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CFC delta-beta is related with mixed features and response to treatment in bipolar II depression

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ABSTRACT

Objective: The aim of this study was to investigate whether differentiation of delta-beta cross frequency coupling (CFC) in bipolar II depressive episode with mixed features and consecutive remission was observed.
Methods: 8 patient diagnosed bipolar disorder type II, depressive episode with mixed features according to DSM-V, were examined during the current episode, at baseline and end of the third week of lamotrigine use. Hamilton Depression Rating Scale (HDRS) and Mood Disorder Questionnaire (MDQ) were applied to each case at the baseline and end of the third week and QEEG was performed. Temperament was evaluated with TEMPS-A.
Results: dPAC-DB and AAC-DB were significantly higher in FP2 at the end of 3rd weeks of lamotrigine use. A linear relationship was found between F3 dPAC-DB and MDQ scores, before and after treatment. P3 dPAC-DB was correlated with HDRS scores initially only. Cyclothymic temperament scores was found related with dPAC-DB and AAC-DB in F4.
Conclusion: In bipolar disorder, delta-beta CFC was first investigated in this study. CFCs may have a neural projection of the physiopathology of bipolar disorder. At the point we reached in this study, we can show it as both state and trait.

1. Introduction

Bipolar disorder is a disease characterized by chronic and recurrent mood episodes. Depression and mania are mood episodes that are opposite to each other. Depressive and manic episodes with mixed features are phenomenologically rich and physiopathologically chaotic periods as they have both poles of the disease together. However, a mixed features of mood episode offers different possibilities to evaluate together and separate phenomenology and physiopathology of opposite poles of the disease. The core symptom of the disease, affective dysregulation and compensatory regulation effort, is available here.

The fMRI findings of the corticosubcortical coupling between the amygdala and the frontal cortex have been defined as the emotion regulation efficiency index (Banks et al., 2007). QEEG reflects neuronal activity directly with very high temporal resolution (Kesebir and Yosmaoğlu, 2018). Affective dysregulation can be manifested by an irregularity in slow and rapid wave formation on EEG. It has been suggested that the relationship between slow and rapid wave activity is a reflection of corticosubcortical interactions involving affective processes (Knyazev, 2007). Cognitive function and psychomotor activity are other components of this relationship. As a matter of fact, there is a valuable relationship between an attention and an efficacy of emotion regulation capacity (Rueda et al., 2005). The increase in beta power induced by slow wave activity is associated with increased cortical activity suggesting that regulation of negative affect is associated with attentional control.

An increased delta-beta coupling in the frontoparietal region serves a better executive function, an increased inhibitory control, a decision-making characterized by advantageous choices, and less interference (Schutter et al., 2006; Putman, 2011). These three functions were injured in bipolar patients. The important question at this point is whether the increase in cross frequency coupling (CFC) delta-beta is adaptive or not, and how independent and trait anxiety or dysthymia are. Previous publications have reported a reduced frontal delta-beta CFC in obsessive-compulsive anxiety, social phobia and trait anxiety (Putman et al., 2012; Poppelaars et al., 2018). In a study conducted with healthy individuals, Morillas-Romero et al. (2015) showed an association between stronger delta-beta CFC at parietal sites and higher self-reported attention control in performance based attentional network functioning. Delta-beta CFC was not only unrelated to orientation and alertness, but also that the expected reduction in theta/beta ratio did not

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accompany this change. According to their results, automatic cognitive processes seems to be less sensitive to state anxiety, providing better executive function in the absence of emotional content. This findings has directed the interest to the role of the affective component.

In the literature, there is no study investigating delta-beta CFC in any affective disorder. The aim of this study was to investigate whether differentiation of delta-beta CFC in bipolar depressive episode with mixed features and consecutive remission was observed.

2. Methods

The study protocol was approved by the local ethics committee. All of our patients have informed consent.

2.1. Sample

For this purpose, 8 patient diagnosed bipolar disorder type II, depressive episode with mixed features according to DSM-V, were examined during the current episode, at baseline and end of the third week of lamotrigine use.

The mean age of the 5 female and 3 male patients was 38.22 ± 6.15 years and the mean age of onset was 21.74 ± 2.39 years.

The common characteristics of eight patients are as follows:

i. They presented with complaints of reluctance, tension and intolerance all day long. So far, there are no psychiatric applications and treatment history.
ii. Psychiatric examination revealed irritable mood, free float anxiety, increased psychomotor activity, obsessive rumination and impulsivity, early insomnia, and diurnal variation.
iii. The history of major depressive disorder and hypomania, alcohol and substance abuse, emotional neglect, upsetting, but above average occupational functionality.

2.2. Assessment and process

Hamilton Depression Rating Scale (HDRS) and Mood Disorder Questionnaire (MDQ) were applied to each case at the baseline and end of the third week and EEG was performed. MDQ has been selected from the opposite pole to determine its properties and the severity of these properties.

Lamotrigine is one of the recommended treatment options for bipolar disorder type II depressive episode. Following the diagnostic interview and measurement application, lamotrigine was started at the first day with a dose of 25 mg/day, 50 mg/day at the end of the first week and 100 mg/day at the end of the second week. Patients did not report any side effects other than headache and dyspepsia, which would not require treatment.

Affective temperament was measured with TEMPS-A (Temperament Evaluation of Memphis, Pisa, Paris and San Diego Auto questionnaire) Temperament Scale (Vahip et al., 2005). Affective temperament is situated in the mildest end of the bipolar spectrum (Kesebir et al., 2005a,b). Affective temperament is a suggested endophenotype for bipolar disorder as well (Kesebir et al., 2005a,b). The predisposition is decisive, it is inherited together with the disease, it gives color to the disease periods, it is also observed outside the disease periods as trait. Affective temperament originates in brain structure, and individual hereditary differences are attributable to differences in neural and physiological function. At this point, it was chosen to demonstrate subthreshold affective dysregulation as a trait at the time of posttreatment remission period.

2.3. QEEG

QEEG aplications were done in a quiet, subtlylit room, in sitting position, with eyes closed. Recording time was 3 minutes. 3 minute artifact free recording corresponds to T = 180 × 125 = 22500 sample points for each electrode which means N = 6 × 22500 = 135000 points for each subject with QEEG. Then PAC and dPAC analysis calculates single value from total 22500 sample point for each channel before statistical tests.

QEEG was recorded continuously at af_s = 125 Hz sampling rate using 10–20 electrode Ag–AgCl electrodes. Linked mastoid electrodes (A1-A2) were used for reference during acquisition. Phase-amplitude coupling (PAC) for delta-beta was calculated for the six electrodes representing brain regions (FP2, F3, F4, C3, C4, P3). Whereas we selected 6 electrodes through distinct ones due to involving multiple channels separated by very small distances. We selected 6 electrodes to prevent capacitive coupling (cross-talk) among electrodes. Cross-talk spatially smooths current source density (CSD) estimates in these recordings and induces artefactual phase shifts especially in the importance of phase amplitude voltage gradients (PAC) occur. The nodes consisting of FP2, F3, F4, C3, C4, P3 were also representing the best locations in depression. FP1 is more affected by the noice of eyeblink and P4 is affected by parietal muscle noise (Tenke and Kayser, 2005).

Offline pre-processing of the QEEG time series was performed using Brain Vision Analyzer (BVA, Brain Products GmbH, 2015). Each time-series was re-referenced to the average of all electrodes and band-pass filtered between 0.5-40 Hz (24 dB/oct slope) with a 50 Hz notch filter (zero-phase shift). Each QEEG channel is segmented into each 8-sec non-overlapping epochs with a length of $n = 1000$ time samples($\Delta t\ (sec) = 1/f_s$) allowing for capturing low-frequency cycles.The total number of epochs is 6 after first and last ten epochs were excluded from the total record. The selected QEEG epochs were band-bass filtered separately for delta (1–4 Hz) and beta (14–30 Hz) using a Butterworth IIR bandpass filter (FieldTrip MATLAB toolbox) by using a zero phase-shift filtering with the orders of 8 for delta and 34 for beta. The order becomes doubled after using both a forward and backward filter to get necessary zero phase values) with using split the filter in two lower-order filters, apply sequentially for removing filter instabilities.

A Hilbert transform (Freeman, 2007) was finally applied for each band in each channel separately to extract phase (φ_t) and amplitude (a_t) information. The first and last 16 samples from each epoch are cut to remove edge artifacts from filtered signals.

2.4. Mathematical approach

Phase-amplitude coupling (PAC) gives the results between delta phase and beta amplitude as

$$PAC = \frac{1}{n}\sum_{t=1}^{n} a_t e^{i\varphi_t}$$

wherea_t denotes the amplitude of the beta amplitude and φ_t denotes the phase of the delta phase, t is the time and n is the total number of time samples.

We calculate the phase clustering ($\overline{PC}$) complex value from mean of the complex vector of phase angles over the n , which is total number of time samples.

$$\overline{PC} = \frac{1}{n}\sum_{t=1}^{n} e^{i\varphi_t}$$

This is correcting value for the complex phase angles of the delta phase.

Finally, we obtain *dPAC* number using the corrected delta phase over, the total number of time samples and taking the modulus of the number.

$$dPAC = \frac{1}{n}\sum_{t=1}^{n}\left|a_t e^{i\left(\varphi_t - \overline{PC}\right)}\right|$$

Where $dPAC = 0$ indicates no coupling and other values greater than zero (absolute) indicate coupling strength.

Amplitude-amplitude coupling (AAC) correlation analysis based on

Pearson correlation coefficient.

The delta and beta power pairs are obtained using following identities.

$$\beta_{pow} = \left| a_t^{\beta} e^{i\varphi_t^{\beta}} \right|$$

$$\delta_{pow} = \left| a_t^{\delta} e^{i\varphi_t^{\delta}} \right|$$

After the mean of 4 Hilbert transformed channels for each epoch is taken, Pearson correlation coefficient is obtained which is based on the covariance matrix to evaluate the coupling strength of the relationship between beta(β) and delta (δ) power vectors (complex modulus) of Hilbert transformed values,

$$P(\beta_{pow}, \delta_{pow}) = \frac{cov(\beta_{pow}, \delta_{pow})}{\sqrt{var(\beta_{pow}) var(\delta_{pow})}}$$

where *var* denotes the variances of beta and delta power vectors for each vector.

Then, the absolute values of Pearson coefficientswere transformed into Fisher's *z* (normally distributed) values. Finally,two-tailed p-value is obtained from *z*-value, based on a normal distribution.

2.5. Statistical analysis

Non-parametric sequential measurements were used to make comparisons between measurements at baseline and at the end of the third week. Correlation analysis was used with Pearson correlation test. All tests were two-tailed and significance was accepted as $p < 0.05$.

3. Results

Phase-amplitude coupling delta-beta (dPAC-DB) and amplitude-amplitude coupling delta-beta (AAC-DB) values before and after treatment are summarized in Tables 1 and 2. Fig. 1 shows the distribution of dPAC-DB before and after treatment. dPAC-DB and AAC-DB were significantly higher in FP2 at the end of 3rd weeks of lamotrigine use (Tables 1 and 2) (Fig. 1).

All patients responded to treatment after three weeks of lamotrigine use.HDRS and MDQ scores are compared in Table 3.

Correlations between dPAC-DB values and HDRS and MDQ scores baseline and at the end of 3rd weeks are summarized in Table 4. There was a relationship between P3 dPAC-DB and pretreatment HDRS scores ($r = 0.271$, $p = 0.042$). There was no correlation between HDRS scores and dPAC-DB at any site after treatment. A linear relationship was found between F3 dPAC-DB and MDQ scores, before and after treatment ($r = 0.412$, $p = 0.003$ ve $r = 0.315$, $p = 0.038$). No relation was found between AAC-DB detected in any electrode and HDRS or MDQ scores.

A relationship was found between F4 dPAC-DB and cyclothymic temperament scores ($r = 0.298$, $p = 0.025$). Another relationship with cyclothymic temperament scores was found in F4 AAC-DB ($r = 0.412$, $p = 0.018$).

Table 1
Pre- vs Posttreatment dPAC-DB.

	Baseline (Pretreatment)	End of 3rd week (Posttreatment)	Analysis ($p <$ 0.05)
FP2	0.21 ± 0.09	0.27 ± 0.08	**0.031**
F3	0.20 ± 0.11	0.17 ± 0.12	0.072
F4	0.17 ± 0.08	0.18 ± 0.05	0.132
C3	0.16 ± 0.10	0.20 ± 0.09	0.070
C4	0.19 ± 0.10	0.21 ± 0.11	0.105
P3	0.19 ± 0.03	0.21 ± 0.05	0.098

Bold signifies $p < 0.05$.

Table 2
Pre- vs Posttreatment AAC-DB.

	Baseline (Pretreatment)	End of 3rd week (Posttreatment)	Analysis ($p <$ 0.05)
FP2	− 0.01 ± 0.01	0.04 ± 0.03	**0.047**
F3	0.06 ± 0.04	0.07 ± 0.06	0.474
F4	0.18 ± 0.11	0.20 ± 0.05	0.232
C3	0.25 ± 0.13	0.29 ± 0.12	0.567
C4	0.21 ± 0.04	0.25 ± 0.14	0.252
P3	0.14 ± 0.06	0.18 ± 0.10	0.428

Bold signifies $p < 0.05$.

4. Discussion

CFCs between different neural oscillations are complex cortical computations of the brain's coordinates, which serve as a kind of stres response (Başar, 2006). In bipolar disorder, delta-beta CFC was first investigated in this study and significant findings regarding the pathophysiology of the disease have been demonstrated.

The corticolimbic seesaw was disrupted in bipolar disorder. The discordance of frontal and limbic activity is favorable to the limbic system in all periods of the disease, in QEEG measurements (Kesebir and Yosmaoğlu, 2018). In fact, frontal activity is decreasing in the inferior frontal gyrus especially in the right side in mania, and particularly usual in euthymia and depression. Limbic system activity is increased independently of mood episodes.

Considering the efficacy of lamotrigine in the treatment of bipolar disorder, it has been reported that it contributes to healing by suppressing the amygdala activity in the depressive period, regulates the emotion and cognitive regulation in the ventro and dorsolateral PFC, and enhances emotional stability by regulating the activity in the prefrontal and cingulate cortex in euthymia (Chang et al., 2010; Pavuluri et al., 2010; Kesebir et al., 2013).

All patients responded to treatment at the end of the third week in this study. The treatment response was reflected in both HDRS and MDQ scores, which meant that the mixed symptoms with depressive symptoms also regressed which would be the possibility of a switch otherwise. Delta-beta CFC was found to be increased in the 5 site at the end of the third week due to treatment response. This increase is significant in FP2.

On the other hand, we found that dPAC delta-beta decreased in F3 at the end of the third week of treatment with lamotrigine, as opposed to the other regions especially right frontoparietal regions. Moreover, it is correlated with MDQ scores before and after treatment in this area. When we examine the MDQ items one by one, we see that the items that are marked as positive are impulsivity related items.

With the control provided at this point, the cost of the decrease in impulsivity is a little bit cognitive impairment we think. The cognitive side effects of fifth and eighth cases can be seen more clearly and in detail. The patient findings are as follows “From the examination room to the interview room, I would had the ability to give the order, now I have to stop and think”, ‘Didn't I say? I've been asking several times in the day, this is not something I've ever done or “I can't find a word in a sentence, I don't like to remember that name” which all are seems in the form of working memory and processing speed, and verbal fluency. We would also like to remind you of some disruptive effects of anticonvulsants on cognitive function (Şentürk Cankorur et al., 2017). In the literature, there is no study of lamotrigine monotherapy among studies investigating the effects of anticonvulsants on cognitive function in bipolar disorder. The most limitation of this study is that the cognitive function is not measured.

On the other hand, delta-beta dPAC was found to be associated with HDRS scores in P3. At this point, the role of the emotional component of frontolimbik seems to be more dominant. To sum up, fronto-limbic system acts like a tilting board which its’ axis can be shifted by displaceable weights. Attention is one of them, as it functions. Another is physical activity, which should be the subject of future studies. Others can be listed as sleep, nutrition, photoperiodicity and temperature (Kesebir, 2018).

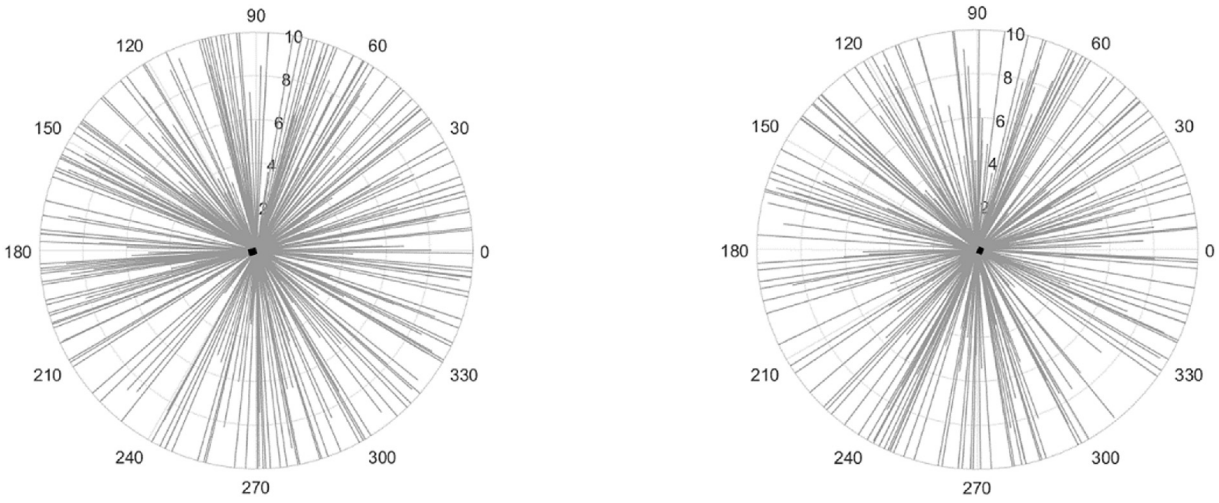

Fig. 1. Polar representation of Phase-amplitude couple values pretreatment (left) and posttreatment (right). - Shorter segments indicate less coupling at a given angle.

Table 3
Pre- vs Posttreatment HDRS ve MDQ scores.

	Baseline (Pretreatment)	End of 3rd week (Posttreatment)	Analysis ($p < 0.05$)
HDRS (Mean ± SD)	24.05 ± 4.31	10.70 ± 1.82	**0.032**
MDQ (Mean ± SD)	33.27 ± 7.83	9.16 ± 2.08	**0.001**

Bold signifies $p < 0.05$.

Table 4
Pre- and Posttreatment correlations between dPAC-DB and HDRS and MDQ.

	HDRS		MDQ	
	Baseline (Pretreatment)	End of 3rd week (Posttreatment)	Basaline (Pretreatment)	End of 3rd week (Posttreatment)
FP2	0.178	0.077	0.244	0.220
F3	0.101	0.086	**0.412**	**0.315**
F4	0.125	0.102	0.201	0.153
C3	0.098	0.115	0.103	0.086
C4	0.103	0.128	0.123	0.093
P3	**0.271**	0.150	0.205	0.178

Bold signifies $p < 0.05$.

Another important finding of our study is delta-beta dPAC and AAC, which correlates with cyclothymic temperament scores in F4. Pretreatment and posttreatment delta-beta coupling, the least change in this region. That is not surprising in the least change of the correlation, because affective temperament is relatively stable which originates in brain structure and it is inherent, and individual hereditary differences are attributable to differences in neural and physiological function. Affective temperament is situated in the mildest end of the bipolar spectrum (Kesebir et al., 2005a,b). It gives color to the disease periods, it is also observed outside the disease periods as trait. Cyclothymic and hypertymic temperament is a suggested endophenotype for BD as well (Kesebir et al., 2005a,b). In our previous study, F4 delta power was found to be correlated with cyclothymic temperament scores, and differentiated from unrelated healthy controls in the patients and first degree relatives (Kesebir et al., 2019).

The most important limitation of this study is the number of samples. The reason for this is to obtain the most homogeneous group according to clinical and temperamental properties. The lack of measurement of cognitive function is an other limitation of this study. On the other hand, we do not have literatüre on the effect of lamotrigine on cognitive function in patients with bipolar disorder.

5. Conclusion

CFCs may have a neural projection of the physiopathology of bipolar disorder. At the point we reached in this study, we can show it as both state and trait.

The dependence of the amplitude of rapid beta rhythm (14–30 Hz) on the phase of delta, which is lower frequency rhythm (1–4 Hz) as referred to phase-amplitude coupling (PAC) is implemented. dPAC-DB values were associated with state impulsivity in frontal and state depression in parietal regions. On the other hand, the amplitude of the slow delta wave regulates the amplitude of the rapid beta wave in amplitude-amplitude coupling as referred to delta-beta AAC. In this case, no correlations with HDRS or MDQ scores for delta-beta AAC have been shown. The AAC-DB seems to be a trait sensitive adaptive mechanism. As a matter of fact, a relationship was found between F4 AAC-DB and cyclothymic temperament scores.

Delta-beta CFC functions as a type of stres response at the beginning of the disease period. This stres response can be considered a cortico-subcortical conversation. As in the case of sunny melancholics (Akiskal and Mallya, 1987), irritability is derived from anxiety (Parker et al., 2002). It is determined temperately that which individuals produce such a stres response.

Depressive mood is limited to alpha frequency and power in a mild to moderate depression, whereas with theta frequency and power with obsessive rumination, delta frequency and power is shaped by increased anxiety and psychomotor retardation. Increased attention at this point is a compensatory change in physical and metabolic activity and reduced need for sleep with phase delay. Delta-beta CFC on the qEEG corresponds to attentional control, reward dependence, irritability and impulsivity and other mixed symptoms. At this point, the keyword is that cortico-subcortical dialogue is stil ongoing.

The severity of any episode, is aggravated from front to back, from top to bottom, from middle to side. The next phase where delta-beta CFC breaks off is the shear of the coil spring and euphoria empties. The assessment of reality is disturbed, paranoia and persecution, hostility and aggression dominated if the next phase is not intervened. The alternative pathway at this breaking point is maximum cognitive loss.

Declarations

Author contribution statement

Sermin Kesebir: Conceived and designed the experiments; Performed

the experiments; Analyzed and interpreted the data; Wrote the paper.

Rüştü Murat Demirer: Analyzed and interpreted the data.

Nevzat Tarhan: Contributed reagents, materials, analysis tools or data.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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