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Original Article

Possible Neuropathological Mechanisms Underlying the Increased Complexity of Brain Electrical Activity in Schizophrenia: A Computational Study

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Abstract

Objective: Schizophrenia is a complex neurodevelopmental illness that is associated with different deficits in the cerebral cortex and neural networks, resulting in irregularity of brain waves. Various neuropathological hypotheses have been proposed for this irregularity that we intend to examine in this computational study.
Method: We used a mathematical model of a neuronal population based on cellular automata to examine two hypotheses about the neuropathology of schizophrenia: first, reducing neuronal stimulation thresholds to increase neuronal excitability; and second, increasing the percentage of excitatory neurons and decreasing the percentage of inhibitory neurons to increase the excitation to inhibition ratio in the neuronal population. Then, we compare the complexity of the output signals produced by the model in both cases with real healthy resting-state electroencephalogram (EEG) signals using the Lempel-Ziv complexity measure and see if these changes alter (increase or decrease) the complexity of the neuronal population dynamics.
Results: By lowering the neuronal stimulation threshold (i.e., the first hypothesis), no significant change in the pattern and amplitude of the network complexity was observed, and the model complexity was very similar to the complexity of real EEG signals ($P > 0.05$). However, increasing the excitation to inhibition ratio (i.e., the second hypothesis) led to significant changes in the complexity pattern of the designed network ($P < 0.05$). More interestingly, in this case, the complexity of the output signals of the model increased significantly compared to real healthy EEGs ($P = 0.002$) and the model output of the unchanged condition ($P = 0.028$) and the first hypothesis ($P = 0.001$).
Conclusion: Our computational model suggests that imbalances in the excitation to inhibition ratio in the neural network are probably the source of abnormal neuronal firing patterns and thus the cause of increased complexity of brain electrical activity in schizophrenia.

Key words: *Computational Modelling; Neurophysiology; Neuropathology; Schizophrenia*

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Schizophrenia is a severe and chronic psychiatric illness that disrupts patients' life at different neurobiological, cognitive, emotional and social levels. Although the onset of schizophrenia often occurs in early adulthood, it has been shown that some traits and symptoms, including cognitive and social impairments, are already manifest in childhood (1, 2). Several studies have pointed out genetic, neurobiological, environmental, social and psychological factors as main contributory processes (3, 4). Meanwhile, many neuroscience studies have focused on neurobiological and neurophysiological factors as abnormal underlying processes. These studies suggest that changes in synapse reorganization and abnormal patterns of neuronal firing are important neurobiological contributory factors, reflecting abnormal neurophysiological activity and irregular brain signals in schizophrenia (5-7). In this regard, researchers in the field of computational neuroscience, considering the concept of time-dependent disorders and dynamical diseases, have utilized chaotic approaches to study patterns of neural activity in schizophrenia (8, 9). Electroencephalogram (EEG)/Magnetoencephalogram (MEG) studies have used nonlinear and chaotic methods to estimate the complexity patterns of brain electrical activity and to investigate the brain dynamics in schizophrenia due to (i) the nonlinear properties of dynamical neural systems, (ii) dynamical nature of schizophrenia symptoms and their severity, reflecting a disturbance in underlying nonlinear processes as state switches in the cortical system, and (iii) deficits in stability, self-organization and hierarchical processes of brain system in schizophrenia (10-15).

Fernandez *et al.* (7), in a comprehensive review, concluded that young, drug-naïve patients with positive symptoms (i.e., paranoia and hallucinations) are expected to show increased complexity in MEG and EEG signals, probably resulting from abnormal firing patterns in neuronal activity in the critical brain areas. Neurons are supposed to be the computational parts of brain function that release a neurotransmitter into the synaptic space due to the action potentials. Any disturbance in this neuronal environment can lead to abnormal firing patterns, resulting in impaired brain activity and subsequent high-level behaviors (16). Postmortem brain studies in schizophrenia have shown that there is an imbalance in the excitation to inhibition ratio due to impairments in the levels of glutamate, as an excitatory neurotransmitter, and N-Methyl-D-aspartate receptor (NMDA-R) signaling, resulting in the raised excitability of pyramidal neurons (17, 18). On the other hand, a variety of impairments in the inhibitory neurotransmitter Gamma-Aminobutyric Acid (GABA) have been observed in postmortem schizophrenia brain researches, which has demonstrated that schizophrenia is closely related to decreased inhibitory neurotransmission (19). Each of these deficits and impairments can be associated with abnormal firing patterns and increased complexity of brain dynamics involved in schizophrenia. In this computational study, we intended to use a mathematical model of a neuronal population to investigate each of these impairments and their effect on brain dynamics. This model, recently developed by our research team (20), is based on cellular automata and uses simple laws of electrical events, called action potentials, and the inherent properties of neurons and the interactions between them, and is well able to simulate real EEG signals. Therefore, we use this model to examine two hypotheses about the neuropathology of schizophrenia: first, reducing neuronal stimulation thresholds to increase neuronal excitability; and second, increasing the excitation to inhibition ratio by increasing the percentage of excitatory neurons and decreasing the percentage of inhibitory neurons in the neuronal population. Then, we compare the complexity of the output signals produced by the model in both cases with real healthy EEG signals and see if these changes alter (increase or decrease) the complexity of the neuronal population dynamics.

Materials and Methods

To test the mentioned hypotheses, we used a model recently developed and published by our research team that has been shown to be able to simulate recorded electrical signals from a healthy human brain. Details on this model can be found in (20), but we will briefly describe it here. This model is based on cellular automata and is designed using the Python programming language and follows simple rules based on the intrinsic properties of neurons and the properties of action potentials. These rules are as follows:

(a) Define a 40 × 40 network,
(b) Define the initial state for each neuron in the network randomly from the four states of resting, firing, hyperpolarization and refractory, which are different parts of an action potential,
(c) Define the number of neighborhoods or synapses for each neuron as the minimum number of synapses (N_{min}) to the maximum number of synapses (N_{max}),
(d) If the sum of input synapses from the neighbor neurons is greater than a resting threshold (T_{rest}), then a resting cell in the network is activated,
(e) After activation, the cell should go through firing, hyperpolarization and refractory states in order and then go back to its resting state,
(f) In the firing and hyperpolarization states, a neuron will never produce the next action potential,
(g) In the refractory state, the neuron may be activated if the sum of input synapses from its neighbors is greater than a relative threshold ($T_{relative}$), where $T_{relative} > T_{rest}$,
(h) The output time series is the sum of the effects of each neuron in the network.

Based on the results of the previous study, we define initial states for neurons as N_{firing} = 40%, $N_{refractory}$ =

35%, N_{rest} = 20% and $N_{hyperpolarization}$ = 5%. Furthermore, 20 percent of the network neurons were considered as inhibitory neurons and the remaining 80 percent as excitatory neurons. Also, we set N_{min} = 14, N_{max} = 60, T_{rest} = 8 and $T_{relative}$ = 12.

As described, some important features of a neuronal network are embedded in this cellular automata model. Our published results on the model proved that this model can produce various dynamics, from limit-cycle to chaotic dynamics, just like the different dynamics and behaviors seen from a real neuron population in the human brain at different conditions. Moreover, output time series from the model showed a high-dimensional chaotic behavior similar to a healthy brain. Quantitative and qualitative comparisons of the model output time series and the real EEG data in both nonlinear and linear domains proved the ability of this mathematical model to simulate the real EEG signals. Therefore, this computational model is useful and can be utilized to investigate healthy and pathological neural populations and gain insight into their various functional mechanisms. As a result, we used this model to test existing hypotheses about the neuropathology of schizophrenia. For the first hypothesis, we reduced T_{rest} and $T_{relative}$ to increase the excitability of neurons; and for the second one, we changed the percentage of excitatory and inhibitory neurons in the network.

Real EEG data

In this work, EEG data available on the PhysioNet website was used to qualitatively and quantitatively compare simulated signals in different conditions with real signals. This database contains 72 EEG signals from healthy adults at rest and during cognitive tasks. EEG signals were recorded using the Neurocom EEG device based on the 10-20 international standard protocol and through Ag/AgCl electrodes. Earlobes were used as references in signal recording. In the pre-processing stage of these signals, a notch filter (50 Hz) and a low-pass filter with a cutoff frequency of 30 Hz were used. In addition, independent component analysis was used to reduce signal artifacts. Therefore, a clean 60-second EEG signal fragment was provided for each individual in this database (21). Here, the O1 channel of 20 resting-state signals from this database was used for further comparison purposes .

Complexity measures

There are various techniques from multiple conceptual approaches to measure complexity (22). In this work, we used maximum lyapunov exponent (MLE) and the embedding dimension to compare nonlinear characteristics and complexity patterns of the real and simulated EEGs qualitatively. Lyapunov exponents are considered as dynamical measures of attractor complexity. They reveal the exponential convergence or divergence of adjacent trajectories of the attractor present in the phase space. MLE is interpreted as a measure of dynamic complexity because it indicates dependence on initial conditions. A dynamical system or time series is determined according to the rate of expansion of the differences between successive samples. Larger MLE values demonstrate more complex patterns in a dynamical system (23, 24). Moreover, the embedding dimension is an important parameter for reconstructing the state space of dynamic systems. In short, in order to reconstruct the state space, the state vectors are replaced by delay vectors, and the number of components in these vectors is the embedding dimension. In this work, we used the well-known Cao algorithm to estimate the embedding dimension (25). Furthermore, Lempel-Ziv complexity was calculated to quantitatively measure the complexity of the healthy EEG signal and the model output time series. It uses the concepts of producibility, reproducibility and exhaustive history of a sequence to estimate the complexity of a time series. For more information and details on these methods for estimating the complexity of EEG signals, you can refer to (7, 22, 23).

Statistical analysis

First, the Shapiro-Wilk test was used to determine the data distribution. This test showed that the data has a normal distribution ($P > 0.05$). Therefore, parametric tests should be used to determine statistically significant differences between features and indices extracted from real and simulated signals in different conditions. As a result, in this study, analysis of variance (ANOVA) and independent t tests were used as parametric statistical tests to compare means. All statistical analyzes were performed using the SPSS software (version 21) and $P < 0.05$ was considered as a significant criterion.

Results

We, first, qualitatively examined and compared the complexity of real healthy EEG signals and the model output time series (simulated EEG) for the mentioned parameters using MLE and the embedding dimension. As shown in Figure 1 (top row), the complexity of the signals generated by the model is very similar in pattern and amplitude to the complexity of real healthy EEG signals. In the Cao algorithm, two functions are used to estimate the embedding dimension of a time series: $E_1(d)$ and $E_2(d)$. When d is greater than or equal to the embedding dimension (i.e., close to 1), $E_1(d)$ does not change. On the other hand, $E_2(d)$ is used to distinguish deterministic signals from chaotic signals. For deterministic signals, $E_2(d)$ is equal to 1 for some dimension, while for chaotic signals, $E_2(d)$ is equal to 1 for almost all values of d. Therefore, as proved in our previous article, this model is well able to simulate the dynamics of the human brain's electrical activity and real EEG signals.

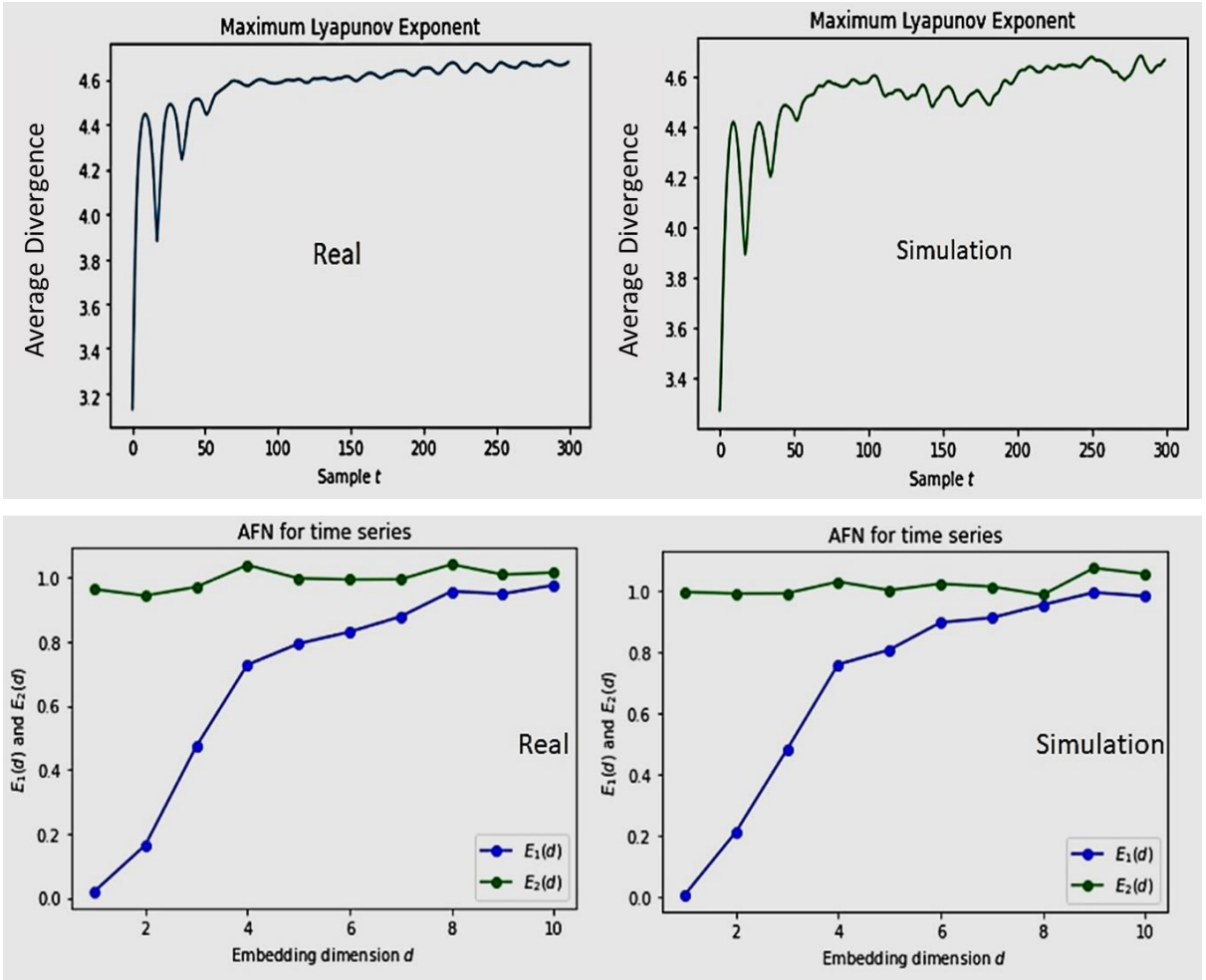

Figure 1. Maximum Lyapunov Exponent (Top Row) and Embedding Dimension (Below Row) Diagrams Calculated for a Real EEG Signal (Blue) and a Simulated EEG Signal Generated by the Cellular Automata Model (Green)

Next, to test the hypotheses under consideration, we made changes to the value of the model parameters and again compared the complexity of the time series generated by the model in different conditions with the complexity of the real EEG signals. To test the first hypothesis, we adjusted the T_{rest} = 6 and $T_{relative}$ = 10 values to lower the excitation threshold of the network neurons and increase the excitability of the neurons. Experiments showed that lower values of these parameters lead to loss of network dynamics. To test the second hypothesis, we increased the percentage of excitatory neurons to 85% and reduced the percentage of inhibitory neurons to 15% to increase the excitation to inhibition ratio in the neural network. These percentages were chosen considering maintaining optimal network dynamics to generate simulated EEG signals after several trials. Finally, we analyzed 20 real healthy EEGs, 20 simulated EEGs for the first hypothesis, 20 simulated EEGs for the second hypothesis, and 20 baseline simulated EEGs (with initial parameter values as the unchanged condition) and extracted their complexity feature using the Lempel-Ziv measure. Table 1 shows the complexity values of the healthy EEG signals and model outputs with and without applied changes (unchanged condition, first hypothesis and second hypothesis). As you can see, by lowering the neuronal stimulation threshold (i.e., the first hypothesis), there was no significant change in the pattern and amplitude of the network complexity, and the model complexity is very similar to the complexity of a healthy EEG signal ($P > 0.05$). However, increasing the excitation to inhibition ratio (i.e., the second hypothesis) led to significant changes in the complexity pattern of the designed network ($P < 0.05$). More interestingly, in this case, the complexity of the output signals of the model significantly increased compared to real healthy EEGs ($P = 0.002$) and the model output of the unchanged condition ($P = 0.028$) and the first hypothesis ($P = 0.001$).

Table 1. Comparison of the Complexity of Real Healthy EEG Signals, the Simulated Signals Produced by the Cellular Automata Model with Initial Parameter Values (Unchanged Condition), with Decreased Neuronal Stimulation Thresholds (First Hypothesis) and with Increased Excitation to Inhibition Ratio (Second Hypothesis) Using the Lempel-Ziv Measure

(I) Label	(J) Label	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Real Healthy EEG	First Hypothesis	0.00385	0.01354	1.000	-0.0296	0.0372
	Second Hypothesis	-0.04794*	0.01354	0.002	-0.0813	-0.0145
	Unchanged Condition	0.00309	0.01745	1.000	-0.0443	0.0505
First Hypothesis	Healthy EEG	-0.00385	0.01354	1.000	-0.0372	0.0296
	Second Hypothesis	-0.05178*	0.01354	0.001	-0.0852	-0.0184
	Unchanged Condition	-0.01751	0.01745	1.000	-0.0649	0.0299
Second Hypothesis	Healthy EEG	0.04794*	0.01354	0.002	0.0145	0.0813
	First Hypothesis	0.05178*	0.01354	0.001	0.0184	0.0852
	Unchanged Condition	0.05103*	0.01745	0.028	0.0036	0.0984
Unchanged Condition	Healthy EEG	-0.00309	0.01745	1.000	-0.0505	0.0443
	First Hypothesis	0.01751	0.01745	1.000	-0.0299	0.0649
	Second Hypothesis	-0.05103*	0.01745	0.028	-0.0984	-0.0036

Discussion

In this work, we used a mathematical and computational model to investigate the neuropathological mechanisms in schizophrenia. Such a study lies within the fields of computational neuroscience and computational psychiatry and has been applied by many researchers in recent years to investigate the relationship between different pathological and phenomenological aspects of psychiatric disorders (26-30). Our model, based on the simple rules of cellular automata, was able to simulate the dynamics of a real neuronal population of the human brain. Our experiments and the results of this model showed that the reduction of neuronal stimulation thresholds does not lead to a significant change in the dynamics of the neuronal population and the complexity of neuronal function. Thus, previous evidence of deficits in glutamate levels and NMDA-R signaling associated with internalization of receptors involved in synaptic and extra-synaptic environments in both inhibitory and excitatory neurons may not possibly be the neuropathological mechanism underlying the dynamic change in brain neurons and the increased complexity of electrophysiology in schizophrenia (6). In addition, the experiments and the results of the model showed that increasing the ratio of excitation to inhibition in a neuronal population can cause substantial changes in its behavioral and dynamical pattern and lead to increased complexity of neuronal function in the schizophrenic brain. Therefore, decreased inhibitory neurotransmission may be the neuropathological mechanism underlying the dynamic change in brain neurons and, thus, the increased complexity of cortical electrophysiology in schizophrenia. Inhibitory neurotransmitter GABA is an important molecule in modulating neuronal firing, and previous studies have shown that schizophrenia is associated with impairments in GABAergic markers (31, 32). One of the main functions of GABA is the synchronization of neuronal populations, which produces bursting or rhythmic neural activity, called brain oscillations. Appropriate oscillating firing activity in different brain regions, especially in the prefrontal cortex, is thought to be a neural mechanism of working memory (33, 34). Given that deficits in working memory have been suggested to underpin a variety of cognitive impairments in patients with schizophrenia, disturbance of brain oscillations can be involved in schizophrenia (35, 36). A reduction in the expression of the GAD67 (GABA synthesizing enzyme) and an impairment in the parvalbumin-positive GABAergic interneurons (PVIs) within the prefrontal cortex are the strongest findings in postmortem schizophrenia studies (37, 38). Given that the expression of PVIs and GAD67 is dependent on the activity, GABAergic drive is decreased within the prefrontal cortex in schizophrenia (39).

Limitation

Like many other researches and studies, this study also suffers from some limitations. The results obtained in this study are based on a mathematical model and therefore their accuracy should be checked by animal models and studies. In addition, in this study, we examined only two neuropathological mechanisms reported in schizophrenia, while other neuropathological mechanisms such as the disconnection hypothesis of schizophrenia have been emphasized in many previous studies, which cannot be examined using the current model.

Conclusion

Various neuropathological mechanisms may lead to distortion of neuronal activity and brain function, and consequently abnormal high-level behaviors associated with the disorder in diseases such as schizophrenia. These mechanisms may alter the dynamics of neuronal function in brain networks by affecting the regular firing pattern of different neurons and may be the source of abnormalities reported in schizophrenia. Our computational model suggests that imbalances in the excitation to inhibition ratio in the neural network are probably the source of abnormal neuronal firing patterns and thus the increased complexity of brain electrical activity in schizophrenia. In addition, this study showed that such a model can be used in the future to better understand the neuropathological mechanisms involved in other psychiatric and neurological disorders. However, findings of the present study should be interpreted with caution due to the nature of computational studies. Indeed, future in vivo and in vitro studies should confirm our theoretical findings.

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Conflict of Interest

None.

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