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Original article

Response to venlafaxine on EEG in unmedicated bipolar depression: which entropy, up or down?

Sermin Kesebir, Sultan Tarlacı, Rüştü Murat Demirer, Nevzat Tarhan

Üsküdar University, NPİstanbul Brain Hospital, İstanbul, Turkey

SUMMARY

Objective

We examined changes in the entropy area in bipolar depression patients at baseline and at the end of the first hour following per oral 75 mg venlafaxine intake.

Methods

For this purpose, 10 patients diagnosed with bipolar disorder type I, depressive episode according to DSM-5, who applied to our outpatient unit and gave voluntary consent for our study were evaluated consecutively. EEG was taken at the end of the first hour following basal and per oral 75 mg venlafaxine intake. Different entropies were calculated by transferring the last sample digital data with EZ-Entropy software. EZ-Entropy software is a free distributed program that automatically and also user friendly calculates entropy. It basically works via the MathLab interface.

Results

Four entropy types among seven types of entropies are increased (ApEn, SampEn, FuzzyEn, PemEn), while three entropy types decreased (DistEn, CEn, SDEn). All these mean entropy changes in increases and decreases were statistically significant under paired samples t-test correlation results.

Conclusions

Pathologies thus seem to reduce the brain's adaptation ability to response stimuli, or in other words make the brain less prone to deviate from equilibrium. This is nevertheless not homogeneous.

Key words: entropy, bipolar depression, venlafaxine

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Correspondence
Sermin Kesebir
Üsküdar Üniversitesi, NPİstanbul Beyin Hastanesi, Ahmet Tevfik İleri C. N: 18, 34768 Ümraniye, İstanbul, Turkey
E-mail: sermin.kesebir@uskudar.edu.tr

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Introduction

Mood disorder is an irregularity between slow and fast wave activity. It has been suggested that the relationship between slow and fast wave activity reflects cortical and subcortical interactions, including emotion processing [1]. Another component of this process is attention. As a matter of fact, it was defined as "mood regulation capacity index" in the fMRI findings showing the cotico-subcortical coupling between the amygdala and the frontal cortex. An increased delta-beta coupling in the frontoparietal region means better executive function, such as an increased inhibitory control and healthy decision-making processes [2]. In bipolar cases, these functions are disabled [3]. On the other hand, previous studies have found entropy lower than healthy controls, not only bipolar cases, even they ve found lower entropy in theirs families [4]. As a matter of fact, bipolar cases have a more rigid structure, they cannot easily show flexibility, whether they use coping strategies, their motivation and ability to change the environment.

The ability to produce a quality alpha wave is associated with the individual's affective repertoire. Brain operates phase synchronizations in healthy

processes in the same way. i) in situations that develop suddenly; ii) in situations that stimulate past memories; iii) in decision making processes. Moreover, under normal circumstances, it tends to consistently create these phase synchronizations. Chaos occurs when entering and exiting these synchronizations due to brain ability to adapt and function in continuously changing conditions. Brain shows the entropy changes due to these transitions with emanating larger instantaneous entropy values.

Completely random distribution and complexity nature has maximum entropy [5]. Aging or diseased status usually emanates with reduced entropy values within the dynamics of physiological structure. The physiologic signals from a healthy system should exhibit a higher complexity value than a pathologic and aging system [6,7]. There are different entropy measures to quantify the complexity.

It has been repeatedly demonstrated in various studies that serotonin noradrenaline reuptake inhibitors are more effective agents on bipolar depression [8]. In bipolar depression, the antidepressant effect should be a decrease in both slow and fast wave activity. The aim of this study is to investigate this change in the field of entropy. We examined changes in the entropy area in bipolar depression patients at baseline and at the end of the first hour following per oral 75 mg venlafaxine intake.

Methods

Sample

For this purpose, 10 patients diagnosed with bipolar disorder type I, depressive episode according to DSM-5, who applied to our outpatient unit and gave voluntary consent for our study were evaluated consecutively. Patients, receiving preventive treatment or any treatment for the current depressive episode were excluded.

The average age of 6 women, 4 men, as total 10 patients is 35.8 ± 7.6 and the duration of the disease is calculated as 8.4 ± 4.1 years.

Assessment tool

EEG was taken at the end of the first hour following basal and per oral 75 mg venlafaxine intake.

EEG and entropy analysis

Nine minutes of analog EEG (sample rate 125 Hz/second) was taken before and after medication. EEGs were cleared of possible artifacts. Analog EEG data was converted to digital with EDFBrowser Ver 1.7. This digital data was downsampleed from 125 Hz to 25 Hz due to the import limitation of the entropy analysis software program. After the downsample of original analog EEG, 12.400 lines of digital data were obtained from the 8.3-minute EEG sample. In this way, an EEG sampling was made in 40 msec as 25 Hz. Different entropies were calculated by transferring the last sample digital data with EZ-Entropy software. EZ-Entropy software is a free distributed program that automatically and also user friendly calculates entropy. It basically works via the MathLab interface, but standalone can work [9].

Seven different entropy types (approximate [ApEn], sample [SampEn], fuzzy [FuzzyEn], conditional [CEn], permutation [PerEn], distribution [DistEn] and sparsity density entropy [SDEn]) were calculated automatically with EZ-Entropy software before and after drug administration from the sampled EEGs. In the analysis of enthalpies, embedding dimension 2 and time delay 1 were taken. For ApEn, SampEn and FuzzyEn, the threshold value of 0.2XSD was taken. For DistEn, bin number 256 is accepted. For CE, quantification level 6 was accepted.

Statistically analysis

The entropy values obtained for different brain regions (frontal, temporal, parietal, occipital and vertex) and left-right hemispheres were compared with the paired sample t-test.

Results

As shown in Table I, seven different entropy type drugs were calculated before-after application. The mean differences over 10 patients between premedication and postmedication periods are calculated for each of seven different type of entropies. Four entropy types among seven types of entropies are increased (ApEn, SampEn, FuzzyEn, PemEn), while three entropy types decreased (DistEn, CEn, SDEn). All these mean entropy changes in increases and decreases were statistically significant under paired samples t-test correlation results.

As shown in Table I, it was determined that there was no statistically significant difference especially in DistEn ($r = 0.10$ and $p = 0.214$) and CEn entropy methods(for pre and post medication periods, $r = 0.150$ and $p = 0.06$).Whether or not the statistically significant change in mean value of entropies over 10 patients is an indirect indicator of treatment efficiency which is an indication that the drug administered has not changed the conditions. From this point of view, ApEn ($r = -450$ and $p = 0.001$), SampEn ($r = -32$ and $p = 0.001$), FuzzyEn ($r = -0.370$ and $p = 0.001$), PermEn ($r = -0.25$ and $p = 0.002$) and SDEn ($r = 0.240$ and $p = 0.003$) continued to a certain degree with moderate or apparent positive-negative statistical significance. This can be taken as an indirect indication that the change of mean entropy values between pre and after drug administration is not distinct or reveal subtle differences.

On the other hand, different type of entropy values were analyzed based on mean entropy change between premedication and post-medication periods in the cer-

TABLE I. *In the whole brain before and after paired samples t-test correlation (n = 10).*

	Mean	Mean difference	Std. deviation	Std. error Mean	Paired sample t-test, *t*	Paired sample t test, *p*	*Correlation, r*	*Correlation p-value*
ApEnPre	1.843		.3358	.0272				
ApEnPost	1.972	-.128959	.1151	.0093	-3.962	*0.001*	-.453	*.001*
SampEnPre	1.573		.4151	.0336				
SampEnPos	1.730	-.156938	.1869	.0151	-3.811	*0.001*	-.326	*.001*
FuzzyEnPre	1.227		.2869	.0232				
FuzzyEnPos	1.330	-.103119	.1547	.0125	-3.405	*0.001*	-.373	*.001*
DistEnPre	.6670		.1070	.0086				
DistEnPos	.6250	.042196	.1183	.0096	3.488	*0.001*	.101	***.214***
PermEnPre	2.568		.0364	.0029				
PermEnPos	2.582	-.013828	.0028	.0002	-4.577	*0.001*	-.252	*.002*
CEnPre	.9844		.4903	.0397				
CEnPost	.8790	.105027	.5522	.0447	1.902	*0.050*	.152	***.062***
SDEnPre	.3871		.1170	.0094				
SDEnPost	.3393	.047740	.1142	.0092	4.132	*0.001*	.242	*.003*

ebral lobes (frontal, temporal, parietal, occipital, vertex) individually. Accordingly, the most obvious changes in entropy were observed in the frontal lobe.Total entropy of frontal electrodes ApEn (mean difference [MD] = -0.565 and p = 0.017), SampEn (MD = -0.179 and p = 0.027), FuzzyEn (MD = -0.122 and p = 0.042) and PermEn (MD = -0.0153 and p = 0.013) were significantly increased. By the contrary, DistEn (MD = 0.0379 and p = 0.105), CE (MD = 0.046 and p = 0.599) did not reveal any significant change in the frontal region. Moreover, SDEn entropy decreased significantly (MD = 0.0482 and p = 0.030).

Entropy changes in other cerebral lobes mostly changed on a single electrode basis. Accordingly, only the ApEn (MD = -0.151 and p = 0.054) and SampEn (MD = -0.192 and p = 0.051) in the temporal lobes revealed a statistically significant change.When the parietal lobe electrodes were analyzed, only a significant entropy reduction was detected in SDEn (MD = 0.064 and p = 0.027) type entropy. When looking at the mean entropy change in vertex electrodes, DistEn (MD = 0.046 and p = 0.039) increased, while PermEn (MD = -0.013 and p = 0.019) and SDEn (MD = 0.048 and p = 0.041) were decreased. As an interesting finding, no change in entropy type was observed in the occipital region electrodes after drug administration.

Seven different types of entropy changes were compared between the right hemisphere related to emotions and the left hemisphere related to cognition (Tab. II). Accordingly, after drug administration, especially in the right hemisphere, Entropy (ApEn), SampEn which has data length independence, Fuzzy Entropy (FuzzyEn) and Permutation Entropy(PermEn) statistically significant increase entropy was observed; A decrease in DistEn, cross-entropy (CE) and SDE methods was detected, but these reductions were not statistically significant changed. In the left hemisphere, there was a change in all entropy methods except CE A statistically significant increase was detected in ApEn, Sample Entropy (SampEn), Fuzzy En and PermEn. On the other hand, while statistically significant decrease was observed in DistEn and SDEn entropies, it did not show a significant change despite the decrease in cross-entropy (CE) method.

Discussion

In our study, at the end of the first hour following PO 75 mg venlafaxine intake, we observed a relative change in the entropy areas of the whole brain. Sparsity / density entropy showed a significant difference between pre and post-medication, while pre and post-medication correlation coefficients differed from each other. We interpret that that there is an increase in chaos. Chaos is a spread over in the widest spectrum, in the range of 0.1-70 Hz. In other words, it is a degree of growth rate in phase space. During chaos stage transition, periods of small frequencies doubling over large periods of fre-

quencies and periods of large frequencies over small frequencies vice versa. This happens in smoothly mixing for a short time. The prolongation or shortening of the chaotic transitions may reveal a disorder.

From application of the seven different type of entropy methods, we performed EEG data before and after Venlafaxine drug administration. We obtained results that may appear inconsistent when viewed superficially. There are different types of entropy approaches, and the mathematical algorithms to calculating these entropies are different from each other. It can be said that while some entropies increase in certain brain lobes or hemispheres, other methods decrease due to differences in basic mathematical assumptions used in entropy analysis rather than inconsistency. In relation to this, in many neurological and psychiatric diseases, different entropy analyzes do not indicate a consistent decrease or increase. For example, while Sample Entropy (SampEn) increased in EEG analysis in Parkinson's disease, ApEn increase was detected in EEG- electrophysiological recordings of globus pallidus internus.Approximate Entropy and Sample Entropy are two algorithms for determining the regularity of EEG data based on the assumptions for the existence of patterns must be known apriori [10]. Theoretical ideas behind those seven type of techniques are different. Even though all seven Entropy methods aim to measure of the amount of uncertainty associated with a given variable (EEG time series on electrodes) but only its distribution of structural changes in the temporal region must be known as an assumption.Moreover, even though those of entropy equations are useful for deterministic processes, small amounts of noise make them very sensitive for chaotic EEG data.

Although increased entropy value is generally associated with a disorder, disorder, or a diseased condition whereas the decrease in entropy is linked to order and well-being. However, there is always an irregularity in nature, and this is a general trend which is the common rule in breathing, physiological increments and brain waves. Outliers in entropy values can be directly related to the disease itself. In this study, the increase or decrease in some types of entropy values can cause illusion in the form of anticipated entropy reduction with the well-being of antidepressant. This expectation is probably based on the preliminary acceptance based on both physical-spiritual order, creativity and their electrophysiological responses reflections are associated with the increase in entropy values. On the other hand, a decrease in entropy may also be an indicator of poor health. Physiological and mental health status are also in duplicate with the ability to create a flexible response that can vary with environmental stimuli. Inelasticity, rigidity or loss of chaotic dynamics of oscillations among neuron populations may be an indication of the diseased state. In some cases, moving away from pure order may cause the symptoms of the disease to be relieved as a clinical appearance.

On the other hand, the entropy decrease occurs in epilepsy disease is such an example. In some epilepsy patients, when seizure control is clinically and electrophysiologically excellent, the psychotic picture may appear. The way to correct psychosis is to reduce the medication of patients with this condition to such an ex-

TABLE II. *Comparison of entropies before and after in right hemisphere-left hemisphere.*

			Paired differences		t	Sig. (2-tailed)
			Mean	Std. deviation		
Right hemispheric electrodes	Pair 1	ApEnPre - ApEnPost	-.140329	.421113	-2.666	**.010**
	Pair 2	SampEnPre - SampEnPost	-.162347	.516499	-2.515	**.014**
	Pair 3	FuzzyEnPre - FuzzyEnPost	-.107468	.379059	-2.268	**.027**
	Pair 4	DistEnPre - DistEnPost	.034550	.148214	1.865	.067
	Pair 5	PermEnPre - PermEnPost	-.014131	.039323	-2.875	**.006**
	Pair 6	CEnPre - CEnPost	.069534	.639844	.869	.388
	Pair 7	SDEnPre - SDEnPost	.033440	.134765	1.985	.056
Left hemispheric electrodes	Pair 1	ApEnPre - ApEnPost	-.118707	.398328	-2.384	**.020**
	Pair 2	SampEnPre - SampEnPost	-.152768	.516954	-2.364	**.021**
	Pair 3	FuzzyEnPre - FuzzyEnPost	-.098316	.380829	-2.065	**.043**
	Pair 4	DistEnPre - DistEnPost	.048758	.151903	2.568	**.013**
	Pair 5	PermEnPre - PermEnPost	-.014053	.037310	-3.013	**.004**
	Pair 6	CEnPre - CEnPost	.146388	.700102	1.673	.099
	Pair 7	SDEnPre - SDEnPost	.064122	.138473	3.705	**.000**

tent that mild EEG disorder occurs [7]. In other words, it aims to compensate clinical reflection by allowing entropy increase change in EEG with same amount of reduced entropy change. Another condition on increase of entropy associated with the disease is caused by the decrease or loss of cardiac RR variability (entropy) that occurs in diabetic autonomic neuropathy. People who normally experience RR variability die 5 years earlier. Another situation is the detection of decreased AppEn and SampEn, which occurs in the case of cognitive impairment in Alzheimer's disease [11].

According to our findings, at the end of the first hour following PO 75 mg venlafaxine intake, the change in the relative entropy, in other words, the increase in chaos, occurred significantly in the frontal lobes and also right hemisphere. Du et al. showed a relationship between Sample Entropy (SampEn) and cognitive impairment in Fp1 and Fp2 that spread over to theta, alpha, beta and gamma frequencies in their study with schizophrenia cases [12]. The first in our two findings is that depressive symptoms evolve into mixed features, which our patients expressed as a subjective sense of tension and increased psychomotor activity, the second finding is that the frontoparietal network had a more dominant role.

In our previous study, we showed that an increased delta-beta coupling in the frontoparietal region which means a better executive function, like an increased inhibitory control and healthy decision-making processes [2]. Indeed, in both schizophrenia and bipolar disorder, entropy decreases during task performance, regardless of pharmacological treatment and structural connectivity [13].

The emergence of mixed symptoms in the form of increased psychomotor activity can be interpreted as a compensating effort during the depressive period, which can be defined as a condition in which hemostasis is disturbed in other words. It will be determined by the temperamental factors to which point it plays a compensatory role and at what point it is a sign of disease. In our cross-frequency coupling (CFC) studies, we found this situation as both a trait and mixed symptoms to cope with depressive symptoms and we found those symptoms as a state that defines mixed symptoms [2]. Mixed symptoms, often occurring in the form of increased psychomotor activity, seem to be a positive feature in depression, such as increased energy in the short term and improvement in cognitive function, but mixed symptoms in longitudinal course are not desired. The mixed period, considered a manic shift counterpart, is associated with an increased risk of suicide and an increase in cycle frequency. As a matter of fact, Areteus stated before 150 BC: "It seems to me that mania is a more severe form of depression following depression".

The propagation of wide range of frequencies at period doubling and chaotic regions of the brain introduces infinite possibilities associated with higher entropy growth. This entropy growth during the chaos is directly proportional to the homogeneity of this spread until a stability region of the fixed point as entropy increases and stops. This increase is directly proportional to the homogeneity of this spread. On the contrary to the density of the scrambled egg at different points as an analogy, we understand how well the egg is whipped and how homogenized it is from the relative increase in entropy. For any psychiatric disorder, the relative change of entropy at any time interval may be another biomarker.

Yanbing et al. (2012) in his study including fMRI signals, sample entropy (SampEn) of the patients characterized for schizophrenia while performing a social exclusion task was higher than healthy controls [14]. EEG signals from patients with Parkinson disease (PD) showed higher entropy in the frequency domain at resting state [15]. Higher neuronal entropy in the globus pallidus interna involved in the regulation of voluntary movement has been reported in the patients with Parkinson Disease [9]. Apomorphine, induce a decrease in entropy measured in the inter spike intervals of subthalamic nucleus. Zanin et al. (2019) compared patients with schizophrenia, Parkinson and epilepsy with permutation entropy (PermEn) in terms of time irreversibility [16]. Evoked Potential responses changed timeseries in patients with schizophrenia and Parkinson's disease, but remained stable in epilepsy cases. Using Approximate entropy (ApEn) and SampEn showed reduced complexities in EEG signals for Alzheimer disease (AH) have been reported [17,19].

The complexity of EEGs at different time scales might represent smaller and larger scales in network connectivity of the brain in AD patients. The neurophysiological mechanism underlying the contradiction between decreased EEG complexity across fine scale factors (shorter time scales) and increased complexity (entropy) at coarser scale factors (longer time scales) for severe Alzheimer Disease patients globally across brain regions remains not clearly understood in characterizing both short and long range temporal correlation dynamics.

Consequently, relative entropy change should not be considered as a simple increase or decrease in diseases such as Parkinson, Alzheimer's, schizophrenia and bipolar disorder. Instead, the observed abnormalities in behavioral patterns reflect a quantifiable dysregulation and disorganization of these functions at different in short and long range scales in hierarchical organization of the brain.

Neurons have a collective behavior. This behavior takes place at the mesoscopic level. An event that takes place at the microscopic level is not projected linearly on the mesoscopic level. Chaos lies in the dynamics of the

collective behavior of neuron populations. The chaotic dynamics of the brain is reflected in mood, decision-making processes and creativity. At this point, a question like which electrode and which region is not very meaningful. Mesoscopic level dynamics behavior also warps large scale macroscopy behavior of the brain which reflects in an extension of the relative entropy change. In other words, the law of the whole/universe is not explained linearly through scales with changing spatio-temporal dimensions. The brain complexity is of same level as Universe complexity. Pathologies thus seem to reduce the brain's adaptation ability to response stimuli, or in other words make the brain less prone to deviate from equilibrium. This is nevertheless not homogeneous.

The small number of the samples considered in this study limits its statistical power. The lack of a control group is another limitation. On the other hand, it is an important advantage that the cases are based on non-drug cases. This is also raising a question of whether chaos has anything to tell us about relative entropy change which states are the not likely to be observed in different diseases. In future, subsequent studies should aim at different periods of the disease with a higher number of cases, comparing the same patients in different longitudinal periods in order to explain temporal dynamics at longer scales.

Ethics approval and consent to participate publication

The Institutional Review Board of Uskudar University approved the study. QEEG is a routine evaluation tools in our NPİstanbul Brain Hospital outpatient clinic. Patients gave written informed consent in accordance with the Declaration of Helsinki.

Consent for publication

Patients gave written informed consent for publication.

Data availability statement

All data and material archived at our institution according to Information and Consent Form on processing and protection of Personal Data.

Conflict of interest

The Authors declare no conflict of interest.

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Authors' contributions

Sermin Kesebir conceived and designed the experiments, performed the experiments, analyzed and interpreted the data with Sultan Tarlacı, Rüştü Murat Demirer and Nevzat Tarhan. She wrote the paper.

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