**Research article**

# QEEG - spectral power density of brain regions in predicting risk, resistance and resilience for bipolar disorder: A comparison of first degree relatives and unrelated healthy subjects

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### ABSTRACT

*Background:* Temperament stems from the brain circuitry. Genetic differences among people are attributable to differences in neurophysiological function. Affective temperament is proposed endophenotype for bipolar affective disorder. QEEG - spectral power density is thought to be an index of general affective and cognitive brain activity. The association of spectral power density with types of affective temperament may enlighten endophenotypes for bipolar affective disorder disposition.

*Method:* TEMPS-A scale and rest QEEG were done on 25 euthymic patients, their healthy first degree relatives (n = 25) and 25 unrelated healthy control subjects. All patients were on lithium maintenance therapy.

*Results:* F4 and T4 delta wave activity were similar between patients and first degree relatives, while Pz alpha activity was similar in first degree relatives and unrelated healthy subjects (p = 0.025, p = 0.001, p = 0.010). Cyclothymic and hyperthymic temperament scores were similar between patients and first degree relatives but higher than unrelated healthy subjects (p = 0.015, p = 0.010). F7 beta and F7–O2 high beta power were correlated with hyperthymic and irritable temperaments respectively in bipolar subjects (r = 0.439, 0.387; 0.405, 0.364; 0.226, 0.351). T3-F4-T4 delta powers were correlated with cyclothymic temperament in patients and their first degree relatives (r = 0.443, 0.420, 505). Pz alpha power and hyperthymic temperament were inversely correlated in first degree relatives and unrelated healthy subjects (r = -0.256 and -0.311).

*Conclusion:* Medial temporal network may be associated with bipolar affective disorder heritability. On the other hand, left dorsolateral prefrontal beta and high beta activities may be a neural marker for disorder resistance together with right occipital high beta power.

## 1. Introduction

The unipolar-bipolar affective disorder differentiation had been introduced by Leonhard in 1957 (Leonhard et al., 1962). Having been supported by studies it was included in official classification in 1980. In first century AD Arataeus the Cappadocian stated "It seems to me that melancholia is the beginning and a part of mania". Kraepelin was the first in conceptualizing "spectrum disorders", including recurrent unipolar depression under the category of bipolar disorder a century ago (Kraepelin, 1921). Affective temperament has been suggested as an endophenotype for bipolar affective disorder. It comprises the mildest end of the bipolar spectrum. In particular, cyclothymic and hyperthymic temperaments have been considered to have a genetic association with bipolar affective disorder. It is thought to be capable of distinguishing bipolar patients and their relatives from healthy controls.

Present psychiatric classification systems ignore family history, longitudinal disorder course and dimenional nosological approach. Cross-sectional dignosis which disengages symptoms from aetiology is emphasized, giving priority to reliability rather than validity.

Regarding only what can be observed, descriptive diagnostic system also ignore neurobiological heterogeneity. Affective temperament emanates from brain structure. Genetic differences are attributable to physiological and neural functional differences.

Particularities of neural function can be detailed using QEEG. The most importants distinction of QEEG compared to other functional imaging techniques is its capability of representing neural activity directly rather than indirectly with parameters such as blood deoxygenation and

**Table 1.** Definition of sample.

|  | Bipolar patients (n = 25) | Healthy relatives (n = 25) | Unrelated healthy subjects (n = 25) | Analysis (F, p) |
|---|---|---|---|---|
| Age (Mean ± SD) | 32.8 ± 5.7 | 36.4 ± 4.1 | 40.1 ± 5.3 | 6.100 0.212 |
| Gender (F/M) | 18/7 | 22/3 | 20/5 | 2.112 0.501 |

glucose usage. QEEG has considerable temporal resolution. 1.5 mV amplitude discharges in the cortex are amplified and decomposed with Fourier transformation. Spectral power density is the power EEG waves carry per unit frequency in a predetermined frequency range. QEEG eliminates the incertitude due to the need to take references. Therefore, it yields more direct results (Tenke and Kayser, 2005).

**Table 2.** Comparison of QEEG spectral power density between bipolar patients, healthy relatives and unrelated healthy subjects.

|  | Bipolar patients | Healthy relatives | Unrelated healthy | Analysis, p |
|---|---|---|---|---|
| Delta F4 | 48.5 | 44.7 | 33.1 | **0.025*** |
| F7 | 40.4 | 35.4 | 30.7 | 0.465 |
| Fz | 48.3 | 51.2 | 50.5 | 0.673 |
| Pz | 43.4 | 45.8 | 46.3 | 0.701 |
| Cz | 31.9 | 38..2 | 28.7 | 0.578 |
| T3 | 28.3 | 27.2 | 26.9 | 0.711 |
| T4 | 24.2 | 25.6 | 16.5 | **0.001*** |
| O1 | 37.8 | 27.4 | 32.1 | 0.456 |
| O2 | 42.4 | 45.1 | 39.3 | 0.342 |
| Theta F4 | 19.3 | 16.8 | 17.1 | 0.398 |
| F7 | 27.1 | 25.3 | 20.1 | 0.401 |
| Fz | 20.9 | 18.4 | 15.4 | 0.178 |
| Pz | 22.1 | 24.1 | 20.2 | 0.395 |
| Cz | 13.5 | 15.2 | 9.9 | 0.201 |
| T3 | 23.5 | 21.5 | 19.0 | 0.312 |
| T4 | 21.2 | 20.4 | 23.5 | 0.473 |
| O1 | 13.8 | 13.4 | 12.4 | 0.712 |
| O2 | 10.7 | 10.1 | 10.6 | 0.801 |
| Alpha F4 | 98.7 | 73.4 | 82.3 | 0.811 |
| F7 | 68.9 | 81.6 | 109.4 | 0.532 |
| Fz | 74.5 | 82.3 | 91.6 | 0.602 |
| Pz | 226.3 | 119.8 | 118.5 | **0.010**** |
| Cz | 110.5 | 100.3 | 95.2 | 0.374 |
| T3 | 115.4 | 122.6 | 132.5 | 0.435 |
| T4 | 136.7 | 130.4 | 120.4 | 0.201 |
| O1 | 70.6 | 91.6 | 118.5 | 0.321 |
| O2 | 80.5 | 90.7 | 100.8 | 0.298 |
| Beta F4 | 16.8 | 19.3 | 17.5 | 0.345 |
| F7 | 21.3 | 21.7 | 22.2 | 0.321 |
| Fz | 19.5 | 23.4 | 25.6 | 0.289 |
| Pz | 15.8 | 24.7 | 32.1 | 0.567 |
| Cz | 14.6 | 20.5 | 30.1 | 0.623 |
| T3 | 24.8 | 17.6 | 21.6 | 0.111 |
| T4 | 33.4 | 30.5 | 26.7 | 0.344 |
| O1 | 32.5 | 27.6 | 24.5 | 0.352 |
| O2 | 24.7 | 25.6 | 23.1 | 0.415 |
| High beta F4 | 6.1 | 5.5 | 5.7 | 0.652 |
| F7 | 7.4 | 5.3 | 3.9 | 0.413 |
| Fz | 12.3 | 12.7 | 13.2 | 0.712 |
| Pz | 11.8 | 11.5 | 12.8 | 0.112 |
| Cz | 15.1 | 13.2 | 14.7 | 0.435 |
| T3 | 9.4 | 9.1 | 9.6 | 0.893 |
| T4 | 11.2 | 8.7 | 5.4 | 0.109 |
| O1 | 3.5 | 5.1 | 4.7 | 0.202 |
| O2 | 3.1 | 3.5 | 3.4 | 0.687 |

Significant figures are shown in bold (r = −0.311, p > 0.05). Covariance analysis, Benjamini-Hochberg correction.
*Delta: Patients = Relatives > Controls (F4, T4).
**Alpha: Patients > Relatives = Controls (Pz).

**Table 3.** Comparison of Affective Temperaments scores between euthymic bipolar patients, their first degree relatives and unrelated healthy controls.

|  | Bipolar patients | Healthy Relatives | Unrelated healthy | Analysis, p |
|---|---|---|---|---|
| Depressive temperament | 16.5 ± 2.5 | 11.1 ± 1.4 | 10.6 ± 1.8 | 0.022* |
| Cyclothymic temperament | 15.9 ± 1.3 | 14.8 ± 1.2 | 7.5 ± 2.4 | 0.015** |
| Hyperthymic temperament | 17.1 ± 1.6 | 17.4 ± 1.2 | 10.2 ± 2.3 | 0.010*** |
| Irritable temperament | 19.1 ± 1.1 | 16.4 ± 1.2 | 13.5 ± 2.7 | 0.245**** |
| Anxious temperament | 19.6 ± 1.2 | 14.7 ± 2.3 | 14.3 ± 1.9 | 0.025***** |

Covariance analysis, Benjamini-Hochberg correction.
*DT: Patients > Relatives = Controls.
**CT: Patients = Relatives > Controls.
***HT: Patients = Relatives > Controls.
****IT: Patients > Relatives > Controls.
*****AT: Patients > Relatives = Controls.

The differentiation of QEEG in cases diagnosed with bipolar disorder and their first degree relatives from healthy individuals suggests QEEG as a trait marker; this will set forth an argument in favor of QEEG as an endophenotype for bipolar disorder. A potential association between QEEG and affective temperament subtypes would give an idea about the neurophysiologic projection of the subsyndromal phenomenology, i.e. the bipolar spectrum. Heritability of some QEEG parameters such as alpha peak frequency and alpha spectral power density was shown in twin and family studies (Vogel, 1970).

Most prominent aim of this study is to investigate into whether QEEG parameters distinguish euthymic bipolar cases from healthy first degree relatives, and unrelated healthy subjects. Secondly, a possible association between spectral power density and affective temperament in bipolar cases and their first degree relatives will be studied.

## 2. Method

### 2.1. Sample

25 cases diagnosed with bipolar affective disorder according to DSM-V diagnostic criteria who were in euthymic period, 25 healthy first degree relatives and 25 healthy individuals without any family history of bipolar disorder were included in the study. The patient group was referred to our outpatient clinics for routine follow up. Patients between 18-65 years of age were included in the study. Patients with diagnosed physical or neurological illness were excluded. Eythymia was defined as HDRS<8 and YMRS<7.

SCID-NP form was applied to healthy relatives and unrelated healthy controls.

### 2.2. Procedure

Informed consent was obtained from all three groups of subjects. The subjects who consented were evaluated consecutively. The study protocol was approved by the Üsküdar University Ethics committee.

QEEG was recorded continuously at 125 Hz sampling rate with 10–20 Ag–AgCl electrodes. Linked mastoid electrodes (A1-A2) were used for reference. Spectral power density was calculated for the nine electrodes representing brain regions (F4, F7, Fz, Pz, Cz, T3, T4, O1, O2). We selected 9 electrodes to prevent cross-talk among electrodes. Cross-talk spatially smooths current source density (CSD) estimates and induces artefactual phase shifts. The nodes F4, F7, Fz, Pz, Cz, T3, T4, O1, O2 represent the most significant locations in depression. Fp1 and Fp2 may be artefacted more by eye blink noise and P4 is more affected by parietal muscle noise (Tenke and Kayser, 2005).

QEEG was applied in a quiet, dimly lit room, in sitting position, eyes closed. Recording time was 3 min, 3 min artifact free recording corresponds to T = 180 × 125 = 22500 sample points for each electrode; meaning N = 6 × 22500 = 135000 points for each subject. Analysis calculates single value from a total of 22500 sample points for each channel.

Affective temperament was evaluated with TEMPS-A (Temperament Evaluation of Memphis, Pisa, Paris and San Diego-autoquestionnaire) Turkish version (Vahip et al., 2005).

### 2.3. Statistical analysis

QEEG data were analyzed using Neuroguide Deluxe v.2.5.1 (Applied Neuroscience, Largo, FL). Intergroup comparisons were made by covariance analysis and paired t-tests. Benjamini-Hochberg procedure was implemented to correct for multiple comparisons. Pearson correlation test was used for correlation analysis. All tests were two-tailed. Level of significance was accepted as p < 0.05.

## 3. Results

### 3.1. Sample

Bipolar patients, their first degree relatives and unrelated healthy control groups are similar in terms of age and gender (Table 1). Duration of illness is calculated as 8.7 ± 3.5 month in bipolar group. Lithium prophylaxis duration is 5.6 ± 2.7 month and current lithium dose is 865 ± 300.5 mg.

Comparison of QEEG spectral power density among euthymic bipolar patients, their first degree relatives and unrelated healthy controls.

F4 and T4 delta activities were similar between patients and first degree relatives, while Pz alpha activity was similar in healhty relatives and unrelated healthy subjects (p = 0.025, p = 0.001, p = 0.010), (Table 2).

Comparison of TEMPS-A scores between euthymic bipolar patient, their first degree relatives and unrelated healthy controls.

Cyclothymic and hyperthymic temperament scores were found to be similar between patients and their relatives and higher than unrelated healthy controls (p = 0.015, p = 0.010), (Table 3).

### 3.2. Relation between QEEG spectral power density and affective temperaments scores in groups

F7 beta and F7–O2 high beta powers were correlated with hyperthymic and irritable temperaments in bipolar patients respectively (r = 0.439, 0.387; 0.405, 0.364; 0.226, 0.351), (Table 4).

T3-F4-T4 delta power were correlated with cyclothymic temperament in bipolar subjects and fisrt degree relatives (r = 0.443, 0.420, 505), (Table 4).

An inverse correlation was found between Pz alpha power and hyperthymic temperament in first degree relatives and unrelated subjects (r = -0.256 and -0.311), (Table 5 and 6).

**Table 4.** Correlations of affective temperament scores and spectral power density of QEEG in bipolar patients.

| | Depressive temperament | Cyclothymic temperament | Hyperthymic temperament | İrritable temperament | Anxious temperament |
|---|---|---|---|---|---|
| Delta F4 | 0.170 | **0.443*** | -0.023 | 0.098 | 0.101 |
| F7 | 0.172 | 0.145 | 0.098 | 0.121 | 0.105 |
| Fz | 0.153 | 0.155 | 0.075 | 0.125 | 0.143 |
| Pz | 0.132 | 0.143 | 0.050 | 0.075 | 0.132 |
| Cz | 0.103 | 0.110 | 0.086 | 0.105 | 0.142 |
| T3 | 0.134 | **0.420*** | 0.100 | 0.162 | 0.101 |
| T4 | 0.141 | **0.505*** | 0.087 | 0.155 | 0.145 |
| O1 | 0.123 | 0.181 | 0.053 | 0.111 | 0.078 |
| O2 | 0.127 | 0.176 | 0.098 | 0.121 | 0.096 |
| Theta F4 | 0.182 | 0.191 | 0.075 | 0.064 | 0.120 |
| F7 | 0.145 | 0.165 | 0.096 | 0.097 | 0.165 |
| Fz | 0.152 | 0.158 | 0.102 | 0.102 | 0.115 |
| Pz | 0.134 | 0.142 | 0.055 | 0.105 | 0.102 |
| Cz | 0.105 | 0.127 | 0.100 | 0.112 | 0.104 |
| T3 | 0.123 | 0.156 | 0.101 | 0.132 | 0.113 |
| T4 | 0.145 | 0.135 | 0.110 | 0.101 | 0.114 |
| O1 | 0.099 | 0.122 | 0.011 | 0.135 | 0.100 |
| O2 | 0.100 | 0.134 | 0.070 | 0.121 | 0.125 |
| Alpha F4 | 0.182 | 0.191 | 0.086 | 0.085 | 0.156 |
| F7 | 0.145 | 0.113 | 0.121 | 0.096 | 0.175 |
| Fz | 0.133 | 0.121 | 0.132 | 0.100 | 0.164 |
| Pz | 0.121 | 0.111 | 0.105 | 0.098 | 0.132 |
| Cz | 0.100 | 0.126 | 0.097 | 0.104 | 0.125 |
| T3 | 0.105 | 0.135 | 0.010 | 0.108 | 0.123 |
| T4 | 0.123 | 0.123 | 0.120 | 0.098 | 0.132 |
| O1 | 0.117 | 0.132 | 0.098 | 0.100 | 0.121 |
| O2 | 0.119 | 0.155 | 0.070 | 0.076 | 0.112 |
| Beta F4 | 0.087 | 0.161 | 0.165 | 0.168 | 0.142 |
| F7 | 0.040 | 0.158 | **0.439*** | **0.387*** | 0.156 |
| Fz | 0.010 | 0.153 | 0.168 | 0.171 | 0.162 |
| Pz | 0.015 | 0.115 | 0.165 | 0.148 | 0.089 |
| Cz | 0.020 | 0.112 | 0.165 | 0.121 | 0.100 |
| T3 | 0.103 | 0.121 | 0.126 | 0.122 | 0.123 |
| T4 | 0.098 | 0.118 | 0.137 | 0.101 | 0.139 |
| O1 | 0.100 | 0.127 | 0.098 | 0.135 | 0.121 |
| O2 | 0.095 | 0.123 | 0.070 | 0.134 | 0.123 |
| High beta F4 | 0.090 | 0.158 | 0.178 | 0.187 | 0.167 |
| F7 | 0.085 | 0.152 | **0.405*** | **0.364*** | 0.178 |
| Fz | 0.092 | 0.142 | 0.189 | 0.168 | 0.155 |
| Pz | 0.100 | 0.135 | 0.155 | 0.197 | 0.123 |
| Cz | 0.117 | 0.120 | 0.162 | 0.181 | 0.142 |
| T3 | 0.129 | 0.105 | 0.143 | 0.159 | 0.123 |
| T4 | 0.126 | 0.102 | 0.138 | 0.182 | 0.111 |
| O1 | 0.010 | 0.100 | 0.121 | 0.198 | 0.125 |
| O2 | 0.007 | 0.010 | **0.226*** | **0.351*** | 0.123 |

Significant figures are shown in bold (r = −0.311, p > 0.05). Pearson correlation test (r).
*p < 0.05.

## 4. Discussion

This study is the first in investigating into whether QEEG differs between healthy subjects and bipolar patients and their first degree relatives. F4 and T4 delta activities were similar between euthymic bipolar subjects and first degree relatives, but higher than unrelated healthy subjects. An increase in slow wave activity is proposed as a state and trait marker for affective disorders (Fink, 2010). Increase in level of delta band activity may predict response to ECT (Nobler et al., 2002). Pervasive increase in delta wave activity indicates unresponsiveness to

antidepressants (Arns et al., 2017). Thus, depressive cases with high episode severity and antidepressant resistance carry a high risk for bipolarity.

The differentiation of F4 and T4 delta activity in bipolar cases and their relatives from unrelated healthy subjects, when assessed regionally, is consistent with the findings of the functional imaging study which suggests the change in activity in the aforementioned regions as an endophenotype. Dorsolateral prefrontal and middle temporal gyrus activity (Wiggins et al., 2017), frontal and cingulate cortex and striatum activity (Pagliaccio et al., 2017) and inferior frontal gyrus activity

**Table 5.** Correlations of affective temperament scores and spectral power density of QEEG in healthy relatives.

|  | Depressive temperament | Cyclothymic temperament | Hyperthymic temperament | İrritable temperament | Anxious temperament |
|---|---|---|---|---|---|
| Delta F4 | 0.167 | **0.258** | 0.183 | 0.096 | 0.110 |
| F7 | 0.174 | 0.169 | 0.142 | 0.122 | 0.109 |
| Fz | 0.158 | 0.172 | 0.107 | 0.121 | 0.139 |
| Pz | 0.134 | 0.140 | 0.145 | 0.070 | 0.135 |
| Cz | 0.105 | 0.120 | 0.122 | 0.108 | 0.145 |
| T3 | 0.144 | **0.334*** | 0.165 | 0.163 | 0.101 |
| T4 | 0.151 | **0.372** | 0.145 | 0.156 | 0.148 |
| O1 | 0.127 | 0.120 | 0.117 | 0.114 | 0.087 |
| O2 | 0.129 | 0.125 | 0.125 | 0.125 | 0.098 |
| Theta F4 | 0.188 | 0.175 | 0.163 | 0.066 | 0.126 |
| F7 | 0.154 | 0.163 | 0.152 | 0.098 | 0.168 |
| Fz | 0.155 | 0.168 | 0.160 | 0.105 | 0.116 |
| Pz | 0.143 | 0.170 | 0.154 | 0.105 | 0.112 |
| Cz | 0.115 | 0.116 | 0.120 | 0.115 | 0.107 |
| T3 | 0.126 | 0.130 | 0.123 | 0.135 | 0.123 |
| T4 | 0.146 | 0.152 | 0.143 | 0.110 | 0.118 |
| O1 | 0.089 | 0.030 | 0.134 | 0.136 | 0.106 |
| O2 | 0.108 | 0.093 | 0.096 | 0.123 | 0.130 |
| Alpha F4 | 0.189 | 0.199 | 0.102 | 0.080 | 0.158 |
| F7 | 0.148 | 0.152 | 0.100 | 0.098 | 0.177 |
| Fz | 0.140 | 0.176 | 0.152 | 0.110 | 0.165 |
| Pz | 0.126 | -0.100 | **-0.256*** | 0.098 | 0.133 |
| Cz | 0.100 | 0.102 | 0.116 | 0.105 | 0.128 |
| T3 | 0.109 | 0.111 | 0.114 | 0.110 | 0.132 |
| T4 | 0.127 | 0.134 | 0.123 | 0.099 | 0.134 |
| O1 | 0.118 | 0.120 | 0.126 | 0.105 | 0.122 |
| O2 | 0.117 | 0.125 | 0.110 | 0.076 | 0.112 |
| Beta F4 | 0.088 | 0.072 | 0.100 | 0.170 | 0.145 |
| F7 | 0.045 | 0.100 | 0.095 | 0.187 | 0.155 |
| Fz | 0.018 | 0.105 | 0.098 | 0.170 | 0.165 |
| Pz | 0.010 | 0.040 | 0.035 | 0.148 | 0.090 |
| Cz | 0.030 | 0.035 | 0.032 | 0.123 | 0.104 |
| T3 | 0.105 | 0.102 | 0.112 | 0.122 | 0.124 |
| T4 | 0.089 | 0.101 | 0.105 | 0.101 | 0.138 |
| O1 | 0.108 | 0.100 | 0.120 | 0.135 | 0.123 |
| O2 | 0.099 | 0.081 | 0.127 | 0.134 | 0.127 |
| High beta F4 | 0.095 | 0.112 | 0.128 | 0.187 | 0.168 |
| F7 | 0.086 | 0.100 | 0.132 | 0.194 | 0.176 |
| Fz | 0.094 | 0.102 | 0.124 | 0.158 | 0.157 |
| Pz | 0.110 | 0.105 | 0.112 | 0.199 | 0.125 |
| Cz | 0.120 | 0.112 | 0.151 | 0.185 | 0.149 |
| T3 | 0.128 | 0.155 | 0.168 | 0.156 | 0.121 |
| T4 | 0.124 | 0.142 | 0.153 | 0.184 | 0.113 |
| O1 | 0.015 | 0.100 | 0.163 | 0.196 | 0.128 |
| O2 | 0.010 | 0.052 | 0.176 | 0.195 | 0.130 |

Significant figures are shown in bold (r = −0.311, p > 0.05). Pearson correlation test (r).
*p < 0.05.

(Roberts et al., 2013) were found to differ in bipolar patients and relatives from healthy controls.

Medial temporal lobe overactivity differentiates bipolarity from schizophrenia in memory and emotion tasks (Whalley et al., 2012); bipolar cases from unipolar cases (Diler et al., 2013, Grotegerd et al., 2013 ); and type I bipolar cases from type II (Gürdal and Kesebir, 2015) in small samples.

Bipolar affective disorder may be conceptualized as a discordance between prefrontal and limbic neuronal activities in QEEG (Güven et al., 2015). Manic episode decreases IFG activity, while it returns to normal in euthymia and depressive episode. Regardless of affective state, limbic activity stays high. An increase in beta wave activity is often present in manic episode, though frequency diversity is higher than in depressive episode (El-Badri et al., 2001, Güven et al., 2015). In this study F7 beta and F7–O2 high beta activities are found to be higher in bipolar patients than in their first degree relatives and higher in first degree relatives than in healthy controls.

On the contrary, Pz alpha activity was similar between first degree relatives and unrelated subjects. Lemere remarked in 1936 that 'the ability to produce an alpha wave of quality is associated with brain's affective repertoire'. Previous studies indicate that an increase in alpha power density implies major depression (Itil, 1983, Ulrich et al., 1984).

**Table 6.** Correlations of affective temperament scores and spectral power density of QEEG in unrelated subjects.

| | Depressive temperament | Cyclothymic temperament | Hyperthymic temperament | İrritable temperament | Anxious temperament |
|---|---|---|---|---|---|
| Delta F4 | 0.183 | 0.100 | 0.170 | 0.072 | 0.100 |
| F7 | 0.142 | 0.095 | 0.187 | 0.100 | 0.095 |
| Fz | 0.107 | 0.098 | 0.170 | 0.105 | 0.098 |
| Pz | 0.145 | 0.035 | 0.148 | 0.040 | 0.035 |
| Cz | 0.122 | 0.032 | 0.123 | 0.035 | 0.032 |
| T3 | 0.165 | 0.112 | 0.122 | 0.102 | 0.112 |
| T4 | 0.145 | 0.105 | 0.101 | 0.101 | 0.105 |
| O1 | 0.117 | 0.120 | 0.135 | 0.100 | 0.120 |
| O2 | 0.125 | 0.127 | 0.134 | 0.081 | 0.127 |
| Theta F4 | 0.163 | 0.128 | 0.187 | 0.112 | 0.128 |
| F7 | 0.152 | 0.132 | 0.194 | 0.100 | 0.132 |
| Fz | 0.160 | 0.124 | 0.158 | 0.102 | 0.124 |
| Pz | 0.154 | 0.112 | 0.199 | 0.105 | 0.112 |
| Cz | 0.120 | 0.151 | 0.185 | 0.112 | 0.151 |
| T3 | 0.123 | 0.168 | 0.156 | 0.155 | 0.168 |
| T4 | 0.143 | 0.153 | 0.184 | 0.142 | 0.153 |
| O1 | 0.134 | 0.163 | 0.196 | 0.100 | 0.163 |
| O2 | 0.096 | 0.176 | 0.195 | 0.052 | 0.176 |
| Alpha F4 | 0.111 | 0.155 | 0.089 | 0.091 | 0.121 |
| F7 | 0.067 | 0.152 | 0.055 | 0.065 | 0.120 |
| Fz | 0.078 | 0.133 | 0.112 | -0.178 | 1.131 |
| Pz | 0.152 | 0.170 | **-0.311*** | -0.162 | 0.113 |
| Cz | 0.161 | 0.156 | 0.098 | 0.122 | 0.114 |
| T3 | 0.102 | 0.105 | 0.071 | 0.132 | 0.120 |
| T4 | 0.113 | 0.200 | 0.102 | 0.101 | 0.131 |
| O1 | 0.099 | 0.117 | 0.125 | 0.142 | 0.120 |
| O2 | 0.159 | 0.076 | 0.154 | 0.111 | 0.098 |
| Beta F4 | 0.100 | 0.183 | 0.072 | 0.100 | 0.183 |
| F7 | 0.095 | 0.142 | 0.100 | 0.095 | 0.142 |
| Fz | 0.098 | 0.107 | 0.105 | 0.098 | 0.107 |
| Pz | 0.035 | 0.145 | 0.040 | 0.035 | 0.145 |
| Cz | 0.032 | 0.122 | 0.035 | 0.032 | 0.122 |
| T3 | 0.112 | 0.165 | 0.102 | 0.112 | 0.165 |
| T4 | 0.105 | 0.145 | 0.101 | 0.105 | 0.145 |
| O1 | 0.120 | 0.117 | 0.100 | 0.120 | 0.117 |
| O2 | 0.127 | 0.125 | 0.081 | 0.127 | 0.125 |
| High beta F4 | 0.128 | 0.163 | 0.112 | 0.128 | 0.163 |
| F7 | 0.132 | 0.152 | 0.100 | 0.132 | 0.152 |
| Fz | 0.124 | 0.160 | 0.102 | 0.124 | 0.160 |
| Pz | 0.112 | 0.154 | 0.105 | 0.112 | 0.154 |
| Cz | 0.151 | 0.120 | 0.112 | 0.151 | 0.120 |
| T3 | 0.168 | 0.123 | 0.155 | 0.168 | 0.123 |
| T4 | 0.153 | 0.143 | 0.142 | 0.153 | 0.143 |
| O1 | 0.163 | 0.134 | 0.100 | 0.163 | 0.135 |
| O2 | 0.176 | 0.096 | 0.052 | 0.176 | 0.095 |

Significant figures are shown in bold (r = −0.311, p > 0.05). Pearson correlation test (r).
*p < 0.05.

The interpretation of our findings up to this point is that increased activity in any region in QEEG can be considered not merely a state marker but also a trait marker for an affective episode. Decision process for treating a patient should take into account the 'impaired daily function' criterion in DSM. The clinical diagnosis of an affective episode must be done considering all diagnostic criteria. Temperament is a form of affective disorder with subclinical symptoms that do not require treatment. It is a rather stable, heritable trait biomarker, in other words, an endophenotype.

In this study cyclothymic and hyperthymic temperament scores were found to be similar between patients and their relatives, but higher than unrelated healthy subjects. This finding has already been shown in our previous study (Kesebir et al., 2005a,b). In the same study while depressive and anxious temperament scores were similar in first degree relatives and healthy controls, irritable temperament score were higher in bipolar patients than in first degree relatives and in first degree relatives than in healthy controls. These findings are consistent with the present study.

This study is the first to assess subthreshold affective disorder by QEEG spectral power density in bipolar patients and their fisrt degree relatives. An inverse correlation was found between Pz alpha power and hyperthymic temperament in first degree relatives and unrelated subjects. Hyperthymic temperament was shown to be in direct and linear relation with resilience in major depressive disorder (Kesebir et al., 2015). The inverse relation between hyperthymic temperament score and Pz alpha power in this study may be associated with resilience in first degree relatives and unrelated subjects.

F7 beta and F7–O2 high beta powers were associated with hyperthymic and irritable temperament scores in euthymic bipolar subjects. QEEG beta activity is associated with anxiety, impulsivity and increased psychomotor activity (Güven et al., 2015). Whereas narcissism, risk-taking behaviour, adventuresomeness and being critical of others are common features of hyperthymic and irrirable temperaments, loving fun, high self esteem and sociability are more distinctive for hyperthymic temperament and restlessness, agressivity and dysphoric emotionality for irritable temperament. There is an association between affective temperament and clinical features of bipolar disorder (Kesebir et al., 2005a,b). Kesebir et al. showed a correlation between irritable temperament and mixed and pychotic affective episodes (2005). Lieber and Newbury (1988a,b) describe two groups of depressive cases according to QEEG parameters, in which a group had an increase in beta and/or slow wave and the other an increase in slow wave activity. We interpret the QEEG findings of the bipolar group as cases of depression with mixed features.

T3-F4-T4 delta powers were correlated with cyclothymic temperament in euthymic subjects and first degree relatives. Cyclothymic temperament is defined by intensity and instability as well as cyclicity (Kesebir et al., 2005a,b). Whalley et al. (2011) compared 93 bipolar patient relatives and 70 unrelated healthy subjects on fMRI with Hayling Sentence Completion paradigm and evaluated depressive mood and cyclothymia scores. Increased activity in left amygdala was shown in the risk group and this was suggested as an inheritable risk factor for bipolar cases. While no difference was shown between the two groups regarding the association between increased activity in any region and subthreshold depression and cyclothymia scores, significant correlation was found between ventral striatum activation and depression scores and between ventral prefrontal activation and cyclothymia scores. Whalley et al. suggested prefrontal and striatal activation to be studied in the differentiation of the biological nature of subclinical states in the presence of familial risk, irrespective of disorder state. These findings are not inconsistent with our study.

All euthymic bipolar patients included in the study were on lithium prophylaxis. The aim of giving a uniform treatment was to standardize the prophylactic treatment. Lithium is a mood stabilizer which, when started in manic episode, improves frontal function in the two weeks. It is rather less effective in depressive episode and its prophylectic role includes cognitive function. Whilst lithium normalizes beta, delta and theta activities, basal delta activity is the best indicator of treatment response (Silverston et al., 2005). In light of our findings, the association between the delta activities of healthy first degree relatives and bipolar patients in ongoing remission with lithium, diverting from unrelated healthy controls, seems meaningful in this aspect.

The most important limitation of this study is the small sample size. On the other hand, the use of the same prophylactic agent reflects the representative capacity of the sample. Future studies should investigate into whether similar results will be achieved with different agents. Replicating the same study with new-onset patients would be most valuable, considering the ethical repercussions of studying on patients not receiving prophylaxis in the euthymic period following the first episode.

In conclusion, medial temporal network mediated cyclothymic temperament looks associated with the bipolar affective disorder heritability. On the contrary, increased beta and high beta activities might be a neural marker of resistance to the hyperthymic and irritable nature of the disorder. The inverse correlation between hyperthymic temperament scores and Pz alpha power may be related to resilience in healthy relatives and unrelated healthy subjects.

## Declarations

### Author contribution statement

### Funding statement

### Competing interest statement

The authors declare no conflict of interest.

### Additional information

No additional information is available for this paper.

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