


# Predictive Value of Slow and Fast EEG Oscillations for Methylphenidate Response in ADHD

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## Abstract

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder and is characterized by symptoms of inattention and/or hyperactivity and impulsivity. In the current study, we obtained quantitative EEG (QEEG) recordings of 51 children aged between 6 and 12 years before the initiation of methylphenidate treatment. The relationship between changes in the scores of ADHD symptoms and initial QEEG features (power/power ratios values) were assessed. In addition, the children were classified as responder and nonresponder according to the ratio of their response to the medication (>25% improvement after medication). Logistic regression analyses were performed to analyze the accuracy of QEEG features for predicting responders. The findings indicate that patients with increased delta power at F8, theta power at Fz, F4, C3, Cz, T5, and gamma power at T6 and decreased beta powers at F8 and P3 showed more improvement in ADHD hyperactivity symptoms. In addition, increased delta/beta power ratio at F8 and theta/beta power ratio at F8, F3, Fz, F4, C3, Cz, P3, and T5 showed negative correlations with Conners' score difference of hyperactivity as well. This means, those with greater theta/beta and delta/beta powers showed more improvement in hyperactivity following medication. Theta power at Cz and T5 and theta/beta power ratios at C3, Cz, and T5 have significantly classified responders and nonresponders according to the logistic binary regression analysis. The results show that slow and fast oscillations may have predictive value for treatment response in ADHD. Future studies should seek for more sensitive biomarkers.

## Keywords

ADHD, electroencephalogram (EEG), delta, theta, beta, delta/beta ratio, theta/beta ratio, classification

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## Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder among children and adolescents with a prevalence approaching 11%<sup>1</sup> and is characterized by symptoms of inattention and/or hyperactivity and impulsivity, which have negative effects on academic, social, and occupational functionality<sup>2</sup> as well as executive functions<sup>3,4</sup> or emotional regulation.<sup>5</sup> In general, there is a decline in symptoms with age; however, 30% to 70% of cases continue to have problems in adulthood.<sup>6–9</sup> According to the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*), ADHD has three different presentations, which are predominantly inattentive (ADHD-I), predominantly hyperactive-impulsive (ADHD-H), and combined (ADHD-C) (ie, children displaying both inattention and hyperactivity) depending on a child's symptoms.<sup>10</sup>

Early diagnosis and intervention are important to prevent functional impairment of ADHD as well as choosing the optimal treatment options among alternatives such as stimulants, atomoxetine, clonidine, and guanfacine.<sup>11</sup> For example, severe

ADHD and low IQ factors were associated with low response rate but their predictive ability is limited.<sup>12</sup> Genetic factors commonly found to be associated with treatment resistance include genes involved in monoaminergic transmission.<sup>13</sup> Neuroimaging studies revealed that dopamine transporter status, and morphometric measurements could be used to predict treatment response.<sup>14,15</sup>

Another biomarker that could be used to predict response is quantitative EEG (QEEG).<sup>16</sup> The interpretation is straightforward

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**Table 1.** Group Characteristics of ADHD Patients Who Were Responders and Nonresponders to the Medication.

Characteristic	Responder (n = 17), Mean (SD)	Nonresponder (n = 34), Mean (SD)
Age, years	9.0 (1.73)	8.35 (1.74)
Gender (M/F), n	16/1	26/8
IQ scores	102.23 (15.71)	102.59 (12.15)
Hyperactivity (before med.)	6.24 (2.17)	6.09 (3.08)
Hyperactivity (after med.)	3.82 (2.01)	5.5 (2.69)
Inattention (before med.)	5.76 (1.95)	5.68 (2.75)
Inattention (after med.)	4.0 (1.66)	4.68 (2.16)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; SD, standard deviation; F, female; M, male; med., medication.

as electrical activity of the brain recorded with electrodes on the scalp are converted into common frequency bands, which are alpha, beta, delta, and theta.<sup>17,18</sup> Various studies have established that ADHD is associated with increased slow waves (theta and delta) and decreased fast band powers (ie, beta power).<sup>19</sup> In addition, theta/beta ratio in QEEG may be helpful as a diagnostic tool.<sup>20-23</sup> Nevertheless, there are also meta-analysis showing that theta/beta ratio may not be elevated in all children with ADHD.<sup>17</sup>

Besides diagnosis, QEEG could also be used to predict treatment response. Several studies explored the use of QEEG in the prediction of response to medication in patients with depression,<sup>24,25</sup> obsessive-compulsive disorder,<sup>26,27</sup> and schizophrenia.<sup>28</sup> There are also a number of studies exploring the role of QEEG as a biomarker for prediction of response to stimulants. Chabot et al<sup>29</sup> reported that several EEG alterations that include theta increase were associated with worse response to stimulants. Loo et al<sup>30</sup> reported that treatment responders (determined using continuous performance test [CPT]) had increased frontal beta as compared with nonresponders. In addition, decreased frontal theta was associated with improvement in attention symptoms. On the other hand, Ogrim et al<sup>31</sup> reported that elevated theta was associated with better stimulant response. Arns et al<sup>32</sup> reported that children with prominent frontal slow waves responded better to stimulants as measured by CPT. In a recent study, Arns et al<sup>32</sup> showed that alpha peak frequency was associated with treatment response whereas no association was found for theta/beta ratio. These results provide mixed results for the role of QEEG powers in predicting clinical response.

Previous studies suggest that qEEG features may be useful as biomarkers for predicting treatment response in ADHD. However, the results of the previous studies are contradicting and inconsistent. Therefore, in this study we aimed to test the hypothesis that slow (delta, theta) and fast (beta) frequency powers as well as slow/fast frequency power ratios predict clinical response in a large group of children with ADHD.

## Materials and Methods

### Participants

This study included a total of 51 patients with ADHD (8 inattentive, 1 hyperactive, 42 combined), identified retrospectively,

aged between 6 and 12 years (mean age = 8.57 years, standard deviation [SD] = 1.75).<sup>33</sup> The diagnosis was first established by a child and adolescent psychiatrist based on *DSM-5* criteria. During patient selection, a second psychiatrist, different from the first checked patient files again and the children were included only in case of agreement. Patients with a history of neurological or another psychiatric disorders (such as mental retardation, autism, anxiety disorder, depression, epilepsy) were not included to the study. Hyperactivity and inattention symptoms were evaluated by Turkish version of Conners' Parent Rating Scale–Short Form.<sup>34,35</sup> Also, levels of intelligence of these patients were evaluated by using Wechsler Intelligence Scale for Children–Revised (all children had a full-scale IQ >80). The study protocol was approved by the local ethics committee.

In order to perform binary logistic regression analysis, ADHD patients were classified as responder and nonresponder according to their response to the medication (>25% improvement after medication).<sup>32</sup> As a result, ADHD patients were divided into 2 groups as 17 responders and 34 nonresponders. Differences between Conners' subcategory (hyperactivity and inattention) scores in the beginning of treatment and Conners' subcategory scores of patients' parents in the thirteenth month of treatment were considered to evaluate the response to treatment. We suggest accuracy of the response to treatment is related to the decline in test scores. The participants who showed 25% reduction in one of the Conners' subcategory were deemed responsive.

The groups' characteristics are shown in Table 1.

Methylphenidate was administered at a dosage of 0.5 mg/kg to the patients after they were diagnosed with ADHD. They were monitored monthly after the treatment started and bimonthly for the rest of the 10-month period. The dosage of the drugs was increased to 1 mg/kg after considering side effects and clinical results in follow-ups. There was no discontinuation for drugs in holidays and weekends. The improvement was monitored through results of Conners' Parents Rating Scale<sup>34</sup> at the beginning of treatment and thirteen months later; height, weight, blood pressure, pulse, and electrocardiogram of subjects were observed in follow-ups. Methylphenidate blood levels were also measured to see whether or not the patient was actually using the medication. Children did not receive any other medication.

## QEEG Recording

After the first assessment before methylphenidate was started, spontaneous EEG was recorded for each participant. EEG was recorded by using 19 electrodes that placed on the scalp, based on the international 10-20 system. Patients sat calmly with eyes closed condition during the recording time of 3 minutes. EEG was digitized at a sampling rate of 125 Hz and the acquired signals were band-pass filtered at 0.1 to 62.5 Hz and notch filtered at 50 Hz. Two linked earlobe electrodes (A1 + A2) served as references. Electrode impedances were kept below 10 kohm.

## EEG Analysis

For preprocessing and data analysis, Brain Vision Analyzer Version 2.1.2 software was used. Before the segmentation of EEG data, artifacts were rejected via raw data inspection method that is a manual off-line technique by a researcher who has 10 years of work experience, then segmented in consecutive epochs of 1 second. The segment numbers change between 108 and 169 and the mean number of segments is 149.10. In order to calculate power spectrum, the digital fast Fourier transform (FFT) was performed with 10% Hanning window over each epoch (0-1000 ms) and all epochs were averaged for each electrode. Then, the area information of delta (0.5-3.5 Hz), theta (4-7 Hz), alpha (8-13 Hz), beta (15-30 Hz), and gamma (30-48 Hz) powers were exported for all locations. In addition, the Conners' difference scores were calculated by subtracting prescores from postscores of each subcategory (hyperactivity and inattention) for each subject who have ADHD.

## Statistical Analysis

Statistical analyses were performed with IBM SPSS Statistics (version 24.0) software. Separately for each location, delta/beta and theta/beta power ratio was calculated as new variables by dividing the power of the slower frequency by the power of the faster frequency in SPSS.

The differences between the groups for all locations were assessed separately for each frequency band by means of repeated measures analysis of variance (ANOVA). In the analysis of power differences, repeated-measures ANOVA included the between-subjects factor as groups (responder and non-responder), and included the within-subject factors as location (F3, F4, F7, F8, C3, C4, T3, T4, T5, T6, P3, P4, O1, O2) and laterality (right, left). Greenhouse-Geisser corrected *P* values were reported. The significance level was set to  $P < .05$ .

Spearman's rank correlation coefficient was calculated to explore the correlation between EEG absolute powers in all locations and difference Conners' scores of hyperactivity and attention deficit for all frequency bands and power ratios (delta/beta and theta/beta). Logistic regression analysis performed to examine predictors of response to medication based on powers in all frequency bands and power ratios (delta/beta and theta/beta), which have the correlation with the difference Conner's

scores of hyperactivity and inattention. A *P* value of less than .05 (2-tailed) was considered to be statistically significant.

## Results

In the current study, there was no group difference between responders and nonresponders in terms of power values for delta band ( $F_{1,49} = 855.069$ ,  $P = .413$ ), theta band ( $F_{1,49} = 895.518$ ,  $P = .529$ ), alpha band ( $F_{1,49} = 841.050$ ,  $P = .890$ ), beta band ( $F_{1,49} = 1312.204$ ,  $P = .136$ ), and gamma band ( $F_{1,49} = 461.689$ ,  $P = .831$ ).

The correlation analysis revealed significant correlations between Conners' score differences for both subscales (hyperactivity and inattention) and several power values/ratios. As pretreatment scores were subtracted from post-treatment scores to calculate difference scores, a negative correlation indicated that as EEG power was greater for patients who showed improvement.

EEG delta powers at F8 was significantly and negatively correlated to Conners' score difference of hyperactivity ( $P = .047$ ). EEG theta power at Fz, F4, C3, Cz, and T5 were significantly and negatively correlated to Conners' score difference of hyperactivity ( $P$  values are .048, .027, .028, .029, and .05, respectively). EEG beta powers at F8 and P3 were significantly and positively correlated to Conners' score difference of hyperactivity ( $P$  values are .042 and .032, respectively). EEG gamma powers at T6 were significantly and negatively correlated to Conners' score difference of hyperactivity ( $P = .042$ ). The correlation between alpha powers and Conners' score difference of hyperactivity did not reach the level of significance for any location (Table 2). Moreover, no correlation was found between power values and Conners' score differences of inattention for any frequency band.

EEG theta/beta power ratios at F8, F3, Fz, F4, C3, Cz, P3, and T5 were significantly and negatively correlated to Conners' score difference of hyperactivity ( $P$  values are .014, .023, .015, .031, .012, .010, .042, and 0.010, respectively). EEG delta/beta power ratios at F8 was significantly and negatively correlated to Conners' score difference of hyperactivity ( $P = .004$ ) (Table 2). On the other hand, there was no significant correlation between Conners' score difference of inattention and power ratios (delta/beta and theta/beta).

These findings indicate that patients with increased delta power at F8, theta power at Fz, F4, C3, Cz, and T5 and gamma power at T6 and decreased beta powers at F8 and P3 showed more improvement in ADHD hyperactivity symptoms. In addition, increased delta/beta power ratio at F8 and theta/beta power ratio at F8, F3, Fz, F4, C3, Cz, P3, and T5 showed negative correlations with Conners' score difference of hyperactivity as well. This means, those with greater theta/beta and delta/beta powers showed more improvement in hyperactivity following medication.

The power values and ratios found to be significant above were further submitted to logistic binary regression to estimate their prediction rate. Theta power at Cz and T5 have significant results for classification of responders and non-responders with

**Table 2.** Spearman's Rank Correlation Coefficient and Associated *P* Values Between Power/Power Ratio Values in Different Location for All Frequency Bands and Conners' Difference Scores of Hyperactivity for ADHD Participants.

	F8	F3	Fz	F4	C3	Cz	C4	P3	Pz	P4	T5	T6
<i>Power values</i>												
Delta												
Spearman's $\rho$ corr. coef.	-0.279	-0.030	-0.142	-0.182	-0.003	-0.122	-0.025	0.004	-0.072	-0.101	-0.004	0.046
<i>P</i>	.047*	.832	.319	.202	.985	.394	.862	.979	.617	.482	.976	.746
Theta												
Spearman's $\rho$ corr. coef.	-0.218	-0.229	-0.278	-0.309	-0.308	-0.305	-0.213	-0.102	0.037	-0.008	-0.275	0.025
<i>P</i>	.124	.106	.048*	.027*	.028*	.029*	.134	.478	.797	.957	.050*	.864
Alpha												
Spearman's $\rho$ corr. coef.	0.096	-0.013	0.030	0.161	-0.178	0.020	0.037	-0.124	-0.018	0.146	-0.126	0.010
<i>P</i>	.501	.930	.833	.258	.212	.889	.795	.387	.901	.305	.379	.943
Beta												
Spearman's $\rho$ corr. coef.	0.285	0.240	0.200	0.180	0.255	0.133	0.223	0.301	0.220	0.224	0.226	-0.079
<i>P</i>	.042*	.089	.159	.207	.071	.354	.116	.032*	.121	.114	.111	.582
Gamma												
Spearman's $\rho$ corr. coef.	0.071	0.139	0.037	-0.034	0.032	-0.028	-0.108	0.146	0.122	-0.053	0.018	-0.285
<i>P</i>	.619	.332	.796	.815	.825	.847	.451	.307	.392	.711	.901	.042*
<i>Power ratios</i>												
Delta/Beta												
Spearman's $\rho$ corr. coef.	-0.399	-0.121	-0.163	-0.215	-0.100	-0.182	-0.129	-0.237	-0.217	-0.174	-0.133	-0.088
<i>P</i>	.004*	.399	.253	.131	.483	.201	.368	.094	.127	.222	.351	.540
Theta/Beta												
Spearman's $\rho$ corr. coef.	-0.341	-0.319	-0.338	-0.303	-0.348	-0.359	-0.269	-0.285	-0.122	-0.154	-0.359	0.079
<i>P</i>	.014*	.023*	.015*	.031*	.012*	.010*	.056	.042*	.392	.280	.010*	.583

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; corr coef, correlation coefficient.

\* $P \leq .05$ .

**Table 3.** Results of Binary Logistic Regression Applied on ADHD Participants Who Grouped as Responders and Nonresponders.<sup>a</sup>

	F8	F3	Fz	F4	C3	Cz	C4	P3	Pz	P4	T5	T6
<i>Power values</i>												
Delta	64.7	—	—	—	—	—	—	—	—	—	—	—
Theta	—	—	64.7	66.7	68.6	68.6*	—	—	—	—	72.5*	—
Beta	66.7	—	—	—	—	—	—	66.7	—	—	—	—
Gamma	—	—	—	—	—	—	—	—	—	—	—	66.7
<i>Power ratios</i>												
Delta/Beta	64.7	—	—	—	—	—	—	—	—	—	—	—
Theta/Beta	64.7	66.7	70.6	66.7	70.6*	76.5*	—	64.7	—	—	64.7*	—

Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

<sup>a</sup>“—” indicates not calculated.

\* $P \leq .05$ .

68.6% and 72.5% overall percentages, respectively (*P* values are .043 and .03, respectively). Moreover, theta/beta power ratios at C3, Cz, and T5 have significant results for classification of responders and nonresponders with 70.6%, 76.5%, and 64.7% overall percentages, respectively (*P* values are .032, .023, and .015, respectively) (Table 3).

## Discussion

In the present study, we analyzed the power spectrum of different frequency bands (delta, theta, and beta) during resting state

EEG in eyes closed condition. In addition, delta/beta and theta/beta power ratios were calculated. Those results indicate that patients with higher slow oscillations, lower fast oscillations and higher slow/fast ratios improved to a greater extent. In addition to correlation analysis, logistic binary regression analysis was performed to classify responders and non-responders. According to the findings, there were significant results to classify responders and non-responders.

Identification of biomarkers predicting treatment response is also important with regard to an emerging concept. The personalized medicine approach prompts the use of genetic or other

type or markers to tailor the healthcare decisions according to patient needs and peculiarities. In that sense QEEG markers could be used to individualize treatment and studies showed promising results for instance in depression,<sup>36,37</sup> obsessive-compulsive disorder,<sup>38</sup> anxiety disorders, and schizophrenia albeit the meta-analyses did not show any consistency.<sup>39,40</sup> With regard to ADHD, various studies emphasized that the increase in theta power and theta/beta ratio and the decrease in beta power can be a useful tool for the diagnosis of ADHD.<sup>21,23,41,42</sup> On the other hand, Arns et al<sup>17</sup> established that theta/beta ratio cannot be a reliable assessment tool for the diagnosis of ADHD but it can be applied as a tool, which may help monitor the prognosis in only 1 subgroup. As stated in the introduction, studies yielded mixed results on the role of fast and slow EEG oscillations for predicting the treatment response in ADHD. To illustrate, one study<sup>41</sup> reported that decreased theta was associated with treatment response whereas another just reported the opposite.<sup>31</sup> Yet another study showed no relationship between theta/beta waves and treatment response but found an association for alpha oscillations.<sup>32</sup> Although we obtained significant correlations between pretreatment EEG powers and change in ADHD symptoms, the magnitude of correlations and classification accuracy rates were not high. These results indicate that although QEEG may be used as one of the several factors for predicting clinical response, based on the prediction accuracies, one would not advocate its use as a sole predictor.

The inconsistencies described above in EEG predictors of treatment response pose a challenge in front of personalized medicine attempts in psychiatry; however, the challenge may be overcome by using more sophisticated EEG analysis methods. Future studies should aim to find more accurate predictors that can be used solely to estimate response to stimulants. These predictors could involve use of multiple imaging methods at the same time (ie, multimodal neuroimaging<sup>43</sup>). In addition, studies using complexity measures such as entropy revealed that this index might be useful for predicting treatment response in depression<sup>44</sup> and obsessive-compulsive disorder (unpublished results from our studies). In addition, restriction of oscillation analyses to specific brain areas using source localization techniques could also increase sensitivity and specificity of biomarkers. For instance, Korb et al<sup>45</sup> demonstrated that restricted EEG analysis to orbitofrontal and medial prefrontal cortices was successful in predicting the treatment response in depression. Another promising EEG-derived measure could be cordance, which is derived from absolute and relative power; however, it is more directly related to brain activity as compared with both. A study reported that theta-cordance was related to response to atomoxetine treatment in young adults.<sup>46</sup>

Besides biomarkers derived from single channel data, electrophysiological measures of brain connectivity could also provide biomarkers for prediction of treatment response. Interestingly Scangos et al<sup>47</sup> recently reported that pretreatment delta coherence may predict response to electroconvulsive treatment. Another depression study also found that right frontotemporal delta/theta coherence predicted treatment

response.<sup>48</sup> In addition, another earlier study showed that across-Rolandic fissure coherence was significantly related to outcome after 2 years in patients with amnesic and vascular dementia.<sup>49</sup> Connectivity measures offer an advantage over standard power-derived biomarkers by providing a more dynamic and long-range interactions between brain regions. However, biomarker studies using connectivity measures are relatively few in number and future studies should aim to fill in this gap.

Meanwhile, our study has a number of limitations. First, our study is retrospective and did not have a control group. Second, the subjects were followed up throughout 13 months but, the first QEEG was not repeated in the process of follow-up. Thus, there is no information about the change in QEEG in current study. Third, the improvement of subjects' symptoms was monitored with just Conners' Parents Rating Scale, and no other tests were applied. Finally, in the current study, only the effect of one type of stimulant—methylphenidate—was investigated. Therefore, although our results do not support the use of QEEG band power for predicting clinical response, future longitudinal studies can elucidate this issue more clearly.

### Authors' Note

The study protocol was approved by the local ethics committee.

### Author Contributions

ESG contributed to conception; acquisition of data; literature search; writing and gave final approval. EET contributed to literature search; analysis and interpretation; writing; critically revised manuscript and gave final approval. BB contributed to analysis and interpretation; writing and gave final approval. MEY contributed to acquisition of data and gave final approval. MKA contributed to the conception and gave final approval. NT contributed to the conception and gave final approval. BM contributed to literature search; conception and design; interpretation; writing; critically revised manuscript and gave final approval.

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