Brain electrical activity mapping in the diagnosis of attention-deficit hyperactivity disorder

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Background

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder of childhood. It affects approximately 4% of all children, although estimates vary widely from 3% to 11% or more. Neuroimaging and neurophysiological tests have been increasingly used to understand the relation between brain functionality and ADHD symptoms. QEEG provides a method that can measure the neurophysiological mechanisms underlying neurodevelopmental disorders. By using spectral analysis is able to find abnormalities of brain functionality and connectivity linked to abnormal ADHD behaviors.

The objective of the current work was to study and compare the efficacy & accuracy of QEEG for diagnosis of ADHD children, to assess the spectral characteristic of QEEG findings within cases of ADHD, to detect the presence of specific EEG findings that might help in diagnosis.

Methodology

The current study was conducted on 60 school aged children range from 6-15 years (60 ADHD children matching DSM-5 criteria) and 20 typically developing children. All cases were subjected to thorough history taking and clinical examination with special attention to neurological examination. Both cases and controls were subjected to QEEG analysis and interpretation. All studied children had undergone assessment with Arabic form of Conners' Parent Rating Scale short form, IQ test, Arabic version of DSM-5.

The present study revealed that: Increased levels of slow waves (predominantly theta) , decreased levels of relative Beta LF activity, and increased levels of Theta/Beta LF ratio, in QEEG of ADHD when compared to QEEGs of normal controls. The present study revealed significant differences between ADHD cases & control at all regions of brain; according to average amplitude of power spectrum of all bands (Theta, Beta LF&HF) and Theta/Beta LF ratio.

From this study we concluded that children with ADHD have QEEG dysfunctions that underlie their symptomatology. QEEG average of power spectral analysis (theta, beta LF and theta/beta LF ratio) can differentiate between ADHD cases (abnormal power) & normal population (normal power).

Keywords:
Attention-deficit, diagnosis, qualitative electroencephalogram

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Introduction

Attention-deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder of childhood that significantly affects the well-being, social interactions, and academic achievement of children (Wolraich *et al.*, 2011). ADHD is considered a lifetime problem, appearing in preschool years, with clinical picture manifestation (full or partial) throughout the adulthood (Singh *et al.*, 2015). ADHD is thought to have strong genetic, neurobiologic, and neurochemical risk factors (Attention Deficit Hyperactivity Disorder, 2009).

The relative prevalence of ADHD is high, affecting nearly 4% of all children, but estimates show wide variation ranging from 3 to 11% or more (Singh *et al.*, 2015). According to a recent report of Center for Disease Control and Prevention (CDC), the prevalence increased by an estimated 3% annually between 1997 and 2006 (Perou et al., 2013). Recent USA national data showed that prevalence of ADHD was 9.5% for those aged 6–11 years, and 11.8% for those aged 12–17 years (Perou et al., 2013). Moreover, reports stated that prevalence was higher for children with low family socioeconomic status than for children

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with high family socioeconomic status (Pastor *et al.*, 2015).

Regarding our national data, prevalence of ADHD among school aged children in Menoufia, Egypt, was 6.9% in 2014 (Farahat *et al.*, 2014). In 2015, the prevalence of ADHD in Fayooum City, Egypt, was 20.5% (Aboul-ata and Amin, 2015). The prevalence of ADHD between 1ry school children in Alexandria, Egypt, in 2013 was 6% (Iskander, 2013). A systematic review of epidemiology of ADHD in Arab countries was done by searching PubMed between July 1978 and July 2014, and on reviewing local journals while cross-referencing each of the 22 Arab countries (Jordan, Egypt, Lebanon, Saudi Arabia, and others), the prevalence of ADHD ranged from 1.3 to 16%. The review concluded that the prevalence in Arab countries is similar to reports in Africa, North America, and other countries of the Middle East (Alhraiwil *et al.*, 2015).

Standard electroencephalogram (EEG) is a diagnostic tool that measures and records the electrical activity of a case's brain to evaluate cerebral functions. The physiological interpretation of recorded signals describe both intrinsic properties of the neurons (such as their ionic conductance), as well as neural networks interactions and connectivity characteristics. The characteristics waves are typically classified in five classic frequency bands: delta band (0–4 Hz); theta band (>4–8 Hz); alpha band (>8–12 Hz); beta band (>12–35 Hz), which is divided into low frequency (LF >12–20 Hz) and high frequency (>20–35 Hz); and gamma (>35–100 Hz) (Okazaki *et al.*, 2015; Gurau *et al.*, 2017).

A more sophisticated form of EEG has been established, called quantitative electroencephalogram (QEEG) or brain electrical activity mapping, in which the brain activity is transformed into a digital form to study the background activity (Hughes and John, 1999). The findings are then showed in topographical diagrams demonstrating electrical activity of the brain known as 'brain maps' (Hughes and John, 1999; Swisher, 2017). Each frequency range is averaged across a sample of data and quantified into mean amplitude. The absolute power in each frequency band is also calculated (Dumermuth and Molinari, 1987).

Food and Drug Administration licensed and approved the first QEEG diagnostic test (Neuro-psychiatric EEG-Based-Assessment Aid device) which uses theta/beta ratios of QEEG measures at electrodes CZ on patients 6–17 years old to help the diagnosis of ADHD in children. However, the Food and Drug Administration also stated that this device is not used as a stand-alone in the diagnosis or evaluation of ADHD, and clinical evaluation remains the most important aspect in diagnosis (Snyder *et al.*, 2015). However, a summary of American Academy of Neurology practice advisory in 2016, on utility of QEEG theta/beta power ratios (TBR) in diagnosis of ADHD, concluded that 'It is not known if combinations of standard clinical evaluation and QEEG TBRs, increase the diagnostic assurance of ADHD, compared with clinical evaluation alone' (Gloss *et al.*, 2016).

The role of QEEG in ADHD diagnosis and its classification has yet to be elucidated. The American Academy of Neurology and the American Clinical Neuropsychology Society concluded that QEEG remains investigational for clinical use.

The aim of the study

The aim of the present study is to assess the spectral characteristic of QEEG findings within cases of ADHD. Such specific EEG findings might help in the diagnosis of ADHD in children by using QEEG.

Patients and methods

This was a cross-sectional case–control study that was carried out on 80 children among those attending the pediatric neuropsychiatry outpatient clinic at Alexandria University Children's Hospital and private clinics. Written informed consent was taken from the parents of all subjects and control. The research protocol and methodology was approved by the ethical committee of Faculty of Medicine, Alexandria University. Children were categorized as follows:

(1) Group I: 60 naive children with a recent diagnosis of ADHD.
(2) Group II: 20 healthy matched control children.

Inclusion criteria

Children aged between 6 and 15 years and children with newly diagnosed ADHD with no history of drug treatment before ADHD diagnosis were included.

Exclusion criteria

Age group less than 6 years old and more than 15 years old, the presence of gross neuropsychiatric or medical disorders, intelligence quotient less than 70, or children with ADHD with history of prior medical treatment were the exclusion criteria.

All the children were subjected to the following:

(1) Complete history taking and through clinical examination with special consideration on neurological examination.
(2) Intelligences quotients using (a) Stanford-Binet scale (Arabic version 5) to exclude cases and controls with IQ less than 70 (Al-Buhaira and Ajlan, 2011).
(3) Diagnosis of ADHD depending on (a) Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria and Arabic version of DSM-4 and Conner rating scale for ADHD (Arabic version) for assessment of activity level (Farag, 2011; Bard*et al.*, 2013).
(4) QEEG was done for all cases. Brain wave speed was measured in Hertz, and it was divided into bands delineating slow, moderate, and fast waves.

Electroencephalogram and quantitative electroencephalogram recording and analysis

The QEEG for the four groups was recorded using Neuron-Spectrum-4/P (Neurosoft, Ivanono, Russia) with a sampling rate of 500 Hz. The settings were set on low-pass filters of 35.0 Hz, high-pass filter of 0.5 Hz, and a 50-Hz notch filter. This software provides mathematical processing of the received data including brain mapping, spectral, and periodometrical correlation analysis, as well as computation of different spectral indices, and calculation, and finally an output of these results to a database developed with Microsoft Access.

Statistical analysis of the data (Kirkpatrick and Feeney, 2013)

Data were fed to the computer and analyzed using IBM SPSS software package, version 20.0. (IBM Corp., Armonk, New York, USA) (Kirkpatrick and Feeney, 2013). Qualitative data were described using number and percent. The Kolmogorov–Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, SD, and median. Significance of the obtained results was judged at the 5% level. The used tests were χ^2 test for categorical variables, to compare between different groups; Student t test for normally distributed quantitative variables, to compare between two studied groups; and Mann–Whitney test for abnormally distributed quantitative variables, to compare between two studied groups.

Results

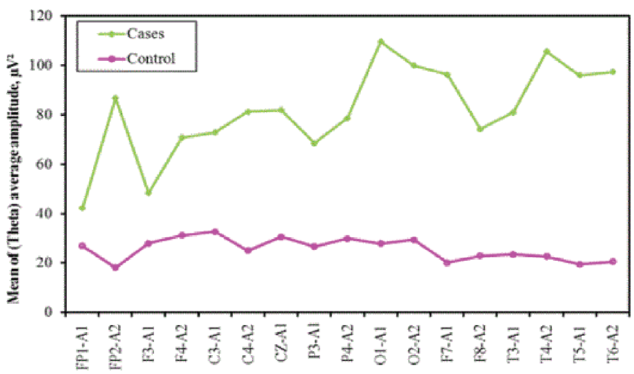
The present study showed no significant differences between group I (ADHD cases) and control according to sex (P=0.4). Alternatively, the mean age of the group I was significantly higher than the control group, with P value less than 0.001 (Table 1).

Quantitative electroencephalogram findings of attention-deficit hyperactivity disorder cases versus control

Theta band

Theta average amplitude of power spectrum was significantly higher in patients with ADHD in comparison with control at all brain regions (FP1, FP2, F3, F4, F7, F8, C3, C4, Cz, P3, P4, O1, O2, T3, T4, T5, and T6), as shown in Fig. 1.

Figure 1



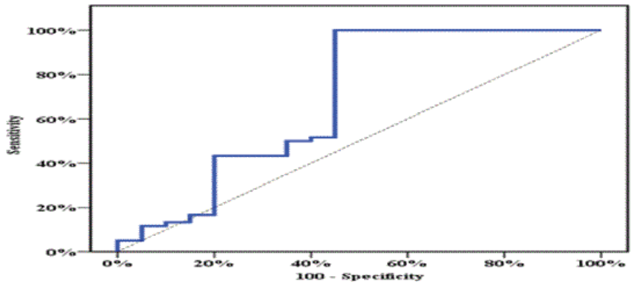
Comparison between ADHD cases and control according to theta (power spectrum, average amplitude). ADHD, attention-deficit hyperactivity disorder.

Table 1 Comparison between attention-deficit hyperactivity disorder cases and control according to sex and age

	ADHD cases (N=60) [n (%)]	Control (N=60) [n (%)]	Test of significance	P
Sex				
Male	42 (70.0)	12 (60.0)	χ^2=0.684	0.408
Female	18 (30.0)	8 (40.0)		
Age (years)				
Minimum–maximum	6.0–15.0	6.0–14.0	F=14.963*	<0.001*
Mean±SD	10.25±2.65	7.40±2.62		
Median	10.50	6.0		

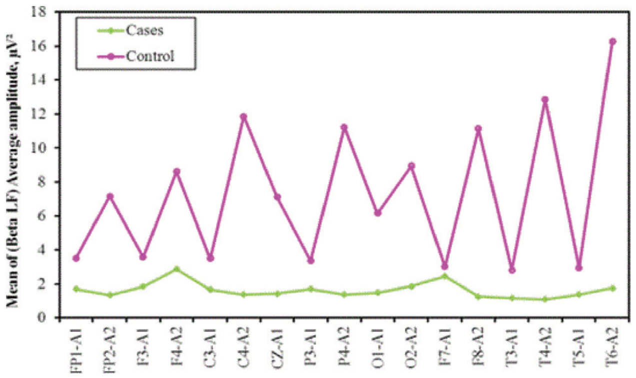
ADHD, attention-deficit hyperactivity disorder. c2: Chi square test P: P value for comparing between the different groups. F: F for ANOVA test, Pairwise comparison bet. each 2 groups were done using Post Hoc Test. *Statistically significant at $P \leq 0.05$.

Figure 2



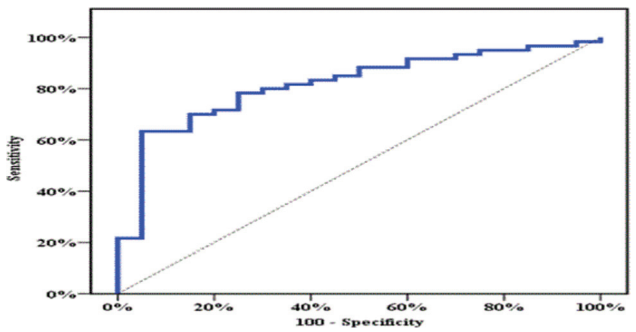
ROC curve for theta (average amplitude, μV^2) to diagnose patients from control. ROC, receiver operating characteristic.

Figure 3



Comparison between ADHD cases and control according to beta LF (power spectrum, average amplitude). ADHD, attention-deficit hyperactivity disorder; LF, low frequency.

Figure 4



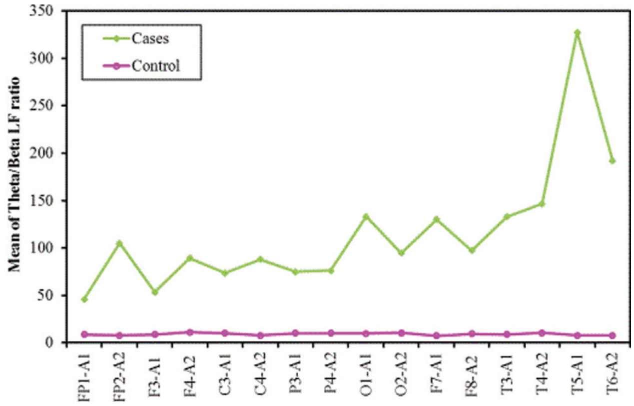
ROC curve for beta LF (average amplitude, μV^2) to diagnose patients from control. LF, low frequency; ROC, receiver operating characteristic.

Our results also showed that average amplitude of power spectrum of theta band at level more than or equal to 30.95 was significantly correlated with the diagnosis of ADHD, with 50% sensitivity and 65% specificity (P<0.001), as shown in Fig. 2.

Beta low frequency band

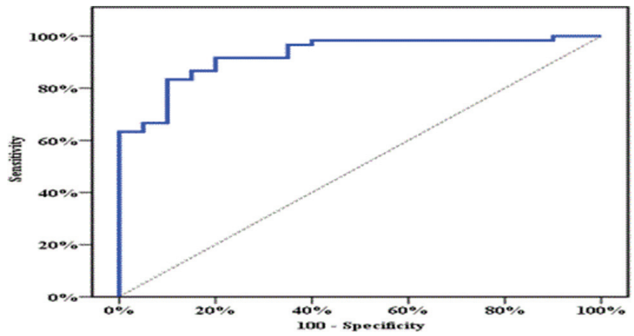
Average amplitude of power spectrum of beta LF band at all brain regions was significantly lower in ADHD in

Figure 5



Comparison between ADHD cases and control according to theta/beta LF ratio (power spectrum, average amplitude). ADHD, attention-deficit hyperactivity disorder; LF, low frequency.

Figure 6



ROC curve for theta/beta LF ratio to diagnose patients from control. LF, low frequency; ROC, receiver operating characteristic.

comparison with control, and the difference was statistically significant (Fig. 3).

Our results showed that average amplitude of power spectrum of beta low-frequency band at cutoff value level less than 1.25, there was 63% sensitivity and 95% specificity for ADHD (P<0.001) (Fig. 4).

Theta/beta low frequency ratio

ADHD cases showed significant higher average amplitude of power spectrum of theta/beta LF ratio at all brain regions than control (Fig. 5).

Our results showed that, it was statistically significant that average amplitude of power spectrum of theta/beta LF ratio at cutoff value level more than or equal to 13.65 has 83.33% sensitivity and 90% specificity for diagnosis of ADHD (P<0.001) (Fig. 6).

Discussion

QEEG spectral analysis of the EEGs of children with ADHD might be helpful in assessing waves activity in children with ADHD (Arns *et al.*, 2012). The current study was conducted on 60 school aged children, with age range from 6 to 15 years (60 ADHD children matching DSM-5 criteria), and 20 typically developing children. All studied children had undergone assessment with Arabic form of Conners' Parent Rating Scale short form (Al-Buhaira and Ajlan, 2011), Stanford-Binet IQ test Arabic version (Farag, 2011), and DSM-5.

The present study showed no significant differences between group I (ADHD cases) and control according to sex (P=0.4). Alternatively, the mean age of the group I was significantly higher than the control group (P<0.001).

Beta LF frequency is related to thinking, focusing, and sustained attention (beta LF is high during performing mental tasks), whereas theta waves are present during presleep state, indicating inattentiveness, distractibility, and lack of focus (theta is low during performing mental tasks) (Boutros *et al.*, 2015).

According to QEEG, the present study showed that average amplitude of power spectrum of theta (arousal from sleep and not concentrating) was significantly high in ADHD cases compared with control in all brain regions, with P values less than 0.001. The receiver operating characteristic (ROC) curve showed that it was statistically significant that average amplitude of power spectrum of significantly high theta band at cutoff level more than or equal to 30.95, there was a 65% specificity and 50% sensitivity for detection of ADHD, with P value of 0.012.

This significantly high theta in patients with ADHD can be explained by two reasons: the first is that children with ADHD are keeping the hypo-arousal state during the whole day even when performing mental tasks that require higher intellectual concentration of the brain. The second cause is that QEEG changes of ADHD are considered mainly a maturational lag (reduced both cortical activity and concentration), so the higher the age, the less the maturational lag (Barry *et al.*, 2003).

Similarly other studies (Snyder *et al.*, 2008; Ogrim *et al.*, 2012) revealed that most children with ADHD display fairly consistent EEG differences in brain electrical activity as compared with normal children, particularly with respect to their increased fronto-central theta (4–7 Hz) activity. Furthermore, meta-analysis of nine studies with a collective sample of 1498 participants found an average excess of 32% in theta band power for children with ADHD relative to controls (Snyder and Hall, 2006; Woltering *et al.*, 2012).

Regarding average amplitude of power spectrum of beta LF (concentrating), the present study showed that beta LF bands were significantly low in ADHD cases compared with control at all brain regions, with P values less than 0.001. The ROC curve showed that, it was statistically significant that average amplitude of power spectrum of significantly low beta LF band at cutoff level less than 1.25, there was a 63% specificity and 95% sensitivity and for detection of ADHD, with P value less than 0.001.These significantly low beta LF bands are explained by deficiencies of fast wave activity, indicating a maturational lag in CNS development. Beta wave is associated with active task engagement, alertness, and motor behavior (Jensen *et al.*, 2001).

Similarly, other studies (Satterfield and Dawson, 1971; Satterfield *et al.*, 1974) revealed that ADHD results from cortical under-arousal. This model is supported by electro-dermal (Satterfield and Dawson, 1971), regional cerebral blood flow and positron emission tomography studies (Lou *et al.*, 1989; Zametkin *et al.*, 1990), which have found indications of cortical under-arousal in this disorder. From EEG studies, other studies (Satterfield *et al.*, 1974) have also found results that are consistent with a hypo-arousal model (Satterfield *et al.*, 1974). Similarly other studies (El-Sayed *et al.*, 2002; Loo *et al.*, 2009; Sangal and Sangal, 2015) reported reduced amplitude in beta band for those with ADHD compared with normal controls. Beta LF frequency is related to thinking, focusing, and sustained attention, so decreased beta LF in children with ADHD is associated with decreased attention.

Regarding average amplitude of power spectrum of theta/beta LF (concentrating), the present study showed that theta/beta LF bands were significantly high in ADHD cases compared with control (theta/beta LF ratio is higher in ADHD cases 2 : 1 while 1 : 1 in normal population) at all brain regions, with P values less than 0.001.

Frontal areas of ADHD cases are much thinner and smaller than frontal areas of normal population, so theta is higher (drowsiness) and beta LF is lower (inattention).

Similarly, other studies (Snyder *et al.*, 2008; Abdel et al., 2015) using QEEG to document underlying neurophysiological dysfunction in ADHD were conducted and revealed that TBR of patients with ADHD was significantly greater than that in the control group (Snyder *et al.*, 2008; Abdel et al., 2015).

As compared with the results of this study, Ogrim *et al.* (2012) in 2012 conducted their study on 62 patients with ADHD and 39 controls (7–16 years old). The study revealed that TBR at Cz did not discriminate significantly between patients and controls. Ogrim *et al.* (2012) also concluded that theta and the TBRs were higher in the younger groups than in the older groups and that the age effect was stronger in the patients than in the controls.

The ROC curve of this study showed statistically significant difference regarding average amplitude of power spectrum of significantly high theta/beta LF at cutoff level ≥more than or equal to 13.65, there was a 83.33% specificity and 90% sensitivity for detection of ADHD, with *P* value less than 0.001. Hence, TBR is indicated to be done to diagnose ADHD cases.

As compared with the results of this study, another study (Markovska-Simoska and Pop-Jordanova, 2017) using ROC analysis indicated that assessed EEG parameters, in particular TBR at theta central, were successful in differentiating children with ADHD from control group (accuracy rates of 81 and 87.6%, respectively) (Markovska-Simoska and Pop-Jordanova, 2017).

Conclusion

(1) Children with ADHD have QEEG dysfunctions that underlie their symptomatology, proving it as a useful method aiding the diagnosis of children with ADHD.
(2) QEEG technique has the advantages of being unbiased, quantitative, and replicable easier to perform, less expensive, and noninvasive compared with other neuro-imaging techniques (e.g. PET and fMRI).
(3) QEEG average of power spectral analysis (theta, beta LF, and theta/beta LF ratio) can differentiate between ADHD cases (abnormal power) and normal population (normal power).
(4) QEEG analysis should be considered and combined with already established diagnostic methods to fulfill the final goal of detection of ADHD, which may open a window for appropriate intervention.

Limitation

(1) Small sample size of the studied group may limit the ability to make a final description of brain mapping characteristics of children with ADHD.
(2) The study participants showed a wide range of age window. It is recommended to use a narrower window of age groups to find more precise differences between different ADHD subtypes.
(3) Different subtypes of ADHD, including inattentive, hyperactive-impulsive, and combined subtypes should be studied to find precise electrical brain mapping characteristic for each subtype.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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