

RELATION BETWEEN FRONTAL ALPHA ASYMMETRY AND ANXIETY IN YOUNG PATIENTS WITH GENERALIZED ANXIETY DISORDER

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Abstract

Frontal alpha asymmetry (the relative difference in power between two signals in different hemispheres) has been suggested as biomarker for anxiety. The goal of this study was to evaluate alpha asymmetry in the frontal region for young people (7–18 years) with generalized anxiety disorder, diagnosed according to two statistic manuals (DMS-IV-R and ICD-10), the medical history and the neuropsychological assessment. The QEEG recording and analysis of the obtained results from alpha spectra power and log of alpha spectra power are made in four conditions (eyes open, eyes closed, VCPT and ACPT). The obtained results for alpha power in general showed higher cortical activity in the right hemisphere, associated with negative emotions. The calculated alpha asymmetry separate for eyes open, eyes closed, VCPT and ACPT conditions showed the right activation in all four conditions. In addition, the right frontal asymmetry was specific for the Fp₁–Fp₂ region, while a greater left frontal activation was recorded for the F₇–F₈ region. The log of alpha power in general was additionally analyzed. The calculated asymmetry score in general (in a way that the left log transformed score was subtracted from the right) confirmed a greater right activation. Testing the power of the whole alpha band (μV^2) in general, for all four conditions and for frontal region confirmed the right alpha asymmetries in all participants. The right alpha asymmetry in the frontal region was specific only for the Fp₁–Fp₂ region (frontopolar region). The only greater left frontal activation was registered between the F₇–F₈ region. Our findings are supported by many other studies using specific localization methods like fMRI or LORETA source localization.

Key words: generalized anxiety disorder, QEEG, frontal asymmetry, spectra power, log spectra power

Background (Introduction)

Generalized anxiety disorder in childhood is characterized by recurrence of excessive, disproportionate and intrusive concerns or worries (related to child's performance at school, sport activities, his/her physical health, family financial situation, catastrophes, possible disasters) in a period of one month at the least. Brain imaging and functional studies have shown some evidence of abnormal function in several regions of the brain in people suffering generalized anxiety disorder (GAD). The amygdale plays a central role in anxiety disorders. This structure

in the limbic system warns us when a danger is present in our environment and triggers "the fight or flight reaction" to get us out of it.

The EEG recording (based on the electrical brain activity) is used generally to evaluate some neurological disorders like epilepsy, but additionally it can be used to evaluate some mental and behavioral problems too. Hundreds of studies have been done investigating quantitative EEG activity in some important areas involved in our daily life functioning, including attention, mood, anxiety, social functioning, learning and thinking skills.

The most interesting and relevant of the EEG recording are the alpha waves, which rhythmically change according to the mental state of the individual. In a relaxing state with eyes closed, the alpha waves are high in both, amplitude and magnitude (Andreassi, 2000). However, when an individual opens his eyes, or begins mental processing, the alpha waves decrease in amplitude and become more frequent. Thus, the alpha wave amplitude is inversely related to the cognitive activity (Tomarken et al, 1990; Peterson et al, 2008). In experimental studies, the removal of the positive images provoke decreased alpha amplitude and increased wave intensity, whereas the removal of negative images increased alpha amplitude and decreased wave intensity.

According to Davidson and Irwin (1999), the ventromedial sector of the prefrontal cortex (PFC) is directly involved in the representation of elementary positive and negative emotional states. Frontal brain asymmetry has been conceptualized as a biological substrate for the fundamental dimensions of emotions, approach and withdrawal (Davidson, 2001; 2003). The interesting work of Fox (1991) is related to brain asymmetries (as measured by scalp recorded EEG activity) localized in the frontal region and associated with the generation of emotions even in infants. This finding motivated extensively use of electroencephalography (EEG) for exploring the connection between frontal asymmetry and emotion and motivation. Fearful face trials induced greater relative right frontal activation, whereas happy face trials induced greater relative left frontal activation (Avram et al, 2010). Even more, Colin and Allen (2004) showed that frontal EEG asymmetry appears to serve, firstly, as an individual difference variable related to emotional responding and emotional disorders, and secondly, as a state-dependent concomitant of emotional responding (Coan and Allen, 2004).

However, frontal alpha asymmetry has been suggested as a biomarker for anxiety. Research in frontal asymmetry focuses on the relative difference in power between two signals in different hemispheres. The goal of our study was to evaluate alpha asymmetry in frontal region in young patients (aged 7–18 years) suffering for generalized anxiety disorder. Activity

within the alpha range (typically 8–13 Hz) may be inversely related to underlying cortical processing. Decreases in alpha can be observed when underlying cortical systems are engaged in active processing. Our hypothesis is that frontal asymmetry in anxious children may be the marker for emotional imbalance. The main questions are whether the general alpha asymmetry is specific, or alpha asymmetry appears only in frontal region, or maybe some separate parts of the frontal region are activated and alpha EEG asymmetry could be distinguished between them?

Methods and Subjects

The evaluated sample comprised 40 children and teenagers, mean age 12 (± 3.5) years. Girls were 17 (42.5%) and 23 (57.5%) were boys. All subjects were patients of the Department for Psychophysiology at the University Pediatric Clinic in Skopje, in the period from January 2008 until December 2010. The diagnosis was made according to two statistic manuals: DMS-IV-R (American Psychiatric Association: Diagnostic and statistical manual of mental disorders DSM-IV, 4th Ed, 1994) and ICD-10 (World Health Organization: The ICD-10 classification of mental and behavioural disorders. Diagnostic criteria for research, 1993). Medical history, neuropsychological assessment and QEEG has been realized in all patients.

The manifested symptoms comprised:

- ✓ Excessive concerns about the quality of one's performance in areas such as school-work, sports or everyday life;
- ✓ Excessive concerns about physical health (despite good health);
- ✓ Excessive concerns about non-health related themes (money, family, disasters...);
- ✓ Free floating anxiety unrelated to specific situations;
- ✓ A frequent need for reassurance;
- ✓ Marked feelings of tension, inability to relax or to concentrate, nervousness, difficulty falling asleep, autonomic symptoms (such as palpitations, sweating, dry mouth, etc.);
- ✓ Recurrent somatic complaints.

Inclusion criteria were: age between 7 and 18 years; absence of actual neurological impairments and absence of the use of psychoactive or psychotropic substances (screened by

a previous anamnesis and clinical examination). All subjects had normal or corrected to normal vision.

Informed consent for QEEG recording has been appropriately obtained from all participants. All of them were assessed with psychological testing (Generalised Anxiety Scale–GAS and Eysenck Personality Questionnaire–EPQ, in a single session). Subjects were without any medication 48 – hours before testing and were asked to have good sleep night before testing. All of them must have meal before testing to avoid effects of hypoglycemia on brain function. They were seated in a comfortable chair with a backrest and were instructed not to move their eyes during testing.

EEG was recorded with Quantitative EEG equipment (Mitsar, Ltd.) amplifier from 19 electrodes, referenced to linked ears (on the International 10–20 system) with 250 Hz sampling rate in 0.3–70 Hz frequency range in the following conditions:

- 1) Eyes opened (EO) – 5 minutes,
- 2) Eyes closed (EC) – 5 minutes,
- 3) Visual continuous performance task (VCPT) – 20 minutes.
- 4) Auditory continuous performance task (ACPT) – 20 minutes.

The ground electrode was placed between Fpz and Fz. The impedance levels for all electrodes were set to 5 K Ω . Two stimulus GO/NOGO task developed specifically for HBI (Human Brain Institute) database were used. VCPT consisted of 400 trials and ACPT of 1000 trials. Subjects were instructed to press a button with index finger of their right hand for GO condition and not to press a button for NOGO condition.

Recorded results were referred and analyzed as data base montage. The 19 electrode positions were allocated to three sagittal regions:

- ✓ Frontal – Fp1, Fp2, F3, Fz, F4, F7 and F8.
- ✓ Central – T3, T4, C3, Cz and C4.
- ✓ Posterior – T5, T6, P3, Pz, P4, O1 and O2.

Scale: 50 mcV/cm, speed – 30 mm/sec, time constant – 0.3 sec, low frequency filter – 30 Hz. The analysis was made after eliminating artifacts resulting from movements, large scale muscle tension, sweat and large eye movements. Vertical and horizontal eye movement

artifact correction was done by means of Independent Component Analysis (ICA). ICA is an information maximization algorithm that derives spatial filters by blind source separation of the EEG signals into temporally independent and spatially fixed components. Recordings in four conditions (eyes closed, eyes open, VCPT and ACPT) were sufficient for calculation of spectra power values for all 19 electrodes. In this examination the special field of interest was frontal region, so we analyzed data for alpha spectra power and log alpha power from Fp1, Fp2, F3, F4, F7 and F8. The obtained results were exported and then calculated for each region separately. The QEEG spectra power data were analyzed using Statistica software (version 7.0).

Asymmetry is defined as a functional difference between the left and right hemispheres measured from absolute amplitude which exists between the homologous electrodes located on these hemispheres (Wheeler et al, 1993). It was calculated using the following equation:

$$\frac{\text{Power(left)} - \text{Power(right)}}{\text{Power(left)} + \text{Power(right)}}$$

where Power (left) corresponds to the alpha power of the electrode located on the left hemisphere, and Power (right) to the alpha power on the right hemisphere. These asymmetry data were submitted to statistical analysis.

Additionally, EEG asymmetry scores can be computed as the difference between natural logarithm (log) of the EEG alpha power at the right recording site and the left recording site:

$$\log(\text{right}) - \log(\text{left}); \text{e.g. } F_{3/4} = \log(F_4) - \log(F_3).$$

Because of the inverse relation between alpha power and activation, positive values of this metric denote left-sided activation and negative values denote right sided activation (12). Brain activity is an inverse measure of alpha power activity, meaning that less alpha power represents more brain activity and vice versa (Shagass, 1972). Consequently, left EEG asymmetry values indicate greater left relative to right brain activity, and right EEG asymmetry values yield the opposite activity pattern. EEG asymmetries were evaluated for Fp1, Fp2, F3, F4, F7 and F8 points as indicators for alpha activity in left and right frontal hemisphere.

Results

Average power in the 8–13 Hz band was taken as an index of alpha power. Consequently, an asymmetry score was computed by taking the difference between alpha power values of left and right locations (Fp₁ and Fp₂, F₃ and F₄, F₇ and F₈) from the equation:

$$\frac{\text{Power (left)} - \text{Power (right)}}{\text{Power (left)} + \text{Power (right)}}$$

The calculation was made in general and in four conditions separately. The obtained results are presented in the following tables.

Table 1

Alpha spectra power in general

Variable	Descriptive statistics (Spectra power anxiety) Include cases 1 : 160			
	Valid N	Mean	Minimum	Maximum
Left-alpha	160	6.443	0.240	40.503

Variable	Descriptive statistics (Spectra power anxiety) Include cases 1 : 160			
	Valid N	Mean	Minimum	Maximum
Right-alpha	160	7.334	0.307	45.028

ALPHA POWER in general	Results	Higher cortical activity in
Left	6.44	Right hemisphere
Right	7.33	
$\frac{\text{Power (left)} - \text{Power (right)}}{\text{Power (left)} + \text{Power (right)}}$	-0.06	

The results showed that, in general, all tested children and teenagers have greater right alpha activation.

Table 2

Alpha power for frontal region

Variable	Descriptive statistics (Frontal asymmetry-spectra power) Include cases 1 : 160				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
Fp ₁	160	1.961	0.144	12.391	1.769
F ₇	160	2.931	1.179	12.421	2.229
F ₃	160	3.276	0.178	16.124	2.292

Variable	Descriptive statistics (Frontal asymmetry-spectra power) Include cases 1 : 160				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
Fp ₂	160	2.281	0.287	12.082	2.014
F ₄	160	3.189	0.187	18.537	2.468
F ₈	160	2.673	0.298	13.357	2.049

ALPHA POWER for frontal region in general	Results	Higher cortical activity in
Left	8.17	Right hemisphere
Right	8.64	
$\frac{\text{Power (left)} - \text{Power (right)}}{\text{Power (left)} + \text{Power (right)}}$	-0.02	

When we made the same tests only for alpha power in frontal region we received results for greater right alpha activation. Then we made

analysis for separate parts of frontal region. So we calculated the frontal asymmetry between Fp₁ and Fp₂; F₃ and F₄ and between F₇ and F₈.

Table 3

Alpha power for Fp₁ and Fp₂

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
Fp ₁	160	1.961	0.144	12.391	1.769

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
Fp ₂	160	2.282	0.287	12.082	2.014

ALPHA POWER for frontal region in general (Fp ₁ -Fp ₂)	Results	Higher cortical activity in
Left	1.96	Right hemisphere
Right	2.28	
$\frac{\text{Power (left)} - \text{Power (right)}}{\text{Power (left)} + \text{Power (right)}}$	-0.07	

Table 4

Alpha power for F₃ and F₄

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
F ₃	160	3.276	0.178	16.124	2.292

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
F ₄	160	3.189	0.187	18.537	2.468

ALPHA POWER for frontal region in general (F ₃ -F ₄)	Results	Higher cortical activity in
Left	3.28	Left hemisphere
Right	3.19	
$\frac{\text{Power (left)} - \text{Power (right)}}{\text{Power (left)} + \text{Power (right)}}$	0.04	

Table 5

Alpha power for F₇ and F₈

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
F ₇	160	2.931	0.179	12.421	2.230

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
F ₈	160	2.673	0.298	13.357	2.049

ALPHA POWER for frontal region ingeneral (F7-F8)	Results	Higher cortical activity in
Left	2.93	Left hemisphere
Right	2.67	
$\frac{\text{Power (left)} - \text{Power (right)}}{\text{Power (left)} + \text{Power(right)}}$	0.05	

After obtaining these results we made calculation of the alpha asymmetry for different conditions and the results are as follows.

Table 6

Alpha power in EO condition in general

Variable	Descriptive statistics (Spectra power anxiety) Include cases 1 : 40			
	Valid N	Mean	Minimum	Maximum
Left-alpha	40	4.084	0.345	11.494

Variable	Descriptive statistics (Spectra power anxiety) Include cases 1 : 40			
	Valid N	Mean	Minimum	Maximum
Right-alpha	40	4.635	0.427	14.503

ALPHA POWER in general for EO condition	Results	Higher cortical activity in
Left	4.08	Right hemisphere
Right	4.63	
$\frac{\text{Power (left)} - \text{Power (right)}}{\text{Power (left)} + \text{Power(right)}}$	-0.07	

Table 7

Alpha power for EO condition in frontal region

Variable	Descriptive statistics (Frontal asymmetry-spectra power) Include cases 1 : 40				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
Fp1	40	1.396	0.144	4.881	1.068
F7	40	2.356	0.501	5.791	1.616
F3	40	2.723	0.448	7.173	1.741

Variable	Descriptive statistics (Frontal asymmetry-spectra power) Include cases 1 : 40				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
Fp2	40	1.612	0.340	5.675	1.198
F4	40	2.588	0.304	8.639	1.774
F8	40	2.081	0.475	6.272	1.444

ALPHA POWER in frontal region for EO condition	Results	Higher cortical activity in
Left	6.46	Left hemisphere
Right	6.28	
$\frac{\text{Power (left)} - \text{Power (right)}}{\text{Power (left)} + \text{Power(right)}}$	0.014	

Table 8

Alpha power for EO condition in Fp1-Fp2

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
Fp1-eo	40	1.396	0.144	4.881	1.068

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
Fp2-eo	40	1.612	0.340	5.675	1.198

ALPHA POWER for frontal region in eo condition (Fp1-Fp2)	Results	Higher cortical activity in
Left	1.39	Right hemisphere
Right	1.69	
$\frac{\text{Power (left)} - \text{Power (right)}}{\text{Power (left)} + \text{Power(right)}}$	-0.73	

Table 9

Alpha power for EO condition in F3-F4

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
F3-eo	40	2.723	0.448	7.173	1.741

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
F4-eo	40	2.590	0.304	8.639	1.774

ALPHA POWER for frontal region in EO condition (F3-F4)	Results	Higher cortical activity in
Left	2.72	Left hemisphere
Right	2.58	
$\frac{\text{Power (left)} - \text{Power (right)}}{\text{Power (left)} + \text{Power(right)}}$	0.03	

Table 10

Alpha power for EO condition in F7-F8

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
F7-eo	40	2.356	0.501	5.791	1.616

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
F8-eo	40	2.081	0.475	6.272	1.444

ALPHA POWER for frontal region in eo condition (F7-F8)	Results	Higher cortical activity in
Left	2.35	Left hemisphere
Right	2.08	
$\frac{\text{Power (left)} - \text{Power (right)}}{\text{Power (left)} + \text{Power(right)}}$	0.06	

Table 11

Alpha power for EC condition in general

Variable	Descriptive statistics (Spectra power anxiety) Include cases 41 : 80			
	Valid N	Mean	Minimum	Maximum
Left-alpha	40	13.006	0.240	40.503

Variable	Descriptive statistics (Spectra power anxiety) Include cases 41 : 80			
	Valid N	Mean	Minimum	Maximum
Right-alpha	40	14.912	0.307	45.028

ALPHA POWER in general in EC condition	Results	Higher cortical activity in
Left	13.01	Right hemisphere
Right	14.91	
$\frac{\text{Power (left)} - \text{Power (right)}}{\text{Power (left)} + \text{Power(right)}}$	-0.06	

Table 12

Alpha power for EC condition in frontal region

Variable	Descriptive statistics (Frontal asymmetry-spectra power) Include cases 41 : 80				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
Fp1	40	2.893	0.149	9.390	2.082
F7	40	4.414	0.179	12.421	2.941
F3	40	4.832	0.178	16.124	3.049

Variable	Descriptive statistics (Frontal asymmetry-spectra power) Include cases 41 : 80				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
Fp2	40	3.224	0.287	10.770	2.466
F4	40	4.849	0.187	18.537	3.515
F8	40	4.232	0.298	13.357	2.803

ALPHA POWER in frontal region for ec condition	Results	Higher cortical activity in
Left	12.13	Right hemisphere
Right	12.29	
$\frac{\text{Power (left)} - \text{Power (right)}}{\text{Power (left)} + \text{Power(right)}}$	-0.006	

Table 13

Alpha power for EC condition in Fp1-Fp2

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
Fp1-ec	40	2.893	0.149	9.390	2.082

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
Fp2-ec	40	3.224	0.287	10.77	2.466

ALPHA POWER for frontal region in ec condition (Fp1-Fp2)	Results	Higher cortical activity in
Left	2.89	Right hemisphere
Right	3.22	
$\frac{\text{Power (left)} - \text{Power (right)}}{\text{Power (left)} + \text{Power(right)}}$	-0.05	

Table 14

Alpha power for EC condition in F3-F4

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
F3-ec	40	4.832	0.178	16.124	3.049

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
F4-ec	40	4.849	0.187	18.537	3.515

ALPHA POWER for frontal region in ec condition (F3-F4)	Results	Higher cortical activity in
Left	4.83	Right hemisphere
Right	4.85	
$\frac{\text{Power (left)} - \text{Power (right)}}{\text{Power (left)} + \text{Power(right)}}$	-0.002	

Table 15

Alpha power for EC condition in F7-F8

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
F7-ec	40	4.414	0.179	12.421	2.941

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
F8-ec	40	4.232	0.298	13.357	2.803

ALPHA POWER for frontal region in ec condition (F7-F8)	Results	Higher cortical activity in
Left	4.41	Left hemisphere
Right	4.23	
$\frac{\text{Power (left)} - \text{Power (right)}}{\text{Power (left)} + \text{Power(right)}}$	0.02	

Table 16

Alpha power for VCPT condition in general

Variable	Descriptive statistics (Spectra power anxiety) Include cases 81 : 120			
	Valid N	Mean	Minimum	Maximum
Left-alpha	40	5.016	0.380	24.050

Variable	Descriptive statistics (Spectra power anxiety) Include cases 81:120			
	Valid N	Mean	Minimum	Maximum
Right-alpha	40	5.495	0.368	20.044

ALPHA POWER in general in VCPT condition	Results	Higher cortical activity in
Left	5.01	Right hemisphere
Right	5.49	
$\frac{\text{Power (left)} - \text{Power (right)}}{\text{Power (left)} + \text{Power(right)}}$	-0.04	

Table 17

Alpha power for VCPT condition in frontal region

Variable	Descriptive statistics (Frontal asymmetry-spectra power) Include cases 81 : 120				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
Fp1	40	1.506	0.289	6.219	1.210
F7	40	2.409	0.305	7.976	1.826
F3	40	2.914	0.258	9.315	1.807

Variable	Descriptive statistics (Frontal asymmetry-spectra power) Include cases 81 : 120				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
Fp2	40	2.007	0.397	12.082	2.017
F4	40	2.821	0.229	10.407	1.853
F8	40	2.275	0.504	6.121	1.459

ALPHA POWER in frontal region for VCPT condition	Results	Higher cortical activity in
Left	6.83	Right hemisphere
Right	7.1	
$\frac{\text{Power (left)} - \text{Power (right)}}{\text{Power (left)} + \text{Power(right)}}$	-0.02	

Table 18

Alpha power for VCPT condition in Fp1-Fp2

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
Fp1-VCPT	40	1.506	0.289	6.219	1.210

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
Fp2-VCPT	40	2.007	0.397	12.082	2.017

ALPHA POWER for frontal region in VCPT condition (Fp1-Fp2)	Results	Higher cortical activity in
Left	1.51	Right hemisphere
Right	2.01	
$\frac{\text{Power (left)} - \text{Power (right)}}{\text{Power (left)} + \text{Power(right)}}$	-0.14	

Table 19

Alpha power for VCPT condition in F3-F4

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
F3-VCPT	40	2.914	0.258	9.315	1.807

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
F4-VCPT	40	2.820	0.229	10.407	1.853

ALPHA POWER for frontal region in VCPT condition (F3-F4)	Results	Higher cortical activity in
Left	2.91	Left hemisphere
Right	2.82	
$\frac{\text{Power (left)} - \text{Power (right)}}{\text{Power (left)} + \text{Power(right)}}$	0.015	

Table 20

Alpha power for VCPT condition in F7-F8

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
F7-VCPT	40	2.409	0.305	7.976	1.826

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
F8-VCPT	40	2.275	0.504	6.121	1.459

ALPHA POWER for frontal region in VCPT condition (F ₇ -F ₈)	Results	Higher cortical activity in
Left	2.41	Left hemisphere
Right	2.27	
$\frac{\text{Power (left)} - \text{Power (right)}}{\text{Power (left)} + \text{Power(right)}}$	0.03	

Table 21

Alpha power for ACPT condition in general

Variable	Descriptive statistics (Spectra power anxiety) Include cases 121 : 160			
	Valid N	Mean	Minimum	Maximum
Left-alpha	40	3.667	0.482	14.833

Variable	Descriptive statistics (Spectra power anxiety) Include cases 121 : 160			
	Valid N	Mean	Minimum	Maximum
Right-alpha	40	4.295	0.351	22.917

ALPHA POWER in general in ACPT condition	Results	Higher cortical activity in
Left	3.67	Right hemisphere
Right	4.29	
$\frac{\text{Power (left)} - \text{Power (right)}}{\text{Power (left)} + \text{Power(right)}}$	-0.08	

Table 22

Alpha power for ACPT condition of frontal region

Variable	Descriptive statistics (Frontal asymmetry-spectra power) Include cases 121 : 160				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
Fp ₁	40	2.049	0.422	12.391	2.093
F ₇	40	2.545	0.580	7.099	1.626
F ₃	40	2.635	0.395	6.668	1.573

Variable	Descriptive statistics (Frontal asymmetry-spectra power) Include cases 121 : 160				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
Fp ₂	40	2.284	0.453	7.399	1.870
F ₄	40	2.499	0.297	6.397	1.436
F ₈	40	2.106	0.303	5.244	1.307

ALPHA POWER in ACPT condition in frontal region	Results	Higher cortical activity in
Left	7.22	Left hemisphere
Right	6.89	
$\frac{\text{Power (left)} - \text{Power (right)}}{\text{Power (left)} + \text{Power(right)}}$	0.02	

Table 23

Alpha power for ACPT condition in Fp1-Fp2

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
Fp1-ACPT	40	2.049	0.422	12.391	2.092

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
Fp2-VCPT	40	2.284	0.453	7.399	1.870

ALPHA POWER for frontal region in ACPT condition (Fp1-Fp2)	Results	Higher cortical activity in
Left	2.05	Right hemisphere
Right	2.28	
$\frac{\text{Power (left)} - \text{Power (right)}}{\text{Power (left)} + \text{Power (right)}}$	-0.05	

Table 24

Alpha power for ACPT condition in F3-F4

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
F3-ACPT	40	2.635	0.395	6.668	1.573

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
F4-ACPT	40	2.499	0.297	6.397	1.436

ALPHA POWER for frontal region in ACPT condition (F3-F4)	Results	Higher cortical activity in
Left	2.63	Left hemisphere
Right	2.50	
$\frac{\text{Power (left)} - \text{Power (right)}}{\text{Power (left)} + \text{Power (right)}}$	0.02	

Table 25

Alpha power for ACPT condition in F7-F8

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
F7-ACPT	40	2.545	0.580	7.099	1.626

Variable	Descriptive statistics (Frontal asymmetry-spectra power)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
F8-ACPT	40	2.106	0.303	5.244	1.307

ALPHA POWER for frontal region in ACPT condition (F ₇ –F ₈)	Results	Higher cortical activity in
Left	2.54	Left hemisphere
Right	2.11	
Power (left) – Power (right) Power (left) + Power(right)	0.09	

The obtained results for alpha asymmetry in general are calculated separately for eyes open, eyes closed, VCPT and ACPT conditions showed right frontal activation in all four conditions. The right frontal asymmetry only for the frontal region in general was specific for eyes closed and VCPT condition. Additionally, for all four conditions the right frontal asymmetry was specific for the Fp₁–Fp₂ region and in all four conditions a greater left frontal activation between F₇–F₈ region was obtained.

In addition, we calculated the asymmetry score in the way that the left log transformed score was always subtracted from the right:

$$\log(\text{right}) - \log(\text{left});$$

e.g. $F_{p1/p2} = \log(F_{p2}) - \log(F_{p1})$ or
e.g. $F_{3/4} = \log(F_4) - \log(F_3)$ or
e.g. $F_{7/8} = \log(F_8) - \log(F_7)$

The calculation was made only in general for 4 conditions. The results are as follows.

Table 26

Asymmetry score in general according log. spectra results

CONDITION-General	Results	Higher cortical activity in
log(right) – log (left)	0.09	Right hemisphere

Variable	Descriptive statistics (Frontal asymmetry-log.spectra power) Include cases 1 : 160				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
Log Fp ₁	160	2.266	0.144	19.361	2.255
Log F ₇	160	3.183	0.179	26.989	2.921
Log F ₃	160	3.311	0.178	17.760	2.392

Variable	Descriptive statistics (Frontal asymmetry-log.spectra power) Include cases 1 : 160				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
Log Fp ₂	160	2.645	0.287	19.625	2.450
Log F ₄	160	3.238	0.187	16.819	2.467
Log F ₈	160	2.967	0.298	20.286	2.497

The calculated asymmetry score in general for all four conditions, in the way that the left log transformed score was always subtracted from the right, showed results which suggest greater right frontal activation.

Asymmetry can be defined either as a functional difference between the left and right hemispheres measured from the absolute amplitude which exists between the homologous electrodes located on these hemispheres. The power (left) corresponds to the relative alpha power of the electrode located on the left hemisphere, and the Power (right) to the relative alpha power on the right hemisphere. So, when

we analyze in general the alpha band asymmetry in all tested examinees we found greater right alpha activation. When we made the same test only for alpha power in the frontal region we obtained again results for greater right alpha activation. Based on this results we can conclude that alpha asymmetry in general and especially in the frontal region can be biomarker for anxiety.

In the following, we made analysis for separate parts of frontal region and we calculated frontal asymmetry between Fp₁ and Fp₂; F₃ and F₄ and between F₇ and F₈. The right frontal asymmetry was specific only for the Fp₁–Fp₂ regions and left frontal asymmetry for the F₃–F₄

and the F₇–F₈ regions. Such results can be explained according to Davidson and Irwin (1999) that the ventromedial sector of the PFC is the most directly involved in the representation of elementary positive and negative emotional states, while the dorsolateral PFC may be involved in the representation of the goal states towards which these elementary positive and negative states are directed. Figure 1 shows asymmetries presented on brain maps.

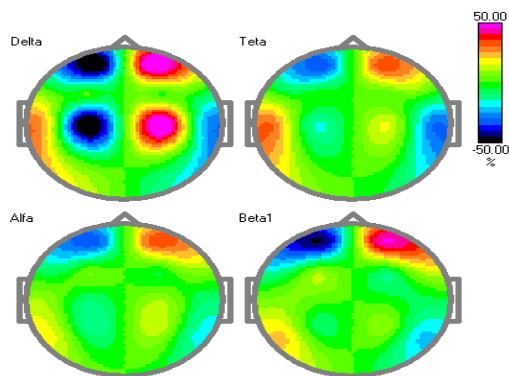


Figure 1 – Asymmetry for all four bands in a patient with GAD

In addition, we calculated separate alpha asymmetry for eyes open, eyes closed, VCPT and ACPT condition and the obtained results suggested right frontal activation in all four conditions. The analysis of the results for the frontal region showed greater right activation in eyes closed and VCPT conditions. The same calculation but for separate regions during all four conditions: Fp₁ and Fp₂; F₃ and F₄ and F₇ and F₈ was made. We found that in all four conditions the right frontal asymmetry was specific for the Fp₁–Fp₂ region while in all four conditions a greater left frontal activation between the F₇–F₈ region was obtained. The described results confirm our hypothesis that frontal asymmetry in anxious children may be considered as a biomarker for emotion imbalance i.e. anxiety in young patients with GAD. In the frontal region a specific interest was focused on the frontopolar part in which the right alpha activation is specific for anxiety patients. Figure 2 shows LORETA for eight old patient with GAD.

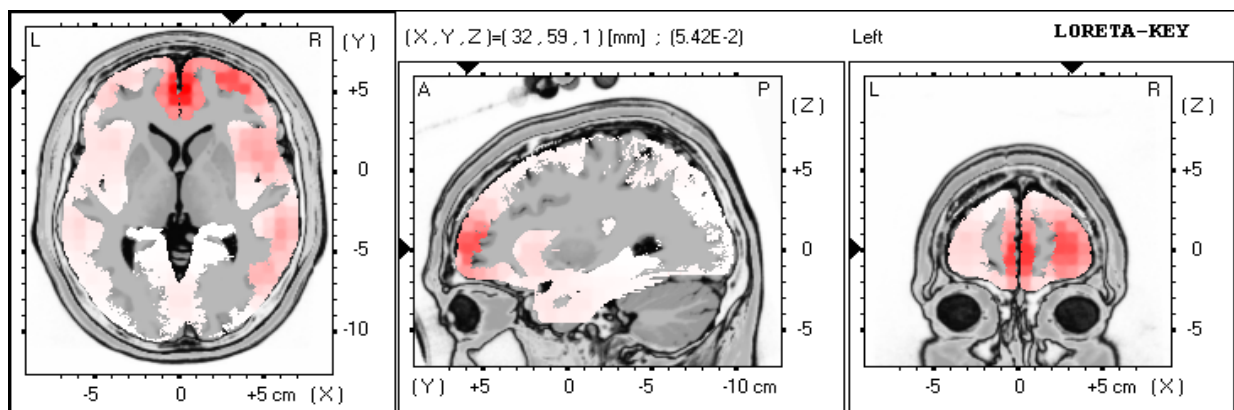


Figure 2 – LORETA during eyes open condition in eight year old girl

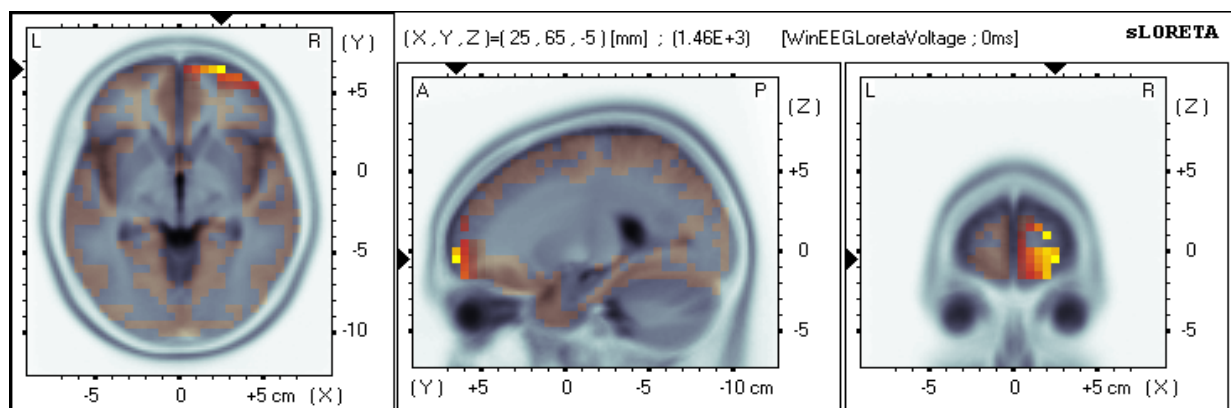
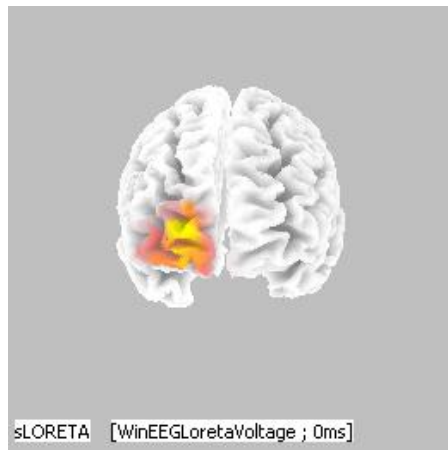


Figure 3 – Standardized LORETA during eyes open condition in the same patient



*Figure 4 – Standardized LORETA
– 3Dcortex/scalp/electrodes – during eyes open
condition in the same patient*

LORETA shows specific localization of the source for alpha activation.

Discussion

Alpha waves originate in the posterior portions of the brain stem and oscillate up through the occipital, temporal, parietal and then frontal lobes. Thus, the frontal lobes are one of the last portions of the brain which receive alpha signals. Alpha waves are also harmonious and synchronized between the left and right hemispheres (Scott, 1976).

The focus on the alpha band derives from the evidence indicating an association between increased alpha activity and decreased cerebral activation. In other words, the activity within the alpha range (typically 8–13 Hz) may be inversely related to underlying cortical processing, since decreases in alpha are observed when cortical systems are engaged in active processing. This assumption has been supported by fMRI and PET studies showing a decrease in cortical blood flow with increase of the alpha power (Cook et al, 1998; Goldmann et al, 2000).

The frontal lobes of the human brain are a processing center for emotional reactions. Electroencephalographic (EEG) research has revealed that increased relative right fronto-cortical activity tends to emerge during the processing of negative information and emotions, while greater relative left fronto-cortical activity is associated with positive affective information processing (Davidson, 1998). In the same direction, Davidson et al (2000) and Fox (1991) theorized that the frontal lobes are differentially involved in positive versus negative

affective states and corresponding motivated behaviors, with left frontal areas of the brain mediating the experience of positive emotions (e.g., joy, happiness, etc.) and approach behaviors, while the right frontal areas mediate the experience of negative emotions (e.g., fear, sadness, etc.) and withdrawal behaviors. Moreover, patterns of frontal electroencephalogram (EEG) asymmetry may serve as an index of risk for a variety of emotion-related disorders, including depression and anxiety. Moskovitch and colleagues (2011) measured alpha asymmetry in anxious patients before and after cognitive behavioral training (CBT) and stressed that, although it is too early to conclude that frontal EEG asymmetry is a biological marker of affective psychopathology and has prognostic value for its treatment, their results show that in treated patients the symptom reduction is associated with reliable changes in EEG asymmetry.

It is very important to make difference between alpha band activity and alpha band activation. The activity will refer to a tonic recording of cortical processes as measured by EEG, while the activation will refer to the change in the EEG activity (in this case alpha band activity) in response to a provocation, such as the presentation of an emotional or, in our case, visual and auditory stimulus. At the time we made these recordings, only VCPT and ACPT were available in our laboratory work. We noticed that in anxious children the visual and auditory stimulus raises the level of anxiety and serves as provocation or as negative stimulus. The results for alpha asymmetry are presented after computing and analyzing an asymmetry index, typically a difference score, usually by subtracting the natural log of left hemisphere alpha power from the natural log of right hemisphere alpha power ($\log [\text{right alpha}] - \log [\text{left alpha}]$). This approach results in a unidimensional scale representing the relative activity of the right and left hemispheres, with the middle point of the scale equaling zero or symmetrical activity. In interpreting this scale, higher scores indicate relatively greater left frontal activity whereas lower scores indicate relatively greater right frontal activity. When we calculated the asymmetry score in general for all four conditions, in the way that the left log transformed score was always subtracted from the

right, the obtained results suggest greater right frontal activation for alpha activity in general.

It is true that most researches including our own (Demerdzieva and Pop-Jordanova, 2011; Demerdzieva and Vujovic, 2014) investigate hemisphere asymmetries in correlation with emotion and motivation based only on EEG. Of course, this method has advantages like the assessment of the baseline neural activity, but it is also limited with respect to localizing the exact regions involved in underlining mental processes. Therefore, it cannot be excluded that different regions of the same cerebral lobe support relatively contradictory processes (such as activation vs. regulation of negative affect). Thus, the right dorsal prefrontal cortex may play a different role in emotion processing than the right ventral prefrontal cortex. Our obtained results showed different activation in the Fp₁–Fp₂ and the F₇–F₈ regions. As it is known, EEG can measure only activity on the surface of the head, so in the previous findings it cannot be differentiated where the activity actually comes from. Therefore, it is useful to combine EEG measures with localization methods such as EEG source localization (like LORETA) or fMRI.

The analysis and the conclusions following the obtained results must be done very carefully. One possible way is to correlate the electrode positions and the corresponding Brodmann's areas. As it is well known, Fp₁ and Fp₂ correspond to the Brodmann area 10 – dorsolateral and anterior prefrontal cortex. These parts are involved in processing the emotional stimuli and decision making involving conflict and reward especially for the right site. The right frontal asymmetry for Fp₁–Fp₂ regions is confirmed by Papousek and Schuster (Papousek and Schuster, 2002) who found that mood changes specifically co-vary with changes of the EEG asymmetry at the frontopolar electrode positions. The higher cortical activity in the right hemisphere for the Fp₁–Fp₂ region is related to the greater activation of the Brodmann area 10 R (right) which is specific (among others) for recalling episodes, reword vs conflict and risk vs benefit. In addition, these results correlate with the findings of Paulesu and colleagues (Paulesu, 2010) who found during the fMRI study that the activation of the anterior cingulate and dorsal medial prefrontal cortex (Brodmann area 32/23 and Brodmann area 10/11) was associated with worry in both

subjects with GAD and normal controls. However, GAD subjects showed a persistent activation of these areas even during the resting state scans that followed the worrying phase. This region was activated during the empathy experiment with representation of sad faces. By searching for similar results we can find a few more studies supporting our work. For example, Isotani and colleagues in 2001 (Isotani et al, 2001) obtained in hypnotically induced anxiety with LORETA maximally stronger activity in the right Brodmann area 10. Monk and colleagues in 2006 (Monk et al, 2006) during a fMRI study found that adolescents with generalized anxiety disorder manifested greater right ventrolateral prefrontal cortex (BA 10) activation in trials containing angry faces. McClure and colleagues in 2007 (McClure et al, 2007) during another fMRI study found that "while attending to their own subjective fear, patients, but not controls, showed greater activation to fearful faces than to happy faces in a distributed network including the amygdala, ventral prefrontal cortex, and anterior cingulate cortex". Karina Blair and colleagues in 2008 (Blair et al, 2008) examined the correlations between severity of the anxiety and engagement within the region Brodmann's area 10, and confirmed the perturbed engagement for angry versus neutral expressions in patients with generalized anxiety disorder.

The F₇ corresponds to Brodmann area 47 which is inferior prefrontal gyrus involved in many functions related to language and emotions. The greater left frontal activation between the F₇–F₈ region correlates to the greater activation of the Brodmann area 47 – the inferior part of the left frontal cortex. It is supported by Sprengelmeyer et al. (1998) in 1998 whose aim was using functional magnetic resonance imaging to locate neural structures that are critical for recognition of facial expressions of basic emotions by investigating cerebral activation. For all three emotions – disgust, fear and anger they found activation of the left frontal cortex (Brodmann area 47). The research based on fMRI partly supports this hypothesis by revealing that left more than right subcortical areas (amygdala, hypothalamus, thalamus) play a role in responses to unpleasant stimuli (Damasio et al, 2000, Lane et al, 1997). In this context, very important are the results obtained with fMRI by Miller et al (Miller et al, 2013)

who found that left inferior frontal gyrus region (Brodmann area 47) is more active for negative words than for neutral ones, significantly much more in subjects scoring high in anxious apprehension.

All described, as well as our own results confirm the hypothesis for greater right frontal activation in the Fp₂ region (Brodmann area 10) – ventrolateral prefrontal cortex and greater left frontal activation of F₇ (Brodmann area 47) – the inferior Frontal Gyrus which are similar in studies performed with more sophisticated equipment (fMRI) and methods (ECPT and Stroop tasks).

It is true that in some conditions or diseases like GAD, alpha asymmetry is specific for the right hemisphere but, there are many regions with specific activation and overlapping of regions specific for some mental processing. For example, it has been shown that the right hemisphere has a clear advantage in creative solution of problems (Bowden and Beeman, 1998), which has been considered as a mental process strongly associated with approach rather than withdrawal behavior. In this context, Friedman and Foster (2005) demonstrated a series of experiments that "positive" approach motivation facilitates a creative problem solving and that this effect is mediated by the right hemispheric activation. In the same work they also showed that avoidance of motivation facilitates analytic problem solving, and that this effect is mediated by the left hemispheric activation. According to all this findings, Rotenberg (2004) stresses that efficiency and activity of a hemisphere differ. To disentangle these two characteristics, it is necessary to jointly apply methods that measure hemisphere activity on the one hand (e.g., EEG), and hemisphere efficiency on the other hand (e.g., reaction times in visual hemifield tasks).

Research studies of many authors has shown that even infants (Fox, 1991) and children who show greater right, relative to left frontal EEG activation (right frontal asymmetry) are likely to be fearful and inhibited and have higher negative affect. Davidson and Fox (1989) found that infants who cried when separated from their mothers revealed greater right frontal activation than those who did not cry. In another research, Julia Avram (2010) and colleagues find that fearful face trials indu-

ced greater relative right frontal activation, whereas happy face trials induced greater relative left frontal activation. Many other authors agree that relatively greater left frontal activity has been associated with a general appetitive, approach, or behavioral activation system, in contrast to the relatively greater right frontal activity that has been related to an aversive, avoidance or withdrawal system (Coan and Allen, 2003b; Hagemann et al, 2002; Harmon-Jones, 2006). However, based on the available literature, meta-analyses support only the moderate effect of anxiety on the right-sided asymmetry of frontal activity (Thibodeau, 2006).

In the last few years many contradictory findings on sub regions of the frontal cortex, including their connectivity to each other and to other regions are published (Miller et al, 2013).

Different articles published on this topic can initiate many fields for further research. For example, Smith and colleagues (Smit et al, 2007) supposed that the asymmetry of the left and the right frontal brain activation should be related to the effects of both, sex and age. They found that the relation between FA and the risk for anxiety and depression is the most robust in young females. In our work we did not obtain any correlation with sex and age of evaluated children. Very interesting is the work of Blackhart and colleagues (Blackhart, 2006) reporting that the relative right frontal EEG activity may even predict future development of anxiety symptoms. The reports of Earle J.B (Earle, 1998) showed that task activity during the event related potentials appeared to play a significant role in the determination of parietal and temporal-lobe asymmetry. So in our further work we must analyze these regions – parietal and temporal, for alpha asymmetry either. Maybe these are ideas for further investigation in this area. In our work we started from the findings of Coan and Allen (2004) who found that frontal EEG asymmetry appears to serve as an individual difference variable related to the emotional responding and emotional disorders and that the frontal EEG asymmetry can serve as both a moderator and mediator of emotion and motivation related constructs. It was the reason why we were focused only on frontal region. Of course, our results are more in correlation with their later work from 2003, (Coan and Allen, 2003b) that the relationship between the

relative right frontal activity and the behavioral inhibition system is likely to be complex and not accounted by behavioral withdrawal alone.

The additional important effects of comorbidity in the regional brain activity during the analyses of all data for frontal asymmetry must be stressed. It is very difficult to explore EEG activity in children especially in those with anxiety disorders. But, we must agree with Baving and colleagues (Baving, 2002) that children suffering from anxiety disorders exhibited a significantly different pattern of frontal brain activation than healthy children without any lifetime diagnosis of mental disorders.

Conclusions

The study of alpha asymmetry as a biomarker for emotion imbalance is proposed. According to the obtained results we can conclude that right alpha asymmetry in general and especially in the frontal region can be a biomarker for anxiety in the evaluated group of children with GAD. The EEG activity analysis showed right alpha asymmetry in general for all four conditions (eyes open, eyes closed VCPT and ACPT). Right alpha asymmetry in the frontal region was specific only for the Fp1–Fp2 region (frontopolar region). Our results suggest greater left frontal activation only between the F7–F8 region. Many other studies support our findings using specific methods like fMRI or LORETA source localization.

Additionally, it can be concluded that not just the right, but some regions of the left hemisphere (Brodmann area 47) and especially the left subcortical areas (amygdala, hypothalamus, and thalamus) play a role in responses to unpleasant stimuli and generation of anxiety symptoms. These results are in context of assumption that different regions of the same cerebral lobe support relatively contradictory processes (such as activation vs. regulation of negative affect). The most important in understanding brain function is the analysis of the functional connectivity of different parts of the same cerebral lobe.

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Резиме

ОДНОС ПОМЕЃУ ФРОНТАЛНАТА АЛФА-АСИМЕТРИЈА И АНКСИОЗНОСТА КАЈ МЛАДИ ПАЦИЕНТИ СО ГЕНЕРАЛИЗИРАНО АНКСИОЗНО РАСТРОЈСТВО

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Фронталната алфа-асиметрија (релативната разлика помеѓу моќноста на два сигнала во разни хемисфери) е сугерирана како биомаркер за анксиозноста. Цел на оваа студија беше да се

евалуира алфа-асиметријата во фронталната регија кај млада популација (7–18 години) со генерализирано анксиозно растројство, дијагностицирано според статистичките мануели (DMS-IV-R i ICD-10), позитивната медицинска историја и неврофизиолошката процена. QEEG-снимањето и анализата на добиените резултати за алфа-моќноста и логаритам на алфа-моќноста е правена во четири услови (отворени очи, затворени очи, VCPT и ACPT). Добиените резултати за спектралната моќност, генерално, покажаа поголема кортикална активност во десната хемисфера, здружена со негативни емоции. Пресметаната алфа-асиметрија посебно за условите отворени очи, затворени очи, VCPT и ACPT покажа деснострани активација во сите четири услови. Дополнително, десната фронтална асиметрија беше специфична за Fr_1 – Fr_2 регионот, додека поголема левострана активација е добиена за F_7 – F_8 регионот. Логаритамот на алфа-моќноста е ана-

лизиран дополнително. Пресметаниот скор за алфа-асиметрија (при што левиот логаритам трансформиран скор е изваден од десниот) потврди дека постои поголема деснострани активација. Тестирањето на моќноста на целиот алфа-бенд (μV_2), генерално, за сите четири услови, како и за фронталната регија потврдија деснострани алфа-асиметрија кај сите испитаници. Деснострани асиметрија во фронталната регија е специфична само за Fr_1 – Fr_2 регијата (фронтална регија). Единствено поголема лева фронтална активација е регистрирана во F_7 – F_8 регионот. Нашите наоди се поддржани од многубројни други студии што користеле локализирани методи, како што се fMRI или LORETA за изворна локализација.

Клучни зборови: генерализирано анксиозно растројство, QEEG, фронтална асиметрија, спектрална моќност, логаритам на спектралната моќност