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Quantitative EEG Spectrum-weighted Frequency (Brain Rate) Distribution in Adults with ADHD

Silvana Markovska-Simoska, MD, MSc, and Nada Pop-Jordanova, MD, PhD

ABSTRACT

Objective: The aim of this study is to explore the applicability of brain rate (f_b) for the diagnosis of attention-deficit/hyperactivity disorder (ADHD), analyzing the spatial distribution of f_b through analysis of its values in sagittal and lateral electrodes' positions, recorded in four conditions (eyes closed, eyes opened, visual continuous performance task and emotional continuous performance task).

Methods: Sixty-seven adults diagnosed with ADHD according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria and 50 age-matched control subjects participated in the study. The brain activity of the subjects was recorded by 19 channel quantitative electroencephalography (QEEG) system and f_b was calculated with the f_b software.

Results: Maximum values of f_b for sagittal topography are obtained in central region and the minimum in frontal region, while lateral topography maximum values are found in the left and right sides and the minimum in midline region. A positive correlation between the f_b values and the QEEG spectra subtypes was

FOCUS POINTS

- Maximum values of brain rate (f_b) for sagittal topography are obtained in central region and the minimum in frontal region, while for lateral topography maximum values of f_b are obtained in the left and right sides and the minimum in the midline region.
- There is a positive correlation between f_b values and quantitative electroencephalography (QEEG) spectra subtypes.
- There is no correlation between behavioral symptoms (obtained with Barkley's scale) and f_b values (as well as QEEG subtypes), illustrating heterogeneous and multifactorial character of attention-deficit/hyperactivity disorder (ADHD).
- The applicability of f_b indicator in the diagnosis of ADHD is especially pronounced for higher subtypes (ADHD III and IV), independently of the subjective behavioral symptoms.

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obtained, with lower values for normals, first and second subtype, and higher values for the third and fourth subtype. On the other hand, there was no correlation between behavioral symptoms and f_b values.

Conclusion: The applicability of an f_b indicator in the diagnosis of ADHD is especially pronounced for the higher subtypes (ADHD III and IV), corresponding to heterogeneous and multifactorial character of this disorder.

INTRODUCTION

Brain-rate (f_b) is defined as a mean frequency of brain oscillations weighted over the all bands of the electroencephalography (EEG) potential (or power) spectrum.[1] It is an integral brain state indicator that, besides being an element of neurophysical substrate, may serve as a simple indicator of the arousal and attention states. Namely, the actual electric field in the brain (and the resulting EEG) is not monochromatic, so that the indicator of real (effective) arousal, reflected in EEG, appears to be the spectrum weighted frequency–f_b.

In recent studies by Pop-Jordanova,[2] Markovska-Simoska and colleagues,[3] and Markovska-Simoska and Pop-Jordanova,[4] f_b is used as indicator of inner arousal. We have shown that the level of this kind of arousal is directly proportional to the increase of f_b from eyes opened to the eyes closed condition. As a general activation of mind, mental arousal may characterize the level of consciousness, irrespective of its content. Simultaneously, it is correlated with the integral (polyrhythmic) EEG spectrum.[5]

Other specific applications are the use of f_b as a simple indicator of sleep quality[6] and as an objective measure of wake-to-sleep transition, or drowsiness period.[7] In the first study, the described f_b indicator has been compared with the spectrum-weighted frequencies from heart rate variability (f_{hv}). The authors conclude that f_b is approximately related to the sleep profile, having the predictive value in identifying shallow sleep versus deep sleep, and helping to assess the quality of sleep. They also note the interesting inverse relation between f_b and f_{hv}. In the second study, EEG coherence, f_b, and spectral delta/alpha band parameters were used as possible solid indicators in sleep onset detection. They found that f_b values were decreased at the sleep onset period, than showed a little increase in the rapid eye movement phase and after the second stage of sleep progressively decreased in the next stages. In addition, f_b could be a useful indicator in cases where lateralization effects in EEG activity are relevant.[8]

Attention-deficit/hyperactivity disorder (ADHD) is a clinically heterogeneous neurobehavioral disorder that is associated with tremendous financial costs, stress to families, adverse academic and occupational outcomes. According to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,*[9] ADHD is characterized by a varying amount of inattention, hyperactivity, and impulsivity symptoms. The *International Classification of Diseases, 10th Editon*,[10] although using a different name (hyperkinetic disorder), lists similar criteria for the disorder. The worldwide prevalence of ADHD is ~5% in children and adolescents.[11] ADHD symptoms decline over time,[12] which may illustrate the developmental insensitivity of the *DSM-IV*.[13-15] However, >50% of all ADHD children continue to display clinically significant symptoms after reaching adulthood. In the last decade, many studies have tried to define the neural correlates of ADHD, particularly changes in quantitative EEG (QEEG) and these results for adult ADHD patients are very divergent.

Recently, a QEEG spectrum classification of ADHD population[16] has been developed defining four subtypes: I (abnormal increase of delta-theta frequency range centrally or centrally-frontally), II (abnormal increase of frontal midline theta rhythm), III (abnormal increase of beta activity frontally), and IV (excess of alpha activities at posterior, central, or frontal leads).

Considering f_b as a pertinent quantitatively characteristics of whole spectrum, here we will analyze f_b values for the four QEEG ADHD subtypes of adult group, aiming at investigating its reliability for the diagnosis of ADHD.

Until now f_b parameter was studied only in Cz electrode position and in only two baseline conditions: eyes closed (EC) and eyes opened (EO). In this study, as an additional improvement we will consider the spatial distribution of f_b through analysis of its values in sagittal and lateral electrodes' positions, recorded in four conditions (EC, EO, visual continuous performance task, and emotional continuous performance task) in normal control group and ADHD adults.

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METHODS

Subjects

Sixty-seven adults (between 18–50 years of age) diagnosed with ADHD and 50 age-matched control subjects participated in the study. Each group consisted of almost equal number of females and males: the ADHD group consisted of 33 females and 34 males (the gender imbalance noted in children has not been established in adults with ADHD) and gender distribution in the control group was 25 females and 25 males. The groups were matched on age, with the mean age being 33.4 (SD=8.39) years for ADHD subjects and 32.8 (SD=8.22) years for the control group.

ADHD subjects were new patients presenting to the Private Practice in Chur, Switzerland or to the Division of Neuroinformatics at the Macedonian Academy of Sciences and Arts for an assessment of ADHD, from 2007 to 2009 until the target number was obtained. The diagnosis was made by a psychiatrist and a psychologist, and both had to agree on the diagnosis for the subject to be included in the study. All subjects met the criteria of Barkley's Semi-structured Interview for adults with ADHD. In order to ensure diagnostic validity, additional information was collected from parents, partners, relatives and friends. According to the *DSM-IV* criteria, the assessment resulted in 26 ADHD subjects being diagnosed with the inattentive type, four with hyperactive-impulsive type, and 37 with combined type.

The control group was recruited through professional colleagues and community organization from Skopje, Macedonia. Inclusion criteria required the control group to be free of history of ADHD or other psychopathological or neurological simptomatology, assessed through personal interview, self-report, and the *DSM-IV* symptom checklist for ADHD. All subjects had normal or corrected to normal vision.

Procedure

All participants were individually assessed with neurophysiological testing in an environment free from distractions, in a single session that lasted ~1.5 hours, during office hours (8:00 AM to 3:00 PM). All participants gave informed consent. Subjects were not allowed to take any medication in the 48-hour-period prior to testing and were asked not to use caffeine or tobacco on the morning of their testing. All subjects were seated in a comfortable chair with a backrest and were instructed not to move their eyes during the recording. Recording was suspended for a short period if the subject was found to be experiencing drowsiness or becoming restless.

The EEG was recorded using a Mitsar 19-channel QEEG system in the following conditions: 5 minutes EC resting condition; 5 minutes EO resting condition (sufficient for 2 minutes artifact-free data EC and EO); visual continuous performance test (VCPT) from Psytask (two-stimulus Go/No Go paradigm) with 20 minutes duration; and emotional continuous performance test (ECPT) from Psytask (two-stimulus Go/No Go paradigm) with 20 minutes duration.

EEG electrode placement was in accordance with the international 10/20 system using an electrocap produced by Electrocap international. Activity in 19 derivations was recorded from Fp1, Fp2, F3, F4, F7, F8, Fz, C3, C4, Cz, T3, T4, T5, T6, P3, P4, Pz, O1, and O2, referenced to linked ears. The ground electrode was placed between Fpz and Fz. To control eye movement artifacts, the electrooculogram (EOG) was recorded, using two 9 mm tin electrodes, above and under the right eye, referenced to Fpz and Oz. The EOG rejection was set at 50 μV. The bandwidth of the amplifiers was set at 0.53 Hz for low frequency filter, 50 Hz for high frequency filter and 45–55 Hz notch filter. The EEG digitization frequency was 256 Hz. The impedance levels for all electrodes were set to 5 kΩ. EEG was continuously recorded on the hard disc for off-line analysis. The VCPT and ECPT were administered using the standard protocol. The 19 electrode positions were allocated to three sagittal regions: frontal (Fp1, Fp2, F3, Fz, F4, F8, F7), central (T3, T4, C3, Cz, C4), and posterior (T5, T6, P3, Pz, P4, O1, O2), and three lateral regions: left (Fp1, F3, F7, T3, C3, T5, P3, O1), midline (Fz, Cz, Pz), and right (Fp2, F4, F8, T4, C4, T6, P4, O2) by averaging the power within each region. The authors visually appraised every epoch and decided to accept or reject it based on the absence or presence of artifact. EEG data was processed with the WinEEG software version 2.82.32. Spectral analysis using fast Fourier transform was carried out for six frequency bands, delta (0.5–4.0 Hz), theta (4–8 Hz), alpha (8–12 Hz), sensory motor rhythm (12–16 Hz), beta 1 (16–20 Hz) and beta 2 (20–24 Hz), for absolute power (μV^2). The transformed data were analyzed separately for each subject, frequency band, and measurement condition. After thorough analysis of EEG spectra and received absolute power of each frequency band, the f_b was calculated with the f_b

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software in which the basis for calculation is the formula from Pop-Jordanova and Pop-Jordanov.[1] All individual spectra's of ADHD subjects were analyzed by the first author and were compared with the Human Brain Institute (HBI) database. According to the Kropotov's classification,[16] ADHD subjects were divided in four subtypes: QEEG subtype I (13 patients), QEEG subtype II (14 patients), QEEG subtype III (16 patients), and QEEG subtype IV (24 patients).

Stimuli

We used the two stimulus Go/No Go task developed specifically for the HBI database. The task consisted of 400 trials. The duration of stimuli is equal to 100 ms. Trials consisted of presentation of a pair of stimuli with inter stimulus interval of 1.1 sec. Interval between trials is equal to 3,100 ms and response interval from 100 to 1,000 ms. Subjects were instructed to press a button with index finger of their right hand as fast as possible every time when animal or angry face was followed by an animal or angry face (Go condition), respectively, and to withhold the suppressing on the other three trials (No Go condition). More detailed explanation of the VCPT and ECPT tasks can be found in the paper of Markovska-Simoska and Pop-Jordanova.[17]

Data Analysis

A series of repeated measures analysis of variance (ANOVA) was performed using the factors sagittal and lateral topography (frontal, central, posterior and left, midline, right), measurement condition/task (EC, EO, VCPT, ECPT), and group (controls, ADHD I, II, III, IV subtype) for f_b values. Then, post hoc Bonferroni test was performed to explain significant interactions. Statistical analysis was performed using the Statistica 7.0 software. Due to space reasons, only significant effects and interactions between groups are reported here.

RESULTS

The values of fb for sagittal topography depend from group classification F (12, 1180)=7.83, $P<.000$, with the highest values of f_b in ADHD III subtype and the lowest in ADHD I subtype (Figure 1).

The post hoc Bonferroni test (summary of significant difference for all groups and conditions is shown in Table 1) showed that the f_b values in frontal, central and posterior regions for ADHD III subtype is significantly higher than the values for normal group, ADHD I, II and IV subtype (only for frontal regions). While, the ADHD IV subtype has greater f_b values only to normals and ADHD I subtype (Table 1).

The ANOVA results have shown the dependence of f_b values from the recording conditions F(9, 1,086)=15.45 $P<.000$, with the statistically highest values of f_b in eyes closed condition for posterior region (Figure 2). The post hoc test did not reveal any significant difference among the conditions for frontal and central regions. While, for the posterior region, EC condition has the greater values of f_b compared to EO, VCPT, and ECPT. The highest

TABLE 1.
Summary of Significant Post Hoc Bonferroni *P*-values for f_b Difference Between Subtypes, Conditions, and Regions

		Frontal	Central	Posterior	Left	Midline	Right
Subtype Effects	Normals vs.ADHD III	0.000	0.000	0.000	0.000	0.000	0.000
	Normals vs.ADHD IV	0.015	0.000	0.003	0.001	0.000	0.003
	ADHD I vs.ADHD III	0.000	0.000	0.000	0.000	0.000	0.000
	ADHD I vs.ADHD IV	0.040	0.001	0.018		0.000	0.010
	ADHD II vs.ADHD III	0.000	0.003	0.010	0.000	0.000	
	ADHD III vs.ADHD IV	0.000			0.007		0.000
Condition Effects	EC vs. EO			0.000	0.005	0.000	0.003
	EC vs. VCPT			0.000	0.043	0.000	
	EC vs. ECPT			0.000		0.000	0.022

EC=eyes closed; EO=eyes opened; VCPT=visual contionous performance test; ECPT=emotional contionous performance test.

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values of f_b are noted in central region and lowest in frontal region (Figures 1 and 2).

Regarding the lateral topography, we found a statistical significant difference among the groups F(12, 1180)=9.99, *P*<.000, with the highest values of fb in ADHD III subtype for left and right hemisphere and midline region (Figure 3). The post hoc analysis found a significant difference in f_b values for left region between ADHD III subtype compared to normals, ADHD I, II and IV subtypes, while ADHD IV subtype had the greater f_b values only regarding to normals. For the right region there are the same findings as the left side for ADHD III subtype, while ADHD IV subtype have greater f_b values not only compared to normals, but and to ADHD I subtype. In the midline region, f_b values are the highest in ADHD III and IV compared to normals and ADHD I subtype (Table 1).

Concerning the influence of the recording condition to f_b values for lateral topography we found a statistical significance with F(9, 1,086)=7.64 *P*<.000, with the smallest values of f_b have been detected in the midline region for all groups and conditions (Figure 4). The post hoc test reveal significant higher values of f_b in eyes closed compared to eyes opened and VCPT for left region, while for right region there were higher values for eyes closed compared to eyes opened and ECPT. In the midline region this difference was prominent between EC and all three other conditions (EO, VCPT, and ECPT) (Table 1). Considering the lateral regions, the smallest f_b values are found in the midline (Figures 3 and 4).

A correlation with r=0.32, *P*<.05, between the f_b values and the QEEG spectra ADHD subtypes (Figure 5) and no correlation between the f_b values and the behavioral ADHD types according to the *DSM-IV* r=0.1, *P*>.05 was found (Figure 6). No correlation between QEEG ADHD subtypes and behavioral symptoms (Table 2) was found, illustrating the multifactorial character of ADHD.

TABLE 2.
Behavioral and QEEG Subtypes of Examined ADHD Subjects

QEEG ADHD Subtypes	*Behavioral ADHD Types*
I	4 inattentive + 9 combined
II	6 inattentive + 8 combined
III	8 inattentive + 8 combined
IV	8 inattentive + 4 hyperactive + 12 combined

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DISCUSSION

Maximum values of f_b for sagittal topography are obtained in central region, while the minimum in frontal region, corresponding to increased arousal (which is in agreement with the neurophysiological considerations.)[16] Maximum values of f_b for lateral topography are obtained in the left and right sides, while the minimum in the midline region, which indicates higher excitability of lateral regions. As expected, a positive correlation between f_b values and the QEEG spectra subtypes was obtained. Lower values were found for normal group, first and second subtype, and higher for the third and fourth subtype. This can be explained by the comparable arousal level for normals, first and second subtype, and higher arousal in the third and fourth subtype. On the other hand, there was no correlation between behavioral symptoms (obtained with Barkley's scale) and f_b values (ie, spectrum gravity), as well as between QEEG ADHD subtypes and behavioral symptoms, illustrating the heterogeneous and multifactorial character of ADHD.

CONCLUSION

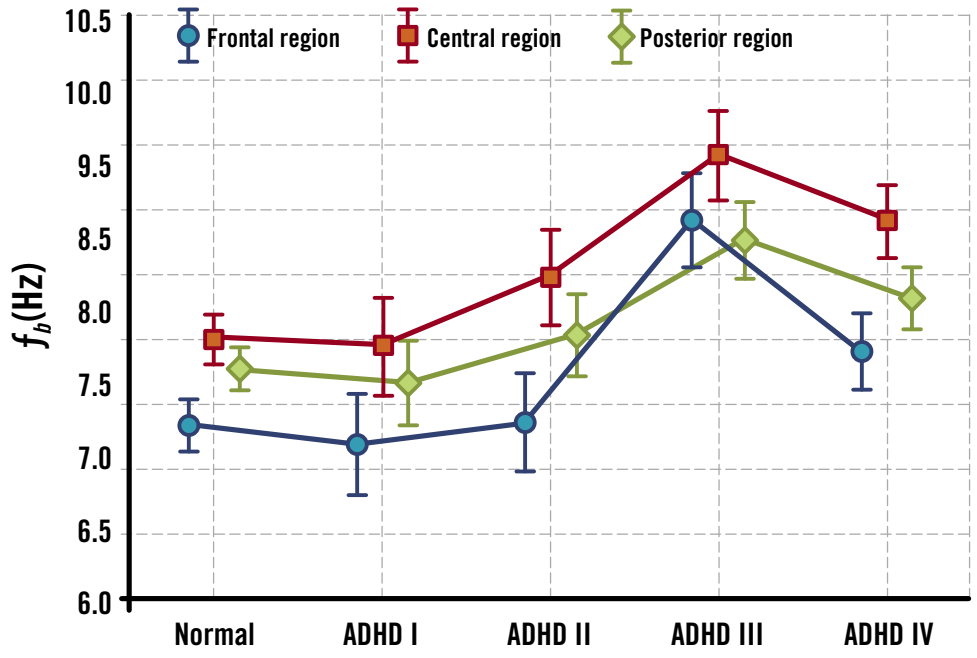
It could be concluded that the measurement of f_b, combined with QEEG, can be used as an objective indicator of arousal related to the level of consciousness. Distribution of f_b values for sagittal and lateral topographies reflects the arousal levels in the corresponding conditions. There is a positive correlation between f_b values and the QEEG spectra subtypes and no correlation with behavioral symptoms. The applicability of f_b indicator in the diagnosis of ADHD is especially pronounced for higher subtypes (ADHD III and IV), independently of the subjective behavioral symptoms, thus illustrating heterogeneous and multifactorial character of this disorder. Follow-up research is needed in order to determine the specificity and sensitivity of f_b as a real diagnostic approach to identify ADHD. ***CNS***

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FIGURE 1.
f_b values for sagittal topography in normals and ADHD subtypes



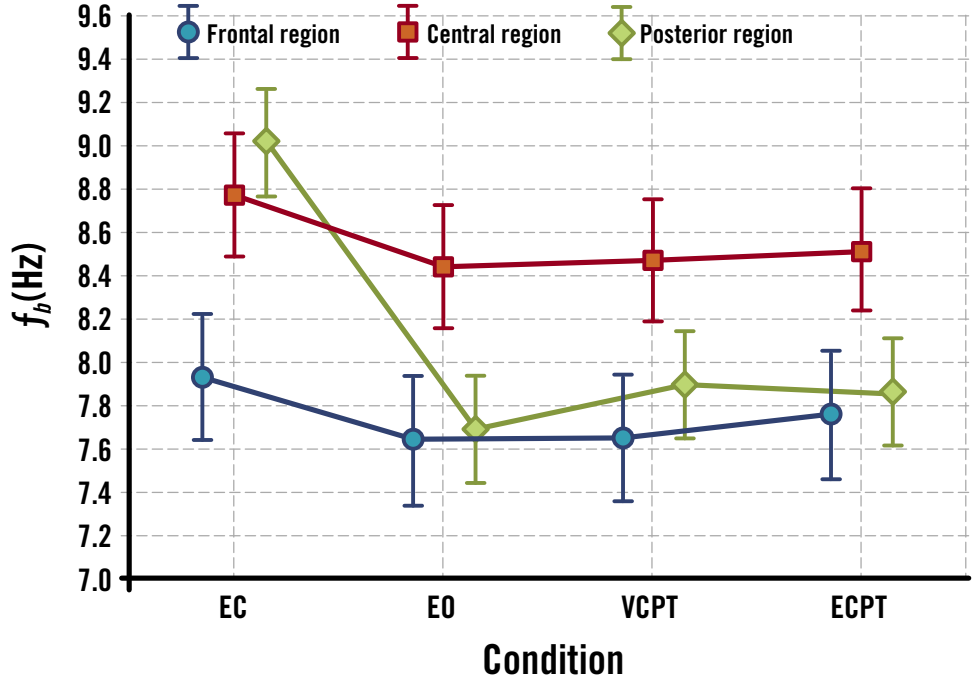
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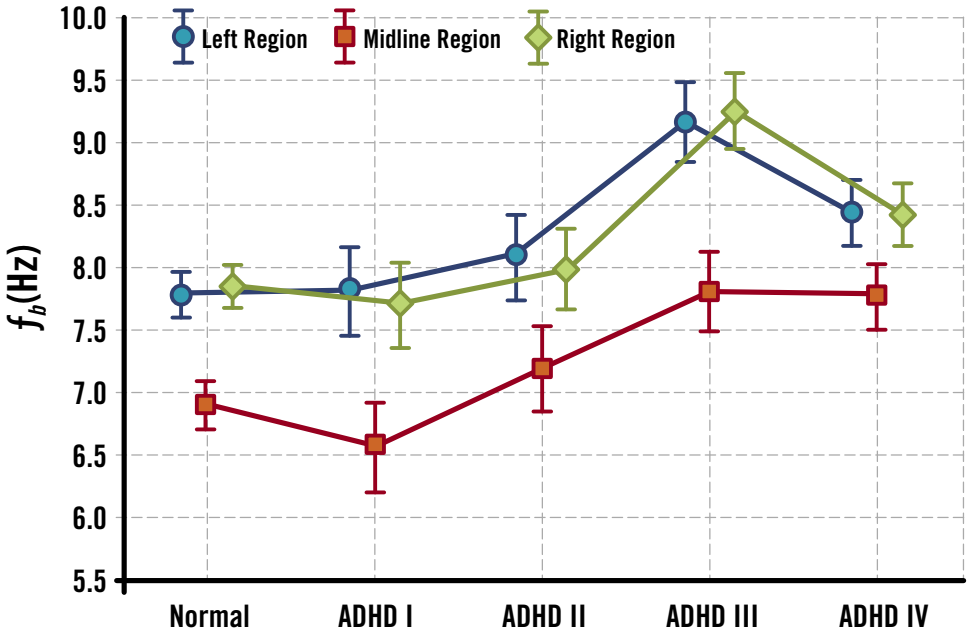
FIGURE 2.
f_b values for sagittal topography according to the recording conditions (EC, EO, VCPT, ECPT)



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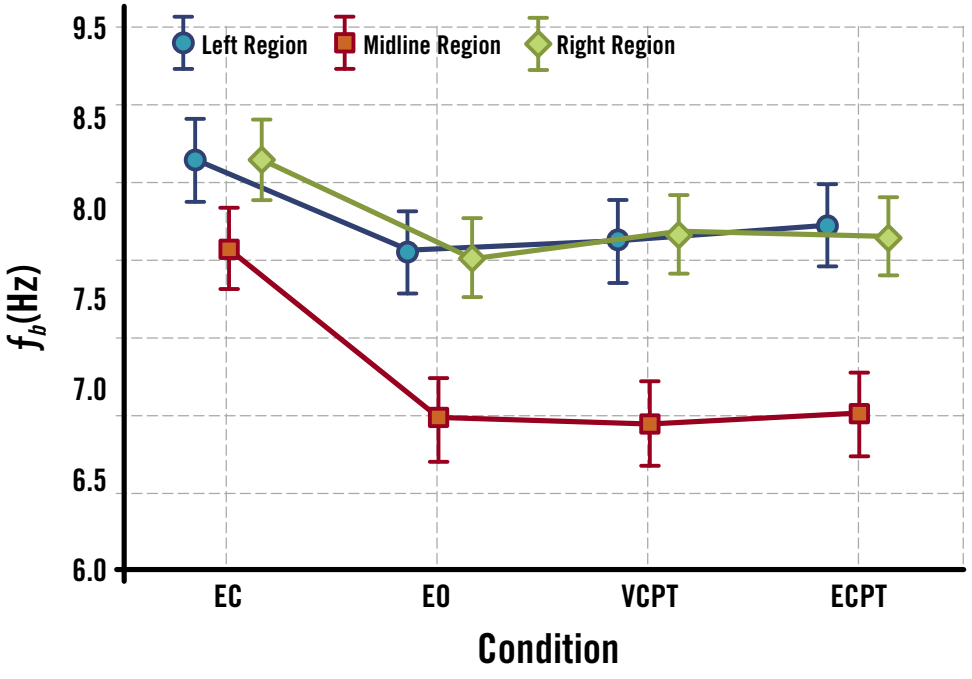
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FIGURE 3.
f_b values for lateral topography in normals and ADHD subtypes



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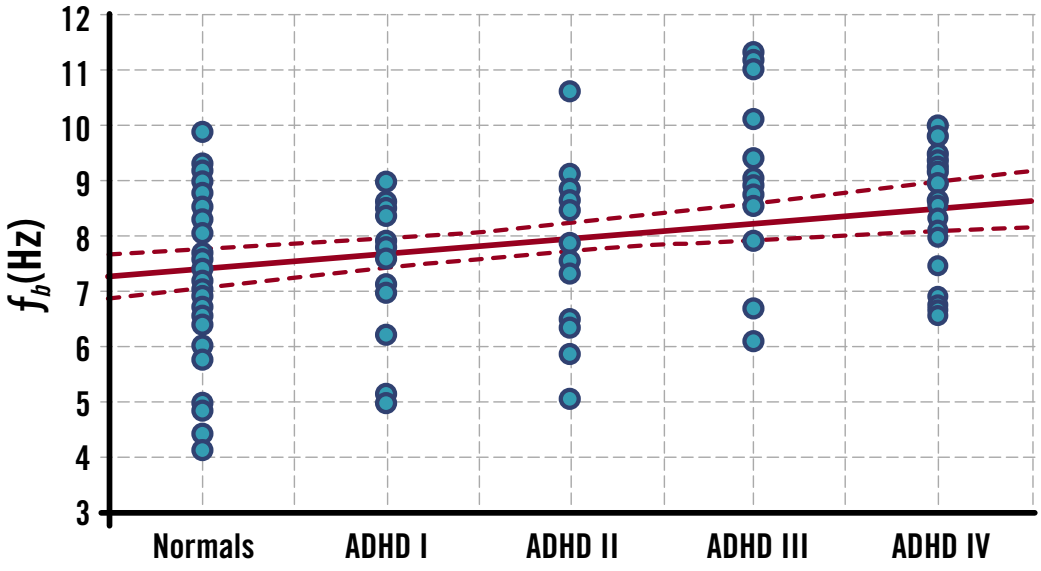
FIGURE 4.
f_b values for lateral topography according to recording conditions (EC, EO, VCPT, ECPT)



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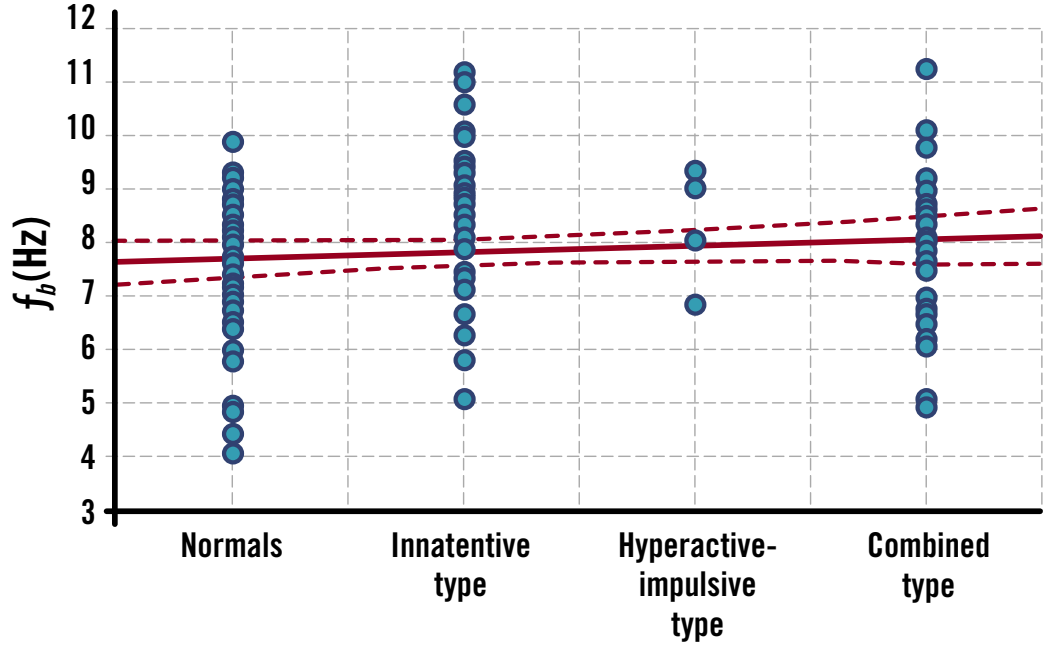
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FIGURE 5.
Correlation between the f_b values and the QEEG spectra ADHD subtypes (the mean [7.83] is presented as a solid line and the SD [±1.40] as dashed lines)



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FIGURE 6.
Correlation between f_b values and the behavioral ADHD types according to the *DSM-IV*



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