Quantitative electroencephalographic biomarker of pharmacological treatment response in anxiety disorder: A retrospective study

Jun Byeon
Daegu Catholic University School of Medicine
Jung Yeon Moon
Daegu Catholic University School of Medicine
Se Ryoung Je
Daegu Catholic University School of Medicine
Jun Won Kim (f_affection@naver.com)
Daegu Catholic University School of Medicine

Article

Keywords: Anxiety, Treatment, Response, Quantitative electroencephalography (QEEG)

Posted Date: March 29th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1431567/v1

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Scientific Reports on March 7th, 2023. See the published version at https://doi.org/10.1038/s41598-023-30994-1.

Abstract

Objectives: This study investigated the effectiveness of a quantitative electroencephalography(qEEG) biomarker in predicting the response to pharmacological treatment in patients with anxiety disorder.

Methods: A total of 86 patients were diagnosed with anxiety disorder by using the Diagnostic and Statistical Manual of Mental Disorders 5th edition and treated with antidepressants. After 8-12weeks, the participants were divided into treatment-resistant(TRS) and treatment-response(TRP) groups on the basis of the Clinical Global Impressions-Severity(CGI-S) score. We obtained the absolute-EEG measurements for 19-channels and analyzed qEEG findings according to the Hz range: delta, theta, alpha, and beta. The beta-wave was subdivided into low-beta, beta, and high-beta. The theta-beta ratio(TBR) was calculated, and an analysis of covariance was performed.

Results: Among the 86 patients with anxiety disorder, 65% were classified in the TRS group. The TRS and TRP groups did not differ regarding age, sex, and medication-dosage. However, the baseline CGI-S was higher in the TRP. After calibration by covariates, the TRP showed a higher beta-wave and high-beta-waves in T3 and T4. The TRP showed a lower TBR, especially in T3 and T4.

Conclusion: These results indicate that patients with a lower TBR and higher beta and high-beta waves in T3 and T4 are more likely to respond to medication.

Introduction

Anxiety disorders, which are the most common psychiatric diseases worldwide and incur high medical costs for patients, include panic disorder, generalized anxiety disorder, social anxiety disorder, specific anxiety disorder, and separation anxiety disorder[1]. Anxiety disorders are common worldwide, with a 21.3% one-year prevalence rate and a 33.7% lifetime prevalence; these disorders are often cormorbid with other psychiatric diseases, necessitating prolonged treatment periods[1]. The most common pharmacological agents used for treating anxiety disorders are selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs)[2]. However, approximately 50% of adults and 40% of children and adolescents are known to be unresponsive to pharmacological treatment[3]. The main reason for the poor treatment response is the difficulty in accurately diagnosing these disorders[4]. For this reason, several attempts have been made to evaluate the treatment response in anxiety disorders, especially through development of predictors of the treatment response[5].

To date, functional magnetic resonance imaging (fMRI)[6, 7], magnetic resonance spectroscopy (MRS)[8, 9], heart rate variability (HRV)[10], brain-derived neurotrophic factor (BDNF)[11], and 5-HT2A gene polymorphisms have been studied as predictors. Among these, quantitative electroencephalography (qEEG) data, which can serve as a biological marker of brain function by providing information about the electrophysiological activity of the brain, can be obtained without invasive approaches such as needle or radiation exposure and can be acquired faster than other diagnostic tools. Due to these advantages, qEEG studies on treatment response in depressive disorder are being actively conducted to the extent that

meta-analyses are now possible. However, EEG studies on the treatment response in anxiety disorders are relatively fewer.

Currently, the most prominent qEEG finding in anxiety disorders is an increase in beta waves in the temporal lobe[12]. Beta waves are the basic human arousal waveforms associated with attention and reflect significant levels of local metabolic activity, particularly in the cortex[13]. These waves can be roughly divided into low-beta waves (12–15 Hz), beta waves (15–25 Hz), and high-beta waves (25–30 Hz). However, high-beta waves are particularly associated with individual fear, anxiety, and hyperarousal[12, 14]. Moreover, a higher theta-beta ratio (TBR) is known to be associated with increased anxiety[15]. This pattern occurs mainly during thalamocortical dysrhythmia (TCD) and is mainly associated with attention problems and overreaction to fear[16].

In this study, we aimed to predict the response to pharmacological treatment for anxiety disorders by considering the characteristics of the various qEEG findings described above.

Results

Demographic characteristics

The study included 56 patients in the TRS and 30 patients in the TRP. The two groups showed no significant differences in age and sex and the history of prescription drugs. The two groups also showed no significant difference in STAI-S, STAI-T, and BDI scores, but the initial CGI-S score was significantly higher in the TRP ($p = 0.043$). Most subscales of the SCL-90-R showed no significant difference between the two groups, but the TRS showed a significantly higher score on the HOS scale ($p = 0.006$) (Table 1).

Table 1
Clinical characteristics in each group

Characteristics	Treatment resistant anxiety disorder (n = 56)	Treatment response anxiety disorder (n = 30)	t-value	P-value
Sex, n(%)				0.983
Male	26(46.4%)	14(46.6%)		
Female	30(53.6%)	16(53.4%)		
Age	50.39 ± 19.23	48.80 ± 15.43	0.391	0.697
CGI-S	4.73 ± 0.73	5.10 ± 0.90	-2.057	**0.043***
AD equivalent	20.32 ± 9.23	23.48 ± 10.3	-1.452	0.150
BZD equivalent	7.05 ± 3.88	8.1 ± 5.98	-1.045	0.299
STAI-S	56.39 ± 11.88	54.18 ± 11.33	0.749	0.456
STAI-T	56.11 ± 12.08	54 ± 12.52	0.686	0.495
BDI	26.64 ± 11.90	23.86 ± 10.11	0.966	0.337
SCL-90-R				
SOM	55.143 ± 11.444	56.682 ± 11.193	-0.538	0.592
O-C	59.054 ± 10.346	56.864 ± 8.38	0.884	0.379
I-S	58.482 ± 11.014	53 ± 10.668	1.995	0.050
DEP	61.964 ± 10.502	58.591 ± 8.573	1.340	0.184
ANX	60.161 ± 10.908	61.682 ± 9.692	-0.571	0.570
HOS	57.518 ± 11.233	49.773 ± 9.981	2.824	**0.006***
PHOB	58.732 ± 10.335	57.364 ± 12.67	0.493	0.623
PAR	55.964 ± 11.654	50.864 ± 11.671	1.739	0.086
PSY	55.875 ± 9.029	53.545 ± 8.14	1.053	0.296
GSI	59.321 ± 9.416	57.272 ± 7.881	0.903	0.369

* $p < 0.05$. CGI-S: Clinical Global Impression – Severity, AD: Antidepressant, BZD: Benzodiazepine, STAI-S: State-Trait Anxiety Inventory – State, STAI-T: State-Trait Anxiety Inventory – Trait, BDI: Beck Depression Inventory, SCL-90-R: Symptom Checklist-90-Revised, SOM: Somatization, O-C: Obsessive-Compulsive, I-S: Interpersonal Sensitivity, DEP: Depression, ANX: Anxiety, HOS: Hostility, PHOB: Phobic Anxiety, PAR: Paranoid Ideation, PSY: Psychoticism, GSI: General Symptom Index

Comparison Of Qeeg Findings

After controlling for covariates, ANCOVA was used to compare the absolute power average values for the total electrode sites between the two groups and for each frequency band. Although no significant differences were observed in the delta, theta, and alpha waves, the T3 ($p = 0.030$), T4 ($p = 0.003$), and T5 ($p = 0.008$) regions of the beta wave showed significant intergroup differences (Table 2). When ANCOVA was performed by subdividing the beta region into low-beta wave, beta wave, and high-beta wave, no significant intergroup differences were observed in low-beta wave and beta wave, but the T3 ($p = 0.043$) and T4 ($p = 0.019$) regions of the high-beta waves showed significant differences (Table 2). When the p-values of beta and high-beta waves were shown in a topographical map, the findings for both temporal lobes were confirmed to be significant (Fig. 1).

Table 2
ANCOVA result of resting electroencephalogram in each group in beta wave

EEG channel	Treatment resistant anxiety disorder (n = 56) (uV^2)	Treatment response anxiety disorder (n = 30) (uV^2)	t-value	P-value
Beta wave				
FP1	7.031 ± 4.204	8.314 ± 4.583	2.150	0.147
FP2	7.318 ± 3.98	8.391 ± 4.807	1.756	0.189
F7	5.728 ± 3.245	6.741 ± 3.852	2.203	0.142
F3	11.41 ± 8.806	12.255 ± 8.452	0.346	0.558
Fz	11.023 ± 8.002	12.1 ± 8.302	0.657	0.420
F4	12.078 ± 9.153	12.952 ± 9.421	0.382	0.538
F8	6.487 ± 3.369	7.304 ± 4.614	1.452	0.232
T3	**6.123 ± 3.268**	**7.784 ± 5.083**	**4.878**	**0.030***
C3	12.212 ± 9.163	13.992 ± 10.879	0.990	0.323
Cz	14.69 ± 13.29	15.917 ± 11.034	0.342	0.561
C4	12.575 ± 8.97	14.472 ± 11.924	1.072	0.304
T4	**5.551 ± 2.771**	**8.052 ± 5.404**	**9.412**	**0.003***
T5	**7.001 ± 3.912**	**10.438 ± 8.637**	**7.539**	**0.008***
P3	12.663 ± 9.455	15.769 ± 12.271	2.102	0.152
Pz	13.221 ± 9.726	16.405 ± 12.817	1.984	0.163
P4	12.631 ± 8.642	15.421 ± 13.431	1.697	0.197
T6	7.288 ± 4.403	9.429 ± 7.999	2.883	0.094
O1	11.211 ± 8.173	14.208 ± 10.371	2.182	0.144
O2	11.701 ± 7.824	15.192 ± 15.404	1.993	0.162
High beta wave				
FP1	17.440 ± 6.028	17.882 ± 7.558	0.138	0.712
FP2	17.540 ± 5.871	17.959 ± 7.406	0.104	0.748
F7	17.261 ± 6.102	18.129 ± 7.262	0.422	0.518

* $p < 0.05$. EEG: Electroencephalogram

EEG channel	Treatment resistant anxiety disorder (n = 56) (uV^2)	Treatment response anxiety disorder (n = 30) (uV^2)	t-value	P-value
F3	20.900 ± 8.076	22.143 ± 8.801	0.527	0.470
Fz	19.382 ± 7.591	20.58 ± 8.984	0.516	0.475
F4	20.762 ± 7.877	22.135 ± 9.354	0.665	0.418
F8	18.446 ± 5.955	18.975 ± 7.487	0.214	0.645
T3	**22.992 ± 6.720**	**26.338 ± 8.513**	**4.238**	**0.043***
C3	22.969 ± 9.015	25.629 ± 10.026	1.713	0.195
Cz	20.722 ± 8.387	22.445 ± 9.628	0.867	0.355
C4	23.466 ± 9.067	25.522 ± 10.667	1.030	0.314
T4	**22.230 ± 7.043**	**26.734 ± 9.490**	**5.765**	**0.019***
T5	21.986 ± 7.326	24.677 ± 9.718	1.901	0.172
P3	23.371 ± 8.828	26.543 ± 9.888	2.225	0.140
Pz	21.170 ± 7.981	24.639 ± 9.014	3.139	0.081
P4	22.928 ± 8.641	25.874 ± 9.500	1.874	0.175
T6	20.894 ± 7.782	22.942 ± 8.959	0.999	0.321
O1	21.084 ± 7.794	22.803 ± 8.659	0.748	0.390
O2	21.099 ± 8.577	22.053 ± 8.387	0.274	0.603

* $p < 0.05$. EEG: Electroencephalogram

Comparison Of Tbr

The TBR is obtained by dividing theta wave by beta wave and serves as an index that can indicate TCD. As mentioned earlier, it is known to be associated with attention problems and phobic reactions[17]. When comparing the differences in TBR at each site between the two groups, the values in TRS were generally higher than those in TRP, and this change was particularly noticeable in the T3 ($p = 0.036$) and C3 ($p = 0.033$) areas, After the covariates were corrected using ANCOVA, significant differences were observed in the T3 ($p = 0.037$) and T4 ($p = 0.044$) regions (Fig. 2).

Discussion

In this study, patients diagnosed with anxiety disorder using DSM-5 and prescribed medications were classified into TRS and TRP on the basis of drug response after 8 to 12 weeks of treatment. qEEG characteristics were investigated. The findings confirmed that qEEG has value as a marker in identifying responders to antidepressant therapy among patients with anxiety disorders.

First, the results showed no difference in the demographic characteristics of the subjects by age and sex. In addition, the two groups showed no significant difference in STAI, BDI, and SCL-90-R scores, other than the score for the HOS subscale, indicasting that subjective symptoms such as depression and anxiety were not significantly different between the two groups. However, the CGI-S score showed a rather significant difference with no significant difference in the medications used, indicating that the clinician judged that the disease was more serious at the first interview in the TRP.

We recorded the patient's EEG in the eye-closed resting state for 5 min and acquired absolute power through power spectrum analysis. In the TRP, overall higher beta waves and high beta waves appeared at T3 and T4 than in the TRS. Notably, when the scores for covariates such as sex, age, STAI-S, STAI-T, and BDI scores were corrected using ANCOVA rather than t-test, the difference in T3 and T4 was more consistent than before.

To the best of our knowledge, no previous studies have evaluated the treatment response in anxiety disorders by using qEEG, although one case report reported a reduction in overall beta waves as treatment progressed in anxiety disorders[18]. Despite the limited number of studies on treatment response, many studies have explored the qEEG characteristics of anxiety disorders. In particular, increases in beta and high-beta waves in both temporal lobes are well known, which have also been associated with fear, panic, insecurity, and phobia[12, 14]. Especially, beta waves in T3 and T4 are known to be associated with excessive activity of amygdalae[19]. Amygdalae act like fear sensors and signal the hypothalamus to secrete CRH and produce ACTH[17]. In addition, beta waves reflect a significant level of local metabolic activity in the cortex, and TBR elevation in anxiety disorders is also well known[13, 15]. Elevated TBR suggests a disturbance in the thalamus-cortex interaction and shows a negative correlation with attentional control and trait anxiety[16].

Two possibilities can be considered to explain the results. First, there may have been differences in the severity of anxiety symptoms between the two groups. STAI-S and STAI-T were performed before the start of treatment and showed no significant differences, but the CGI-S evaluated by the clinician showed a difference between groups. In fact, existing studies have repeatedly reported that the more severe the symptoms of anxiety disorder, the higher the probability of responding to treatment[20]. Second, the TRS may have included patients with comorbid diseases other than anxiety disorder. In fact, anxiety is a common symptom that accompanies depressive disorder and is often comorbid with depression[21]. However, we considered that the two groups showed biological differences since there was no significant difference in the BDI scores between the two groups and the difference in T3 and T4 remained even after adjusting for BDI, STAI-S, and STAI-T scores. Anxiety disorder is a heterogeneous disease that includes several diseases, and its pathophysiology has not yet been clearly elucidated, but it is known that the

above-mentioned abnormalities in the amygdalae circuit and the abnormalities in the HPA axis are the main causes[22]. In this study, the TRP showed high beta waves in T3 and T4 compared to the TRS, which is considered to be closer to the type of anxiety disorder characterized by excessive activity of amygdalae[19]. On the other hand, the TRS can be expected to be close to abnormalities of Raphe nuclei or hippocampus, other factors that can affect the HPA axis other than amygdalae[23]. In addition to HPA axis abnormalities, oxidative stress in the central nerve system(CNS) has also been shown to cause anxiety disorder. Therefore, this group of patients may also need antioxidants in addition to the usual antidepressant treatment[24].

The limitations of this study are as follows. The primary limitation was that the study was conducted by reviewing medical records retrospectively. Therefore, additional tests could not be performed. Future follow-up studies should include other prospective assessments, including an initial evaluation and EEG after 8 to 12 weeks. Second, only CGI-S was used to determine the therapeutic effect. As a result, assessment of the treatment response was based only on the clinician's judgment. Subjective evaluation of patients would have been possible if an STAI assessment, which was performed at the beginning of treatment, was also performed after treatment. Lastly, this study evaluated treatment response by recruiting a patient group from a broad category of anxiety disorders. Therefore, future studies should explore the quantitative EEG characteristics for treatment response according to each disease group.

Conclusion

In clinical practice, qEEG is being used as an auxiliary tool in the treatment of anxiety disorders, and is gradually proving its usefulness. In addition to diagnosing anxiety disorders, predicting their reactivity prior to treatment is also important, and qEEG has shown promise in this regard. Patients with anxiety disorders who show elevated T3 and T4 and decreased TBR in beta waves are more likely to respond to drug treatment using antidepressants and benzodiazepines. For patients with anxiety disorders who do not show such characteristics, combination with agents such as antioxidants or other non-pharmaceutical treatment modalities may be preferable.

Methods

Participants

A retrospective study based on medical records was conducted by selecting patients who underwent outpatient treatment for anxiety disorders at the Department of Psychiatry at Daegu Catholic University Hospital from March 01, 2016 to December 31, 2020. Before starting treatment, the patients underwent a qEEG examination, and they subsequently received drug treatment for more than 8 weeks. Patients who had been previously diagnosed with neurological conditions such as convulsive disorders, had undergone intracranial surgery or insertion of magnetic material into the head or eyeball, had not received antidepressants for the first treatment, or showed poor-quality EEG findings were excluded from the study. In accordance with a previous report, patients with a CGI-S score of 4 or higher after 8 weeks of sufficient

antidepressant treatment were stratified in the treatment resistance group (TRS), and those with a CGI-S score of 3 or less were classified in the treatment response group (TRP)[25].

Informed consent

This study was approved by the Institutional Review Board (IRB) of the Daegu Catholic University Medical Center (DCUMC IRB approval No. CR-21-121) and was performed in accordance with the Declaration of Helsinki (World Medical Association: Ethical Principles for Medical Research Involving Human Subjects, 1964). The ethics committee approved of the waiver for the informed consent because this was a retrospective study.

Detailed Methods

A total of 86 patients who had undergone diagnoses of the category of anxiety disorders, including generalized anxiety disorder, social anxiety disorder, and panic disorder, by a psychiatrist using the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) during the study period were included. The patient's medical records were checked to determine their sex, age, type and dose of prescription drugs, and status from the start of treatment to 8 or 12 weeks. Assessments based on the State-Trait Anxiety Inventory (STAI), Beck Depression Inventory (BDI), and Symptom Checklist-90-Revised (SCL-90-R) were performed, and the CGI-S scale was used for disease severity assessment by clinicians. To analyze the dose of the prescribed drug, it was converted into an equivalent dose. For antidepressants, fluoxetine was used as the standard, and for benzodiazepines, diazepam was used as the standard[26, 27]. Finally, the results of qEEG examinations performed before starting drug treatment were analyzed.

Measures

(1) State-Trait Anxiety Inventory

STAI is a self-reporting tool that has been proven to be useful for measuring anxiety in general populations and clinical samples. It consists of two subscales: the "State," which evaluates the current state, and the "Trait," which evaluates the general state. Each subscale includes 20 items that are evaluated on a 4-point Likert scale of 1-4 points, and a score of 40 or higher is considered to be clinically significant. The internal consistency coefficient of the subscales was 0.86 to 0.95; the test repeatability coefficient was 0.65 to 0.75 for 2 months; and the composition and validity of the test are widely known[28].

(2) Beck Depression Inventory

The BDI is a self-reported test developed by Beck et al., and is the most commonly used tool to measure depressive symptoms[29]. It consists of a total of 21 items that are rated on a 4-point Likert scale with 0-3 points. This scale was used to evaluate depressive symptoms that may be associated with anxiety.

(3) Symptom Checklist-90-Revised

The SCL-90-R is a self-reported test and is commonly used to measure overall psychiatric symptoms. The test evaluates somatization (SOM; 12 items), obsessive-compulsive characteristics (OC; 10 items), interpersonal sensitivity (IS; 9 items), depression (DEP; 13 items), anxiety (ANX; 10 items), hostility (HOS; 6 items), phobic anxiety (PHOB; 7 items), paranoid ideation, (PAR; 6 items), and psychoticism (PSY; 10 items) using symptom-level detailed scales, and each item is scored on a 4-point Likert scale consisting of 0-3 points. This scale was used to evaluate the patient's other psychiatric symptoms[30].

(4) Clinical Global Impression-Severity

As one of the most commonly used evaluation tools in the field of psychiatry, the CGI-S can be used to directly evaluate patients to measure the severity of symptoms, cure rates, and treatment effectiveness. It consists of a score from 1 to 7, and the severity of the patient's symptoms was evaluated according to standardized scoring guidelines[31].

(5) EEG recording and pre-processing

For EEG measurement, 19 channels of the international 10-20 system (Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, O2) were used, and a 64-channel Comet digital EEG unit (Grass, Natus neurology, USA) was used for measurements with a recording frequency of 800 Hz with reference to the ear electrode. EEG measurements were obtained for 5 minutes with eyes open while lying on a comfortable bed, and then for 5 minutes with the eyes closed immediately afterwards. The patient was instructed to keep an eye on the “+” sign in the front when the eyes were open, to refrain from movement as much as possible, to remain in a state of not thinking about anything as much as possible, and to not fall asleep when the eyes were closed. EEG analysis was performed using the fast Fourier transforms (FFT) algorithm for each frequency band for each selected epoch: delta wave (1-4 Hz), theta wave (4-8 Hz), alpha wave (8-12 Hz), and beta wave (12-30 Hz). Beta waves were subdivided into low-beta (12-15 Hz), beta (15-25 Hz), and high-beta (25-30 Hz). MATLAB 7.0.1 (MathWorks, Massachusetts, U.S.A) and EEGLAB toolbox were used for analysis. To calculate the TBR, the theta wave was divided by the beta wave and used for analysis. For analysis, downsampling of EEG data to 250 Hz, detrending, and mean-subtracting were performed to remove the DC component. Then, less than 1 Hz and 60 Hz affected by electrical noise were removed through the filter, and the noise caused by blinking and muscle movement was then removed through independent component analysis (ICA). Finally, an experienced clinician performed a power spectrum analysis on EEG data for at least 2 minutes without noise.

(6) Statistical analysis

The Student t-test was used to compare continuous sociodemographic variables between the two groups (TRS and TRP), and the chi-square test was used for comparison of categorical variables. For each frequency and TBR at each site between the two groups, the total score of sex, age, and BDI, STAI-S, and STAI-T scores was set as a covariate, and then the difference between groups was analyzed using analysis of covariance (ANCOVA). Equality of variance was tested using Levene's test. The p-value was

set as 0.05 and all analyses were performed using SPSS Version 25.0 for Windows (IBM Corp., Armonk, NY).

Declarations

Data availability

- The datasets used and analysed during the current study available from the corresponding author on reasonable request.

References

1. Bandelow, B. & Michaelis, S. Epidemiology of anxiety disorders in the 21st century. *Dialogues in clinical neuroscience***17**, 327 (2015).
2. Wehry, A. M., Beesdo-Baum, K., Hennelly, M. M., Connolly, S. D. & Strawn, J. R. Assessment and treatment of anxiety disorders in children and adolescents. *Current psychiatry reports***17**, 52 (2015).
3. Strawn, J. R. & Levine, A. Treatment Response Biomarkers in Anxiety Disorders: From Neuroimaging to Neuronally-Derived Extracellular Vesicles and Beyond. *Biomarkers in neuropsychiatry*, 100024 (2020).
4. Bystritsky, A. Treatment-resistant anxiety disorders. *Molecular psychiatry***11**, 805-814 (2006).
5. Nasrallah, H. A. *Biomarkers in neuropsychiatric disorders: Translating research to clinical applications*. (Elsevier, 2019).
6. Frick, A.*et al.* Anterior cingulate cortex activity as a candidate biomarker for treatment selection in social anxiety disorder. *BJPsych open***4**, 157-159 (2018).
7. Kujawa, A.*et al.* Prefrontal reactivity to social signals of threat as a predictor of treatment response in anxious youth. *Neuropsychopharmacology***41**, 1983-1990 (2016).
8. Brennan, B. P.*et al.* Acute change in anterior cingulate cortex GABA, but not glutamine/glutamate, mediates antidepressant response to citalopram. *Psychiatry Research: Neuroimaging***269**, 9-16 (2017).
9. Howells, F. M.*et al.* 1H-magnetic resonance spectroscopy in social anxiety disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry***58**, 97-104 (2015).
10. Kircanski, K., Williams, L. M. & Gotlib, I. H. Heart rate variability as a biomarker of anxious depression response to antidepressant medication. *Depression and anxiety***36**, 63-71 (2019).
11. Shen, Z.*et al.* The roles of brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) in predicting treatment remission in a Chinese Han population with generalized anxiety disorder. *Psychiatry research***271**, 319-324 (2019).
12. Ribas, V. R.*et al.* Pattern of anxiety, insecurity, fear, panic and/or phobia observed by quantitative electroencephalography (QEEG). *Dementia & neuropsychologia***12**, 264-271 (2018).

13. Cook, I. A., O'Hara, R., Uijtdehaage, S. H., Mandelkern, M. & Leuchter, A. F. Assessing the accuracy of topographic EEG mapping for determining local brain function. *Electroencephalography and clinical neurophysiology***107**, 408-414 (1998).
14. Price, J. & Budzynski, T. Anxiety, EEG patterns, and Neurofeedback, Introduction to QEEG and Neurofeedback . ISBN.(2009).
15. van Son, D.*et al.* Acute effects of caffeine on threat-selective attention: moderation by anxiety and EEG theta/beta ratio. *Biological psychology***136**, 100-110 (2018).
16. van Son, D., Angelidis, A., Hagenaars, M. A., van der Does, W. & Putman, P. Early and late dot-probe attentional bias to mild and high threat pictures: Relations with EEG theta/beta ratio, self-reported trait attentional control, and trait anxiety. *Psychophysiology***55**, e13274 (2018).
17. Porzionato, A., Macchi, V., Rucinski, M., Malendowicz, L. K. & De Caro, R. Natriuretic peptides in the regulation of the hypothalamic–pituitary–adrenal axis. *International review of cell and molecular biology***280**, 1-39 (2010).
18. Tas, C., Erensoy, H., İbadi, Y., Brown, E. & Tarhan, N. QEEG related changes following the treatment of anxiety disorders: case series. (2014).
19. Othmer, E., Othmer, J. P. & Othmer, S. C. Brain functions and psychiatric disorders: A clinical view. *Psychiatric Clinics***21**, 517-566 (1998).
20. Bunford, N.*et al.* Neural reactivity to angry faces predicts treatment response in pediatric anxiety. *Journal of abnormal child psychology***45**, 385-395 (2017).
21. Tiller, J. W. Depression and anxiety. *The Medical Journal of Australia***199**, S28-S31 (2013).
22. Craske, M. G.*et al.* What is an anxiety disorder? *Focus***9**, 369-388 (2011).
23. Tafet, G. E. & Nemeroff, C. B. Pharmacological Treatment of Anxiety Disorders: The Role of the HPA Axis. *Frontiers in psychiatry***11**, 443 (2020).
24. Fedoce, A. d. G.*et al.* The role of oxidative stress in anxiety disorder: cause or consequence? *Free radical research***52**, 737-750 (2018).
25. Kinrys, G., Vasconcelos e Sa, D. & Nery, F. Adjunctive zonisamide for treatment refractory anxiety. *International journal of clinical practice***61**, 1050-1053 (2007).
26. Hayasaka, Y.*et al.* Dose equivalents of antidepressants: evidence-based recommendations from randomized controlled trials. *Journal of affective disorders***180**, 179-184 (2015).
27. Strang, J. & Group, I. E. W. Drug misuse and dependence: UK guidelines on clinical management. (2017).
28. Spielberger, C. D. Manual for the State-Trait Anxiety Inventory STAI (form Y)(" self-evaluation questionnaire").(1983).
29. Beck, A. T., Ward, C. H., Mendelson, M., Mock, J. & Erbaugh, J. An inventory for measuring depression. *Archives of general psychiatry***4**, 561-571 (1961).
30. Kim, J.-W. & Kim, K.-i. The Standardization Study of Symptom Checklist-90-Revision in Korea . *Mental Health Research***2**, 278-311 (1984).

31. Busner, J. & Targum, S. D. The clinical global impressions scale: applying a research tool in clinical practice. *Psychiatry (Edgmont)***4**, 28 (2007).

Figures

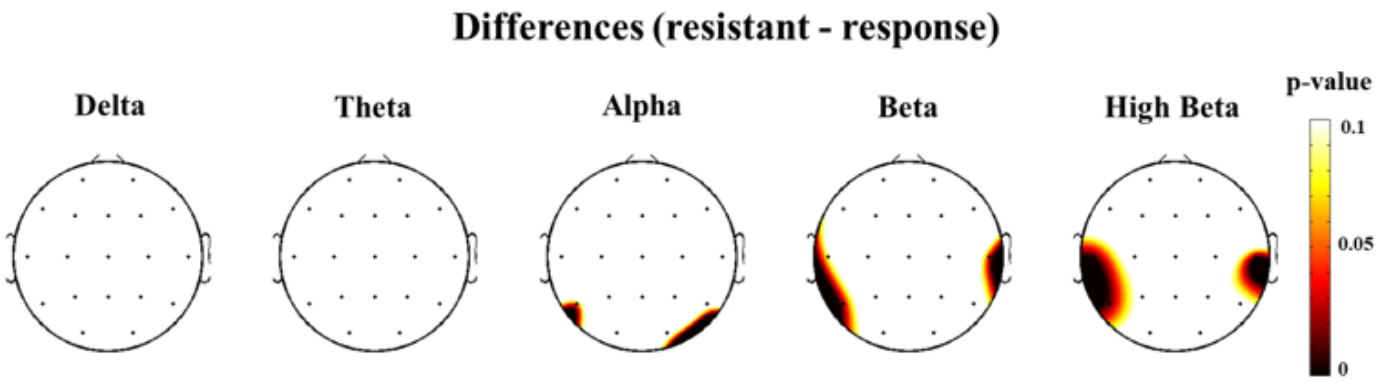

Figure 1

Topographic maps between channel in each frequency

The topographic maps represent the probability of analysis of covariance (ANCOVA) between two groups. A colored area means an increase of difference in absolute powers. In beta wave and high-beta wave, significant differences showed in T3 and T4

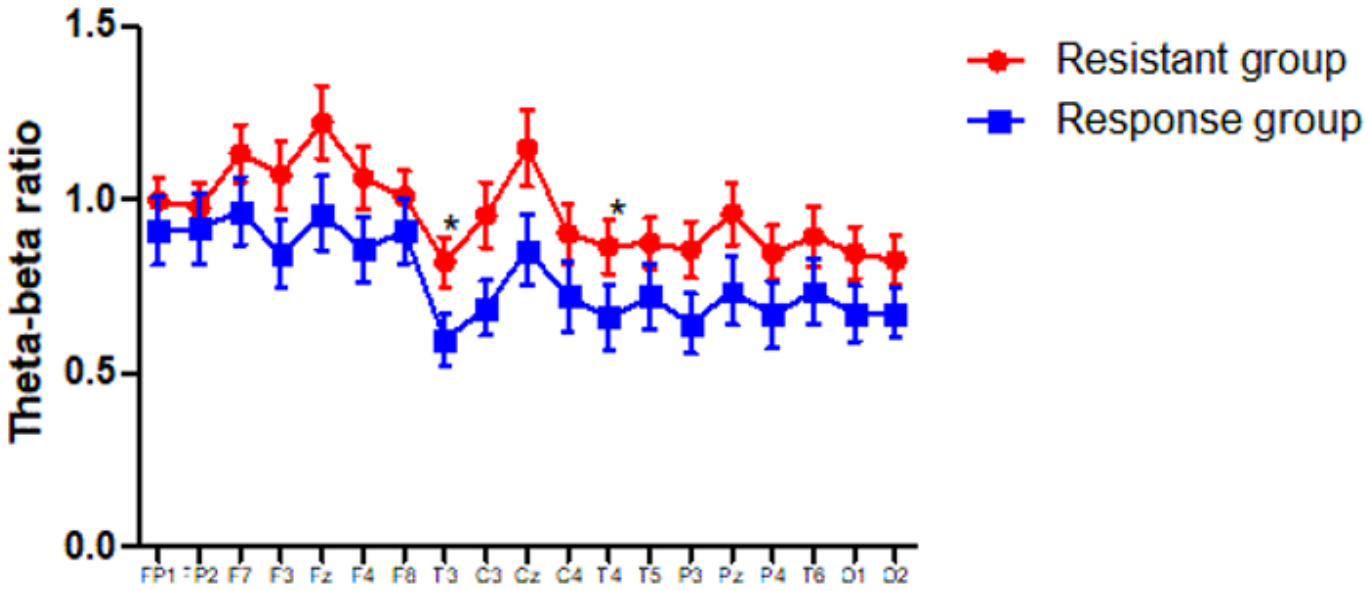

Figure 2

Theta-beta ratio between channel in each group

Figure 2 shows the difference in Theta-Beta ratio (TBR) between two groups for each channel. Each graph move in a similar pattern for each channel. Even after age, gender, STAI score, and BDI score were corrected by ANCOVA, significant differences showed in T3 and T4.

* $p<0.05$. STAI-S: State-Trait Anxiety Inventory, BDI: Beck Depression Inventory, ANCOVA: analysis of covariance