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Rüştü Demirer

Üsküdar University

Sermin Kesebir (✉ serminkesebir@hotmail.com)

Üsküdar University

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Rüştü Murat Demirer¹, Sermin Kesebir²

¹Assist. Professor, Biomed. Engineering, Üsküdar University, İstanbul, Turkey

²Professor of Pschiatry, Üsküdar University, NPIstanbul Brain Hospital, İstanbul, Turkey

Corresponding Author:

Sermin Kesebir

NPIstanbul Beyin Hastanesi

Ahmet Tevfik İleri C. N: 18 Ümraniye

İstanbul Turkey

E-mail: serminkesebir@hotmail.com

GSM: 0090 532 5922080

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 NPIstanbul 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.

Competing interests

The authors declare no conflict of interest.

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Authors' contributions

Sermin Kesebir conceived and designed the experiments, performed the experiments. Rüştü Murat Demirer analyzed and interpreted the data. Rüştü Murat Demirer and Sermin Kesebir wrote the paper.

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ABSTRACT

The application of chaos theory measures in the association of EEG signals which allows for differentiating pre and postmedicated epochs for bipolar patients. We propose a new approach on positive Schwarzian chaos necessary for a proof of EEG power spectrum of metastability. Shannon entropies of those concealed patterns of positive Schwarzian derivatives from canonical angle transformations of EEG phases from Hilbert transform are compared and found significantly statistical different between pre and post medication periods. Entropy change of chaotic transition measures were compared at first baseline and then at the end of first hour of 300 mg lithium carbonate intake for the same subject in depressive patients. With an application of Schwarzian derivative on the prediction of the von Bertalanffy's models, integration and segregation of phase growth orbits of neural oscillations can be understood as an influence of chaos on mixing of frequencies. A first order curve-fitting function was performed to determine bifurcation parameter of von Bertalanffy's model at each given overlapped EEG segment. Schwarzian derivative was positive near the origin which revealed robust chaos. We founded that treatment with Lithium carbonate significantly altered Schwarzian spectrum of chaotic structure and entropy change in Schwarzian amplitudes even though it was not observed in classical EEG power spectrum. Lithium carbonate reduced the strong chaos spectrum of EEG Schwarzian dynamics and removed sharp boundaries in bipolar spectrum.

Keywords: Bipolar disorder, lithium, entropy, chaos.

INTRODUCTION

Bipolar disorder is characterized by recurrent depressive and manic episodes¹. A mixed episode offers possibility to evaluate compensatory regulation effort with affective dysregulation. Brain is a complex adaptive system that actively minimizes the entropy through our sensory and physical states. The quasi-attractor states are producing self-organized action-perception cycles from higher cortical states to lower cortical states vice versa². There exists a mathematical field theory of the hierarchically organized emergence dynamics (i.e. creation and annihilation) of spatial and

temporal dimensions at micro, meso, and macro scales by behavioral patterns in mental processes. Haken introduced a circular causality (both top-down and bottom-up approach), order parameter and complexity reduction in relation to those processes. Typical cortical transitions are not merely random but are in the framework of transitory and chaotic dynamics with fractal or nested modular hierarchy^{3,4}. The chaotic itinerancy among quasi-attractors are defined as memories which allow the brain to learn new input patterns while maintaining memories in the situation of human communication. Memory is built in hierarchical architecture as simple memory, episodic memory and relational memory. Chaotic itinerancy appears in bifurcating processes at different levels of brain regions. This stage of higher memory formation can be a marker through communication as output-driven information processing⁵.

Collective dynamics of neural populations oscillate across a wide range of topologically transitive states. They are aperiodic, non-equilibrium, transitive and dense oscillations in different brain regions which lives in a high-dimensional electrode space of whole cortical neural activity. The EEG oscillations cause the appearance of a temporal sequence of aperiodic quasi-attractors which are weakly spatially coupled together for cognitive processes as shown in **Error! Reference source not found..** We are based on the collective dynamics of neural populations. With an application of Schwarzian derivative of von Bertalanffy's models, integration and segregation of phases of EEG oscillations spread through different regions can be explained as a causality of chaos. We proposed a new method which captures concealed chaotic patterns and transitive points of rhythms as shown in **Error! Reference source not found..** The positive Schwarzian derivative value shows a good continuity and monotonicity of topological entropy in a wide range of oscillations, and depicts the order in the succession of transitive bifurcations in cognitive processes. We are being able to differentiate pre and postmedicated epochs for bipolar patients. Positive entropies of those concealed phase patterns of positive Schwarzian derivatives are compared and found significantly statistical different between pre and postmedication periods.

The aim of this study was to investigate chaotic transitions in the bipolar disorder. For this purpose, entropy of chaotic transitions were compared at baseline and at the first hour of 300 mg lithium carbonate intake.

METHODS

Sample

In our study, patients with major depressive episode, recurrence, current episode moderate or severe were evaluated consecutively according to DSM-V (n= 10). Our inclusion criteria were

- i) psychotic findings,
- ii) atypical features and / or mixed symptoms,
- iii) presence of bipolar disorder in family history,
- iv) cyclothymic or hyperthymic temperament.

The presence of comorbidity and chronic physical illness exclusion criteria for any psychiatric disorder. In addition, patients were not required to take medication for current depression.

Assessment

The permission required for this study was obtained from the ethics committee of our university. After each diagnostic interview, HDRS (Hamilton Depression Rating Scale), MDQ (Mood Disorder Questionnaire) and TEMPS-A (Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire) were applied. EEG was performed. 300 mg of lithium carbonate was then administered orally. EEG was repeated at the end of the first hour.

EEG was recorded at a sample rate of 125 samples/s. Impedances for each electrode referring channels were kept below 30 k Ω . EEG processed offline for artifact rejection. A high pass filter was applied at 0.1 Hz and a low pass filter was applied at 70 Hz.

Statistical analysis

Comparisons were made with SPSS 20.0 Wilcoxon test before and after medication.

Mathematical Approach of Chaotic EEG Brain Dynamics Embedded in Phase Growth Models

The general system architecture of system architecture for each electrode is shown in **Error! Reference source not found..**

The analytic phase $\varphi(t)$, in radians and canonical form is derived by using the Hilbert transform in MATLAB. The EEG channel, for each j is denoted by $v_j(t)$ on each second trial which is contained in a two element vector, $V_j(t)$ with a real part the same as EEG, $v_j(t)$ and an imaginary part, $v'_j(t)$ from Hilbert transform of the $v_j(t)$ where $i = \sqrt{-1}$.

$$V_j(t) = v_j(t) + iv'_j(t), j = 1, \dots, 21$$

where

$$v'_j(t) = \frac{1}{PV} \int_{-\infty}^{\infty} \frac{v_j(t')}{t - t'} dt'$$

PV denotes Cauchy Principal value. At each sampling step, we obtain one point in a complex plane. Analytic amplitude of the each point can be represented by

$$A_j(t) = [v_j^2(t) + v'^2_j(t)]^{0.5}$$

and the arctangent of each sample point will give us the analytic phase value at a t ,

$$\varphi_j(t) = \text{atan} \left[\frac{v'_j(t)}{v_j(t)} \right]$$

for $j = 1..21$ EEG channels. The phase values are transformed from $[-\pi, \pi]$ to canonical $[0, 2\pi]$ range.

We then consider one dimensional EEG dynamical model independently for each channel represented by von Bertalanffy's function of instantaneous phase values $f_r: [0,1] \rightarrow [0,1]$. We omitted the channel index, j for the sake of simplicity. Then the model

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

with $x = \frac{\varphi(t)}{\varphi_\infty} \in [0,1]$ the normalized phase of canonical phase values, t is the discrete time index and

$$r = r(K, \varphi_\infty) = \frac{K}{3} \varphi_\infty^{2/3} > 0$$

is an intrinsic growth rate of EEG phase for one channel. K denotes von Bertalanffy growth rate constant and φ_∞ is the asymptotic phase value. The model of phase growth dynamics for each channel satisfies the following conditions:

- a. f_r is continuous on $[0,1]$
- b. f_r has an unique critical phase value $c = (2/3)^3 \in (0,1)$

- c. First order derivative $f'_r \neq 0, \forall x \in (0,1) \setminus \{c\}, f'_r(c) = 0$ and second order derivative, $f''_r(c) < 0$
- d. The model dynamics $f_r \in \mathbb{C}^3$ must be three times differentiable.

Finally, we can explore the chaotic dynamics of phase growth model by analyzing Schwarzian derivative given by

$$\mathcal{S}(f_r(x)) = \frac{f_r'''(x)}{f_r'(x)} - \frac{3}{2} \left(\frac{f_r''(x)}{f_r'(x)} \right)^2$$

$\mathcal{S}(f_r(x)) > 0$ shows the bifurcation stability of the EEG phase dynamics. In terms of flip bifurcations, $\mathcal{S}(f_r(x)) > 0$, we define the transitions between the stability dynamics and the period doubling dynamics at a value of $r = \frac{5}{3}$. The chaotic semistability i.e. metastability dynamics corresponds to the transitions among chaotic conditions and depicts no continuous stable admissible condition. In other words, brain dynamics has a distinct attractor (**Error! Reference source not found.**) jumping intermittently from one to another which can disappear in a small range to cause to a new attractor. In the new attractor, EEG trajectories of brain dynamics would stay for a longer time in different regions of brain [11]. The entropy of this phase growth dynamics for each electrode can be defined as

$$H := - \sum_{x \in \mathcal{S}} p_x \log p_x$$

where $p_x := \text{Prob}(\xi = x), x \in \mathcal{S}$. A random variable ξ takes values in a finite set of Schwarzian positive values.

RESULTS

The mean age of the patients was 43.6 ± 5.7 years and the mean age of onset was 20.3 ± 2.8 years. The mean number of depressive episodes was 3.5 ± 1.2 . HDRS score was 27.4 ± 3.7 , MDQ score was 13.4 ± 1.1 , cyclothymic and hyperthymic temperament scores were 17.8 ± 1.2 and 21.3 ± 2.1 .

We founded that EEG dynamics covers a wide range of a scrambled set of frequencies through periodic doubling of across delta, beta, alpha, gamma etc. bands in a given topology.

The p-values of entropies for 10 patients based on 20 electrodes are given in Table 1 for Wilcoxon signed rank test from pre and post medication terms on all electrodes. p-associations to Wilcoxon-sign test of entropy were less than ≤ 0.001 for eight patients and ≤ 0.05 for one patient among total 10 patients. These data and approach support decreased entropy change in the whole-brain network that is specific to Lithium carbonate medication and introduces a general chaotic attractor state which causes to a scrambling effect through a wide range of frequencies that might explain cognition in healthy subjects and mental disorders (Figure 2 and 3).

DISCUSSION

Chaotic itinerancy appears in the brain activity of communicating people in the form of chaotic phase transition disorders between synchronization and desynchronization⁶. The brain resists a tendency to this disorder and therefore minimize the entropy change of their sensory states as shown in **Error! Reference source not found.** Measures for energy, entropy and temperature can be defined with models using the Carnot cycle and then using the Rankine cycle to incorporate criticality and phase transitions⁷. The knowledge is expressed with the dynamics of two interactive fields of neural activity, one at high and the other at low energy density, and the two operators that create and annihilate the fields. Extremely high density of brief energy in cortical activity patterns can account for the vividness, richness of associations, and emotional intensity of memories in widespread task conditions as shown in **Error! Reference source not found.**^{8,9}. Successful interregional communication depends on the transient synchronization between harmonization of multiple oscillatory components into an integrated signal through phase-coordinated local neuronal spiking, where the phase of one oscillation modulates in harmony with amplitude fluctuations in another oscillation. Widespread slow of coupled chaotic oscillations modulate faster oscillations of local events⁹. This is a chaotic system synchronize suddenly and completely from one global activity pattern state to another with minimal duration of transient "amplitude fluctuations". The EEG dynamics shows sequences of patterns, each carried by an aperiodic waveform around a chaotic attractor as shown in **Error! Reference source not found.** The synchronization of EEG network as coupled chaotic oscillators depends on the strength of the coupling, the connectivity topology and the dynamic characteristics of the system that exists at each brain region. Positive Schwarzian derivative in high-dimensional chaotic systems exhibit the capacity to create information as well as to destroy it. Chaotic dynamics endows brains with the capacity to create

new kinds of trials by which to generalize across inputs from equivalent sensory receptors. Chaos in the model arises when the mesoscopic populations are interconnected with the cortex, so that each excites the other¹⁰ in continuing update of cortical populations as shown in **Error! Reference source not found.** Each has its own characteristic frequency, but they differ and cannot agree. Neither can escape the other, so that stable aperiodic oscillation persists. If the three parts are disconnected, the chaos in the model disappears¹¹.

We propose a Schwarzian derivative which is invariant under the von Bertalanffy's model¹² of phase growth. This model is a family of unimodal inverse transformation map as which it can be used to determine the EEG dynamics of a higher derivatives. With the neuron populations considered in a Bertalanffy's growth model, the size of the its activated pool is inversely related to the frequency of synchronization. The slower the oscillation, the more neurons can participate in a larger size of pool hence the integrated mean field is larger. Perturbations at slow frequencies like 4-8 Hz EEG band can trigger a cascade chain of energy dissipations mixing up to higher gamma frequencies (20-50 Hz) which means that widespread slow oscillations modulate faster local EEG oscillations. We consider the Schwarzian derivative represents a dimensional feedback coupling constant. The corresponding brain dynamics undergoes stable evolution but for one fixed point solution as shown in **Error! Reference source not found.** The dynamics is in metastability conditions. Even though both phase growth spectrums remain constant shown in both **Error! Reference source not found.** and **Error! Reference source not found.**, before and after medication terms, whereas power spectrum values of Schwarzian coupling in a whole frequency range decreases after medication and depicts excellent uniformity in diffusivity mixing in a whole frequency range. Before medication, Schwarzian spectrum remains in narrow uniformity with increasing bias values and the Schwarzian power spectrum in a whole frequency range increases. In terms of entropy change (ΔE) in positive values of Schwarzian amplitudes, before medication, this disorder is high in bipolar patients over all electrodes. After medication, those entropy change (ΔE) remain low for all electrodes.

According to our entropy change (ΔE) results, there were no statistical significance in one patients between pre and postmedication. In subject 8, there was a diagnosis of non-Hodgkin lymphoma after this research was over. The entropy change of chaotic transition was first examined in trait bipolar disorder, in other words bipolar spectrum disorder.

According to our results, lithium carbonate effects the strong chaos spectrum and removes narrow boundaries. We concluded that EEG dynamics covers a wide range of a scrambled set of frequencies through periodic doubling of across delta, beta, alpha, gamma etc. bands in a given topology. Schwarzian derivative as a coupling constant is a mathematical method for precise prediction of chaotic points in the scrambling EEG dynamics. Schwarzian derivative is being positive near the origin which shows robust chaos where phase growth is in the terms of average L^p - norms as an estimator of free energy that is approximated by from the square of the EEG phase growth on spheres of radius $r > 0$ as $r \rightarrow \infty$ for $1 < p < \infty$ (**Error! Reference source not found.** and **Error! Reference source not found.**).

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Figures

Figure 1

The general architecture of chaotic model for each electrode associated with Schwarzian derivative

Figure 2

Before medication, entropy change (ΔE) is high in bipolar patients, disordered over electrodes

Figure 3

After medication, (ΔE) entropy change is low in bipolar patients, disordered over electrodes

Figure 4

Power Spectrogram of Schwarzian coupling and von Bertalanffy's EEG Phase Growth Model before medication for Fp2 electrode for an interval of 60000 time points at $f_s=125$ Hz.

Figure 5

Power Spectrogram of Schwarzian and von Bertalanffy's EEG Phase Growth Model after medication for Fp2 electrode for an interval of 60000 time points at $fs=125$ Hz.

Figure 6

Phase space of model output with the derivative (attractor)

Supplementary Files

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