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A Novel Hypothesis for Migraine Disease Mechanism: The Creation of a New Attractor Responsible for Migraine Disease Symptoms

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ABSTRACT Migraine Disease (MD) is one of the common primary headaches that can prevent patients from their everyday life. Despite the high prevalence, the pathophysiology of the disease has not been clearly understood yet. Here, the brain is considered as a dynamical system. The Chua's circuit with a chaotic attractor is the proposed model. This attractor has a one-scroll mode representing a healthy brain and a double-scroll mode representing a migraine sufferer brain. We believe that MD and Chua's systems have certain behavioral similarities. The boundaries of the attractor are the sensitive brain areas in which any small trigger can start the ictal phase of the migraine. The transition from the inter-ictal phase to the ictal phase in migraine patients occurs due to a decrease in serotonin levels when the brain is within the boundaries of the first attractor. Here, this is the results of the increase of system parameters. In addition, the transition from the ictal phase to the inter-ictal phase in a migraine sufferer brain is caused by a disruption of coordination in the brain's structures and this lasts for a certain period for every migraine patient. The structures which are the result of the Migraine Generator Network (MGN) and Cortical Spreading Depression (CSD). This explanation may propose newer methods for preventing or curing MD. To better understand MD to control it and shrink the areas involved in this disease, it is better to know the dynamic systems better. It may help prevent the formation of migraine ictal attractor or even make the migraine ictal phase attractor smaller even after it has been formed.

KEYWORDS
Headache
Ictal
Migraine sufferer
Complex dynamic system
Chaotic attractor
Chua's system

INTRODUCTION

Migraine Disease (MD) is one of the primary headaches affecting one in every seven individuals worldwide (Aslan 2021). This prevalent disease is a neurological disorder characterized by numerous symptoms, including headache, nausea, vomiting, photophobia, phonophobia, osmophobia, etc. The foremost critical and bothering symptom of the MD is the throbbing headache. The frequency of incidence of the migraine ictal can range from infrequent to weekly or even daily. MD is regarded as a chronic disorder with episodic manifestations (Ashina *et al.* 2021). The mechanism of MD is still not fully understood. However, the activation of some regions in the brainstem called Migraine Generator Network (MGN) and activation of Cortical Spreading Depression (CSD) during a migraine ictal are considered to be theories involved in the pathophysiology of MD. These theories have difficulty explaining the difference between a healthy brain and a migraine sufferer's brain in the inter-ictal phase. In this disease, there are one normal phase and four abnormal phases, including the pre-ictal, aura, ictal, and post-ictal phases. In some patients, only one or two phases of the disease are observed (Lane and davies 2006).

Two common subtypes of MD are migraine with aura (MA) and migraine without aura (MO), depending on whether the migraine sufferer experiences the aura phase. The diagnosis of MD is based on the clinical symptoms described by the patient and the opin-

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ion of the physician. Some studies focus on the classification of migraine patients and healthy controls based on the extracted features from the electroencephalography (EEG) signal (Aslan 2021; Bellotti *et al.* 2007; Jindal *et al.* 2018). According to some researchers, the brain is a dynamic system that enters the MD state by alternation in its parameters (Dahlem *et al.* 2013, 2015; Scheffer *et al.* 2013). In 2003, Charles described migraine as a brain state. He stated that headache happens due to changes in the state of the brain. During the start of the ictal phase, certain brain networks either become active or inactive. As a result, coordination between different parts of the brain is disrupted. Also, during the ictal phase, arousal decreases and symptoms like fatigue and yawning occur. As awareness grows, the brain becomes more responsive to light, smell, and other stimuli.

In migraine, not only does it activate pain-sensing networks, but it also disrupts the physiological communication between different parts of the brain. Several studies have indicated alterations in neuronal connections during the inter-ictal phase, along with a reduction in theta wave activity on Quantitative Electroencephalography (QEEG) during the pre-ictal and ictal phases (Charles 2013). In 2013, Scheffer et al. considered a minimal model for migraine. According to their report, when a group of neurons is stimulated by an input stimulus, it causes an increase in the intracellular level of potassium and glutamate, which enhances the excitability of the neurons. This excitability is further amplified by the local neuronal activity and positive feedback, ultimately leading to the initiation of a contagious process called CSD by a small trigger in the neurons. This study suggests that within each small region of the brain, there exists a dynamic equilibrium. This equilibrium arises from the generation and decay of pulses. When the baseline excitability increases, this equilibrium is disrupted, and the brain reaches a tipping point. In this case, every small trigger initiates the ictal phase (Scheffer *et al.* 2013).

Dahlem et al. in 2013 considered migraine to be a dynamic disease. It was stated that when the headache starts, the brain transitions from the normal phase and enters a tipping point or bifurcation point and then enters the headache phase. They declared this stage as the prodromal stage and stated that it could be detected with dynamical network biomarkers. It is important to identify the prodromal stage since it is reversible while the headache stage is not, and this may help prevent the headache (Dahlem *et al.* 2013). Dahlem et al. in 2014 also found that when the brain reaches a tipping point, even a small trigger can start the headache. In contrast, if the brain is not in this area, even things known to be major triggers of migraine headaches do not cause pain.

They considered a path with one or two wells as two states of health and pain. As the height between the two wells decreases, the brain enters the tipping point area, and any small trigger causes the onset of the headache (Dahlem *et al.* 2015).In 2018, Bayani et al. extended the model proposed by Scheffer et al. and considered a group of neurons for 3 different trigeminovascular, descending modulatory brainstem, and cortex units, then obtained 3 equations for neuronal activity. They also announced that the inter-ictal and the ictal stages are chaotic phases, and the pre-ictal phase is unstable and periodic (Bayani *et al.* 2018).

According to previous studies, it may be an appropriate method to consider the brain as a dynamic system and then propose a complex system model for that as a migraine patient or a healthy subject. For this reason, it seems possible to gain a good understanding of the performance of MD by studying the behavior of dynamic systems that exhibit similar behavior to MD. This may also serve a better understanding of the changes in the brain during the ictal phase to enable better diagnosis and possibly better therapy.

HYPOTHESIS

MD is considered a chronic disease with episodic manifestations. If the frequency of headaches increases, it can lead to chronicity of the disease. A chronic migraine is present if the headaches occur 15 times or more per month and last longer than 3 months. It is assumed that there is a pre-ictal phase prior to the ictal phase of the migraine. This phase can be a warning sign of the headache initiation. Symptoms that accompany this phase include behavioral changes, hunger, fatigue, and etc. Despite some theories about the cause of the MD such as CSD or MGN, the pathophysiological mechanism of MD is still not fully understood.

Since 1970s, there have been numerous computational models attempting to explain the spreading depression. Some studies also considered the role of Central Nervous System (CNS) as a function of a complex dynamic system. When the parameters of the dynamic system change, the symptoms of the disease become visible. A theoretical model from the perspective of the complex dynamic system is presented here. This is used to explain the clinical signs and manifestation of MD. The dynamics of individual neurons are not considered here, but the interaction between whole neurons is analyzed. As a model for the healthy brain, a complex system with a chaotic strange attractor is considered. It is assumed that this attractor changes from one scroll to double scroll when the system parameters in the brain of migraine patients change. It is considered that the one scroll attractor can represent a healthy brain, while the double scroll attractor represents the brain of a migraine patient.

The size of the two scrolls can change by varying the model parameters to represent the Chronic Daily Migraine (CDM) or episodic migraine. For a migraine patient, certain triggers such as neck pain, bright light, certain foods, and other factors can sometimes initiate the ictal phase, while having no effect on other days. It is believed that the brain becomes sensitive in certain situations where any trigger can initiate the ictal phase. In the proposed system, the boundaries of the normal attractor are the regions where any small trigger can change the phase and thus initiate the ictal phase. In the proposed model, the inner regions of the normal attractor are the non-sensitive brain situations.

COMPUTATIONAL MODEL

In order to choose a suitable model for MD, different dynamic systems were considered. Our goal was to find a system that has one attractor representing a healthy brain and able to generate two attractors by changing the parameters. This attractor can simulate the behavior of the brain of a migraine patient. The assumed system should have a "one scroll" mode and a "double scroll" mode representing a healthy brain and the brain of a migraine patient. Switching between the modes is done with a parameter change. One of the best-known systems with these features is Chua's system. Chua is a non-linear and well-known dynamic model (Chua 1993).In 1983 Leon Chua developed a chaotic electronic circuit with 2 linear capacitors (C1, C2), a linear inductor (L), a linear resistor (R), and a voltage-controlled non-linear resistor (RN) known as Chua's diode. The Chua's diode is capable of generating chaotic behavior. This circuit is shown in Figure 1(a). The Chua's diode has 3 regions; a piecewise linear region with 2 unstable points. The driving points of Chua's diode are shown in Figure 1(b).

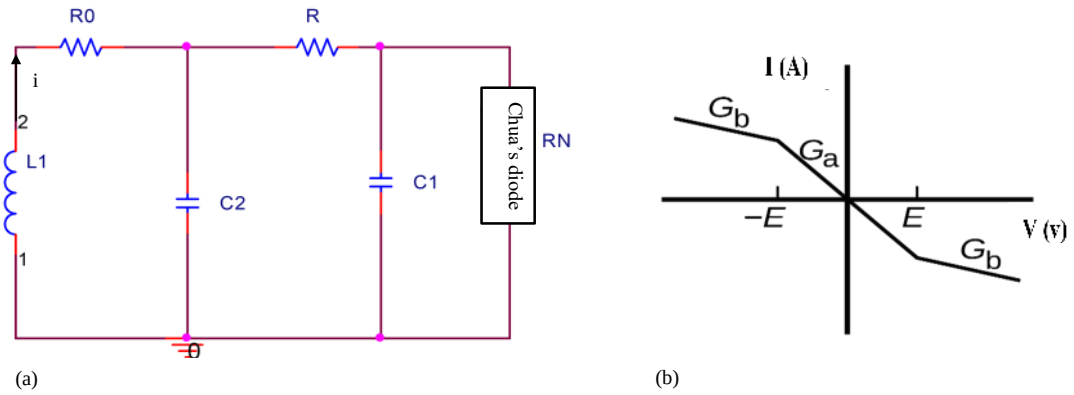

Figure 1 Representaion of (a) Chua's circuit and (b) the driving point characteristics of the voltage controlled resistor (Chua's diode)

The equations of the circuit, which are derived by applying Kirchoff's laws to nodes and loops, are as follows:

$$C_1 V'_{C1} = \frac{V_{C2} - V_{C1}}{R - g(V_{C1})} \tag{1}$$

$$C_2 V'_{C2} = \frac{V_{C1} - V_{C2}}{R + i} \tag{2}$$

$$Li' = -V_{C2} - R_0 i \tag{3}$$

C1 and C2 are the capacitances of the capacitors, L is the inductance of the inductor, R is the resistance of the resistor, and g(x) is the three-segment piecewise linear characteristic of the Chua's diode, which is shown in Figure 1(b) and mentioned here:

$$g(x) = G_b x + 0.5(G_a - G_b)(|x+1| - |x-1|) \tag{4}$$

G_a is the slope of the inner region of the non-linear resistor, and G_b is the slope of the outer part. Then the variables of these equations are replaced with x1=v1, x2=v2, x3=Ri, and the parameters with

$$\alpha = \frac{C_2}{C_1}, \beta = \frac{R^2 C_2}{L}, \gamma = \frac{R R_0 C_2}{L}, m_0 = R G_a, m_1 = R G_b \tag{5}$$

Chua's system equations are achieved as:

$$x'_1 = \alpha(x_2 - x_1 - h(x_1)) \tag{6}$$

$$x'_2 = x_1 - x_2 + x_3 \tag{7}$$

$$x'_3 = \beta x_2 - \gamma x_3 \tag{8}$$

Where

$$h(x) = m_1 x + 0.5(m_0 - m_1)(|x+1| - |x-1|) \tag{9}$$

For different values of the parameters, this attractor changes from a spiral attractor to a double scroll attractor. The spiral attractor can be the representation of a healthy brain, while the double scroll attractor can be the representation of the brain of a migraine patient. Each region can show the ictal or inter-ictal phases, and the lines connecting the two areas show the pre-ictal and post-ictal phases.

The similarities between MD and Chua's system

A healthy brain that does not experience a migraine ictal has only one normal phase. This mode is the one scroll or spiral mode of Chua's attractor, as shown in Figure 2(a).

The value of the parameters for this mode is as:

$$\alpha = 6.5792, \beta = 10.9, \gamma = -0.446, m_0 = -1.182, m_1 = -0.652 \tag{10}$$

A healthy brain has only the normal phase, which is free of headaches. In the proposed model, changing the alpha parameter can transform the healthy brain into a migraine prone one. Increasing the alpha parameter, gives the attractor, which has two scrolls indicating two phases of a migraine patient's brain. The inter-ictal or headache-free phase and the ictal or headache phase are connected by some lines. Figure 2(b) is a representation of the double scroll attractor. The value of the parameters are as:

$$\alpha = 10.3515, \beta = 16.79, \gamma = -0, m_0 = -2, m_1 = -0.2601 \tag{11}$$

Each region of the attractor represents the ictal and inter-ictal phases. Suppose the size of one of the regions is smaller than the size of the other one as shown in Figure 2(c). In this case, the small region may represent the ictal phase for the situation of episodic migraine, in which the headache occur with less frequency. However, if the two areas are the same size, this may represent the brain of a chronic migraine sufferer, where the migraine sufferer experiences headaches 15 days of a month or more. For the parameter values as:

$$\alpha = 11.3515, \beta = 10.79, \gamma = -0.14, m_0 = -2, m_1 = -0.2601 \tag{12}$$

The representation of the Chua's attractor for the given parameter values is in Figure2(c) . This is the proposed model for the brain of an episodic migraine sufferer.

The representation of x(t) in healthy mode, in the ictal phase, and in the inter-ictal phase are shown in Figures 3(a), 3(b), and 3(c). As can be seen in figure 3, the behavior of x (t) in the 3 states of healthy mode, inter-ictal phase, and ictal phase of migraine does not seem to make any significant difference. When we compare the EEG of these 3 groups, there is no noticeable difference in the appearance of the EEG in the time domain of these 3 groups. But in general, these behaviors indicate whether there is MD or not. As a result, we can say that what happens in epilepsy does not occur in MD. In epilepsy, these differences can be seen in the EEG

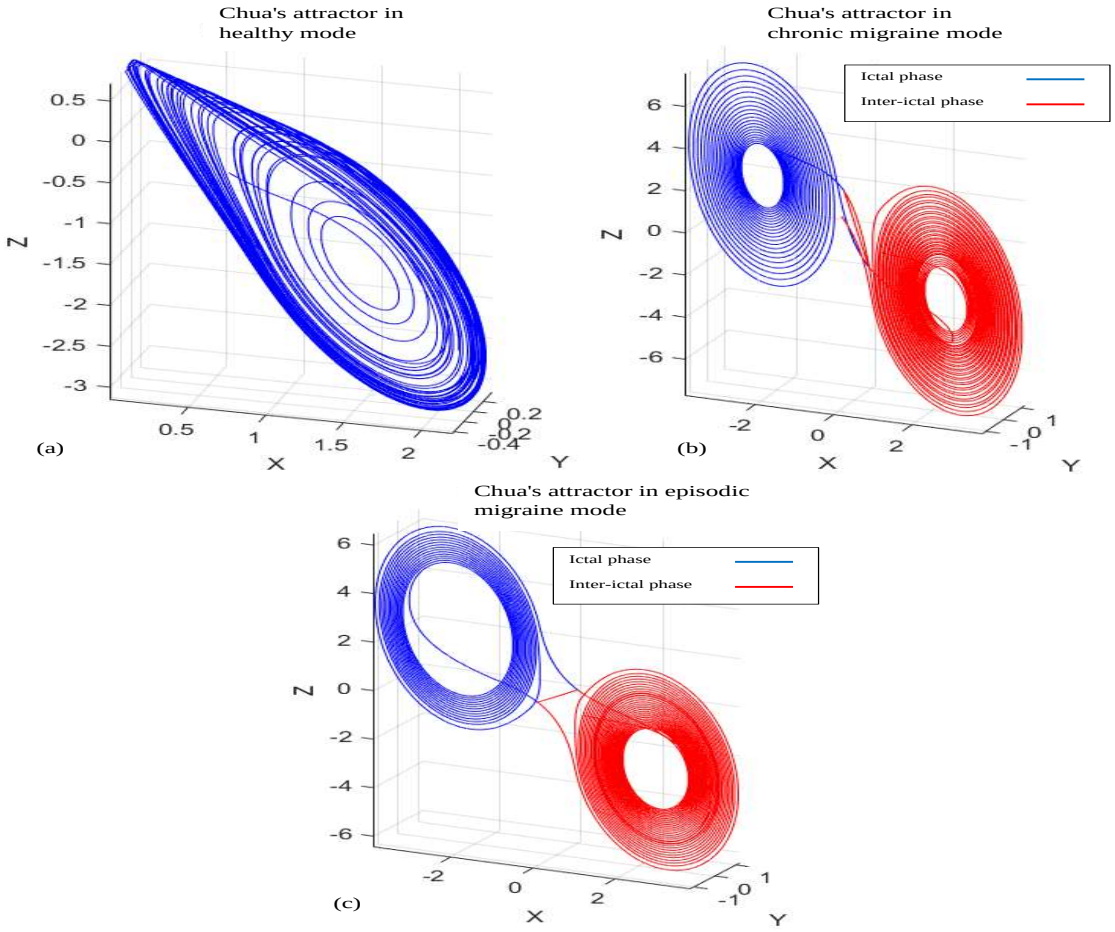

Figure 2 (a) Chua's system in the spiral mode representing a healthy brain and (b) . Double scroll Chua's attractor representing a chronic migraine sufferer brain (c) Double scroll Chua's attractor representing an episodic migraine sufferer brain

due to synchronization. In MD, however, there is no noticeable difference in the appearance of the EEG. In this figure, there is also no significant difference between the behavior of the three groups. Nevertheless, they originate from different phases and modes of the Chua's attractor and lead to different states.

The energy level of x(t) in the different modes of the Chua's system was also compared. The energy level was lower in Chua's spiral mode (considered here as the healthy mode), than the double scroll mode (considered as the MD mode). By calculating the energy levels of the EEG recordings of the migraine patients and healthy controls in the inter-ictal phase using the publicly available Carnegie Mellon University datasetl (Chamanzar *et al.* 2020), this higher value of average energy was also seen in migraine sufferer brain compared to a healthy brain. These values are listed in Table 1.

The researchers also point out that the glutamate level is higher in migraine sufferer brain than a healthy brain(Hoffmann and Charles 2018). Since glutamate plays an important role in the energy metabolism of the brain and the neuron excitation (Ramadan 2003), the reason for the higher energy level could be the higher glutamate level in a migraine sufferer brain.

Migraine patients believe that sometimes any small trigger can

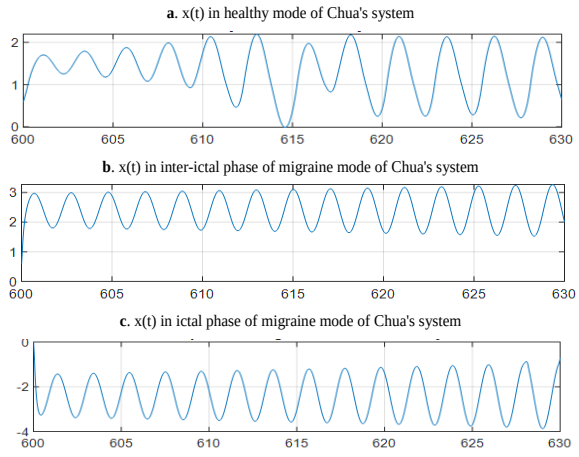

Figure 3 Shape of the x(t) in the healthy mode. (b). Shape of the x(t) in inter-ictal phase of the migraine mode. (c). Shape of the x(t) in ictal phase of the migraine mode.

Table 1 Comparison of the average energy of different modes of the Chua's system and EEG recordings of the migraine patients and healthy controls

Energy level in one scroll mode of chua's system (healthy mode)	Energy level in double scroll mode of chua's system (disease mode)	Average energy level in healthy controls' EEG recordings in rest (mean of all channels)	Average energy level in migraine patients' EEG recordings in rest (mean of all channels)
1.9574e+06	5.8743e+06	15839	22957

initiate a migraine ictal, while in other situations even major triggers may not initiate the ictal phase. To test whether this situation occurs in the proposed model, a point at the edge of the inter-ictal phase ia chosen, as shown in Figure 4. Here, a small noise is added to test if the point enters the ictal phase or not. This point enters the lines between two phases, which represent a path to the ictal phase. This noise can simulate the small trigger which initiates a headache. In addition, the lines between the two phases can be considered pre-ictal and post-ictal phases of the migraine. Another point is also selected in the inner region of the inter-ictal phase; then the same noise is added to the system. Since the trajectory is in the inter-ictal phase and far from the boundries, the same noise cannot trigger the headache and bring the trajectory into the ictal phase.

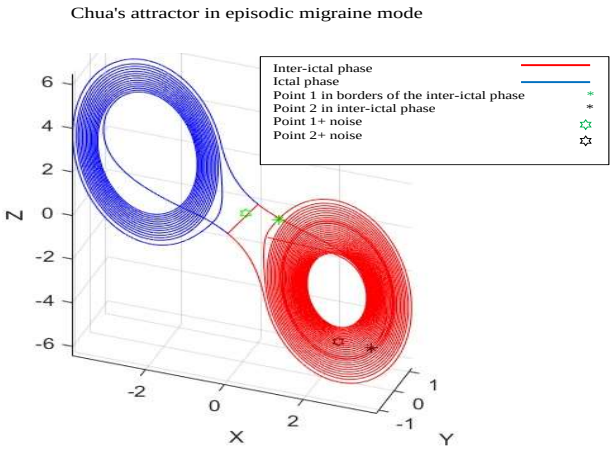

Figure 4 A point in the edge of the inter-ictal phase entering ictal phase while adding noise

DISCUSSION

Headaches are one of the most common disorders that 90% of people experience at least once in their lives. Episodic migraine is a common primary type of headache, affecting 15% of women and 6% of men worldwide (Hauser and Josephson 2010). 20% of the migraine patients suffer from migraine with aura (Lane and davies 2006). The prevalence of migraine increases from childhood to the age of 40 after which it decreases (Stovner *et al.* 2007). In some migraine patients, the frequency of the headaches increases. These people experience migraine without aura 15 times a month. If it lasts longer than three months, this disorder is referred to as CDM (Lipton and Bigal 2006). MD has affected many people globally, particularly young individuals, and has prevented the patients from their daily activities. 53% of migraine patients report a need for bed rest, and one third miss one day a year of school or work (Lipton and Bigal 2006). There is no specific cure to prevent the onset of this disease.

Despite the high prevalence of MD and the disability attributed to the severe pain during the migraine ictal phase, the cause of the disease is not yet clearly understood. Although many studies have addressed the pathophysiology of the disease (Goadsby *et al.* 2017; Hargreaves and Shepheard 1999; Pietrobon and Moskowitz 2013), some questions about MD have remained unanswered. What is the real reason for the onset of MD? Medical texts cite two mechanisms for MD, but it is not yet clear how these mechanisms relate to the headaches and why new manners occur? How are the periods of migraine ictal determined? Why can any minor trigger sometimes initiate a migraine headache and even major triggers may not start the headache in other situations? What is the reason that the headache gets stronger or weaker? What are the pre-ictal and post-ictal phases of migraine headaches?

It seems that the study of individual neurons and changes in MD is not very suitable to assess and recognize the function of the disease. We believe that we will get a better understanding if we have a global view of the neuronal areas. Given what we know about the performance of the dynamical systems and various studies that have compared CNS performance of dynamical systems, it can be concluded that looking at dynamical systems to analyze brain function can lead to a better understanding of MD. Therefore, we hypothesize that different neuronal regions from the normal behavior of the brain can be considered as attractors and the system response remains in this healthy attractor. In the case of MD, a new attractor is added to the responses of different areas of the CNS, which may indicate the disease attractor.

Entering the abnormal area distorts brain function and forms classic migraine pain. Although there are no sensors for pain recognition in large parts of the brain (Hauser and Josephson 2010), severe migraine pain can be caused by a mismatch of information between the different brain regions. The best example of this mechanism is the moment an airplane take off. The vestibular system detects high acceleration during take-off, but the visual and auditory systems do not, resulting in mismatch of information that leads to headaches. According to this theory, some neuronal regions, referred to as MGN in medical texts, form migraine attractor regions. When the number of these neuronal regions geater, the mismatch rate is higher and severe headaches occur.

The model of the creation of a new attractor is closer to reality. In fact, there is no headache when the brain is in the first attractor, and headaches occur when the second attractor is created and the brain enters this attractor. It can be said that the creation of the second attractor occurs through the activation of MGN or CSD as a result of changes in the content of substances such as serotonin, glutamate (Park and Chu 2022) or potassium. Then the brain enters the second attractor. After the creation of the second attractor, when the brain enters this attractor, it has been observed that the

brain energy function increases. This results in an elevation of the cell metabolism, an increased number of action potentials and an enhancement of ATP consumption. The dysfunction of energy metabolism and demonstrable mitochondrial damage has also been reported for migraine patients in recent studies (Haemmerl and Kraya 2023).

The EEG recordings of the brains of the migraine patients also show an increase in energy levels and more spikes than in healthy controls. This ATP consumption cannot continue indefinitely and must be reduced to a certain extent to return to the previous state. The creation of the second attractor occurs through the activation of MGN and CSD, then the increased glutamate level leads to entry into the second attractor. The increase in the glutamate levels have been seen in plasma of the migraine patients which can be the result of its increase in platelets and neurons (Park and Chu 2022). Then there is an increase in energy levels and ATP consumption. After a while, the brain is forced to leave this second attractor and return to the normal state.

It has recently been demonstrated that ATP sensitive potassium channels (KATP) open during migraine attacks (Al-Karagholi *et al.* 2021). This study assumes that the energy level in one part of the brain suddenly rises due to an increase in glutamate levels and that other parts of the brain are unable to adapt to these energy changes, resulting in a mismatch. One of the standard dynamical systems that exhibit complex behavior is Chua's system. Chua's system has been widely studied and applied in various fields of science and engineering, such as mathematics, physics, biology, and control theory. A remarkable similarity can be observed between the behavior of this system and that of MD. The proposed theory is that when a person does not experience migraine, the glutamate and serotonin levels are a little altered, the brain compensates for these changes and most of the neuronal areas of the MGN in the attractor function normally. Then the maladaptation rate in different areas of the brain is low and the headache does not occur. When the alternation of glutamate and serotonin is high, the neuronal states of the MGN are activated, the brain enters the second attractor, energy increases and there is a mismatch of information, resulting in headaches. As only the normal attractor is formed in healthy people, the attractor associated with the headache area gradually develops in migraine patients.

Therefore, the growth of the disease can be explained by an enlargement of the ictal area of the attractor. By comparing the size of the ictal migraine attractor with the inter-ictal attractor, the length and brevity of the headaches and the frequency of migraine headaches can be justified. In some cases, patients become severely sensitive to stimuli, depending on how close the trajectory is to the branch area, which represents the transition to the ictal attractor. The farther the trajectory is from the branch, the greater the stimulus required to enter the ictal area. In contrast, the closer the trajectory is to the branch, the less stimulus is required to enter the migraine ictal area. According to the drawn trajectory and the phase space of Figure 4, the attractor transition areas can be medically considered pre-ictal and post-ictal areas. In the pre-ictal area (the transition pathway from an inter-ictal attractor to the ictal attractor), it gradually deviates from normal function. The headache rate gradually increases. The transition period can be short or long in different people. In the post-ictal area (the transition pathway from the ictal attractor of migraine to the inter-ictal attractor), we move away from the migraine-related areas with severe headaches and approach the inter-ictal attractor, then the amount of pain gradually decreases.

CONCLUSION

It is assumed that the anatomical differences between the brains of healthy people and migraine patients, which may be caused by genetic factors or other circumstances, are the reason for the creation of the second attractor, which is the attractor of the ictal phase of migraine. CSD and MGN can occur in a migraine sufferer brain leading to the ictal phase of migraine. Then the differences between the structure of a migraine sufferer brain and a healthy brain has created a second attractor.

The transition from the inter-ictal phase (first attractor) to the ictal phase (second attractor) in migraine patients occurs due to a decrease in serotonin levels when the brain is within the boundaries of the first attractor.When the serotonin level drops in a migraine sufferer brain for any reason, which is normal in the daily behavior of the brain, and the brain is also at the boundaries of the attractor, it enters the ictal phase of migraine (second attractor). On the other hand, if the brain is not at the attractor boundaries can compensate the decrease in serotonin level and does not enter the second attractor. For this reason, minor triggers can sometimes cause a headache, while in some cases, even major stimuli have no impact.

The transition from the ictal phase to the inter-ictal phase in a migraine sufferer brain is caused by a disruption of coordination in the brain's structures. The structures which are a result of CSD and MGN activation. When the neurons in this region fail to generate necessary action potentials, these structures become disconnected. When the neurons' ATP intake increases due to high energy levels, a lack of ATP and energy can occur resulting in the neurons being unable to generate action potentials, causing the cessation of the headaches. In other words, a migraine sufferer brain has a higher energy level. Eventually, the body cannot sustain this level of energy, leading to deactivation of neurons in the affected area of the brain and interruption of the second attractor. This results in a reversal to the first attractor, ultimately stopping the headache.

The cause of headaches in migraine sufferers is due to a mismatch of energy levels in the brain. A migraine sufferer brain is initially adapted to a lower energy level. When a certain part of the brain experiences a sudden increase in energy level, the brain is unable to adapt to this heightened level of energy, leading to the onset of a headache. According to the above mentioned items, ATP plays a key role in the migraine cycle. Thus, high fat and high calorie foods keep the second attractor on standby. In this case, a brief stimulus starts the headache phase. When migraine patients consume high-fat and high-calorie foods, they are more likely to experience headaches and enter a the second attractor (Bic *et al.* 1999). In addition, high-calorie and high-fat foods consumption during an ictal phase can prolong headaches. It is recommended that migraine patients reduce their fat and calorie intake, especially when they feel a migraine attack coming on.

In this study, we attempt to explain the disease function and offer a theory that reasonably justifies the behavior of the MD. This explanation may propose newer methods for preventing or curing MD. To better understand MD to control it and shrink the areas involved in this disease, it is better to know the dynamic systems better. It may help prevent the formation of migraine ictal attractor or even make the migraine ictal phase attractor smaller even after it has been formed. A series of electrical stimuli when the headache starts can take us back from the migraine ictal area to the inter-ictal area, which should be further studied.

Availability of data and material

Not applicable.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Ethical standard

The authors have no relevant financial or non-financial interests to disclose.

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