A Physical Review of Epilepsy

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ABSTRACT

Epilepsy is a neurological condition that has been recognized since ancient times. It is characterized by recurrent seizures and is often stigmatized and ostracized from society. In recent years, significant progress has been made in our understanding of the underlying causes and developing more effective treatments. In this review, we focus on the physical aspects of epilepsy and how exploring these modalities may contribute to a more comprehensive understanding of the underlying mechanisms involved. After a brief overview, we focus on the specific physical aspects of epilepsy, such as the impact of pressure, volume, heat, and relevant comorbidities on the condition. The paper concludes by discussing the main findings and limitations and potential areas for future research, highlighting the importance of understanding the physical aspects of epilepsy.

HIGHLIGHTS

- The physical aspects of epilepsy are often overlooked.
- To gain a deeper comprehension of the underlying mechanism, understanding the involvement of the physical aspects is crucial.
- The relation between epilepsy and pressure, volume, and heat introduces a consistent framework.
- In conjunction with certain theoretical works, it is possible to establish a unifying and coherent framework for epilepsy.

Key Words: Epilepsy, physical aspects of epilepsy, epilepsy comorbidities.

1. INTRODUCTION

Epilepsy has been recognized as a medical condition since Babylon, with references to seizures and convulsions (Reynolds, 2008). In the Middle Ages, epilepsy was often attributed to demonic possession or witchcraft as a continuation of the Greek concept of Sacred Disease, and people with epilepsy were often stigmatized and ostracized from society.

The first modern classification of epileptic seizures was proposed by Hughlings Jackson in the late 19th century (Reynolds, 1988), and the first successful surgical treatment of epilepsy was performed by Victor Horsley in 1886 (Meador, 1989). In the early 20th century, electroencephalography (EEG) was developed, which allowed doctors to measure the electrical activity of the brain and identify abnormal patterns associated with epilepsy.

Advances in antiepileptic medication began in the mid-20th century, with the development of drugs such as phenytoin (Duncan et al., 2006). The first randomized controlled trial of surgery for epilepsy was conducted in 2001, which demonstrated the effectiveness of surgical interventions in treating temporal lobe epilepsy (Wiebe et al., 2001).

Today, epilepsy is recognized as a common and treatable neurological condition, and ongoing research is focused on improving our understanding of the underlying causes and developing more effective treatments.

In this review, we focus on the physical aspects of epilepsy. We posit that exploring the commonly overlooked physical modalities of epilepsy may contribute to a more comprehensive understanding of the underlying mechanisms involved. We start with an

overview of epilepsy, including its definition, different types, physiological mechanisms, diagnosis, and treatment. The subsequent sections of the paper focus on specific physical aspects of epilepsy, such as the impact of pressure, volume, heat, and comorbidities on the condition. The paper also includes a discussion of the main findings and limitations, and potential areas for future research. Overall, this review highlights the importance of understanding the physical aspects of epilepsy.

2. OVERVIEW OF EPILEPSY

2.1. Definition

According to the International League Against Epilepsy (ILAE), epilepsy is a chronic brain disorder characterized by recurrent unprovoked seizures (Fisher, 2014). Seizures are defined as "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" (Fisher, 2014).

Epilepsy can be diagnosed after two unprovoked seizures, or after one unprovoked seizure with a high probability of recurrence (Fisher, 2014).

2.2. Types

Epilepsy can be classified into two broad categories (Berg et al., 2010): focal epilepsies and generalized epilepsies. Focal epilepsies, previously known as partial epilepsies, are characterized by seizures that originate from a specific region of the brain, and can be further classified based on the underlying cause, such as structural, genetic, or unknown. Generalized epilepsies, on the other hand, are characterized by seizures that involve both

hemispheres of the brain from the onset. They can be further classified based on the specific seizure type (Fisher, 2017):

1. Absence epilepsies: Brief episodes of impaired consciousness without convulsions.
2. Myoclonic epilepsies: Sudden brief jerks of the body or limbs.
3. Clonic epilepsies: Repetitive jerking movements affecting the face, neck, and limbs.
4. Tonic epilepsies: Sudden stiffening of the body and limbs.
5. Tonic-clonic epilepsies: A combination of tonic (stiffening) and clonic (jerking) movements.
6. Atonic epilepsies: Sudden loss of muscle tone, resulting in falls or drops.
7. Myoclonic-astatic epilepsies: A combination of myoclonic (jerking) and astatic (lack of muscle tone) seizures.
8. Epileptic spasms: Brief, frequent, symmetrical contractions of the axial muscles.
9. Lennox-Gastaut syndrome: A severe epileptic encephalopathy characterized by multiple seizure types, cognitive impairment, and a characteristic electroencephalogram (EEG) pattern.

2.3. Physiological Mechanisms

There are various mechanisms that lead to epilepsy.

1. Ion channel dysfunction: Mutations in ion channels, such as voltage-gated sodium channels, can lead to abnormal neuronal excitability and increased risk of epilepsy (Catterall, 2014).

2. Neurotransmitter imbalances: Imbalances in neurotransmitters, such as gamma-aminobutyric acid (GABA), glutamate, and serotonin, can affect neuronal excitability and contribute to the development of epilepsy (Akyuz, 2021).

3. Structural abnormalities in the brain: Structural abnormalities in the brain, such as cortical dysplasias, hippocampal sclerosis, and tumors, can disrupt normal brain function and increase the risk of epilepsy (Blumcke et al., 2011).

4. Genetic mutations: Mutations in genes related to ion channels, neurotransmitters (Poduri, 2011), and brain development can increase the risk of epilepsy (Pandolfo, 2011).

5. Autoimmune mechanisms: Autoimmune mechanisms, such as antibodies against voltage-gated potassium channels or glutamate receptors, can contribute to the development of epilepsy (Bien and Bauer, 203).

2.4. Triggers

Seizures can be triggered by various factors (Schachter, 2023):

1. Lack of sleep: A lack of sleep or changes in sleep patterns can trigger seizures in some people.

2. Stress: Emotional stress and anxiety can increase the likelihood of seizures.

3. Flashing lights and patterns: This is known as photosensitivity and can be triggered by flickering lights, such as strobe lights, or patterns on screens.

4. Alcohol and drugs: Alcohol and recreational drugs can increase the risk of seizures.

5. Medications: Certain medications, both prescription and over-the-counter, can trigger seizures in some people.

6. Hormonal changes: Women with epilepsy may experience seizures related to hormonal changes during their menstrual cycle.

7. Illness and fever: Seizures can be triggered by high fevers, especially in children.

8. Skipping meals or dehydration: Low blood sugar levels or dehydration can increase the risk of seizures.

2.5. Diagnosis and treatment

Epilepsy can be diagnosed through a variety of approaches, including EEG testing, brain imaging techniques, and clinical observation (Fisher, 2014). EEG testing remains the primary method for diagnosing epilepsy, as it can detect abnormal brain activity during a seizure and can provide important information on the type and location of the seizure. Magnetic resonance imaging (MRI), computed tomography (CT) scans, and positron emission

tomography (PET) scans are commonly used brain imaging techniques that can help identify structural abnormalities in the brain that may be causing seizures.

In terms of treatment, medication is the most common approach, with antiepileptic drugs (AEDs) being the primary treatment option for the majority of patients (Moshe, 2015). However, for some patients, surgical intervention may be necessary to remove the part of the brain causing seizures (Moshe, 2015). Additionally, dietary interventions, such as the ketogenic diet, have shown promising results in the management of seizures (Winesett, 2015). Other complementary and alternative therapies, such as acupuncture (Chao, 2013; Lu, 2023), biofeedback (Tan, 2009; Nagai, 2014), and cognitive-behavioral therapy (Charyton, 2010; Tang, 2014), may also be used as adjunctive therapies.

3. PRESSURE AND VOLUME

Repetitive action potential generation is induced at high pressure, that is, pressure has an excitatory effect (Kendig, 1977), and hyperbaric pressure induces seizures (Kendig, 1988).

Intracanial pressure (ICP) is increased during epileptic seizures (Gabor, 1984). The ICP levels peaks at the onset of the seizure and gradually decreases thereafter (Gabor, 1984) . ICP may lead to sudden unexpected death in epilepsy (Dibue, 2020).

Artificially induced increase in ICP on animals yields similar results. When ICP is artificially increased by repeated lumbar infusions of saline into the brain ventricles of rabbits, significant increases in ICP and a subsequent increase in seizure activity are observed, suggesting a potential link between ICP and epileptic activity (Caldarelli, 1980).

Brain volume is another critical factor that affects epileptic seizures. Effect of volume can be analyzed globally and locally. Global brain volume changes have been observed in patients with epilepsy, and these changes can vary depending on the type of epilepsy and the location of the seizure focus (Bernasconi, 2005).

Several studies have shown that patients with epilepsy have a reduced brain volume compared to healthy controls (Bernasconi, 2005; Natsume, 2003). For example, a study using MRI found that patients with temporal lobe epilepsy had a reduced gray matter volume in several brain regions, including the hippocampus and amygdala (Bernasconi, 2005). Another study found that patients with idiopathic generalized epilepsy had a smaller thalamus volume compared to healthy controls (Natsume, 2003).

In addition to reduced brain volume, patients with epilepsy may also experience exacerbated changes in brain volume over time. For instance, a longitudinal study found that patients with temporal lobe epilepsy had a greater reduction in gray matter volume over time compared to healthy controls (Keller, 2002).

The relationship between epilepsy and global brain volume is complex and not fully understood. It is thought that recurrent seizures can lead to neuronal loss and gliosis, which can result in brain volume changes. However, other factors, such as genetics and age of onset, may also play a role in brain volume changes in patients with epilepsy.

Local volume changes are also correlated with epilepsy. Brain interstitial system (ISS) accounts for approximately 20% of the total brain volume, far more than the cerebral blood vessels, which account for 3% (Sun, 2021). ISS is a network of channels that allow the flow of fluid between the brain's cells. This system plays a crucial role in maintaining the brain's

homeostasis and regulating its response to injury or disease. ISS is critical for the volume regulation of the brain, for which imbalances can lead to epileptic seizures (Sun, 2021). Even contents of the extracellular matrix can be effective. For instance, lack of hyaluronan leads to a reduction in the volume of ISS, which in turn either triggers or intensifies epileptic activity (Arranz, 2014).

After the review of the relation of epilepsy to the fundamental concepts of pressure and volume, we proceed with three closely related phenomena in the following subsections.

3.1. Brain Tumors

A brain tumor is a mass or growth of abnormal cells that develop in the brain. The tumor can be cancerous (malignant) or noncancerous (benign). Brain tumors can grow and interfere with normal brain function by putting pressure on the surrounding tissue, and can cause a range of symptoms, including seizures (Alentorn, 2016). Brain tumors can calso impact the brain and its function by direct infiltration and disruption of the blood-brain barrier (Alentorn, 2016).

Many patients with brain tumors develop epilepsy (Cascino, 1990). Up to 85% of patients with brain tumors experience at least one seizure before or after the diagnosis (Ruda, 2010). The location of the tumor influences the risk of epilepsy (van Breemen, 2007). Cortical tumors have a higher incidence of associated epilepsy than noncortical ones (Ruda, 2010). The tumors that are entirely within the white matter are rarely epileptogenic (Ruda, 2010).

The pathogenesis of tumor-related seizures is multifactorial and is not completely understood. Studies have shown that epileptogenesis mechanisms differ between various types of tumors, which may account for the variations in the occurrence frequency of the

seizures (Ruda, 2010). These mechanisms include mass effect, which refers to the pressure that a tumor can exert on surrounding brain tissue, leading to disruption of normal brain function and the development of seizures. Cortical irritation is another mechanism by which brain tumors can cause seizures. In this case, the tumor may be located in close proximity to the cortex, and can cause irritation or damage to cortical neurons, leading to hyperexcitability and the development of seizures. Finally, some brain tumors can cause changes in neuronal excitability, which can also lead to the development of seizures.

3.2. Age

Age is a significant factor in epilepsy, as it can affect people of all ages. However, the age groups most commonly affected by epilepsy are children and older adults, latter being the most common age group (Beghi, 2020; Sen, 2020; Stephen, 2000). In children, epilepsy can be caused by genetic factors, brain malformations, or brain injuries. In older adults, epilepsy is often caused by strokes, tumors, or neurodegenerative brain diseases (Beghi, 2020).

According to Beghi (2016), epilepsy is most commonly diagnosed in the first year of life and decreases until it reaches adult levels by the age of 10. There is then a gradual decrease in incidence until around the ages of 40-50, after which the incidence of epilepsy starts to increase in a steady pattern.

Brain volume increases rapidly throughout infancy and childhood before reaching a peak in early adulthood (Giedd, 1999). The increase in brain volume is most pronounced in the first few years of life, with a rapid expansion of the cerebral cortex. After peaking in early adulthood, brain volume gradually declines starting around age of 40, with a more rapid decline in older adulthood (Jernigan, 2001).

The number of neurons in the human brain is estimated to be around 86 billion (Herculano-Houzel, 2009). This number remains relatively stable throughout adulthood, with only minor variations in neuron number observed in some brain regions in response to environmental factors such as stress or learning (Pakkenberg, 1997).

During brain development, the number of neurons increases rapidly in embryonic and fetal development, with peak neurogenesis occurring during mid-gestation. However, the rate of neurogenesis slows considerably after birth, and most of the brain's neurons are already present by the time of birth (Rakic, 2009).

While the overall number of neurons in the human brain remains relatively constant throughout adulthood, there are still ongoing changes in the brain's cellular composition due to ongoing processes such as synapse formation and pruning, as well as changes in the size and complexity of individual neurons in response to environmental factors and experience (Hillman, 2008).

When we take into account the number of neurons and volume of the brain, we see that the minimum density of neurons in the brain, in relation to brain volume, occurs at around the age of 40, which is also when the incidence of epilepsy is at its lowest.

3.3. Alcohol

Alcohol consumption has been shown to increase the risk of developing seizures and epilepsy. Studies have found that individuals with alcohol use disorders are at a higher risk of developing epilepsy compared to the general population (Bhalla, 2011).

It's worth noting that the relationship between alcohol and epilepsy is complex and can vary depending on several factors. Alcohol can affect the brain in several ways that can lead to seizures. For example, alcohol can interfere with the balance of neurotransmitters in the brain, including GABA and glutamate, which can lead to seizures (Valenzuela, 1997).

The risk of developing seizures is highest during the acute phase of alcohol withdrawal, which typically occurs within the first few days of cessation (Jesse, 2017). However, seizures can also occur in individuals who continue to consume alcohol regularly.

Alcohol consumption also induces structural changes in the brain. Lesions and atrophy are encountered (Buttner, 2008). Several studies found negative association between alcohol consumption and the brain volume (Harper, 1990; Paul, 2008). For instance, the contributory rate of alcohol consumption for frontal lobe shrinkage was found to be more than 10 percent (Kubota, 2001).

4. HEAT

The temperature of the mammalian brain is tightly regulated, and even small changes in brain temperature can affect the physiology and function of neurons (Kim, 2012). The impact of hyperthermia on brain function has been studied extensively, and it has been found that high temperatures alter the electrical activity of the brain (Heuvel, 2020). Such changes can include an increase in neuronal excitability and a decrease in the amplitude of inhibitory postsynaptic potentials, which are important for regulating neuronal activity (Kim, 2012). However, most of these changes are reversible, and the parameters return to normal levels once the temperature is lowered (Kim, 2012).

Hyperthermia can also exacerbate epilepsy and increase the frequency or severity of seizures in some individuals. This can be due to environmental factors such as hot weather or fever, or as a side effect of certain medications or treatments. Even prolonged exercise at high temperature increases the risk of seizures (Arida, 2008). Additionally, client change poses a threat to exacerbate epilepsy (Gulcebi, 2021). In contrast to hyperthermia, hypothermia has been found to reduce seizures (Pineda, 2021).

Fever is a common cause of seizures in infants and young children, known as febrile seizures, which occur during a febrile illness such as an infection (Dube, 2009). Although febrile seizures are generally considered to be benign, children with a history of febrile seizures are at an increased risk of developing epilepsy later in life (Dube, 2009). Elevated body temperature appears to be an important precipitant of seizures and can be caused by fever, warm baths, ambient warmth, or physical exercise (Verbeek, 2015).

Hot water epilepsy (HWE) is a rare form of reflex epilepsy triggered by immersion in hot water (Bebek, 2001). Seizures in HWE occur within seconds of immersion in hot water with a temperature above 40°C (Satishchandra, 2003). HWE can also be self-induced for pleasure (Bebek, 2001).

While the role of heat shock proteins in hyperthermia-induced seizures is not fully understood, they have been shown to be upregulated in epileptic brain regions compared to non-epileptic ones (Achar, 2021). Some studies suggest that heat shock proteins may serve as useful indicators of stressed neurons in the acute phase of epilepsy (Yang, 2008). However, their role in neuroprotection during an epileptogenic state remains unclear. Further research

is needed to determine the precise mechanism by which heat shock proteins contribute to hyperthermia-induced seizures in individuals with epilepsy.

5. COMORBIDITIES AND SYNDROMES

Epilepsy is not an isolated neurological condition but is often accompanied by comorbidities, including psychiatric disorders, cognitive impairment, migraine, and sleep disorders (Keezer, 2016). Recognizing and treating comorbidities can have a significant impact on quality of life and seizure control. However, comorbidities can be underrecognized and undertreated, partly due to the limited understanding of the underlying mechanisms linking epilepsy and comorbidities.

Epilepsy spans a very broad spectrum of symptoms. For diagnostic, prognostic, and therapeutic purposes classification and definition of epilepsy syndromes are very important. Epilepsy syndrome is defined as “a characteristic cluster of clinical and EEG features, often supported by specific etiological findings (structural, genetic, metabolic, immune, and infectious)” (Wirrell, 2022).

Here, our aim is to make a representative list of comorbidities and syndromes with their relation to physical aspects.

Comorbidity	**Physical Aspects**
Aicardi Syndrome (Rosser, 2003)	Complex brain malformation with cystic formations and microcephaly (Aicardi, 2005).
Angelman Syndrome (Samanat, 2021)	Microcephaly is common (Williams, 2010).

Cerebral folate deficiency (Scheffer, 2017)	Causes delayed development with deceleration of head growth (Gordon, 2009).
Cerebral malaria (Scheffer, 2017)	Causes hyperthermia (Newton, 2000).
Cerebral toxoplasmosis (Ngoungou, 2015)	Forms cysts in the brain and establishes a chronic infection (Carruthers, 2007).
Cytomegalovirus (Scheffer, 2017)	Increases microcephaly risk significantly (Messinger, 2020).
Dravet Syndrome (Diagnostic Manual, 2023)	Hyperthermia triggers seizures (Wirrell, 2016).
Febrile Infection Related Epilepsy (Diagnostic Manual, 2023)	Occurs after a febrile illness (Diagnostic Manual, 2023).
GLUT1 Deficiency (Alter, 2015)	Causes microcephaly (DeGiorgis, 2013).
Landau–Kleffner Syndrome (Pearl, 2001)	Volume reduction is observed (Takeoka, 2004).
Lennox-Gastaut Syndrome (Markand, 2003)	Inflammation and tumors are encountered (Mastrangelo, 2017).
Neurocysticercosis (Scheffer, 2017)	Forms cysts in the brain (Kraft, 2007).
Ohtahara Syndrome (Beal, 2012)	Severe developmental delay is seen and microcephaly may occur (Diagnostic Manual, 2023).
Rasmussen Syndrome (Diagnostic Manual, 2023)	Progressive athropy (grey matter shrinkage) occurs over time due to inflammation (Diagnostic Manual, 2023).
Sotos syndrome (Nicita, 2012)	Macrocephaly (Nicita, 2012) and enlarged ventricles (Schaefer, 1997) are observed.
Sturge-Weber Syndrome (Diagnostic Manual, 2023)	Hydrocephalus may occur due to increased venous pressure; athropy and calcification occurs in the affected cortex (Diagnostic Manual, 2023).
Subacute sclerosing panencephalitis	Causes inflammation (Garg, 2002).

(Scheffer, 2017)	
Tourette Syndrome (Wong, 2016)	Lesions causing tics can be localized to specific regions (Zouki, 2023).
Tuberculosis (Scheffer, 2017)	Causes hydrocephalus (buildup of fluid in the ventricles deep within the brain that puts pressure on the brain) and tuberculoma (a firm spherical intracranial mass) (Garg, 1999).
Zika virus (Scheffer, 2017)	Causes fever and increases microcephaly risk significantly (Paixao, 2016).

Table 1. Physical aspects of comorbidities and syndromes of epilepsy.

6. DISCUSSION

The relationship between epilepsy and the fundamental physical properties (pressure, volume, and heat) is evident. The general trend is apparent: increased pressure and heat, and decreased volume increases the likelihood of epileptic seizures. Therefore, it would not be unnatural to conclude that structural impairments, either environmentally or genetically caused, that result in these physical conditions will increase the risk of epilepsy.

We should note that relative changes in the physical conditions with respect to normal values are effective. When we look at incidence of partial epilepsy and volume of the corresponding brain region (refer to Table 1), we see a disproportionate relationship. In addition to regional volume, we can take into account the number of the neurons in the region. Recent estimates of number of neurons in the entire human brain is in the range 67-86 billion, whereas cerebellum estimates are in the range 54-69 billion (Bartheld, 2016).

However, cerebellum appears to have a very low epilepsy incidence. Absolute values of volume or neuron density are not the primary factors of epilepsy. For instance, energy consumption of cerebrum is highly greater than cerebellum, especially after adolescence (Kuzawa, 2014). Additionally, cerebellum has very small number of non-neuronal cells (15 billion in cerebellum vs 55 billion in entire brain (Andrade-Moraes, 2013)) which my indicate limited activity in terms of amount and variety.

Region	**Relative Volume (%) (Akeret, 2021)**	**Epilepsy Incidence (%) (Semah, 1998)**
Temporal lobe	11	66
Frontal lobe	18	25
Parietal lobe	12	2
Occipital lobe	7	3
Basal ganglia	2	<3
Cerebellum	11	<3

Table 1. Region wise volume and epilepsy incidence. Regional epilepsy incidence percentages are deduced from the patients with partial epilepsy (Semah, 1998)**.**

Volume reduction is not valid for only Sotos syndrome, where macrocephaly occurs (Nicita, 2012). Here, we should note that macrocephaly is accompanied with enlarged ventricles (Schaefer, 1997). This is interesting. It may indicate that the volume change in the immediate surroundings of the neurons (i.e. extracellular space) is the main factor instead of the change in the entire volume. This would not be unexpected when we consider the elastic structure of the brain.

Brain tissue is softer than any other tissue in the human body (Budday, 2020). It even deforms noticeably due to gravity (Budday, 2020). It contains more than 80% water, more than half of which resides inside the cells and extracellular matrix (Budday, 2020). Interestingly, brain tissue is stiffer when compressed than when pulled (tension), in other words cerebrospinal fluid (CSF) trapped inside the solid network of cells and extracellular matrix provide noticeable resistance to compression but only marginal resistance to tension (Budday, 2020). Incompressibility of the surrounding fluid increases the pressure resilience of the mesh like cellular skeleton, so that pressure is transferred to other regions in order to alleviate its local impact. In this regard, the structure of the brain serves to protect the proximity of the neurons. Any discrepancy in this region would alter the electrical activity abnormally. In Sotos syndrome, surrounding volume of the neurons may be reduced due to the enlarged ventricles and this in turn exacerbates the likelihood of seizures.

Another factor that reduces the volume and triggers seizures is brain tumor. Benign tumors also causes epilepsy (Japp, 2013). Surgical removal of the tumors can put an end to seizures (Cascino, 1990). These facts indicate that mass effect of the tumors is the predominant factor to cause seizures.

Another phenomenon related to volume and heat is the sleep. Even if there are seizures exclusive to sleep, their rate is very small (Young, 1985). The diurnal occurrence of seizures is influenced by several factors, including the epilepsy type (generalized or focal) and the location of the seizure onset (Nobili, 2022). Generalized seizures have a tendency to occur in the morning following sleep (Nobili, 2022). On the other hand, in focal epilepsies, frontal lobe seizures occur predominantly during sleep, while temporal lobe seizures, which are the most frequent type (Semah, 1998), arise mostly in wakefulness (Hofstra, 2011). Brain

temperature drops at night and rises during the day (Rzechorzek, 2022). The transition from wakefulness to sleep is accompanied by a marked expansion of the extracellular space, but during the transition from sleep to wakefulness, this alteration is reversed (DiNuzzo, 2017). It is obvious that these observations align with the correlation between epilepsy, volume, and heat.

Although the physical aspects of epilepsy constitutes a consistent picture, there is no unifying explanation yet. At this point, some other related phenomena may be inspiring.

In regard to neuronal activity, epilepsy and anesthesia can be considered symmetric. Hyperbaric conditions can cause seizures (Kendig, 1988), while having a reverse effect on anesthesia (Miller, 1973). Furthermore, anesthetics are utilized in the treatment of status epilepticus (Zaccara, 1997) and under anesthesia ICP may not cause seizures (McNamara, 2003). In a recent speculative work, volume and viscosity of ISF are proposed to be the dominant modulating factors of anesthesia (Esen, 2022). In that perspective, reduced volume (and hence increased pressure) and low viscosity (which may correspond to increased heat) can be associated with epilepsy. Reduced volume and low levels of viscosity of ISF increase the contact likelihood of nearby neurons. As a consequence, firing rates of neurons and hence chance of occurring of bursts increase.

Another phenomenon is the effect of flickering light. It can also cause hallucinations in healthy subjects (Allefeld, 2011), in addition to inducing seizures. The reason is not known. However, a theoretical work (Esen, 2021) that introduces electrokinesis as a physical process that governs the contact likelihood of neighboring neurons can be helpful. In this framework, electrical activity of neurons induce fluid flows in ISF, which in turn exert pressure on

dendrites and axon. Freely moving dendrites and axon terminals are displaced according to the pressure that fluid flow causes. Energy of the fluid motion impacts the pressure and the resultant displacement. In the end, high contrasted repetitive inputs increase the possibility of more distant temporary synaptic connections. In this way, visual signals can activate the regions in the hippocampus and ignite hallucinations. A similar reasoning can be applied to epileptic seizures that are caused by flickering light. Epilepsy patients have suitable conditions (reduced ISF volume and viscosity) for high contrasted repetitive visual inputs to start an avalanche of spikes.

7. CONCLUSION

Epilepsy is a complex neurological condition that requires a comprehensive understanding of its physical aspects. This review has focused on exploring the physical modalities of epilepsy that are often overlooked. We have shown how pressure, volume, heat, and comorbidities can all impact the course of epilepsy, and how understanding these factors can lead to more effective treatments. However, more research is needed to fully understand the physical mechanisms of epilepsy. Theoretical works that we have mentioned can be inspiring in this regard. In conclusion, the study of the physical aspects of epilepsy is critical to advancing our understanding of the condition and improving the lives of people living with epilepsy.

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