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Detection of abnormalities for diagnosing of children with Asperger disorder using of quantitative electroencephalography analysis

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Abstract

Asperger disorder, one of the autistic spectrum disorders, is characterized by impairments in reciprocal social interaction and communication. In this study, spectrogram and coherence values with statistical analysis are used for evaluating quantitative electroencephalography (qEEG).Seventeen children with Asperger disorder (aged between 6 to 11)and thirteen control children (same age) were examined. It is shown that gamma frequency band (34-44Hz) could be used to separate the two groups very well (96.7%) in relaxed eye-opened condition. The children with Asperger disorder showed significant lower spectrogram criteria value ($p<0.01$) at Fp1 electrode and ($p<0.05$) at Fp2 and T6. Coherence values at 112 pairs of EEG neighbor electrodes indicated that the connectivity at electrode pairs (T4, P4), (T4, Cz), (T4, C4) and (T4, O1) had significant differences ($p<0.01$). More abnormalities were related to the connectivity of right temporal lobe with the other lobes. The results demonstrate that analysis of qEEG is useful for diagnosis of children with Asperger disorder using spectrogram and coherence values.

Keywords

Asperger and Autism Disorders, Quantitative Electroencephalography, Spectrogram and Coherence Values

1. Introduction

Asperger's disorder (AD) is characterized by impairments in reciprocal social interaction and communication. AD is one of autism spectrum disorders and shares several features with autism, but is regarded as a separate clinical entity [1, 2]. Language development in AD is usually normal [3] but there are problems in understanding hidden meanings of the spoken message and in using language in a social context [4, 5].

The literature on EEG of autism subjects is usually general and nonspecific i.e. changes in prevalence of slow bioelectrical and alpha rhythm suppression is not very precise [6, 7, 8]. While Ogawa et al. [9] found elevated frontal alpha in autistics, Cantor et al. [8] showed that autistic children had elevated power in frontotemporal regions, especially in delta band. Murias et al. [9] found autistic adults had greater relative theta (3-6 Hz) and beta1 (13-17 Hz) than controls. Orekhova et al. [11] obtained an increased gamma activity under the controlled condition of visual attention and behavioral stillness. Although some authors observed lower activation in the left anterior areas in comparison with the

right ones [12, 13], others showed higher activation in the left hemisphere in delta, theta and alpha frequency bands [14]. It was observed that there are the right hemisphere abnormalities, in the AD, in neuroimaging studies [15, 16]. While Lazarev et al. [17] observed significantly lower activity in the right hemisphere, findings by Coben et al. [18] included excessive theta band in right posterior regions, in autistics that were recorded during an eyes-closed resting condition.

Abnormalities in EEG are one aspect of brain dysfunction. Dawson et al. [12] investigated the individuals with autism had atypical patterns of cerebral lateralization, involving right hemisphere dominance for both verbal and spatial functions. The reversal in lateralization indicated a lack of left hemisphere specialization for linguistic function. Excesses of theta power over the right posterior region of the brain in autistics suggest that this is an area of abnormal functioning [18]. Excess theta activity is commonly found in children with executive functioning and mental activity problems, including attention deficit/hyperactivity disorder [19], learning disabilities [20] and mental retardation [21]. Different patterns of coherence and abnormal connectivity have been associated with social cognition deficits and facial and sensory processing impairments in autistics [22, 23].

Some of methods are used to show abnormalities in EEG of AD individuals but they were not used to distinguish this group [18, 14]. The aim of this study was to extract significant abnormalities in qEEG of children with AD that can be used for diagnosis of this group in comparison to control children. Since possibility of functional neuroimaging is limited in the investigations of young children, qEEG can be an alternative and it may even be used in infants. Therefore, this method is of potential interest to characterization and diagnosis of children with AD.

2. Materials and Methods

2.1. Participants and EEG Recording

Seventeen children (12 boys and 5 girls) were diagnosed as AD, according to the DSM-IV-TR criteria [24] by two child and adolescent psychiatrists, and 13 healthy control children (9 boys and 4 girls) were matched on age [mean± standard deviation (SD), range: 8.31±2.58, 6-11 years old, and 8.37±2.09, 6-11, respectively] and full-scale IQ [108± 16.8 and 110.5±15.4, respectively]. The results of the t-test on age ($t(28) = 0.074$, $p > 0.53$) and IQ ($t(28) = 0.503$, $p > 0.71$) demonstrated that were not any significant differences between the two groups. Their IQ levels were obtained according to the WISC-III intelligence test[25] and all participants had a full-scale IQ higher than 92.The clients were recruited from the autism clinic of University Hospital and private clinic one of the authors (Tehran). All of the children with AD were medication-free for at least two weeks prior to EEG recording. The control children group was selected from healthy regular schools without history of neurological and psychiatric disorders.

Handedness was measured using the Edinburgh Handedness Inventory [26].This inventory assesses using 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. Two left-handed and one ambidextrous subject were in the control group and there were two 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 was described to the parents of control children and the caregivers or parents of children with AD. An EEG was recorded from every one of the children; and a print of the recorded EEG signal was given to each child's parents.

The EEG signals were recorded at the sampling rate 256 Hz by ESI-128 (Neuro Scan Company, USA) at 19scalp points (International 10-20 system) Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2. A1 and A2 on the both earlobes are chosen as common referential electrodes.

Aid was taken from additional external electrodes in upper and lower eye-lid dye to extraction eye artefact too. EEG recording more than 20 minute of data was conducted only when the subjects were wakeful with the relaxed eye-opened condition throughout the experiment seated on chair in a calm state.

The recordings were visually inspected by two expert neurologists 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. EEGs were organized in 3 second artefact-free epochs (768 points) that were copied for off-line analysis on a personal computer. The numbers of 24 artefact-free epochs were selected from each electrode for every subject in the relaxed eye-opened condition.

We used a Hamming window FIR (finite-duration impulse response) band-pass filter with cut-off frequencies at 0.5 and at 100 Hz and then data were processed with a notch filter of 50/60 Hz electricity interference with MATLAB7.1 (The Mathworks, Inc.). Finally EEG signals were divided into frequency bands of delta (0.5-3 Hz), theta (3-7 Hz), alpha (8-13 Hz), beta (14-36 Hz) and gamma (36-44Hz).

2.2. Spectrogram and Coherence Values

The Short-time Fourier transform (STFT) is obtained from the usual Fourier transform by multiplying the time signal $f(t)$ by a window function $\psi(t)$ [27, 28].

$$STFT(\omega,\tau) = \int_{-\infty}^{+\infty} f(t)\psi^*(t-\tau)e^{-j\omega\tau}dt \quad (1)$$

Spectrogram (magnitude of STFT) is very powerful in showing frequency characteristics of signals in the time domain. In this research the values of spectrogram greater than the 70 percent was averaged (spectrogram criteria) and used as a discriminating tool for separating the two groups [29, 30, 31, 32]. As seen in Fig. 1, the maximum value of

spectrogram is 0.4, therefore spectrogram criteria is equal to 0.28 (0.7 × 0.4).

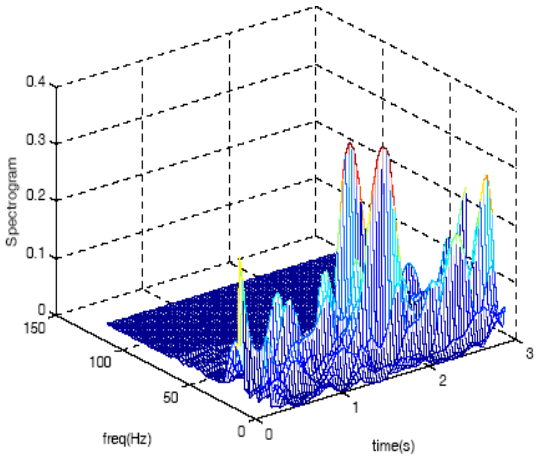

Figure 1. *Magnitude of spectrogram of Fp1 electrode for a control subject.*

The 70 percent was arrived by trying many different thresholds and it was the value that resulted in best group's classification. In practice, the stronger magnitudes of spectrogram of the two groups were compared. In order to decrease cranial bones and skin effects on EEG recordings, Z standard distribution were used in spectrogram criteria calculations. The spectrogram criteria were obtained for all electrodes and averaged based on all the artefact-free 3 second epochs.

Averaged periodogram was calculated over the all 3 second epochs for each recording with a Hanning window with 50% overlapping. Auto and cross-power spectra were estimated for the 112 electrode pairs in order to obtain magnitude squared coherence (MSC) values. 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 value was given at each frequency bin by the following equation [33]:

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

The functional connectivity was investigated by coherence values that estimated by averaging MSC at 112 pairs of EEG neighbor electrodes. In order to obtain MSC values, averaged periodogram was calculated over all epochs using auto spectra and cross-spectrum of the two signals (Fp1 and Fp2 for example).

2.3. Statistical Analysis and Classification

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 spectrogram criteria and MSC values in the two groups. To avoid of multiple t-testing, every test was performed separately. If significant differences between two groups were found, the ability of this method to discriminate AD from control children was evaluated by using receiver operation characteristic (ROC) curves [34].

For classifying the two groups, we used nearest neighbor classifiers. They consist in assigning 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 [35].

3. Results

3.1. Spectrogram Criteria

The spectrogram criteria values were obtained for all of the 19 electrodes of EEG recording in the five frequency bands. 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. The values and standard deviations of spectrogram criteria for AD and control children and the corresponding p values for gamma band in the relaxed eye-opened condition are summarized in Table 1.

Table 1. *The average spectrogram criteria values of the EEG for the Asperger disorder (AD) and control children for all the electrodes in gamma band (34-44Hz)*

Electrodes	AD children (Mean±SD)	Control children (Mean±SD)	Statistical analysis (p value)
Fp1**	0.185±0.089	0.477±0.138	0.001
Fp2*	0.242±0.162	0.383±0.163	0.026
F7	0.315±0.223	0.327±0.193	0.884
F3	0.248±0.156	0.340±0.161	0.16
Fz	0.307±0.212	0.375±0.179	0.395
F4	0.285±0.214	0.398±0.155	0.15
F8	0.342±0.207	0.453±0.157	0.149
T3	0.318±0.191	0.331±0.193	0.867
C3	0.313±0.241	0.303±0.187	0.917
Cz	0.392±0.191	0.404±0.152	0.862
C4	0.327±0.202	0.366±0.202	0.632
T4	0.351±0.226	0.402±0.107	0.495
T5	0.327±0.187	0.307±0.174	0.78
P3	0.302±0.247	0.363±0.156	0.477
Pz	0.350±0.234	0.375±0.154	0.765
P4	0.305±0.214	0.424±0.141	0.125
T6*	0.271±0.193	0.444±0.146	0.012
O1	0.340±0.217	0.369±0.164	0.714
O2	0.349±0.223	0.395±0.228	0.615

** $p<0.01$ and * $p<0.05$

The AD group had significant lower spectrogram criteria value ($p<0.01$) at Fp1 electrode and ($p<0.05$) at Fp2 and T6 electrodes in gamma band frequency.

3.2. 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 in gamma band. Value of Fp1 had an excellent precision (area under the ROC curve is equal to 0.955) and

Fp2, T6 held precision in far fair and good in distinguishing the two groups (0.729 and 0.824, respectively).

It is found that the spectrogram criteria is able to classify seventeen out of seventeen AD children and twelve out of thirteen control children correctly with Mahalanobis distance in gamma band. Therefore in this classification 96.7% of samples (with 0.8521 and 0.7801 sensitivity and specificity, respectively) were placed correctly in their own class. It was found that significant difference values in alpha and beta bands cannot distinguish the two groups.

3.3. MSC Values

The functional connectivity was investigated by computing MSC values at 112 pairs of EEG neighbor electrodes. The results were averaged based on all the artefact-free 3 second epochs of EEG recording. The MSC values with significant difference values ($p<0.01$ and $p<0.05$) between the two groups(AD and control children) in gamma band frequency are summarized in Table2.

We observed that MSC values at electrode pairs of (T4, Cz), (T4, C4), (T4, P4) and (T4, O1) had significant differences ($p<0.01$) in the two groups. Fig. 2 illustrates the obtained results with calculated MSC values in gamma band frequency.

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	0.556±0.204	0.349±0.166	0.025
Fz-C4	0.611±0.173	0.451±0.170	0.049
Fz –T4	0.389±0.223	0.193±0.103	0.031
F4 -T4	0.397±0.193	0.247±0.078	0.05
F8 –T4	0.492±0.221	0.254±0.112	0.011
F8 -T5	0.401±0.132	0.256±0.125	0.021
T4 -Cz**	0.465±0.198	0.225±0.110	0.005
T4–C4**	0.483±0.235	0.224±0.122	0.009
C4-T5	0.462±0.162	0.322±0.113	0.045
P3 -T4	0.415±0.210	0.227±0.118	0.032
Pz -T4	0.440±0.208	0.253±0.118	0.031
T4 –P4**	0.496±0.189	0.246±0.096	0.002
P4-T5	0.472±0.162	0.296±0.110	0.013
P4-O2	0.692±0.164	0.534±0.146	0.035
T4–O1**	0.457±0.207	0.215±0.075	0.005
O2 -T4	0.500±0.171	0.297±0.180	0.017
O2 -T5	0.526±0.118	0.385±0.176	0.036
O2–O1	0.707±0.125	0.580±0.139	0.041

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

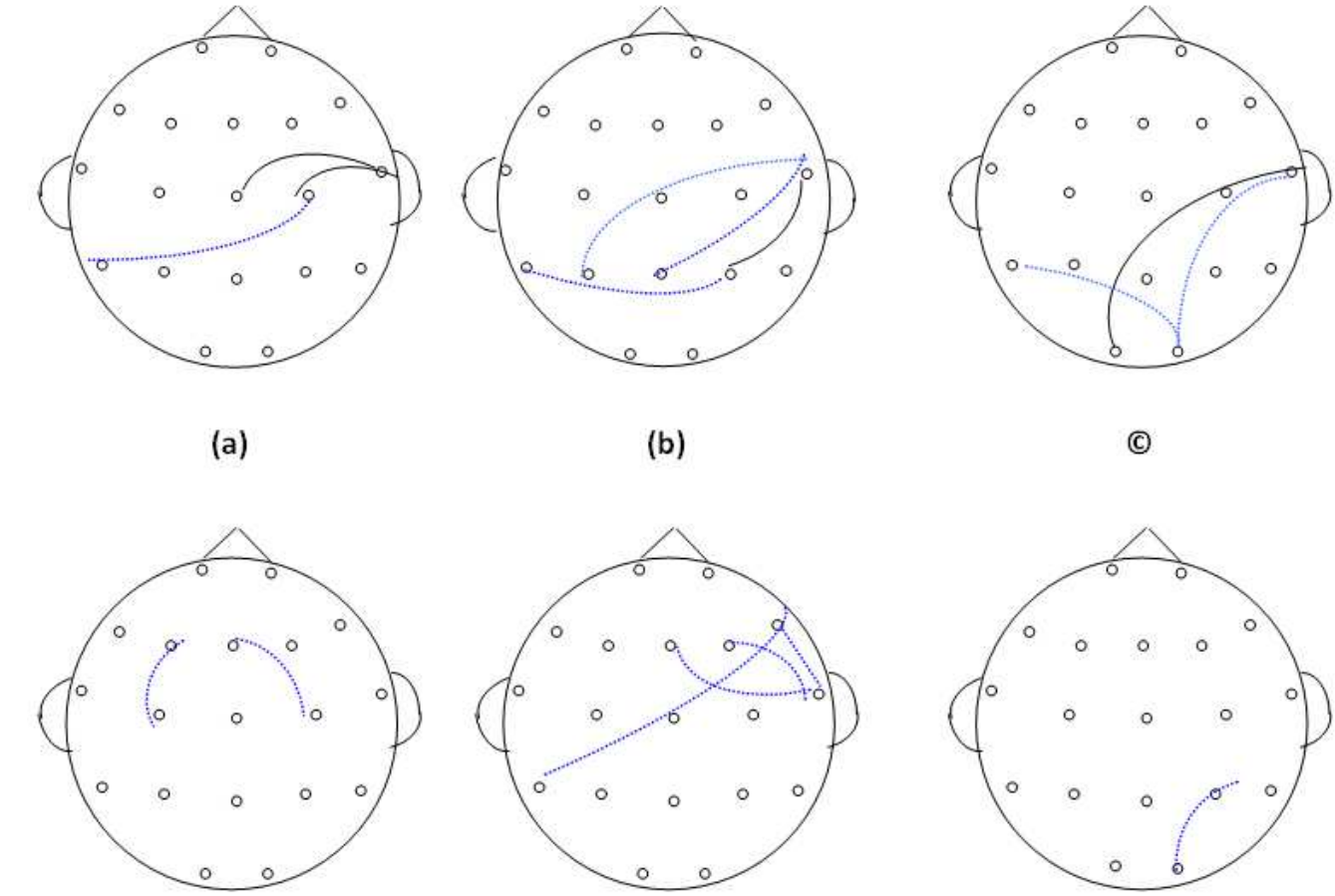

Figure 2. *Significant differences of Magnitude squared coherence (MSC) values between the brain lobes of the two groups of children, control children and children with Asperger, in gamma frequency band. (a)Temporal and central lobes. (b) Temporal and parietal lobes. (c) Temporal and occipital lobes (d) Frontal and central lobes. (e) Frontal and temporal lobes. (f) Occipitals and parietal lobes. Significant differences of MSC values (p<0.01) shown with solid lines and (p<0.05) shown with dotted lines.*

The MSC values with significant differences between temporal and central lobes shown in Fig. 2a. It demonstrates that MSC values at the electrode pairs of (T4, C4) and (T4, Cz) indicate significant differences($p<0.01$), shown with solid lines. In addition, electrode pair (T5, C4) indicates a significant difference ($p<0.05$), shown with dotted line. Fig. 2c-2f demonstrates other significant differences of MSC values between temporal and parietal lobes, temporal and occipital lobes, frontal and central lobes, frontal and temporal lobes, and, occipitals and parietal lobes. Furthermore Fig. 2 illustrates more significant differences are related to MSC values of right temporal lobe with the other lobes (frontal, central, parietal and occipital).

The values of the area under the ROC curves showed that MSC values in those of the electrode pairs that had significant differences did not have proper precisions for classifying the two groups.

4. Discussion

In this study the qEEGs of 17 children with AD and 13 control children were 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 demonstrated that children with AD have significant lower values at Fp1, Fp2 and T6 electrodes in gamma frequency band using spectrogram criteria. The results showed spectrogram criteria did have proper precision and was able to separate the two groups well.

Our findings in gamma abnormalities are in agreement with that of Von Stein and Sarnthein [36] and Grice et al. [37].We know this frequency band in EEG plays the synchronization role of cortical nets regions[38]. Thus, it appears that abnormalities in gamma band in AD can be related to synchronization of cortical nets. High frequency rhythms are generated in neuronal network involving excitatory pyramidal cells and inhibitory gamma-amino butyric acid (GABA)-ergic interneurons. The morphological integrity of GABAergic interneuron connections within cortical minicolumns is important for generation of normal gamma oscillations [39].Therefore, decreases of spectrogram criteria in gamma band frequency can be related to quality of GABAergic interneurons in children with AD.

Other frequency bands of EEG were also evaluated using spectrogram criteria and statistical analysis. The alpha band showed significant differences in F4 and C4.Fp1, Fz and O2 in beta band indicated significant differences. Abnormalities in alpha and beta bands are in agreement with findings of Bashina et al.[6]. Since alpha band reflect coordination of wider areas of brain and beta band shows an integration role in the areas of brain that are neighbors [40, 41], these abnormalities are noticeable.

The current findings illustrate that most abnormalities in MSC values are related to the connectivity's of right temporal lobe with other lobes. An increase of MSC values between the right temporal lobe and the other lobes are interpreted as a reflection of genuine increased correlated cortical activities. Consistent with our findings, other researchers have also reported findings of atypical cortical connectivity pattern in adults with autism spectrum disorders [38, 39]. Murias et al. (2006) and Rippon et al.[10, 44]found a combination of higher and lower coherences in different regions of the brains of adult autistics. Higher coherence in the autistic group indicated a lack of cerebral differentiation [7]. The findings of abnormalities in EEG coherence are suggesting increased white matter in ASD [45, 46]. Evidence of abnormal connectivity has been associated with social cognition deficits [22], frontal system dysfunction [47], and facial and sensory processing [23] impairments in autistics.

5. Conclusion

In this study it is observed that qEEGs of children with AD have two kinds of abnormalities in gamma band frequency. The first, to decrease activity in prefrontal lobe that was detected by spectrogram criteria and the second, to increase MSC values of the connectivity's of right temporal with other lobes. The findings of this research show that abnormalities in qEEG of prefrontal lobe are specific and able to separate this group much better. Limitations of this study include limited sample size and heterogeneity of samples indicating presence of different biological etiologies for various subtypes of autism. The important difference, between our method and that of others is how we analyzed EEG signals. We used spectrogram criteria with more information of signal in two dimensional maps (time- frequency) instead of spectral power. This method to the best of our knowledge is the first to employ spectrogram and coherence values of qEEG for classification and diagnosis of children with AD.

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