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QEEG RELATED CHANGES FOLLOWING THE TREATMENT OF ANXIETY DISORDERS: CASE SERIES
ANKSİYETE BOZUKLULUKLARINDA TEDAVİSİ SONRASINDA QEEG DEĞİŞİKLİKLERİ: OLGU SERİSİ

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Abstract

Patients with anxiety spectrum disorders are a highly heterogeneous group, requiring new therapeutic strategies and individualized treatment monitoring. Today, there is a growing interest for implementing biological approaches to clinical practice in psychiatry. Quantitative EEG is an excellent tool in this regard, though it has been widely underestimated when compared to recent neuroimaging techniques. In this case series, we presented four cases with a different diagnosis of anxiety spectrum disorder and evaluated their qEEG changes before and after the treatment. In addition, we also calculated the so-called EEG cordance values as an index of cerebral perfusion and cingulate cortex activity. According to the results, there appears to be an increase in the frontal beta and theta band in our cases, which has responded to treatment. In regards to the cordance values, we found that there was a reduction in the prefrontal regions up to %38 percent following the treatment. Based on previous studies, this may also indirectly suggest reduction in the cingulate cortex activity. The possible implications of these findings were discussed. Taken together, this case series highlighted the potential use of qEEG power values, normative z-scores and cordance values in treatment response monitoring of anxiety spectrum disorders.

Keywords: Anxiety disorders, qEEG, cordance, treatment monitoring

Özet

Anksiyete bozuklukları yeni tedavi ve bireye özel izlem stratejilerinin geliştirilmesi gereken heterojen bir hastalık grubudur. Günümüzde biyolojik yaklaşımların psikiyatri klinik pratiğine aktarılmasına her geçen gün artan bir ilgi olmaktadır. Bu bağlamda kantitatif EEG, diğer nörogörüntüleme yöntemlerine göre değeri görece olarak göz ardı edilse de oldukça etkin bir araçtır. Bu olgu serisinde, farklı anksiyete spektrum bozukluklarına sahip dört olgunun tedavi öncesi ve sonrası qEEG ölçümlemelerisunulmuştur. Buna ek olarak, "EEG kordans" değeri olarak tanımlanan, beyindeki yerel kan akımının ve singulat korteks aktivitesinin göstergesi olarak kabul edilen değerlerin, teta frekans bandındaki sayısal değerleri hesaplanmıştır. Sonuçlara göre, tedavi öncesinde vakalarda frontal bölgede teta ve beta bandında izlenen artış tedavi sonrası normale dönmüştür. Ayrıca, prefrontal bölgedeki teta kordans değerlerinin tedavi sonucunda %38 oranında azaldığı saptanmıştır. Önceki yapılmış çalışmalar ışığında bu azalma singulat korteks aktivitesindeki tedavi sonrası azalma ile ilişkili olabilir. Bulguların olası sonuçları makalede tartışılmıştır. Bütün olarak ele alındığında, bu olgu serisi qEEG güç, z-skoru ve kordans değerlerinin anksiyete bozukluklarında kullanılmasının potansiyel faydalarının altını çizmektedir.

Anahtar Kelimeler: Anksiyete bozuklukları, qEEG, tedavi izlem, kordans değeri

1. Introduction

When the perception of fear becomes disproportioned than the actual source of worry and higher levels of arousal due to fear hinders normal social functioning, then the criteria for an anxiety spectrum disorder is met (APA,2000). Within this definition, it is plausible to expect the range of people diagnosed with anxiety spectrum disorders to be highly heterogeneous. However, systematic evaluation of treatment response for anxiety disorders has relied only on a handful of subjective self-report measures. Nowadays, researchers have devoted substantial efforts in an attempt to use biological measures to monitor treatment response, though many of these efforts are still experimental and have not yet reached clinical practice. With this in mind, quantitative electroencephalogram (qEEG) has become a popular tool to explore potential biomarkers of pathological anxiety by classifying electrical activity of the brain in different frequency bands (Kropotov et al.,2009).

With regards to qEEG research, a number of studies have concluded that anxiety disorders are accompanied by increased signs of hyperactivation of the frontal cortex. For instance, patients with obsessive compulsive disorder (OCD) have shown an increase in the theta band at frontotemporal regions (Karadag et al., 2003). Bucci et al., (2004) found a relative decrease in alpha band activity in a group of patients with OCD, when compared to healthy participants, which was then

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normalized following treatment. In addition, decreased alpha activity was accompanied by an increase in the power of the beta band activity, which has also been shown to be in close relationship with the characteristics of anxiety disorders in other studies. For instance, Tot et al., (2002) found that OCD patients with increased alpha and decreased beta activity during hyperventilation had superior treatment response than those with the converse pattern. Furthermore, many studies have highlighted differences in frontal alpha band asymmetry in depression and anxiety spectrum disorders (Kropotov et al.,2009). Notably, frontal asymmetries shifted from greater right to greater left alpha band activity following treatment in patients with social anxiety disorder (Moscovitch et al., 2011).

Nevertheless, the locations of the source of these differences in electrical activity cannot be reliably identified with conventional qEEG techniques. Therefore researchers have turned their focus to alternative techniques using EEG source density methods, such as low resolution brain electromagnetic tomography (LORETA), to localize the source of the activity. A thought-provoking LORETA study demonstrated that increased beta band activity in patients with anxiety disorders was associated with posterior cingulate cortex activity, and has potential to predict treatment response in depression and anxiety disorders (Sherlin and Congedo, 2005). In addition, Leuchter and his colleagues developed a qEEG method (EEG cordance) by using a formula that gives us an index of the absolute and relative EEG power of each band separately. They also used a different electrode montage to make power values more informative for specific brain regions (Leuchter et al., 1999). A few studies have demonstrated that increased frontal theta cordance is due to an overactive anterior cingulate cortex activity (Pizzagalli et al., 2003; Korb et al., 2009). In addition, an intriguing pharmacological clinical trial found that "ketamine", a pharmacological agent which is thought to reduce the metabolism in the anterior cingulate cortex (Salvadore et al., 2009), reduced the severity of depressive symptoms. Interestingly, the same study also found decreased levels of theta cordance in the prefrontal region following ketamine administration (Horacek et al., 2010). Although it is important to note that we are not aware of any studies evaluating EEG cordance values in anxiety spectrum disorders. However, focusing on individual changes in the qEEG could be informative for the development of individualized, biological treatment response criteria of these patients.

Given all, the aim of this case series is to illustrate the potential use of qEEG and cordance changes in a small group of patients with anxiety spectrum disorders as an index of treatment response. Here, we present four different cases with different types and severities of anxiety disorder. We recorded resting state qEEGs and calculated the theta cordance values before and six months after treatment with antidepressant medication. All patients provided written informed consent and all procedures met institutional ethical review.

2. EEG recordings and Cordance calculations

All subjects were instructed to rest with eyes-closed in a quiet room with subdued lighting. Three minutes of eyes-closed resting state EEG was acquired using a Scan LT EEG amplifier and electrode cap (Compumedics/Neuroscan, USA), with the sampling rate of 250 Hz. Nineteen sintered Ag/AgCl electrodes were positioned in the cap according to the 10/20 International System with binaural references. The raw EEG signal was filtered through a band-pass filter (0.15-30 Hz) before artifact elimination. Artifact-free EEG data epochs (minimum 2 minutes) were manually selected based on visual inspection. Cordance calculations and age referenced z-score deviations based on a commercially available normative qEEG database (NeuroGuide Deluxe 2.5.1 ; Applied Neuroscience; St. Petersburg, FL). A Fast-Fourier-Transform was used to calculate absolute and relative power in each of two non-overlapping frequency bands: delta (1-4 Hz) and theta (4-8 Hz) by using NeuroGuide Deluxe 2.5.1 software (Applied Neuroscience; St. Petersburg, FL). The comparisons were made based on the absolute and relative powers of each electrode referenced to the left ear. All spectral analyses were completed by using Neurostats software (Applied Neuroscience; St. Petersburg, FL).

The cordance values were calculated in several steps. First, we used a bipolar montage which is based on the calculation of electrical differences of the electrodes which are topographically close to each other. Second, we reattributed the power from bipolar pairs of electrodes to individual electrodes. Third, we normalized the absolute and relative power across brain areas by calculating their z values. Forth, we summed the z score of the absolute power and the relative power of each electrode. The value could be either a positive or a negative value which was attributed as cordant and discordant respectively.

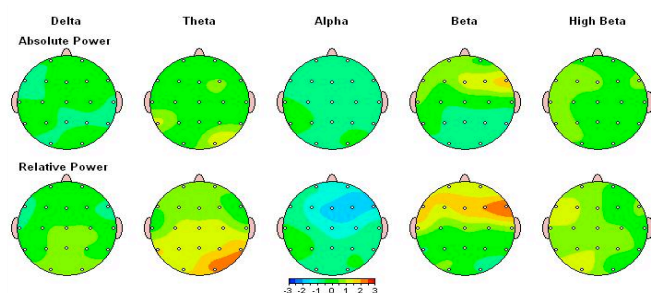## 3. Case series

3.1. Case one

Figure 1: Z-scored topographical brain mapping of Case-1 before the treatment
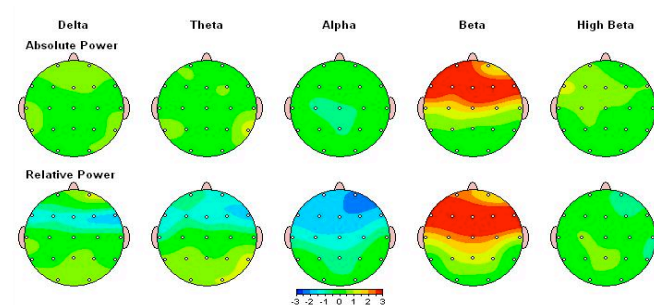
Case R.S was 21 years old, male and a university student. He admitted to the Istanbul Neuropsychiatry Hospital in May 2012 with fear of death, obsessions with religion, perceived anxiety, palpitation and sleep problems. Following the psychiatric interview, he was diagnosed with obsessive compulsive disorder according to the DSM-IV-TR. Prior to treatment, he had a Beck Anxiety Scale total score of 33, and a Yale-Brown Scale total score of 35. Six months after the selective serotonin reuptake inhibitor treatment augmented with aripiprazole (effective dose titrated by plasma drug monitorization), his Beck Anxiety and Yale-Brown Scale total scores

dropped down to 7 and 20, respectively. The topographical analyses based on the z-score deviations before and after the training are illustrated in figure 1 and 2. Accordingly, in comparison with the normative database of z-scores, there was an increased left dominant beta band activity, that was changed to normal level for his age following the treatment. Notably, we also observed relatively decreased alpha band activity in frontal regions before the treatment.

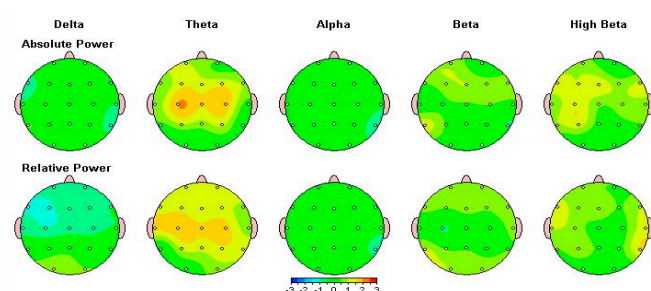**Figure 2:** Z-scored topographical brain mapping of Case-1 after the treatment.

3.2. Case two

Figure 3: Z-scored topographical brain mapping of Case-2 before the treatment.
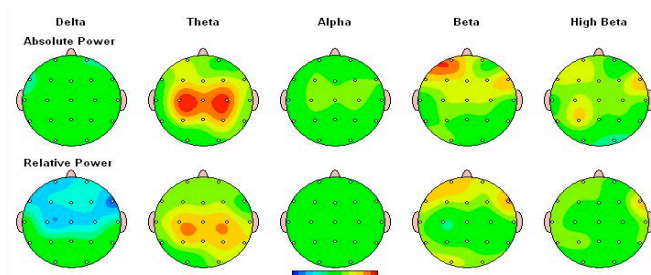
Case S.C. was 22 years old and a female university student. She admitted to the Istanbul Neuropsychiatry Hospital in May 2013 with fear of death, overthinking, hypochondriac thoughts and behaviors, sleep problems, perceived anxiety and palpitations. Following the psychiatric interview, she was diagnosed with anxiety disorder not otherwise specified according to the DSM-IV-TR. Prior to treatment, she had a Beck Anxiety Scale total score of 36. Six months after the selective serotonin reuptake inhibitor treatment (effective dose titrated by plasma drug monitorization) her Beck Anxiety Scale total scores dropped down to 12.
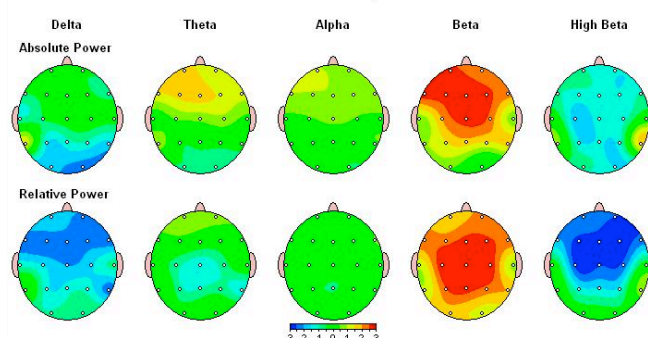
Figure 4: Z-scored topographical brain mapping of Case-2 after the treatment.

The topographical analyses based on the z-score deviations before and after the treatment are illustrated in figure 3 and 4. According to the qEEG, an increased fronto-central theta activity was resolved following the treatment. In addition, we observed increased left fronto-central beta power, which was was changed to normal level for his age following the treatment.
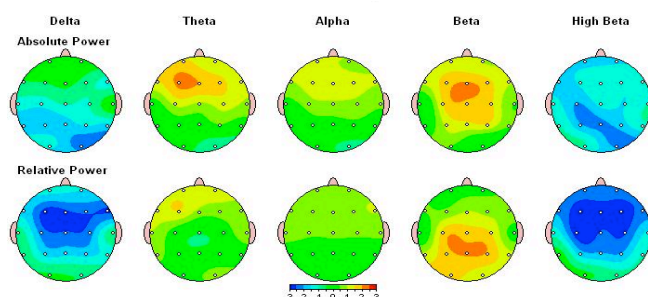
3.3. Case three

Figure 5: Z-scored topographical brain mapping of Case-3 after the treatment.

Case Z.S was 43 years old, female and a factory worker. She admitted to the Istanbul Neuropsychiatry Hospital in October 2012 with palpitation, sweating, hypochondria and depressive mood. Following the psychiatric interview, she was diagnosed with anxiety disorder not otherwise specified according to the DSM-IV-TR. Prior to treatment, she had a Beck Anxiety Scale total score of 38. Six months after the selective serotonin reuptake inhibitor treatment (effective dose titrated by plasma drug monitorization) her Beck Anxiety Scale total scores dropped down to 11. The topographical analyses based on the z-score deviations before and after the training are illustrated in figure 5 and 6. Here we observed an increased absolute power in the beta band, together with lower relative power in the delta band before treatment. We also found a decreased relative power in the high beta band. The relative power of the high beta and delta activity were not affected by the treatment. Nevertheless, the absolute power in the beta band was changed to normal level for her age after the treatment. Lastly, there was a moderate increase in the theta band relative to the normative data, which was not affected by treatment.

Figure 6: Z-scored topographical brain mapping of Case-3 after the treatment.
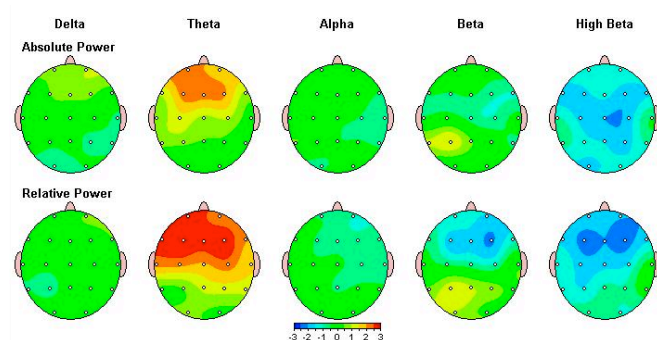

3.4. Case four

Case P. K. was 19 years old, female and a university student. She admitted to the Istanbul Neuropsychiatry

Figure 7: Z-scored topographical brain mapping of Case-4 after the treatment.

Figure 9: Prefrontal theta cordance values before and after the treatment

Hospital in June 2013 with a previous diagnosis of generalized anxiety disorder (GAD) according to the DSM-IV-TR. Following the psychiatric interview, in addition to GAD, a comorbidity of cannabis abuse was also determined. Prior to treatment, she had a Beck Anxiety Scale total score of 38. Six months after the selective serotonin reuptake inhibitor treatment (effective dose titrated by plasma drug monitorization,) together with treatment from 30 sessions of repetitive transcranial magnetic stimulation (rTMS), her Beck Anxiety Scale total scores dropped down to 12. The topographical analyses based on the z-score deviations before and after the treatment are illustrated in figure 7 and 8. Here, we found a significantly increased deviation of the absolute and relative theta power compared with the normative database. Notably, theta activity had resolved following the treatment.

Figure 8: Z-scored topographical brain mapping of Case-4 after the treatment.
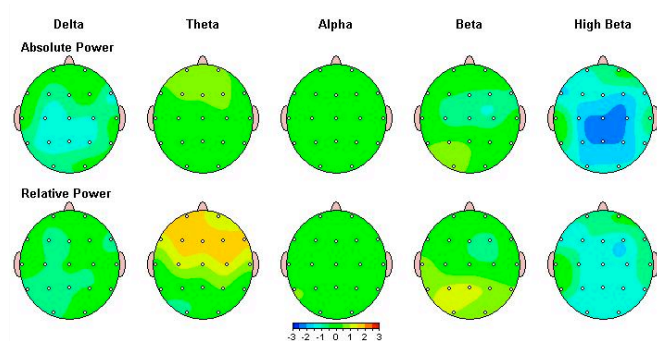

3.5. Theta cordance results

Here we pooled the prefrontal theta cordance values of all cases and calculated mean values. Accordingly, we found a moderate reduction of theta cordance values following the treatment (see figure 9). Specifically, the cordance values reduced approximately 38,3% percent six months after the treatment. Due to the small number of cases, we did not perform hypothesis tests here in this step.

3.6. Discussion

The ultimate goal of this case series was to highlight the different topographical EEG power spectrums of anxiety spectrum disorders and their change following the treatment. In addition to this, we presented theta cordance values, which appeared to be a reliable and consistent measure across different types of anxiety
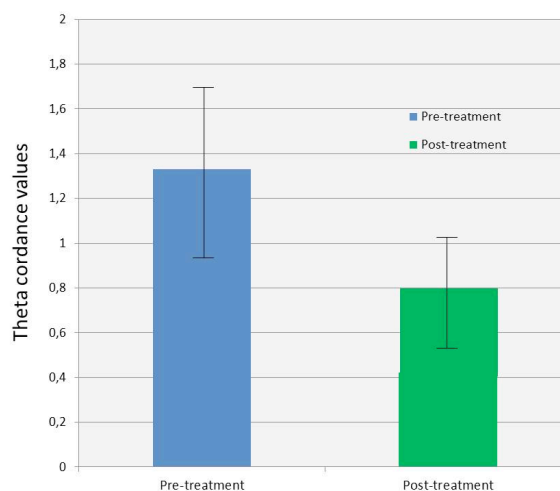
spectrum disorders and thus, may be considered for treatment monitoring of anxiety spectrum disorders in the future. In line with the literature, we found an increased theta and beta activity in the frontal areas. As expected, these activities successfully responded to the treatment. Regarding theta cordance, we replicated the cordance findings of patients with depression (Hunter et al., 2007). Specifically, previous studies calculating cordance values of depressive patients demonstrated an approximately 20% percent of reduction 2 weeks after the treatment (Bares et. el., 2007, 2008).

In our cases, we observed a non-specific increase in the beta band accompanied by a decrease in alpha band. These changes may indirectly suggest that using the absolute and relative power values could not be sufficient to classify anxiety disorders. However, this could not be stressed for the observed changes following the treatment. Because, all power deviations from the normative database disappeared following treatment and thus provided important insights for the clinicians to observe the effects of their treatment.

Previous studies underlined the potential use of cingulate cortex (CC) activity to predict treatment response for depression and anxiety disorders. Greater CC activity was associated with poor improvements following the treatment of patients with post-traumatic stress disorder (Bryant et. al., 2008). In a fMRI study, grater pre-treatment activity of CC in response to the fearful faces has predicted the magnitude of treatment response in patients with generalized anxiety disorder (Whalen et al., 2008). In addition, subsequent to a surgical procedure for removing right posterior CC, OCD patients with higher CC metabolism before operation had a significantly better post-operative outcome than those with smaller metabolism in a neurosurgery study (Rauch et al., 2001). Here we used theta cordance values as an index of cingulate cortex activity. The observed reduction in the theta power suggests that although these patients had different diagnoses, theta cordance may be utilized as an easy to use, non-invasive tool for anxiety disorders.

In light of our cases, although speculatively it would be

legitimate to expect similar spectral changes in the qEEGs of a patient in his or her subsequent episodes, which may require medication or hospitalization. In such occasions, clinicians may consider using the previous qEEG's of their patients in order to follow up the progress. Taken together, although qEEG methods may still require development, the current approaches provide us the initial steps on the way to biological, individualized treatment monitoring for patients. Lastly, theta cordance values may be useful to use to monitor treatment response in anxiety spectrum disorders.

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