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RESEARCH ARTICLE

Reclassification of Mood Disorders with Comorbid Medical Diseases based on Sinai-Ruelle-Bowen/ SRB Entropy Measures

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ABSTRACT

Background: Current classification systems ignore the family histories of patients and psychiatric and medical comorbidity.

Methods: We study a new approach of applying spectral clustering to determine distinct bipolar disorder subtypes, which is data whose clusters are of various sizes and densities. We discovered clusters by processing a SRB (Sinai-Ruelle-Bowen) similarity matrix that reflects the proximity of Von Bertalanffy's functions fitted to phase growth dynamics of EEG (electroencephalography) within a new pipeline architecture. For this purpose, 109 patients diagnosed with bipolar disorder according to DSM-V (Diagnostic and Statistical Manual of Mental Disorders, fifth edition) were evaluated in remission period cross-sectionally.

Results: We found three distinct bipolar disorder subtypes with the p-values < 0.001. We exhibit mixing sub-shifts of EEG phase gradients such that there are chaotic phase transitions but higher order phase gradients in a cone basin is always strictly convex. More surprisingly, we show that the SRB entropy measures on some time interval although there exist several equilibrium states each corresponds to equilibrium state.

Conclusion: It seems subtypes of the bipolar spectrum were shaped according to seasonality, comorbidity for anxiety disorder and presence of psychotic symptom.

Keywords: Bipolar disorder, entropy, EEG, comorbidity, family history, oxidative stress, neuroinflammation, autoimmunity

Introduction

Current classification systems ignore the family histories and the longitudinal course of patients. In this approach, temperamental and neurobiological heterogeneity are neglected[1,2]. Disease transmission modeling through family studies has suggested that bipolar disorder is most likely caused by at least three interacting susceptibility genes[3]. It has been hypothesized that for complex diseases such as bipolar disorder, rare non-synonymous coding variants of moderate to large effect might explain a substantial part of the so-called missing heritability[4]. Genome-wide association studies identified significantly associated loci carrying common variants that explain altogether only a small fraction of the genetic component of bipolar disorders[5]. Carney syndrome, multiple endocrine neoplasia (type I and II), breast and prostate cancer, carcinoid tumors and vascular diseases are found to be associated with mood disorders according to epigenetic principles[6]. A bipolar spectrum is possible, including medical dideases. Important results can be obtained in intrafamilial designs.

Comorbidity for bipolar disorder is almost the rule, not the exception, and is not limited to psychiatric disorders. The answers to two questions are important: i) whether the two diseases start simultaneously or not. It is whether the onset of two diseases starts simultaneously or not is called the epidemiological comorbidity. In our study, where we evaluated 1,816 consecutive patients who have examined the process of diagnosis and treatment of MetS (Metabolic Syndrome) according to NCEP-ATP III (National Cholesterol Education Program-Adult Treatment Panel III) criteria[7]. The patients were diagnosed with schizophrenia, bipolar disorder, recurrent major depressive disorder, and anxiety disorder (generalized anxiety disorder, panic disorder, and obsessive-compulsive disorder) based on the DSM-IV criteria[8]. When we examined periods of both psychiatric disorder and MetS since the same onset, the duration of the progressive course periods was found similar in the affective disorders group. However, this correlation is not relevant in anxiety disorders and schizophrenia groups. ii) whether the other illness persists between mood episodes. This is the definition of clinical comorbidity. In a 2014 study, we showed that while the levels of adhesion molecules in the blood increased differently from healthy individuals during the manic period, they returned to normal when the same patients entered remission period[9]. We re-evaluated after five years in remission period. They were higher than healthy controls[10].

The real comorbidity is also based on a family history of longitudinal progression. In other words, it is intimately associated with the presence and frequency of the other disease in the relatives of individuals throughout the illness in the period. In our previous study, we differentiated bipolar patients into three groups according to the medical diseases present in their family history[11].

This study aims to distinguish and examine the subtypes of bipolar disorder in a history of genetic transmission through the longitudinal neuroprogression of familial/epigenetic alterations. We study a new approach of applying spectral clustering of measures on transitive Anosov diffeomorphism of phase dynamics in EEG (Electroencephalography) gamma-band to determine distinct bipolar disorder subtypes. This measure tends to cluster, or occur the distinct groups of populations of bipolar patients. Epigenetic modifications, described as hereditary but potentially reversible alterations, have been consistently implicated in the pathogenesis of bipolar disorder, with several studies suggesting that epigenetic alterations may alter the regulation of gene expression in bipolar disorder, with a great potential use both for discovering disease biomarkers and for therapeutic interventions. Epigenetic alterations cause changes in mitochondrial bioenergetics and morphology in bipolar disorder. SRB (Sinai-Ruelle-Bowen) entropy measure of 10-20 standard EEG dynamics was able to sense this diffeomorphism in energy and morphology.

Brain phase synchronizations are occurred in the same way in healthy traits: i) in processes that develop suddenly in an emergent manner ii) in processes that stimulate past memories and iii) in decision making processes[12]. Moreover, under healthy circumstances, the processes tend to consistently create these phase synchronizations. Chaos occurs when entering and exiting these synchronizations. When entering and exiting synchronization, uncertainties in phase change are perceived by the change of entropy. Multichannel spontaneous EEG introduces a space-time joint data which is called spatio-temporal data. 1-Hertz component of EEG is completed in a one-second cycle in time. Chaos has characteristics of distinct various frequencies spread in the widest coupled spectrum, in the range of 0.1-70 Hz. In other words, it is some sort of degree of growth change in phase space with creating uncertainty in instability under certainty. Periods of low frequencies diffused into large frequencies (bottom-up) and vice versa (top-down) in a mutual manner during chaos event in intermittent period.

This happens very smoothly as mixing which is a condition to create chaos and it happens for a short time interval. The prolongation or shortening of this time interval during chaos may reveal a disorder.

The strength of the diffusion of different frequencies at different time points cause to draw single event from among infinite possibilities very quickly[12]. Meanwhile, entropy increases to a point during a chaos process. This increment is directly proportional to the homogeneity of the diffusional spread rate. Contrary to the density of the scrambled egg at different points, we understand how well the egg is whipped and how homogenized it is from the change of entropy. Neurons have shown a different collective behavior at a mesoscopic scale than a single neuron behavior. An event that takes place at a single neuron level is not superimposed on to each other at the mesoscopic level. Chaos occurs in the dynamics of the collective behavior of neuron populations emanating with phase transitions. This chaos is reflected in mood, decision-making processes and creativity. At this scale level, a question like which electrode and which brain region is not so meaningful. The dynamics at mesoscopic scale of sub-cortical neural populations can warp space-time at macroscopic scale of the cortical structures. There is no linear transformation from one neuron up to the global cortical scales.

Anxiety accompanied by hypervigilance; this mood reactivity was linked with irritability[13]. On the other hand, delta power, found to be associated with anxiety scores, too. At this point we propose a continuity between slow wave activity and fast wave activity, such as the CFC (Cross Frequency Coupling) between delta and beta power. CFC between different neural ossilations is a key functionality which the brain coordinates complex cortical computations. It can be thought of as a kind of stress response, aberrant and regulatory. An increase power of delta reflects increased activity of subcortical affective processes e.g., anhedonia, reward dependency and impulsivity whereas an increase power of beta reflects an effort for cortical regulation of negative emotion with cognitive process e.g., working memory and sustainable attention. Relationships between slow and fast wave frequency bands are considered to be interest in here of dispositional affective traits as a continuity between depression and mania proposed first by Areteus such as mania is a severer form of depression and anxiety accompanied by hypervigilance and vegetative symptoms is a severe form of anxiety characterized by retardation.

Methods

SAMPLE

For this purpose, 109 patients diagnosed with bipolar disorder according to DSM-V (Diagnostic and Statistical Manual of Mental Disorders, fifth edition) were evaluated in remission period (Hamilton Depression Rating Scale -HDRS< 8, Young Mania Rating Scale –YMRS< 7 for concurrent validity). These cases were the cases who applied to our outpatient unit for their usual control and gave informed consent for our study by the Declaration of Helsinki. The Institutional Review Board of Uskudar University approved the study.

A semi-structure patient questionnaire was requiring to each patient to describe the individual and family history of medical disease and degree of consanquinity if it is present. MetS (Metabolic Syndrome) defined according to NCEP ATP III (National Cholesterol Education Program- Adult Treatment Panel III) as hypertension, dislipidemi, diabetes, obesity[14]. The individual and family history of medical disease includes diabetes, ischemic heart disease, thyroid disease, cancer (gastrointestinal cancers, breast and prostate cancer, leukemia, and lymphoma), cerebrovascular disease and epilepsy. If they are diagnosed and treated at any time for this medical disease this case was accepted as an inclusion criterion. Relatives who had died due to one of the medical conditions above were marked as positive. Alcohol and substance abuse were excluded except nicotine addiction. Clinical features were recorded.

The statistical analyses were performed using the SPSS 20.0 software. All tests were two-tailed and $p < 0.05$ was considered significant.

ELECTROENCEPHALOGRAPHY AND MATHEMATICAL APPROACH

The EEG (Electroencephalography) was recorded using SCAN 4.1, SynAmps, (C) Neurosoft, Inc with a 21-electrode cap using Ag/AgCl electrodes; the sampling rate was 125 Hz with 12-bit resolution and the analog filter was set from DC to 100 Hz. Continuous records were taken and analyzed approximately 5 min. of records. The offset of each channel was removed and each epoch was normalized by dividing by the global standard deviation. Temporal digital band pass zero-phase reverse and forward FIR filter with the order of 200 for each channel were then applied to extract gamma band (20–50 Hz) and finally the Hilbert Transform was applied to decompose the EEG into the analytic amplitude and analytic phase[14-18]. Amplitude modulated and phase modulated neural

populations is observed in the large scale brain functional activity[20]. Depending on analytic phase transitions over multiple channels classifiable radial phase gradient patterns are observed in the form of phase cones which is defined by maksimum instantaneous frequency acquired from Hilbert space (Figure-1).

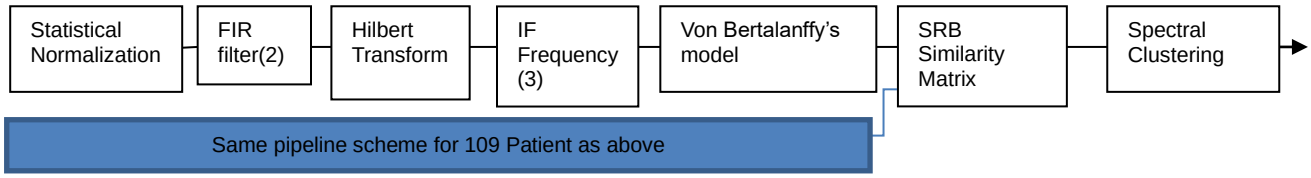

Figure 1. The SRB clustering pipeline architecture

$y(t)$ is the Hilbert transform (HT) of band-pass and normalized $s(t)$ as EEG signal for each channel ranging from $t = 1 \ldots 40000$ discrete time samples.

$$y(t) = H\{s(t)\}$$

Given an EEG signal for each channel, $s(t)$, we can construct the analytic signal from the statistically normalized filtered signal after Hilbert transform is applied over each channel

$z(t) = s(t) + iH\{s(t)\}$.

$z(t)$ is the analytic derivation of the the signal, $s(t)$ which is along with phase and amplitude information.

EEG signal is composed of multiple oscillations with a wide range of frequencies (0.1 Hz-100 Hz). However, we are limited in analyzing the gamma band (up to max. 62 Hz) using a sampling rate of 125Hz due to Nyquist theorem.

EEG signal can be considered as the superimposition of the multiple oscillations as

$$z(t) = \sum_{i=1}^{M} a_i(t) e^{i\phi_i(t)}$$

where $a(t)$ is the instantaneous amplitude and positive for each component embedded in EEG signal for eah channel.

$\phi(t)$ is the instantaneous phase for each component where $a(t)$ and $\phi(t)$ are spectrally disjoint.

M denotes the number of distinct oscillations and admitted as a M manifold in which we are interested in frequency (phase) transitions in a range between 20 Hz and 50 Hz of beta-gamma oscillations.

Instantaneous frequency is simply time derivative of the instantaneous phase which reflects the phase gradients of EEG signal for each distinct frequency change as called a transitive diffeomorphism. For each channel ranging in, instantaneous frequency which reflects the phase gradient of the signal over one channel is calculated.

$$W_t = \frac{1}{2\pi} \frac{d\phi(t)}{dt}$$

The output of the block 3, W_t and the output of the block 2 as shown in figure 1 can be seen as follows in figure 2. The 20-50 Hz beta-gamma band actually 0-60 Hz frequency sweep through the band (Figure-2).

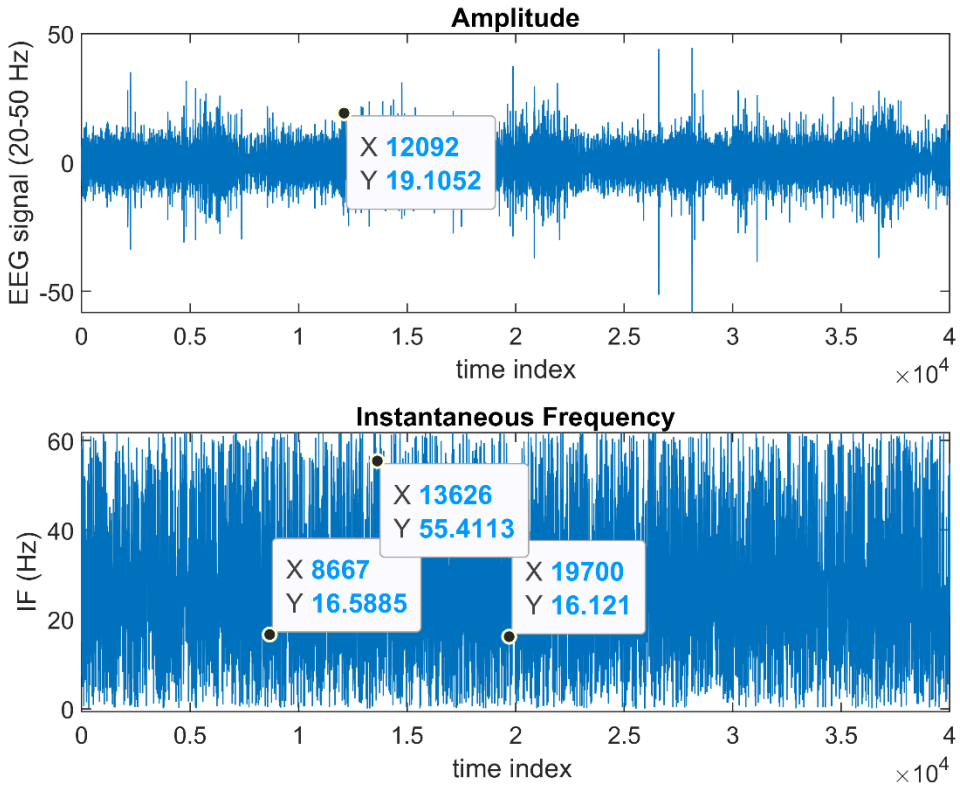

Figure 2. Absolute (IF), W_t , of the statistical normalization of beta-gamma band for one channel

The dynamic brain trajectory is embedded into high-dimensional state space (container) in chaotic itinerancy which is a characterizes phase transitions of the brain. Von Bertalanffy's functions can easily be mapped onto instantaneous phase signal dynamics of each channel. We define the function of each channel which is in a form of an unimodal map that means $f_r: [0,1] \rightarrow [0,1]$ volume preserving as

$$f_r(x) = rx^{\frac{2}{3}}(1 - x^{\frac{1}{3}})$$

With $x = \frac{W_t}{W_\infty} \in [0,1]$ and $r = \frac{K}{3} * W_\infty^{\frac{2}{3}} > 0$ is an intrinsic growth rate parameter of the von Bertalanffy's model representing dynamics, bifurcations and synchronization properties of brain. is the growth rate constant of instantaneous phase gradients. W_∞ is the asymptotic (maximum) frequency of each channel during the time interval concerned. A single function fitted onto each channel is determined on the two-dimensional parameter space[21]. A single model corresponding to one-dimensional map was built for each channel giving total 21-different functions representing each full volume of local dynamics, $B(\mu_{f_r})$, where the manifold lives in two-dimensional parameter space. The transitive behaviour of instantaneous frequencies which form a phase gradient bundle in a manifold of beta-gamma range are expressed by intrinsic growth rate *r* (Figure-3).

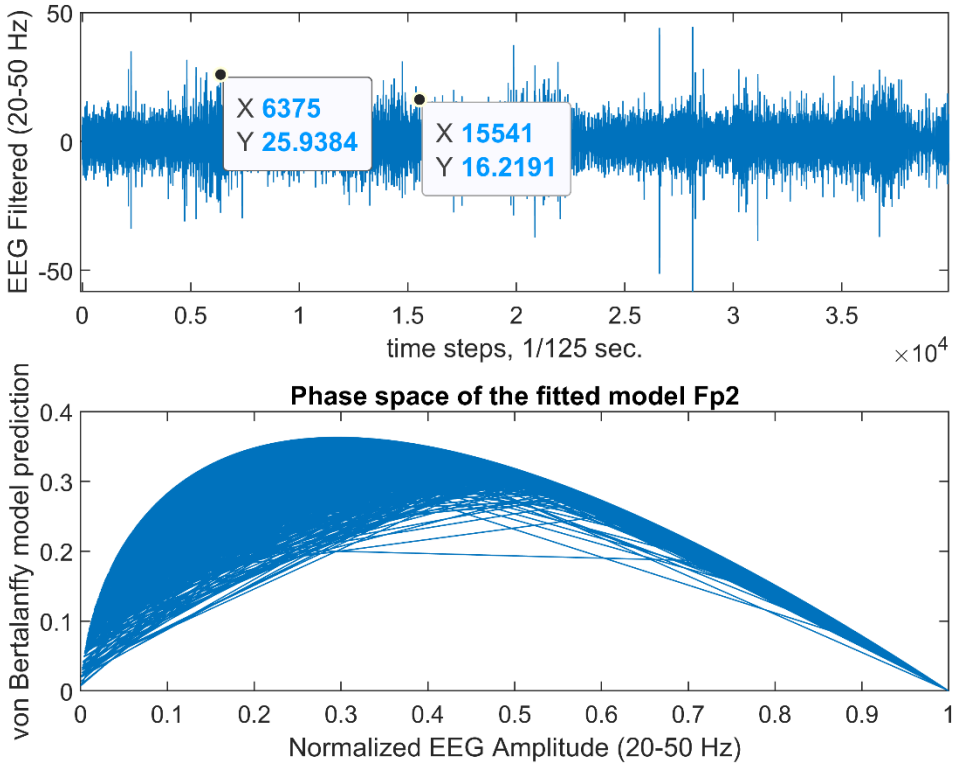

Figure 3. Phase gradient space, $B(\mu_{f_r})$ of single subject to the output of the model with respect to different intrinsic growth rate parameters, different r for each channel

We then admitted a linear Anosov diffeomorphism on this compact manifold, created by spatiotemporal phase gradient dynamics of individual channels. Our goal is to classify those manifolds based on a different kind of entropy measure, μ_{f_r} on each unimodal map, $f_r: M \to M$. In a transitive Anosov diffeomorphism i.e higher order instantaneous frequencies there exists a unique SRB (Sınai, Ruelle and Bowen) measure supported on a phase gradient cone manifold, M. $B(\mu_{f_r})$ is of full volume in a basin which supports all beta-gamma frequencies transitions i.e phase gradients and higher order phase gradients in a cone basin[22,23].

$$B(\mu_{f_r}) = \{x \epsilon M : \frac{1}{n} \sum_{k=0}^{n-1} \delta_{f_r^k x} \to \mu_{f_r}\}$$

The Dirac delta can be consşdered as a function on the one-dimensional real space which is zero everywhere except at the origin, where it is infinite as taken 1 in our model.

$$\delta_{f_r^k x} = \left\{ \begin{matrix} 1, ||[x^{(k)}] - [f_r{}^{(k-1)}(x)]|| < \epsilon \\ 0, otherwise \end{matrix} \right\}$$

If a manifold representing phase gradients is lagged in time by $k = 0..n-1$ times and compare them whether how many total points are approximately equal to each other $\delta_{f_r^k x}$ which each shift, k is relative to previous lag, then a unique measure, μ_{f_r} can be determined. This means that we count the number of fixed points in a tangent (differentiation) bundle of a phase gradient manifold based on Poincaré recurrences while subjected to repeated Anosov diffeomorphic transformations. This is a new biomarker that we introduce using SRB measure which explains how a subject is covering up beta-gamma frequency transitions very quickly in cognitive decisions. We considered cognitive decisions in single diffeomorphisms concatenation of all channels on a unique phase gradient manifold by $n-$ times Anosov diffeomorphisms, i.e. $[\dot{\boldsymbol{x}}] = f_{[r]}([\boldsymbol{x}])$ in which $[x] = \{Fp1, Fp2, F3, \dots\}$ vector includes all channels (electrodes) dynamics with each own intrinsic growth rate, $[\boldsymbol{r}]$ vector. $f_{[r]}([\boldsymbol{x}])$ is the mathematical model of phase gradient behavior of the brain (von Bertalanffy's model) over standard 10-20 EEG channel montage .

$$x^{(1)} = f_r^{(0)}(x)$$
$$x^{(2)} = f_r^{(1)}(x)$$
$$\vdots$$
$$x^{(k)} = f_r^{(k-1)}(x)$$
$$\vdots$$
$$x^{(n-1)} = f_r^{(n-2)}(x)$$

The SRB measure which is a function of an entropy is defined in successive diffeomorphisms. The measure denotes us how any phase transition (instantaneous frequency) in beta-gamma band changes quickly. $[\boldsymbol{\mu}]$ is a container of all channels in a given temporal interval. DE is the new etymological biomarker which is the first time in psychiatry.

$$\boldsymbol{DE} = [\boldsymbol{\mu}]_{fr} = \#\{\frac{i}{n} : |||[x^{(k)}] - [f_r^{(k-1)}(x)]|| < \epsilon\}$$

where $\epsilon \simeq 0$ is a small number and $\#$ denotes the number of impulse functions. The invariant measure is the number of the fixed points arithmetic progressions of transitive n-times diffeomorphisms which makes the measure invariant from the given time interval. In other words, each subject covers n- order differentiable from SRB measures. SRB measure shows a gap between the number of the same values of arithmetic k-progressions ($k = 1 \cdots n$) of each channel.

Results

SAMPLE

The average age of 109 patients, 58 women, and 51 men was calculated as 38.6 ± 11.2. The age of onset is 23.3 ± 4.9, duration of the disorder is 15.3 ± 6.3 years.

The distribution of clinical characteristics among the three groups is summarized in table-1. There is a positive association between epilepsy and psychotic symptom (r = 0.589, p <0.001), between diabetes and seasonal course (r = 0.542, p = 0.001), and between anxiety disorder and neuroleptic sensitivity (r = 0.439, p = 0.025).

Vagus sensitivity and neuroleptic sensitivity were differentiated in the first group, MetS, mixed symptoms, seasonality, delayed sleep phase syndrome and nicotine addiction in the second group, and left handed in the third group (Table-1).

Table-1. Clinical features

	1, n= 29	2, n= 53	3, n= 27
MetS (n, %)	13 44.8	53 100	6 22.2
Mixed symptoms (n, %)	18 62.1	38 71.7	6 22.2
Psychotic symptoms (n, %)	-	-	20 74.1
Neuroleptic sensitivity (n, %)	22 75.8	12 22.6	2 7
Seasonal course (n, %)	10 34.5	48 90.6	10 37
Delayed sleep phase (n, %)	3 10.3	42 79.2	12 44.4
Vagus sensitivity (n, %)	17 58.6	15 28.3	-
Nicotine addiction (n, %)	6 20.7	45 84.9	14 51.9
Left handed (n, %)	2 6.9	5 9.4	17 63

SPECTRAL CLUSTERING

Spectral clustering is a graph-based algorithm for finding k arbitrarily shaped clusters in data. The technique involves representing the data in a low dimension using k-means clustering. This low dimension is based on eigenvectors of a Laplacian matrix. A Laplacian matrix is one way of representing a similarity graph that models the local neighborhood relationships between SRB values as an undirected graph. The algorithm also provides a way to estimate the number of clusters as corresponding to bipolar subtypes in our data as shown in figure 4. The three bipolar subtypes show us very distinct, perfect non-overlapped SRB (Sinai-Ruelle-Bowen) value intervals shown.

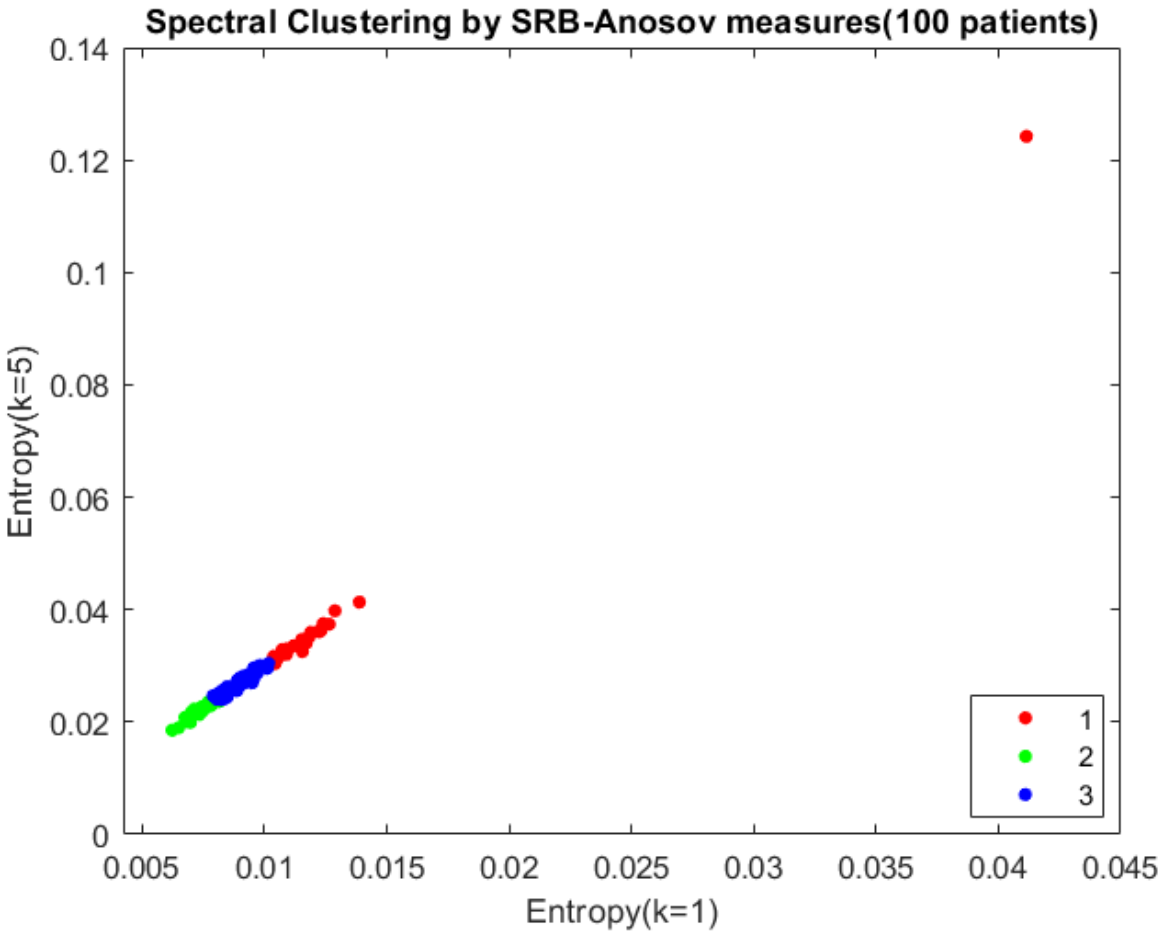

Figure 4 SRB Entropy Clustering Space by the number of clusters, k

The table-2 denotes the number of patients for each class. The class p-values come from eigenvalues of the spectral matrix which is a function of the counting normalized values by unit volume of phase gradient cone basin of cortex.

Discussion

Spectral Clustering is then based on SRB (Sinai-Ruelle-Bowen) measure vectors contained in a classification scheme that gives total 109 patient vectors with each includes the number of same return values in up to n-times diffeomorphism values over 40000 temporal points. We proposed this spectral clustering based on SRB features for 109 patients and found 3 types of bipolar patients which was the first in the literature. We found three distinct bipolar subtypes with p< 0.001 (table-2). The first group consists of anxiety spectrum comorbid bipolar cases. When the literature is reviewed, anxiety disorders rank first or second among psychiatric diagnose that are comorbid to bipolar disorder. Comorbidity in these rates suggests that the two diseases are inherited together in nature. This subgroup which can be defined as personal and family history positive (FH+) thyroid disease. This is a subgroup that can be elicited by linkage data in the literature and it corresponds to comorbidity for panic disorder in which familial aggregation had been shown[3]. Bipolar disorder is a result of diverse interaction mechanisms in pathological rewiring of the neuroprogression including neurobiological factors, mitochondrial dysfunction with oxidative stress, inflammation, and epigenetic mechanisms[23,24].

Table-2. Bipolar subtypes

Class Number	n %	p-values
1	29 26.61	0.000000000000000
2	53 48.62	0.001998365182510
3	27 24.77	0.006766444144567

TLR (Toll-like receptors) are endosomal pattern recognition receptors related to molecular patterns that promote pathogenesis to cytokines which are responsible for innate immunity. TLR receptors are primarily expressed on microglia. They are located in the thyroid gland, adrenal gland, intestines and for a certain developmental period in the thymus gland[25, 26]. It must to remember that the first term designating mood stabilizing agents was thymoleptics, at this point. On the other side HLA (human leukocyte antigen), as adaptive, is acquired immunity referred to immunosuppression. The notion of autoimmune mood disorder come to the fore at this point [27].

The anxiety disorder comorbid bipolar group is characterized by the presence of autoimmune and allergic diseases in their personal and family history. There is a relation between anxiety comorbid bipolar group and neuroleptic sensitivity. Again, at this point, we can talk about autoimmune limbic encephalitis such as NMDA (N Metil Aspartik Asit) and GAD (Glutamik Asit Dekarboksilaz) encephalitis. These are cases characterized by mood symptoms, accompanied by neurological symptoms, and showing neuroleptic sensitivity.

The third group of cases is epileptic spectrum comorbid mood disorder cases. In our previous study, we showed that there is a linear association between leukemia-lymphoma and epilepsy (+) FH (Family History) and bipolar disorder[11]. A strong correlation was found between FH (+) epilepsy and psychotic symptoms of bipolar disorder.

Vitellus sac derived erythro-myeloid progenitors enter the central nervous system to form microglia in the post-insemination embryonic period. BRAF (B-Raf proto-oncogene/ V600E) genes somatic mutation disrupts the continuity of macrophage in adult life[28]. The gene BRAF is under expressed in bipolar patients olfactory neuroepithelial progenitor cells undergoing relatively heritable neurodegenerative diseases in the brain and cerebellum which can be prevented by BRAF inhibitors. This changes are associated in many tissues with tumor or leukemia.

Most of the second group are characterized by mixed symptoms rather than hypomanic and manic episodes. The dominant mood is irritability rather than euphoria. Mood periods are largely seasonal. All of this group meets at least one of the metabolic syndrome criteria according to NCEP-ATP III (National Cholesterol Education Program-Adult Treatment Panel III) [13].

Emotional hyper-reactivity is another characteristic of this group. Indeed, the predominance of comorbid eating disorders in this group can be explained by this emotional impulsivity[29]. It is consistent with cardiometabolic risk reported by Kesebir[6].

A strong correlation was found between diabetes and seasonality in the second group which had the highest rates of comorbidity with medical conditions of metabolic syndrome[6]. Diabetes is a component of metabolic syndrome of which seasonal course is a predictor[19]. The interface between bipolar disorder and diabetes, ischemic heart disease, proliferative cancer (breast, prostate, and gastrointestinal cancers) involves inflammatory effector systems and glucocorticoid/insulin signaling mechanisms [31-34]. In the literature, this group matches FH+ bipolar disorder type II, too[3]. Metabolic syndrome is more common in bipolar disorder type II than in bipolar disorder type I on epigenetic grounds where seasonality plays a mediating role[6]. The role of climate change and migration in the epigenetic framework and their interactions with temperament has been reviewed under the title of "Epigenetics of metabolic syndrome as a mood disorder"[6].

LIMITATIONS

The most important limitation of this study is that it did not include a control group. Secondly, alcohol and substance use disorders were excluded. However, it is a group as large as comorbid anxiety disorder. In another study, comorbidity of alcohol substance use disorder was included in the second group[29].

Conclusion

The literature of EEG-based approaches for Bipolar Spectrum Disorders diagnosis is limited[12]. Our results further suggest that classification based entropy of SRB patterns offer promise as new biomarkers which are through comorbidity passages for bipolar disorders from an inheritance. Individual and/or family history to autoimmune disorders as comorbid anxiety spectrum disorder, metabolic syndrome as seasonal affective disorder and epileptic spectrum disorder as bipolar disorder with psychotic symptoms. Anxiety, reactivity and cyclicity, and psychosis are the three dimensions of the bipolar spectrum. i) Generalized and social anxiety disorder, panic disorder ii) alcohol and substance use disorder, eating disorder, borderline personality disorder iii) psychotic disorder, dissociative disorder, obsessive compulsive disorder without insight were more common in the family histories than in bipolar patients as three dimensions[29]. Delayed sleep

phase, any addiction, cardiovascular disease, diyabetes, breast, prostate or gastrointestinal cancer +FH, vagus tenderness, presence autoimmune disease, left handedness, presence of febril convulsion or migraine and/or epilepsy, leukemia, lymphoma + FH are listed as ''Bipolarity Trait Index'' in factor analysis[30].

The interactions between individual genetic properties and environmental factors regulates neurodevelopmental and neuroprogressive sensitivity and endurance in the early stages of life and defines the individual's clinical profile in the future. Genetic diversity also regulates the stress response, determines the type and severity of the environmental factor we are vulnerable to, and governs disease severity and comorbidity. Current treatment strategies are between common leading pathways of symptoms and symptoms. However, interactions between stress and neural circuits underlying the pathophysiology of the disorder should be determined as treatment targets. This interaction should contribute to the use of biological indicators for tools of diagnosis.

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