

## INVESTIGATING THE RELATIONSHIP BETWEEN THETA/BETA RATIO AND INTENSITY OF DISEASE IN CHILDREN WITH ADHD

FARNIA SAMANEH<sup>1</sup>, ALIPOUR ABBAS<sup>2</sup>, SHAFAT AREFEH BEYGUM<sup>3</sup>, FATTAHI SAMINEH<sup>4</sup>, ALAGHBAND RAD JAVAD<sup>5</sup>, GHAHREMANLOO MAHYA<sup>6</sup>

<sup>1</sup>Psychiatry and Behavioral Sciences Research Center, Addiction Institute, Department of Psychiatry, Mazandaran University of Medical Science, Sari, Iran

<sup>2</sup>Associate professor of epidemiology, faculty of medicine, Mazandaran University of Medical Science, Sari, Iran

<sup>3</sup>Psychiatry and Behavioral Sciences Research Center, Addiction Institute, Department of Psychiatry, Mazandaran University of Medical Science, Sari, Iran

<sup>4</sup>Psychiatry and Behavioral Sciences Research Center, Addiction Institute, Department of Psychiatry, Mazandaran University of Medical Science, Sari, Iran

<sup>5</sup>Associate professor of psychiatry, faculty of medicine, Tehran University of Medical Science, Tehran, Iran

<sup>6</sup>Faculty of Medicine, Mazandaran University of Medical Science, Sari, Iran

**CORRESPONDENCE: GHAHREMANLOO MAHYA**, E-mail: mahya.ghahremanloo@gmail.com

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### ABSTRACT

#### OBJECTIVE

To examine the relationship between theta/beta ratio on EEG with disease intensity in ADHD children as well as sensitivity and theta/beta ratio characteristic to detect ADHD and healthy children and the accuracy of this ratio to differentiate diseased children from healthy ones in terms of ADHD.

#### STUDY DESIGN

Case-control

#### PLACE AND DURATION OF STUDY

The study was conducted at pediatric and adolescent psychiatric clinic at Zareh Hospital, Sari, Iran in 2015.

#### SUBJECTS AND METHODS

A total of 120 children (61 patients and 59 children in the control group) had been chosen through simple random sampling. All patients were examined in terms of disease intensity using parental Conner's questionnaire. The theta/beta ratio in Cz and Fz points was tested and recorded individually each once during waking hours with open eyes with no mental task, and another time during a specific mental task by neurofeedback.

#### RESULTS

The theta/beta without test was larger in the Fz region in cases than in the controls ( $p < 0.001$ ). There was a medium relationship between theta/beta ( $p < 0.001$ ) in Fz region and Conner's score. The theta/beta without test in Fz (sensitivity=62%; specificity=71%) and in Cz (sensitivity=51%; specificity=73%) differentiate two groups only at a medium level.

#### CONCLUSION

It seems that further research should be conducted using more precise tools like QEEG with a larger sample volume and more limited age group.

#### KEY WORDS

EEG, Attention deficit, Hyperactive, Child Psychiatry

### INTRODUCTION

Attention Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder, in which the children's ability in concentration and impulse control is clearly less than the natural level, such that it causes impaired academic and social function for the affected child.<sup>1</sup>

This disorder is the most common disorder of childhood period. The prevalence of the disease differs given the population out of which sample is taken, diagnostic criteria, and the diagnostic tools used. Studies have reported the prevalence as around 4%<sup>2</sup> to 6%<sup>3</sup>. A meta-analysis has reported this value as 5.3% around the world.<sup>4</sup> DSM-IV has also estimated ADHD prevalence as 3-5% among children in school ages. This suggests that ADHD is one of the most common psychiatric conditions during school ages.<sup>5</sup> Currently, ADHD has widely been accepted as a heterogeneous disorder resulting from impaired function of central nervous system (CNS). There is some evidence suggesting different impairments in neurological function, which develop similar behavioral profiles.<sup>6</sup>

Studies indicate that the main cause of ADHD is genetic (75%). The clinical symptoms of this disease are a result of interaction between the neuroanatomical and neurochemical systems. Most ADHD children have no structural developmental disorder in their CNS.<sup>7</sup>

This disease usually manifests itself with disorders like learning disorders, anxiety disorders, and mood disorders. The main symptoms including inattentiveness, impulsivity, and hyperactivity can be inferred by accurately examining the child's primary evolutionary pattern especially in conditions requiring attention and concentration. Hyperactivity may be severe in some situations like school, or sometimes it may be mild in one-person interview.<sup>7</sup>

ADHD diagnosis needs presence of hyperactivity/impulsivity

or attention deficit symptoms in at least two different situations.<sup>7</sup> The Quantitative Electroencephalography (QEEG) data can be useful in predicting response to treatment with stimulants and in selection of neurofeedback protocols.<sup>8</sup> Biomarkers based on EEG including measurement of the brain's theta/beta waves ratio in vertex(Cz) region can be helpful as a noninvasive method to achieve diagnostic and therapeutic objectives.<sup>9</sup> These biomarkers add a new dimension to the current diagnostic criteria, and for this reason EEG biomarkers have been widely used in ADHD research, though they have not been confirmed so far.<sup>10</sup>

EEG studies indicate that in ADHD children, theta-wave activity increases,<sup>11-13</sup> which is primarily in the frontal zone<sup>14-16</sup>. Also, elevated delta in posterior regions<sup>13,17</sup> and diminished alpha and beta<sup>18</sup> in posterior regions are evident.<sup>13-15</sup>

Further, in ADHD children, during alteration of a task given to the patient, abnormal pattern in EEG activity is observed.<sup>19</sup> Nevertheless, Clark et al<sup>13</sup> revealed that 15% of ADHD children have significantly higher levels of beta activity in the EEG. Most results reported on ADHD are related to increased range of theta-to-beta ratio, which has been measured during rest in frontocentral regions.<sup>20-24</sup>

As currently there is no objective diagnostic test for ADHD, and the reports published out of studies are related to theta/beta ratio measurements, which are heterogeneous and incongruent, and also since no study has considered both of the confounding factors of age and gender together,<sup>25-27</sup> it seems that the relationship between the disease intensity and theta/beta has not been extensively investigated<sup>28</sup>. Various studies have examined the behavioral and neurological results in theta/beta through neurofeedback, though limited results are available about the mechanism of action of theta/beta in neurofeedback<sup>29</sup>.

Assuming that the size of relationship between theta/beta ratio and the disease intensity degree is large according to Kohen's criterion, this study attempted to determine the relationship between theta/beta ratio and disease intensity in ADHD children as well as the sensitivity and theta/beta ratio characteristic to identify children with ADHD and healthy children and accuracy of this ratio to differentiate diseased children with healthy ones in terms of ADHD. The results obtained from this study will help to either confirm or reject incongruencies of the previous studies. The results can also be used to confirm neurofeedback diagnostic test in diagnosing patients and determining the disease intensity.

## SUBJECTS AND METHODS

### Participants

This study is a treatment-control test, in which the study population consisted of healthy and ADHD five-to-ten-year-old children visiting pediatric and adolescent psychiatric clinic at Zareh Hospital, Sari, Iran. A total of 120 children (61 patients and 59 children in the control group) were included in the study. The exclusion criteria included:

1. Child's lack of cooperation in neurofeedback
2. Existence or history of any psychiatric disorder causing ADHD and passive-aggressive disorder, as confirmed by pediatric and adolescent psychiatry subspecialist (mental retardation,

learning disorders, depression, anxiety, etc.)

3. Studying at exceptional schools or history of a serious problem in academic measurement performed at the very beginning of entrance to school by training and education authorities
  4. History of consuming or current use of psychiatric drugs (antidepressants, antipsychotics, stimulants, etc.)
  5. Use of any drug in the assessment day (including stimulants, anti-cold drugs, antipyretics, etc.)
  6. History of neurological diseases including epilepsy with confirmation of a neurologist or consumption of antiepileptic drugs (even history of fever and convulsion)
  7. Parents' or children's refusal to participate in the study
- The sample volume was considered 60 children in each group.

Out of the children visiting Psychiatric Clinic at Zareh Hospital, Sari in 2015, 61 children who had received ADHD diagnosis were selected through convenient sampling. The control group were chosen out of the same age range randomly from typical schools around the hospital. For preliminary screening of the control group, SDQ was used. Finally, 59 children were included in the study as the control group after the preliminary screening and diagnostic interview and confirmation of pediatric and adolescent psychiatry subspecialist stating absence of any psychiatric disorder.

### Instruments

The patients who received ADHD diagnosis by a pediatric psychiatry subspecialist were evaluated by K-SADS interview for complete assessment. Kiddie-Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present & Life Time (K-SADS-PL) interview is a diagnostic semi-structured interview, designed to assess the recent and previous episodes of psychopathology in children and teenagers between 6 and 18 years of age. In this interview, the required information is taken from parents, children, and other information sources, and eventually scoring is done based on the clinician's judgment. Most children get a score of 0-2: "0" represents insufficient information; "1" means absence of symptom, and "2" signifies presence of symptoms. The reliability and validity of this instrument have been reported to be acceptable in Iran. In research conducted in Iran, it was found that this instrument has good-to-excellent concurrent validity in diagnosing major disorders. Further, its retesting validity in ADHD and ODD diagnoses has been reported as excellent<sup>30,31</sup>.

### Strengths and difficulties questionnaire (SDQ)

It is a brief behavioral screening questionnaire for 3-16-year-old individuals with 25 items, which is filled by parents or teachers. This questionnaire was developed by Goodman et al (1997) according to ICD-10 to assess 3-16-year-old children. This questionnaire has been normalized in Iran by Tehranidoost et al<sup>32,33</sup>.

### The Revised Conner's Parent Rating Scale (CPRS-R)

all patients were evaluated in terms of disease intensity based on parental Conner's questionnaire. Conner's et al have standardized this questionnaire in 1998. It is a 26-part questionnaire, which is filled by parents. The following indices are extracted from this scale: oppositional problems, hyperactivity-impulsivity problems, attention deficit problems and hyperactivity index. Rating of this questionnaire is performed at four levels (0= never, 1= only a little, 2= somehow much, 3= very much). The minimum score obtained from

this questionnaire in every subscale is <sup>35</sup>, while the maximum score is 90. Overall and according to degree of importance of ADHD diagnosis, this questionnaire has been used as one of the inclusion criteria and to assess intensity of symptoms. Validity of the original version and Persian translation of this questionnaire has been shown in studies.<sup>36,35</sup> Conner's et al (1999) reported reliability of this scale as 0.90. Validity of this questionnaire has been reported to be 0.85 by Institute of cognitive sciences.<sup>19,36</sup>

The questionnaire of the subjects' information was also completed for all patients. The questionnaire of the subjects' information included questions about age, gender, level of education, and the method of treatment.

### Procedure

To record the brain theta/beta ratio, the subjects were requested to avoid consuming stimulant drugs during the measurement day, in case they consumed. Neurofeedback was performed by Procomp2 device as well as thought technology software. It was performed for all subjects within a specific and the same time interval during the day by a trained psychologist in cooperation with a medical student. Theta/beta ratio was measured and recorded in Fz and Cz points separately each once during waking hours with open eyes without mental task and another time during a specific mental task. In spite of the short duration of the measurement and recording by neurofeedback (2 minutes and 10 seconds), due to the probability of hyperactivity of the participants and problem in recording, it was not possible to repeat the measurement and recording process. The mothers were also trained important points including sufficient sleep of the child during the night before measurement, not consuming stimulants like Ritalin, anti-cold medications, caffeine containing foods, etc. in order to prevent any disruption in the accuracy of the job. Recording brain waves was performed on all children in the control group again in the same sites and with the same method, after completing the subjects' information questionnaire.

### STATISTICAL ANALYSIS

To determine whether the data have been distributed normally or not, Shapiro-Wilk test was used. The basic descriptive characteristics of the two groups (patient and control) were tabulated as mean (SD), median (interquartile range (IQR), or as a number (percentage). Comparison of the two groups in terms of comparative data was analyzed by chi-square or Fisher-exact test. To compare EEG data obtained from neurofeedback in the patient and control groups, the raw scores of age and the child's ranking were used as ANCOVA. The impact size was evaluated using eta squared ( $\eta^2$ ). To associate EEG data with behavior, partial correlation (by controlling the age and child rank) was employed. Receiving operational characteristic (ROC) curve (as a statistical validation tool to determine the relationship between a continuous variable and a binary result), was utilized to determine the accuracy of EEG neurofeedback parameters to separate ADHD children and the members of the control group. The accuracy of neurofeedback parameters was measured by area under curve (AUC) of ROC. An area of 1 represents a complete test, while 0.5 denotes a worthless test. Using a guideline, guess is considered for classification of accuracy of a diagnostic test as follows: 90-100%=

excellent, 80-90%= good, 70-80%= fair, 60-70%= poor, and 50-60%= failure. All data were analyzed by SPSS 22. The significance level was considered 0.05.

### RESULTS

A total of 120 children (61 patients and 59 children in the control group) were included in the study. The basic demographic data as well as the clinical characteristics are provided in Table 1. As can be seen in the table, no significant difference was observed between the two groups in most basic characteristics. The child rank was higher in the patients' group than in the control group ( $p=0.03$ ).

**Table 1**  
Basic demographic and clinical characteristics in patients and control group members

	Group		P
	Case (n=61)	Control (n=59)	
Age, year, mean (SD)	8.33 (1.52)	8.25 (1.53)	0.79
Sex, F/M ratio	12/49	12/47	0.92
Education, n (%)	kindergarten	2 (3.4)	0.57
	Pre School	4 (6.6)	7 (11.9)
	School	54 (88.5)	50 (84.7)
Child number, median (IQR)	2 (1-2)	2 (1-2)	0.23
Child rank, median (IQR)	1 (1-2)	1 (1-2)	0.03
Diagnosis age, mean (SD)	4.72 (1.64)	-----	-----
Drug use, n (%)	28 (45.9)	-----	-----

The CPRS-R score was examined among the group members. The mean (SD) of the scores was 75.51 (19.22), and only two subjects had a score below 34 (min=35, max=90). EEG recorded results by neurofeedback for both patient and control groups are provided in Table 2. As shown in the table, beta, theta, and theta/beta without test were higher in Fz region in the patients' group than in the control group ( $p<0.001$ ). Beta and theta with the test in Fz region were higher in the patients' group ( $p<0.05$ ). Beta with test in Cz was higher in the patients' group, when compared to the control group ( $p<0.05$ ).

The relationship between CPRS-R score and neurofeedback parameters is provided in Table 3. As shown in the table, there is a medium relationship between theta/beta ( $r=0.48$ ;  $p<0.001$ ) in Fz region and Conner's score.

Theta without mental task ( $\eta^2=0.05$ ;  $p=0.02$ ), beta without mental task ( $\eta^2=0.04$ ;  $p=0.04$ ), theta/beta without mental task ( $\eta^2=0.06$ ;  $p=0.01$ ) in Fz region, theta without mental task ( $\eta^2=0.09$ ;  $p=0.001$ ), beta without mental task ( $\eta^2=0.04$ ;  $p=0.03$ ), theta/beta without mental task ( $\eta^2=0.05$ ;  $p=0.02$ ) in Cz region, and theta with mental task ( $\eta^2=0.03$ ;  $p=0.05$ ), beta with mental task ( $\eta^2=0.08$ ;  $p=0.02$ ) in Cz region separate the patients' and control groups.

Other EEG parameters recorded with neurofeedback do not differentiate between the patient and control groups ( $p>0.05$ ). ROC curve in Fig. 1 indicates the relationship between sensitivity and theta/beta characteristic in Fz and Cz. The diagonal curve reveals null hypothesis (0-hypothesis). As can be observed, theta/beta without test in Fz (AUC=0.62; 95%CI: 0.52-0.72;  $p=0.02$ ; sensitivity=62%; specificity=71%) and in Cz (AUC=0.61; 95%CI: 0.51-0.72;  $p=0.03$ ;

sensitivity=51%; specificity=73%) separates the two groups only by a medium level.

**Table 2**  
Electroencephalogram (EEG) neuro-feedback parameters (median (IQR)) are presented in patients and control group members

	Group		P
	Case (n=61)	control (n=59)	
Fz theta Without task	16.76	14.21	0.03
Fz beta Without task	7.25	6.7	0.03
Fz theta/beta Without task	2.21	1.89	0.02
Fz theta With task	18.03	15.45	<0.001
Fz beta With task	7.89	6.84	<0.001
Fz theta/beta With task	2.36	2.22	0.2
Cz theta Without task	16.20	12.95	0.009
Cz beta Without task	7.21	6.09	0.11
Cz theta/beta Without task	2.32	1.96	0.03
Cz theta With task	18.76	16.21	0.13
Cz beta With task	7.63	6.12	0.04
Cz theta/beta With task	2.42	2.4	0.86

**Table 3**  
Correlations between Conners' Parent Rating Scale and EEG neuro-feedback parameters are presented in patients and control group members.

	Fz theta_beta (without task)	Fz theta_beta (with task)	Cz theta_beta (without task)	Cz theta_beta (with task)	conners
Conners	.124	.478**	-.056	.059	1.000
Fz theta_beta (without task)	1.000	.498**	.301*	.098	.124
Fz theta_beta (with task)	.498**	1.000	-.007	.104	.478**
Cz theta_beta (without task)	.301*	-.007	1.000	.688**	-.056
Cz theta_beta (with task)	.098	.104	.688**	1.000	.059

**DISCUSSION**

This research aimed to determine the relationship between theta/beta ratio and intensity of disease in ADHD children and specify the power of theta/beta ratio to differentiate healthy children from ADHD counterparts. The results indicated that there is a medium relationship between theta/beta ( $r=0.48$ ;  $p<0.001$ ) in Fz region and Conner's score. Further, theta/beta without mental task ( $\eta^2=0.06$ ;  $p=0.02$ ) in Fz region and theta/beta without task ( $\eta^2=0.05$ ,  $p=0.02$ ) in Cz differentiate the control and patients' groups. In addition, a medium relationship was observed between theta/beta ( $r=0.48$ ,  $p<0.001$ ) in Fz region and Conner's score.

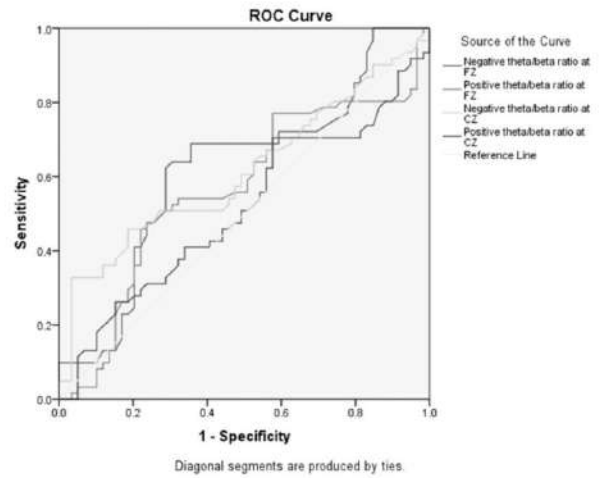


Fig 1. ROC curve showing accuracy of with task and without task theta/beta ratios at Fz and Cz.  
\*negative theta/beta: without task  
\*\*positive theta/beta: with task

Vollebregt MA et al investigated theta/beta index and Individual alpha peak factor (IAPF) and its relationship with behavioral function in ADHD children. Theta/beta and Theta values were significantly correlated with central symptoms of ADHD.<sup>37</sup> The results of this study emphasized that theta/beta and theta values are related to behavioral symptoms in ADHD children. In the present study, there is a medium relationship between theta/beta ( $r=0.48$ ;  $p<0.001$ ) in Fz region and Conner's score. However, in the study by Vollebregt MA et al, the site of theta/beta measurement and whether it is with task or not have not been differentiated.

In a case-control study, Wiersma JR examined EEG activity before and after a mental task with the help of a computer software called 3n-back in ADHD children. Three-minute EEG with closed eyes in rest state regarding theta/beta or theta or other frequency bands before and after 3n-back in 21 ADHD children was compared with 22 normal children. No significant difference was observed neither prior to nor after the test ( $p>0.05$ ). This suggests that theta/beta or theta cannot be considered universal for this disorder.<sup>38</sup> However, in our study, theta/beta without mental task in Fz region was higher in the patients' groups than in the control group ( $p<0.001$ ). Also, theta/beta with mental task in Fz region had  $p=0.2$ .

Usage of neuropsychiatric EEG based assessment Aid was confirmed by FDA in 2013 as the first instrument to assess ADHD. However, until 2014, no study examined the size of theta/beta1 (beta:15-18Hz) and theta/beta2 (beta: 18-21Hz) separately, and no data have been released suggesting that EEG can differentiate between diagnostic ADHD subgroups.

In a cross-sectional study in 2014, Delgado-Mejía et al investigated theta/beta value in 6 to 2 patients between eight and 17 years of age. The aim of that study was to measure theta/beta values in terms of QEEG in a sample of patients with completely proper ADHD diagnosis to compare neurophysiological patterns based on

diagnostic subtopics. The patients were divided into two groups in terms of diagnostic subtopics. Elevation of theta/beta-1 and theta/beta-2 which had been recorded in Cz region was higher than the levels in C3 and C4 regions. Medium and significant differences were observed between the two subsets only at beta:15-18Hz in the occipital region. Therefore, although NEBA evaluation may be helpful in differentiation of ADHD in control samples and other neurodevelopmental disorders, this study showed that beta-1 and beta-2 should be assessed separately<sup>39</sup>.

In the present study, theta/beta in both Fz and Cz regions were measured both with mental tasks and without any mental task. The results suggested that theta/beta without the test in Fz region was higher in the patients' groups than in the control group ( $p < 0.001$ ). In this study, the age group of patients and control groups had an average age of 8 years, which is mostly in the age group defined for prevalence of the disease (7-8 years)<sup>7</sup>.

In the studies by Dupuy FE et al<sup>40,41</sup>, EEG differences were examined among girls with ADHD, of attention deficit type and combined type. Only girls were included in the study and they did not report theta/beta results. In contrast, the present study included both girls and boys and in addition to beta and theta, theta/beta ratio were recorded in Fz and Cz regions in both states of presence of mental task and its absence.

GeirOgrim, JuriKropotov, Knut Hestad<sup>28</sup> conducted a case-control study (62 patients and 13 nine healthy individuals) to investigate whether theta/beta, theta, and beta values separately are associated with behavioral symptoms or not. The other objective was to see whether these criteria are different among children and adults with ADHD and those in the control group. A major increase was observed in theta values in 25.8% of the patients, while it was observed only in one person in the control group (2.6%). In the patients' group, theta in Cz had a positive relationship with functional and attention deficit issues, while it had a negative relationship with hyperactivity. A significant growth was seen in theta among ADHD patients' subgroup, associated with attention deficit and executive problems. In this study, it was assumed that the accuracy of theta/beta, theta, and beta may be 80% for differentiating ADHD and healthy children, which was not obtained. Indeed, none of the three EEG scales differentiated patients from the control individuals significantly. The negligible errors in GO/NOGO differentiated between the patients' and control groups with an accuracy of 85% (theta made a differentiation of 63%, while theta/beta managed to differentiate the two groups by 58%). Nevertheless, finding a considerable increase in the theta band may be considered a supportive evidence for ADHD diagnosis. Based on the data of this study, it can be predicted that these patients are identified behaviorally with attention deficit and executive problems, a pattern which is observed in ADHD-C as well as ADHD-I. The elevated theta as a marker of attention deficit and executive problems in ADHD children may be the most important finding of this study. It does not confirm the results of this research study suggesting that elevated theta/beta ratio can identify most cases of ADHD. However, it is mostly congruent with the studies indicating different EEG patterns in ADHD children. This diversity in the results may reflect different data collection methods and creation of artificial data. In this study, 30% of patient children had an IQ below 80. A large number of patients had also an IQ between 70 and 80, limiting generalizability of the results. In our study, the IQ of the

children was not measured, and only patients with a history of being mentally challenged and based on diagnosis of a podiatry psychiatrist were excluded from the study.<sup>28</sup>

In the research by Tieme W. P. Janssen et al to determine the relationship between brain theta/beta levels during a mental task training through neurofeedback to children with ADHD, the results suggested lack of change in theta level and linear growth of beta level.<sup>29</sup> The sample volume in that research was considered 38, and no control group was taken into account.

This study has also some limitations. The group of ADHD children was compared only with healthy children, and thus no data were obtained as to whether theta, beta, or theta/beta can differentiate ADHD from other psychiatric and evolutionary diseases or not. The IQ of the patients was not measured with any instrument, and to exclude patients with mental retardation, only parental report, academic background, measurements done by training and education authorities and studying in typical schools and evaluation by a podiatry and adolescent psychiatry subspecialist were relied on. In this study, only neurofeedback was employed, and other instruments including QEEG and ERP which may function more accurately either alone or in combination with other parameters to diagnose ADHD were not employed. Beta band in individual beta 1 and beta 2 was not assessed. Out of the brain cortical regions, only Fz and Cz were examined. Finally, this study did not investigate executive problems neither at questionnaire level nor through computer software.

Strong points: both male and female children were included in the study. They were screened in terms of other psychiatric diseases and mental retardation. The most important interfering factors on brain waves including having a disease or consumption of medication and even time of data registration were taken care of.

## CONCLUSION

The diagnostic importance of theta and beta brain waves in ADHD has still remained unknown. Further, whether training elevation of theta and beta activity in ADHD children is possible or not, or whether such training effects can influence underlying behavioral changes are still equivocal. Indeed, the theta/beta ratio in neurofeedback may be helpful in altering brain activity using major effective situations with the aim of promoting the level of neurocognitive function and behavior in ADHD children. Nevertheless, few studies have shown that real learning occurs during treatment with neurofeedback in ADHD children, where this is an element that is essential for effectiveness of the treatment.<sup>19</sup>

Neurofeedback can also affect a larger cortical area. Future studies may add more electrodes to measure EEG effects more extensively.

## SUGGESTIONS

Future studies are encouraged to obtain electrophysiological training data and reports various training components in the treatments. This type of data can play a significant role in developing more effective neurofeedback interventions for ADHD through separating trainable components and enhancing our knowledge

about the underlying mechanisms of neurofeedback.

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