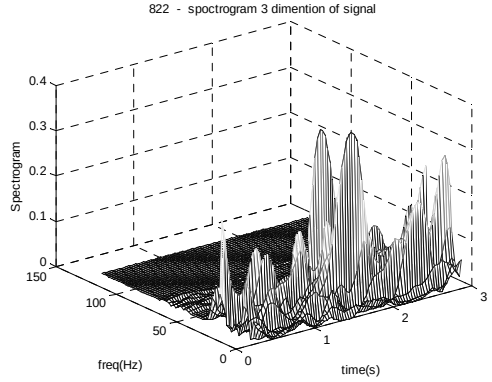

Figure 2. Spectrogram of Fp1 electrode for a subject

For a given frequency (f_0), $MSC(f_0) = 0$ indicates that the activities of the signals in this frequency are linearly independent, whereas a value of $MSC(f_0) = 1$ gives the maximum linear correlation for this frequency. Coherence values were estimated by averaging MSC for adjacent frequency bins on each of the five frequency bands. The functional connectivity was investigated by coherence values which were estimated by averaging MSC at 171 pairs of EEG electrodes. In order to obtain MSC function, averaged periodogram was calculated over all epochs using auto spectra and cross-spectrum of the two signals (Fp1 and Fp2 for example).

Statistical analysis and classification

The statistical analysis on the two-tailed tests (t-test) with 95% confidence interval was used to compare the data in the groups. When significant differences between the two groups were found, the effectiveness of this method of analysis in discriminating AD from control children was evaluated using receiver operating characteristic (ROC) curves (22).

The value for the area under the ROC curve can be interpreted as follows: an area of 0.90 (at Fp1 electrode for example) means that a randomly selected individual from the control group has a spectrogram criteria value larger than that of a randomly chosen individual from the AD group in 90% of the time. A rough guide to classify the precision of a diagnostic test is related to the area under the ROC curve. With values between 0.90 and 1, the precision of the diagnostic test is considered to be excellent; good for values between 0.80 and 0.90; far fair if the results are in the range of 0.70-0.79; poor when the value of the area under the ROC curve is between 0.60 and 0.69 ; and bad for values between 0.50 and 0.59 (23).

To classify the children with AD and the control children, we used nearest neighbor classifiers; they assign a feature vector to a class according to its nearest neighbor(s). This neighbor can be a feature vector from the training set as in the case of k nearest neighbors (KNN), or a class prototype as in Mahalanobis distance. They are discriminative nonlinear classifiers. According to the so-called Mahalanobis distance $d_c(x)$ (24):

$$d_c(x) = \sqrt{(x - \mu_c) M_c^{-1} (x - \mu_c)^T} \qquad (3)$$

Mahalanobis distance is based on correlation between samples using average of the samples (μ_C) and co-variance matrix of the samples (M_C).

Results

Information and demographic factors on the two groups are presented in Table 1. Since the assumptions of normal distribution and similarities were valid, statistical analysis of two-tailed tests (t-test) with 95% confidence interval was used to compare the data in the

Table 1. Characteristics of two groups children with Asperger disorder (AD) and control children

Samples	AD (n=15)	Control (n=11)	t Statistic (df)
Age (Mean±SD)	9.15 ± 2.7	9.1± 1.7	-0.202 (24)
Sex (male, female)	10 m , 5 f	7 m , 4 f	
Verbal IQ (Mean±SD) (Range)	114.28± 19.9 85-140	111.36± 14.67 90-135	-0.370 (24)
Handedness	Right (14) Left (1)	Right (9) Left (1) Ambidextrous (1)	

two groups. The results of the t-test on age and IQ demonstrate that there were not any significant differences between the two groups.

Spectrogram criteria

In this research, the averaged values of spectrogram greater than 70 percent were used as a discriminating tool for separating the two groups. Averaged spectrogram values greater than 70 percent of the maximum (the chosen threshold) were used for comparison that was 0.28 (0.7× 0.4) for Fig. 2.

The 70 percent criterion was arrived by trying many different percentages and it resulted in best group classifications. It was also used in calculations to decrease cranial bones and skin affects with Z standard distribution (25).

The spectrogram criteria values were obtained for Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 electrodes and O2.The results were averaged based on all the artefact-free 3 second epochs within the 20- minute -period of EEG recording. This criterion of spectrogram for EEG recording was evaluated in the frequency bands of delta (0-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-36 Hz) and gamma (36-44 Hz) .It was observed that delta and theta bands had no significant differences; however, F4 and C4 ($p<0.01$) in alpha band and Fp1, Fz and O2 ($p<0.05$) in beta band showed significant differences. More significant differences that could separate the two groups were obtained in gamma band. The AD group had significant lower spectrogram criteria value ($p<0.01$) at Fp1 electrode and lower values ($p<0.05$) at Fp2 and T6 electrodes .Spectral power in the two groups showed significant differences ($p<0.01$) with higher values at Fp1 (0.189 ± 0.029 and 0.116 ± 0.019 mean standard deviation (SD) in children with AD and control children, respectively) and at Fp2 ($p<0.05$) with (0.179 ± 0.145 and 0.145 ± 0.023) in gamma band. However, the values of spectral power in contrast to the spectrogram criteria were higher in children with AD.

ROC curves and classification

We evaluated the effectiveness of spectrogram criteria to discriminate AD from control children at the electrodes in which significant differences were found using ROC curves. The values of the area under the ROC curves for Fp1, Fp2 and T6 electrodes had the most validation for classifying the two groups. Value of Fp1 had an excellent precision level (area under the ROC curve is more than 0.9) and Fp2, T6 held precision in far fair and good levels in distinguishing the two groups (0.939, 0.782 and 0.812 respectively) . Classifications of results with Mahalanobis distance in gamma band and in the relaxed eye-opened recording condition were obtained. We found that the spectrogram criteria are able to classify fifteen out of fifteen AD children and ten out of eleven control children correctly. In total, in this classification 96.2% of the samples were placed correctly in their own class. It was found that alpha and beta bands can not distinguish the two groups.The values of the area under the ROC curves for spectral powers of Fp1 and Fp2 (0.025 and 0.219) didn't have proper precision levels for classifying the two groups. Therefore, the spectral power was not able to discriminate the two groups .

Coherence values

The functional connectivity was investigated by computing MSC at 171 pairs of EEG electrodes in five frequency bands. The results were averaged based on all the artefact-fee 3 second epochs of EEG recording. The MSC values with significant difference among AD and control children are summarized and presented in Table 2. We observed that connectivity at electrode pairs of (T4, P4), (T4, Cz), (T4, C4) and (T4, O1) had significant differences ($p<0.01$) in the two groups; Table 2 demonstrates many significant differences at the electrode pairs ($p<0.05$).

Figure 3 illustrates the obtained results with calculated MSC values in alpha, beta and gamma frequency bands. Fig. 3-C demonstrates that connectivity at the electrode pairs of (T4, P4), (T4, Cz), (T4, C4) and (T4, O1) indicate significant differences ($p<0.01$) shown with solid lines in the two groups. In this lobe, many electrode pairs indicate the significant differences ($p<0.05$) shown with dot lines. Further, Fig. 3 illustrates that more abnormalities are related to temporal lobes connectivity with the other lobes in gamma band. ROC curves showed that MSC values in those electrode pairs that had significant differences didn't have proper precision levels for classifying the

Table 2: The average coherence values of the EEG for the Asperger disorder (AD) and control children for electrode pairs in gamma band (34-44Hz)

Electrode pairs	AD children (Mean±SD)	Control children (Mean±SD)	Statistical analysis (p value)
F3-C3	0.204±0.556	0.166±0.349	0.025
Fz-C4	0.173±0.611	0.170±0.451	0.049
Fz –T4	0.223±0.389	0.103±0.193	0.031
F4 -T4	0.193±0.397	0.078±0.247	0.050
F8 –T4	0.221±0.492	0.112±0.254	0.011
F8 -T5	0.132±0.401	0.125±0.256	0.021
Cz -T4**	0.198±0.465	0.110±0.225	0.005
C4 -T4**	0.235±0.483	0.122±0.224	0.009
C4-T5	0.162±0.462	0.113±0.322	0.045
P3 -T4	0.210±0.415	0.118±0.227	0.032
Pz -T4	0.208±0.440	0.118±0.253	0.031
P4 –T4**	0.189±0.496	0.096±0.246	0.002
P4-T5	0.162±0.472	0.110±0.296	0.013
P4-O2	0.164±0.692	0.146±0.534	0.035
O1 -T4**	0.207±0.457	0.075±0.215	0.005
O2 -T4	0.171±0.500	0.180±0.297	0.017
O2 -T5	0.118±0.526	0.176±0.385	0.036
O1 -O2	0.125±0.707	0.139±0.580	0.041

**p<0.01 and the others with p<0.05

two groups. Therefore, MSC values such as spectral power were not able to discriminate the two groups .

Discussion

In this study, the QEEG signal of 11 control children and 15 children with AD was analyzed, and the results of the two groups were compared against one another using spectrogram criteria and coherence values in the relaxed eye-opened condition. Our results demonstrate that children with AD have significant lower values ($p<0.01$) at FP1 electrode and Fp2 and T6 electrodes ($p<0.05$) in gamma frequency band. Using spectral power AD children have been significant differences with higher values at FP1 ($p<0.01$) and FP2 ($p<0.05$) in gamma frequency band.

The results of classification with Mahalanobis distance in gamma band indicate an excellent diagnosis of AD disorder in 96.2% of the cases.

Decrease of fast EEG oscillation activities in AD is in agreement with the gamma band power reduction given by Von Stein(26). On the other hand, our results with spectrogram criteria did not agree with the induced gamma band regions of the face perception of adults with autism (27). However, using spectral power, we observed that the increase of gamma activity in Fp1 and Fp2 was in agreement with them. The results, however, were obtained by two different methods of spectrogram criteria and spectral power. In classification of the two groups, area under the ROC curves of Fp1 and Fp2 with spectral power did not have a proper precision level (values were less than 0.5).. However, these areas had excellent and good precision levels for Fp1, Fp2 and T6 in spectrogram criteria (greater than 0.8).

In view of the fact that gamma band plays the synchronization role of cortical nets region especially in recognition and perception tasks (28), the results of this study suggests that there are abnormalities in synchronization of cortical nets in children with AD. High frequency rhythms are generated in neuronal network involving excitatory pyramidal cells and inhibitory gamma-aminobutyric acid (GABA)-ergic interneurons. The morphological integrity of GABAergic interneuron connections within cortical minicolumns is important for generation of normal gamma oscillations (29). The cortical minicolumns, which reduces neuropil space in the periphery, should be more numerous, smaller and less compact in autistic disorders than in controls(30). Casanova et al. suggested that such an abnormal minicolumn organization may result in a deficit of inhibitory GABAergic fiber projection, which in turn may facilitate the occurrence of epilepsy in autism (31). Hermann and Demiralp summarized available data on gamma activity in different forms of psychopathology (e.g., epilepsy, attention deficit hyperactivity disorder [ADHD], schizophrenia and Alzheimer's disease) and concluded that disturbances in gamma synchronization mechanisms may contribute to too many psychopathological symptoms (32). In children with AD, the increase of spectral power and decrease of spectrogram criteria in gamma band may be related to quality of cortical minicolumns and GABAergic interneurns .

Other frequency bands of EEG were also evaluated using spectrogram criteria and statistical analysis. The alpha band showed significant differences both in F4

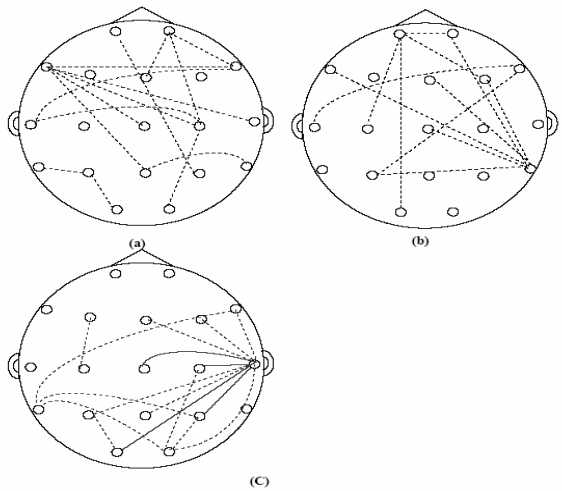

Figure 3. Results of connectivity in 171 pairs of electrodes that had significant differences in frequency bands, Significantly differences with p<0.05 in two groups control subjects and Asperger disorder shown with dot lines and with p<0.01 shown with solid lines, a) alpha, b) beta and c) gamma frequency band.

and C4 with ($p<0.01$); Fp1, Fz and O2 all with the ($p<0.05$) in beta band indicated significant differences.
Abnormalities in alpha and beta bands are in agreement with findings of Bashina et al.(9) Alpha band reflect coordination of wider areas of the brain and beta band shows an integration role in the neighboring areas of the brain (33, 34) .
In this study, it is was observed that significant differences in alpha and beta bands didn't provide a proper sensitivity and specificity for classification of the two groups using ROC curves whereas in gamma band an excellent distinction (96.2%) between the two groups was observed.
Figure 3 shows 171 pairs of EEG electrodes in three frequency bands in the relaxed eye-opened condition using MSC. Fig. 3 illustrates that more abnormalities in connectivity are related to the connectivity of right temporal lobe with the other lobes in gamma band. The increased coherence between the right temporal lobe and other lobes can be interpreted as a reflection of genuine increased correlated cortical activities. Our results are consistent with recent evidence demonstrating altered resting state connectivity in adults with autism spectrum disorders (35).
This inconsistency may well be a result of well known heterogeneity in AD, different age range, IQ and sex of the subjects, and/or dissimilarity in behavioral condition during EEG recording. Autistic groups usually comprise both autism and asperger disorders whilst we have only studied children with AD. Another difference between our study and others is how we evaluated EEG signals. In this study, we have used spectrogram criteria with more information of the signal in two dimensional maps (time-frequency) instead of spectral power .
One of the limitations of our study that merits consideration is that the sample size was small. As a result, our findings are preliminary and require more replications in a larger disorder population before any conclusive valuable clinical diagnosis can be made. This study, to the best of our knowledge, is the first to employ spectrogram and coherence values to QEEG in children with AD and using it for classification and diagnosis of AD. Nevertheless, since no other researchers have used the method in this area, we were unable to assess our results. Another limitation was that the AD children could not be taken off their medication for along time; all of these children were only medication-free for at most two weeks prior to EEG recording .
In conclusion, in this work we have evaluated the QEEG signal in the relaxed eye-opened condition between the two groups of control children and children with AD. We observed that gamma frequency band can discriminate 96.2% of the two groups using the spectrogram criteria. In addition, it was perceived that there are abnormalities in gamma band ,and also significant differences ($p<0.01$) were observed at Fp1 and ($p<0.05$) at Fp2 and T6 that may be related to a problem in cortical net. Connectivity in 171 pairs of EEG electrodes was evaluated with coherence values. Furthermore, it can be stated that there are more abnormalities in connectivity of right temporal lobe with the other lobes. Future research should be carried out to replicate and increase the depth of this study by using more participates and trials and using spectrogram criteria for evaluation of EEG in the other disorders.

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