Objective: Anxiety is commonly observed together with skin diseases and can aggravate them, while skin diseases can increase anxiety. The relationship of skin diseases observed in panic disorder with quantitative electroencephalography (QEEG) findings has not been investigated yet. The aim of this study is to compare the absolute alpha and delta power of panic disorder patients with and without skin disease.

Methods: 246 panic disorder patients, 19 of whom had skin disease and 227 of whom did not have skin disease, were included in the study. Panic disorder severity scale (PDSS) scores of patients were recorded, and QEEG recording was performed. Absolute alpha and delta power and PDSS scores were compared between the two groups.

Results: It was found that the absolute delta power in the left hemisphere was lower and PDSS scores were higher in the patients with skin diseases compared to the control group. In the patients with skin disease, decreased delta power in the left hemisphere may cause impairment in the processing of positive emotions and may cause trait anxiety.

Conclusion: Trait anxiety may increase susceptibility to skin diseases by disrupting cutaneous homeostasis resulting from the prolonged sympathetic nervous system activation.

1. Introduction

Panic disorder is an anxiety disorder that progresses with paroxysmal anxiety attacks and anticipation anxiety [2] and is observed in the community at a rate of 3–4% [31].

Due to dysfunction in information processing in panic disorder, external stimuli and bodily sensations are misinterpreted as a dangerous signal, sympathetic activation is triggered, and as a result, bodily sensations of anxiety arise [2,49,6,11]. These disturbing sensations are misinterpreted as verifying the threat potential of the stimulus, and this interpretation increases anxiety [6]. The mechanism that triggers panic attacks is assumed to be this vicious circle.

In the pathophysiology of panic disorder, the dysfunction of different brain areas such as the amygdala, locus coeruleus, hippocampal area, and prefrontal cortex (PFC) plays a role [47], and disorders are observed in the cortico-subcortical circuits [54]. According to the hypothesis of Gorman, the cause of the anxiety observed in panic disorder is the amygdala hyperactivation occurring as a result of the dysfunctional interaction between PFC and the limbic system [24]. Thus, behavioral, autonomic, and neuroendocrine stimulation, and the symptoms occur [24]. A functional magnetic resonance imaging (fMRI) study that examined the amygdala and PFC functions in panic disorder patients demonstrated a decrease in PFC activation and an increase in amygdala activation [16]. PFC is responsible for executive functions, including inhibitory control [45]. Hipoactivity in PFC causes the failure of the amygdala inhibition required for the regulation of the fear response, and the cascade of neural events reflecting on the clinical picture as panic attacks may start [23,16,43,56].

Cerebral cortical hyperactivation was demonstrated, especially in the frontal and temporal cortices in electroencephalography (EEG) studies conducted on panic disorder patients [50,28,10,13,41]. There are contradictory results showing that the activity increase is in the right [76,63,46] or in the left hemisphere [18]. Although the most common EEG finding in panic disorder is the decrease in the alpha power and the increase in the beta power [76,23,64], there are also studies showing that there is an increase in theta, delta, and alpha power and a decrease in beta power [34].

Keywords:
Panic disorder
Skin disease
Dermatological disorder
QEEG
Delta
Trait anxiety
and that there is a decrease in theta, alpha-1, alpha-2, and beta power [65].

While delta and theta are associated with the brainstem and limbic system activity, respectively; alpha is considered as the thalamocortical rhythm [38]. The alpha band (8–13 Hz) reflects the inhibition done by the cortical regions to the subcortical area, and, therefore, a decrease in alpha power is associated with neural excitation [33]. The increase in beta power (13–30 Hz) may also result in the disruption of cognitive control and is a parameter that indicates overstimulation [21]. The task of inhibitory effects arising from the medial PFC (mPFC) involved in the production of delta oscillations (1–3 Hz) [1,44] is to selectively suppress the inappropriate or unrelated neuronal activity that may be involved in the event while performing any mental task such as behavior, speech, or cognition [35,22]. An inverse relationship was found between anxious features and delta power observed in individuals [39]. Moreover, there is also a reciprocal relationship between alpha and delta activity, and this relationship may be reflecting the inhibitory control of PFC over motivational and emotional impulses [44,38].

The two-way relationship between skin diseases and psychiatric disorders has been widely discussed in the literature [7]. For dermatologists, the general view is that skin diseases such as psoriasis and eczema create susceptibility to psychiatric disorders by causing stigmatization, social isolation, and thus the impaired quality of life because of being visible [36,58,17]. On the other hand, there is an opinion that psychiatric disorders can be included in the etiology of skin diseases [85,32].

Electrodermal activity (EDA) increases due to the sympathetic nervous system (SNS) activation in panic disorder [56,8,52]. Autonomic and especially sympathetic nerves play a role in the continuity of cutaneous homeostasis by regulating vasomotor and pilomotor functions and the activity of apocrine and eccrine sweat glands [26]. There are case reports demonstrating the association of panic disorder and skin diseases [62,27]. Anxiety is commonly observed together with skin diseases and can aggravate them, while skin diseases can increase anxiety.

Conducting analysis over all of the EEG bands or all of the EEG regions in the head may reveal a statistical fact called p-hacking [62]. It is suggested to study certain bands and certain areas to get rid of p-hacking. In this study, we preferred to investigate alpha and delta activities that play a role in inhibitory processes [35,37,38,22].

The aim of this study is to compare the absolute alpha and delta power of panic disorder patients with and without skin disease. We hypothesize that the possibility of skin disease will increase when anxiety cannot be neutralized in patients, and this situation can be observed as disinhibition patterns in EEG findings.

2. Materials and Methods

2.1. Participants

Two hundred forty-six patients, who applied to Kemal Arıkan Psychiatry Clinic (a private psychiatric practice) between May 29, 2012, and February 14, 2020, and were diagnosed as panic disorder in the psychiatric interview (Structured Clinical Interview for DSM-5 = SCID-5) [20], were included in the study. All of the patients were diagnosed as panic disorder for the first time, and none of them received medication. Other psychiatric disorders were excluded by applying SCID-5 [20]. There was no physical trauma history, such as head injury, etc. in patients. The participants were divided into two groups as having a skin disease (n = 19) -none of them had a primary psychocutaneous disease- and not having a skin disease (n = 227). Patients with a skin disease were defined as group 1, and those without a skin disease were defined as group 2. The Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HARS), and Panic Disorder Severity Scale (PDSS) were applied to all participants, and EEG was performed.

2.2. EEG recording

All the participants underwent EEG recording following the first psychiatric examination and all were free of neuropsychiatric medications for at least 1 month during recording. The participants were informed about the procedure prior to EEG recording. In order to reduce anxiety, the participants were allowed to rest in a quiet room for 30 min prior to the procedure. EEG recording was performed in a soundproof, dimly lit, and well-ventilated room. A 19-channel (FP1, F7, T3, T5, F3, C3, P3, O1, FZ, CZ, PZ, F4, C4, P4, O2, FP2, F8, T4 and T6) electro-cap that was compatible with each participant’s head measurements was properly fixed to the head of each participant. Electro-gel was used between the electrodes and the scalp to increase conductivity and the signal-to-noise ratio. A sufficient amount of gel was applied to each electrode area using a blunt tip injector. The ground electrode was placed in the FPz position. Reference electrodes were extra electrodes attached with EEG paste to both earlobes, which had first been cleaned with cleansing gel and alcohol.

A vertical electrooculogram (v-EOG) and horizontal EOG (h-EOG) were recorded to determine simultaneous eye movements in EEG imaging; the Ag-AgCl disc electrodes used for this purpose were attached to the relevant area using the EEG paste and fixed to the area with a plaster. Following these procedures, all electrodes were checked for impedance, and additional electro-gel was used, as necessary. EEG recording was initiated when impedances were < 5000 Ω. EEG recordings were made using a Neuron-Spectrum-4/P device, and only while the participants were at rest; no activation method was applied. The participants were instructed to sit comfortably, remain awake, and blink as little as possible during EEG recording.

2.3. Data conditioning

Neuron-Spectrum.NET software was used for EEG impedance measurement, as follows: notch filter: on; scale: 10 mV/mm−1; sweep: 30 mms−1. As used for standard EEG recording, high pass filter (HPF) was set to 0.5 Hz and low pass filter (LPF) was set to 70 Hz. The EEG range was reinforced using a 0.5–70-Hz bandpass filter, with the resistance of the electrodes set at < 5000 Ω, and the sampling rate was 250 Hz. All EEG recording data were transferred to a computer hard drive. EEG recordings were made with the participants’ eyes open during 2 individual 5-min periods and with their eyes closed during 2 other 5-min periods. Continuous EEG recordings that were made during 20 min periods were cleared of EEG ranges contaminated by both eye movement and motion-related artifacts using a combination of visual inspection and a computerized artifact identification algorithm [9].

2.4. Data analysis

Fast Fourier transformation (FFT) was used for spectral analysis of EEG ranges without artifacts [9]. Spectral analysis is a standard method for EEG quantification that facilitates determination of the distribution of power according to frequency [59], which provides information about the frequency content of a signal. For each of the 19 monopolar derivations, absolute power (µV2) was calculated for the delta (0.5–4 Hz) and alpha (8–13 Hz) frequency bands [71,59,57].
2.5. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows v.24.0 (IBM Corp., Armonk, NY). The age and gender differences between the groups were compared by Student’s t-test and chi-square test, respectively. No significant difference was detected between the groups in terms of age (p = 0.79) and gender (p = 0.387) (Table 1).

The Mann-Whitney U test was performed in the HAMD, HARS, and PDSS scores provided that the presence of a skin disease was a dependent variable (Table 2). Since the number of cases with skin diseases was below 30, the nonparametric Mann-Whitney U test was applied to delta and alpha power in all channels (Table 3). Alpha = 0.005 was determined as the acceptance criterion for Mann-Whitney U test and covariance analyses [50]. Although any age and gender differences were not found at the baseline, to be sure that the differences in EEG measurements were not affected by age and gender, each band-channel combination, for which significant results were obtained in the Mann-Whitney U test, was subjected to the ANCOVA test including age and gender covariates. Alpha was considered to be 0.05 for the ANCOVA test. The difference in four of the six band-channels tested was observed to be independent of age and gender (Table 4).

3. Results

No significant difference was determined between the groups in terms of age (p = 0.79) and gender (p = 0.387) (Table 1).

While there was no significant difference in terms of HAMD (p = 0.875) and HARS (p = 0.342) scores between the two groups, PDSS scores were found to be higher in group 1 (those with a skin disease) (p = 0.034) (Table 2).

When the delta and alpha power of two groups were compared, the log-transformed absolute power of T3 alpha1 band (p = 0.003) and C3 (p = 0.001), Fp1 (p = 0.001), T3 (p = 0.001), T5 (p = 0.002), F4 (p = 0.003), and O1 (p = 0.003) delta band were found to be lower in group 1 (those with a skin disease) (Table 3). From these channels, the difference observed in Fp1, C3, O1, and T3 delta band power was determined to be age and gender independent (Table 4).

4. Discussion

In this study, it was demonstrated that the delta power in the left hemisphere was lower and PDSS scores were higher in panic disorder patients with skin disease compared to the group without skin disease.

In studies investigating the correlation between positron emission tomography (PET) and fMRI signals and EEG, the origin of delta waves was demonstrated to be mPFC [13,1,44]. Accordingly, the delta wave is vital in the regulation of anxiety responses and inhibition of amygdala activity [24]. And the amygdala hyperactivity observed in cases with the decreased delta power may trigger the activity of some subcortical regions and typical panic attack symptoms, respectively [23,16,43,56]. These findings are consistent with the result of our study, which demonstrates the association of high PDSS scores and delta power decrease in the group with skin disease.

According to Gray’s theory, the behavioral inhibition system (BIS) is sensitive to punitive stimuli and protects individuals from negative and painful outcomes by increasing avoidance behavior and anxiety in the presence of these stimuli [25]. The extreme level of the BIS is associated with anxious personality traits and anxiety-related disorders [3–5]. In individuals with high BIS activity, the resting-state alpha power was found to be higher and delta power was found to be lower [39]. In contrast, when panic provocation was performed in EEG studies, change was demonstrated from fast frequencies to slower (delta and theta) frequency bands [41,40,36]. While alpha power increase and delta power decrease reflect trait anxiety, alpha power decrease and delta power increase may be reflecting state anxiety. Although there is no difference in terms of HARS scores between our two groups, the fact that the decreased delta power in the group with skin disease may be indicating that trait anxiety is higher in them. This situation may cause the impairment of cutaneous homeostasis and, thus, increase susceptibility to skin diseases, depending on the affection of the autonomic nervous system chronically [26].

According to the valence hypothesis, the pattern of hemispheric dominance depends on the emotional value of the stimulus. Accordingly, the left hemisphere is dominant for positive emotions [15], and the left frontal activity is associated with behavioral activation [51]. There is a high correlation between the task

<table>
<thead>
<tr>
<th>Table 1</th>
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<tbody>
<tr>
<td>Demographical characteristics of groups.</td>
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<tr>
<td>n</td>
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<tr>
<td></td>
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<tr>
<td>Group 1 (DD)</td>
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<tr>
<td>Group 2 (Control)</td>
</tr>
<tr>
<td>p</td>
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</tbody>
</table>

* There was no statistically significant difference between the groups in terms of age (p = 0.79) and gender (p = 0.387). DD: dermatological disease, SD: standard deviation.
performance and the number of slow waves in the EEG [61]. In the group with skin disease, the delta power decreased in the left hemisphere. This situation may indicate that there is a problem in the processing of left hemisphere-related positive emotions and in behavioral activation [5,14]. This finding is consistent with the results of the studies demonstrating the presence of hemispheric asymmetry, which is against the left hemisphere in panic disorder patients [76,63,46].

As a result, it was demonstrated that PDSS scores were higher and the delta power in the left hemisphere was lower in the patients with skin disease compared to the patients without skin disease. Decreased delta power in the left hemisphere may be associated with left hypofrontality, and this situation may impair the processing of positive emotions and the behavioral activation. In parallel to this, PDSS scores increased in the group with skin disease. Anxiety is commonly observed together with skin diseases and can aggravate them, and skin diseases can also increase anxiety. When trait anxiety increase observed together with decreased delta power is interpreted as longer exposure to anxiety, cutaneous homeostasis may have been impaired, and susceptibility to skin diseases may have been increased due to prolonged autonomic activation in these patients [26].

The strong aspect of our study is that the relationship of the presence of skin disease with EEG findings was investigated for the first time in panic disorder patients. Since none of our patients received medication, pharmacotherapy had no effect on EEG findings. Since there was no difference in terms of HAMD scores between the groups, the effect of depression on EEG findings was eliminated. Moreover, since all of our patients were diagnosed with panic disorder for the first time, the possible effect of the disease duration on skin disease was eliminated.

5. Study limitation

The limitation of our study is that patients were evaluated not with questionnaires that might show their anxious personality traits, but only with HARS scores indicating their current anxiety status. The application of the questionnaires, which evaluate personality traits, could have enabled us to evaluate the physical effects to which the patients were exposed as a result of chronic anxiety they experienced due to their personal characteristics prior to diagnosis. Another limitation is that our study is a retrospective study. A prospective study that will be conducted on this subject will make it more possible to evaluate the state and trait anxiety characteristics.

6. Conclusion

In summary, although a relationship between EEG findings and skin disease was found in this study, the study design does not allow further interpretation of this relationship, and more studies are needed on this subject.

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Table 4

<table>
<thead>
<tr>
<th>Source</th>
<th>Type III Sum of Squares</th>
<th>Df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
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<td>14,261</td>
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<td>3,764</td>
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<tr>
<td>C3-Delta</td>
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<td>3,935</td>
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<tr>
<td>O1-Delta</td>
<td>12,505</td>
<td>1</td>
<td>12,505</td>
<td>4,777</td>
<td>.030*</td>
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<tr>
<td>T3-Delta</td>
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<tr>
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<td>4,107</td>
<td>2,430</td>
<td>.120</td>
</tr>
</tbody>
</table>

*ANCOVA; The decreased delta power in FP1, C3, O1, and T3 observed in the dermatological disease group is independent of age and gender.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References
