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(Maybe Not) All of the Lights

By Babiker Higazi

"A Light painting curve move" by Sérgio Valle Duarte Obtained from Wikimedia commons (CC BY-SA 3.0).

"Cop-lights, flash lights, spotlights, strobe lights, street lights" - shouts the electrifying Kanye West, as the music video bombards viewers with an extensive range of bright, neon lights. Ten year old me came across this video, which displayed a frightening message at the beginning in all caps, "WARNING: THIS VIDEO HAS BEEN IDENTIFIED BY EPILEPSY ACTION TO POTENTIALLY TRIGGER SEIZURES FOR PEOPLE WITH PHOTOSENSITIVE EPILEPSY. VIEWER DISCRETION IS ADVISED." I paused and stumbled over the words, then ultimately decided to continue just as 272 million other viewers would eventually do. The next 4 minutes strained my eyes as my face was glued to the screen. However, what caused a few minutes of discomfort for me could have induced a serious malfunction of the nervous system in someone with epilepsy.
Epilepsy Action is a British charity advocating for and supporting those suffering from epilepsy. Since their inception in the 1950s, they have led various campaigns aimed at protecting those suffering with epilepsy, eventually prompting the eerie warning preceding this Kanye West music video. With the surge of popularity of television, screen games, and smartphone usage after the turn of the century, such warnings have become more common across various forms of media. The 2010s marked the beginning of wildly popular social media platforms such as Instagram, Snapchat, and Tiktok; all of these platforms give users immense freedom to distribute their own animations and videos with minimal oversight. To understand why such freedom can be troublesome, one must take a closer look at epilepsy, and the smaller subset of photosensitive epilepsy.

Despite it being the fourth most common neurological condition behind dementia, the definition of epilepsy is still debated [2]. Most recently, the definition has been broadened, describing epilepsy as a susceptibility to recurrent epileptic seizures [3]. Susceptibility is defined as having two or more unprovoked seizures in less than 24 hours, or having a single unprovoked seizure and a significant risk of recurrence afterwards. As of 2015, epilepsy afflicts 1.2% of the American population [4]. Among the most common adult-onset neurological disorders, epilepsy ranks third behind stroke and Alzheimer's disease. Susceptibility to seizures can fall under two major pathological frameworks, both of which depend on synchrony between neurons. When too many excitatory neurons (neurons that release neurotransmitters increasing the chance of action potentials) fire synchronously, the chances of a seizure event increase dramatically [3]. The same result occurs when too many inhibitory neurons (neurons that release neurotransmitters that decrease the chance of action potentials occurring) are blocked, thus making excitatory neurons more likely to induce a seizure.

As scary and common as they are, seizures are poorly understood by the general public. When most people think of seizures, they think of the tonic-clonic seizures that manifest through a combination of muscle stiffness, repeated jerking, and a short loss of consciousness. A seizure, however, extends much further and is defined as a sudden, uncontrolled electrical disturbance in the brain [6]. There is a wide array of seizure types, and each manifests differently. The two broadest categories

are focal seizures and general seizures. In focal seizures, abnormal electrical activity is limited to a single area of the brain, while in general seizures, all areas of the brain are involved [6]. Photosensitivity is more commonly associated with general seizures than focal seizures, though it plays a role in both subsets [7]. Most seizures last between thirty seconds and two minutes, but seizures lasting more than 5 minutes are considered medical emergencies [6].
Though a common occurrence for those with epilepsy, seizures are just as dangerous as they sound. Every year, an estimated 3000 people in the United States die from sudden unexpected death in epilepsy (of SUDEP) [5]; SUDEP is an umbrella term that refers to deaths among people with epilepsy not caused by known causes such as drowning, injury, etc. Due to the many ways seizures manifest, possible factors for these deaths include altered breathing rates, abnormal heart rhythms, or a combination of the two during a seizure event. With susceptibility at an all-time high, and healthcare disparities getting worse every day, it is more important than ever to understand the physiology of photosensitive epilepsy: a subcategory of epilepsy triggered by flashing lights and/or contrasting visual patterns [2].

Photosensitive epilepsy was first described by british neurologist Dr. William Gowers [8]. Gowers was one of the most prominent clinical neurologists of his time and practiced at the National Hospital for the Paralyzed and Epileptics in London. In 1885, Gowers singled out the sun as a key factor in provoking seizures in a small subset of individuals [8]. When the sun (or any other light source) shines, it releases bundles of electromagnetic energy, referred to as photons. Whether coming from the sun, a smart phone, or an action-packed video game, these photons enter the human nervous system through the pupil of the eye, which is essentially a hole; the pupil can increase or decrease in size (dilated or constrict, respectively) depending on the availability of light due to the iris, the colored part of one's eye (Figure 1). After entering the pupil, these photons are refocused to a particular area of the eye by the lens, a clear eye structure which adjusts its curvature to do so. Finally, the photons reach the back of the eye, otherwise known as the retina. The retina contains specialized cells tasked with converting this influx of photons into a language the brain can interpret: action potentials. An action potential is a rapid sequence of voltage change across a single neuron, which is how messages propagate throughout the nervous system. After the transduction of light energy into action potentials, the signals propagate through the thalamus, which is the relay center of the brain processes stimuli before interpretation); they eventually make their way to the occipital lobe. The occipital lobe is located at the back of the brain; it is the center for all things involving visual perception, colors, forms, and motion. In the occipital lobe, the visual information received at the retina is integrated and processed in a region aptly named the primary visual cortex (Figure 2).

Not just any significant light source can induce seizure in those with photosensitive epilepsy. Many factors of a light source are at play in such stimulation, including the quality and wavelength of light. For example, deep red light

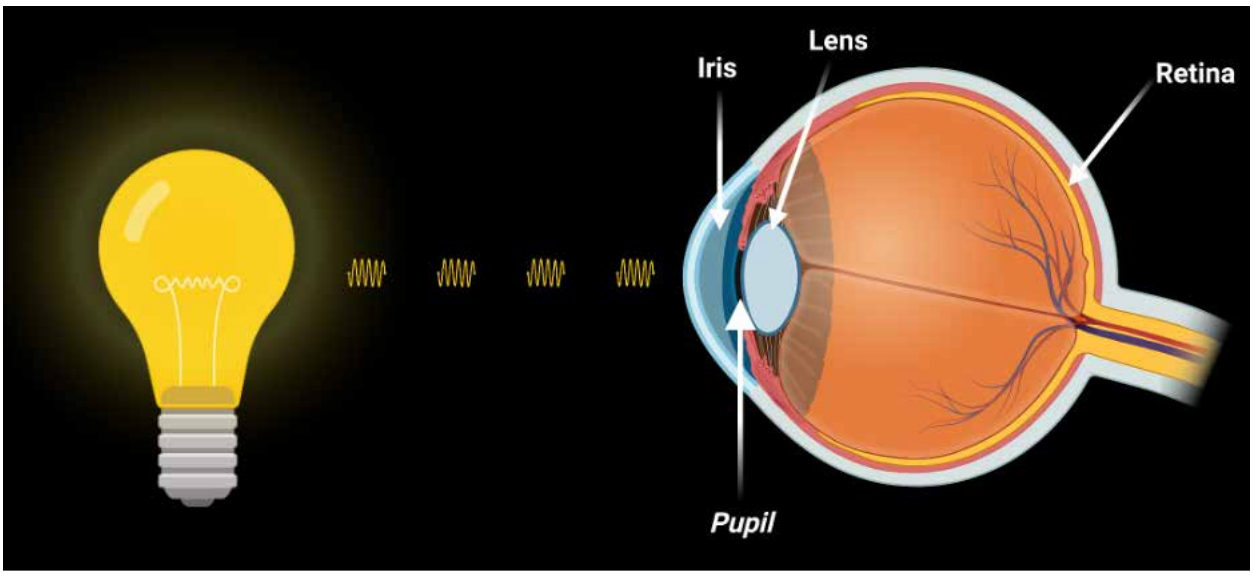


***Figure 1**: The structure of the human eye, including the iris, lens, retina and pupil, which regulate the amount of light entering the eye.*

has been shown to have an especially provoking effect [9]. Spatial and temporal aspects of the light patterns play a major impact as well. The most common rates of light flashing that induce seizures in photosensitive patients range between 4 and 30 Hz [9]. Further, the area at which such images are displayed also have an impact on seizure susceptibility; the area of the flashing stimulus should not exceed greater than 25 percent of the viewers visual field, hence why many photosensitive epilepsy patients are encouraged to cover one of their eyes when viewing such stimuli [9]. At the specified range of light frequencies; neurons in the visual cortex have been shown to synchronize their firing. If these synced neurons fire at too high a rate, their discharges can hyper synchronize in a way that propagates through networks [10]. In the case of a seizure, it may be helpful to think of the brain as a community gym, neurons as the gym equipment, and people working out as action potentials (neuronal signals). In a typical gym, there are moments when the gym is busy and when the gym is quiet, but rarely is the gym ever completely filled or completely empty. Thus, there is always equipment in use and people can perform their workout routines as they please. Further, everyone works out independently for the most part; when one person is in the middle of the lift, another person can be taking a break or getting a drink of water. We can think of this typical gym as the non-seizure brain model. There are always action potentials, the neurons are a constant, and the action potentials fire independently for the most part (though some areas of the brain may be firing more and other areas firing less at various time points). Now imagine a moment where the gym is busy, and a significant portion of the gym members begin to synchronize their workout sets; this subgroup of members all begin to bench press, leg press, and run on the treadmill simultaneously. If they synchronize to a high enough level, other subgroups of the gym will be forced to wait for them to finish their workout routines. In doing so, these other subgroups will also find themselves synchronizing. So now a gym that relied on the members being out of sync, will become heavily disrupted due to the syncing of workout routines. When particular patterns or magnitudes of photons are transduced by the visual system, a similar synchronization occurs in the visual cortex. This synchronization also causes other networks and brain regions to synchronize and function abnormally [10]. Earlier we defined a seizure to be an uncontrolled electrical disturbance in the brain; now we see these disturbances arise, ironically, from too many action potentials firing in sync.

The exact cause of epilepsy has yet to be pinpointed, yet there is a general consensus that it arises as a result of an excitatory-inhibitory balance in the brain [11]. Glutamatergic neurons (neurons that release the neurotransmitter chemical glutamate) are the most common neurons in the brain, they produce an excitatory response. GABAergic neurons (neurons that release the neurotransmitter chemical GABA) are the second

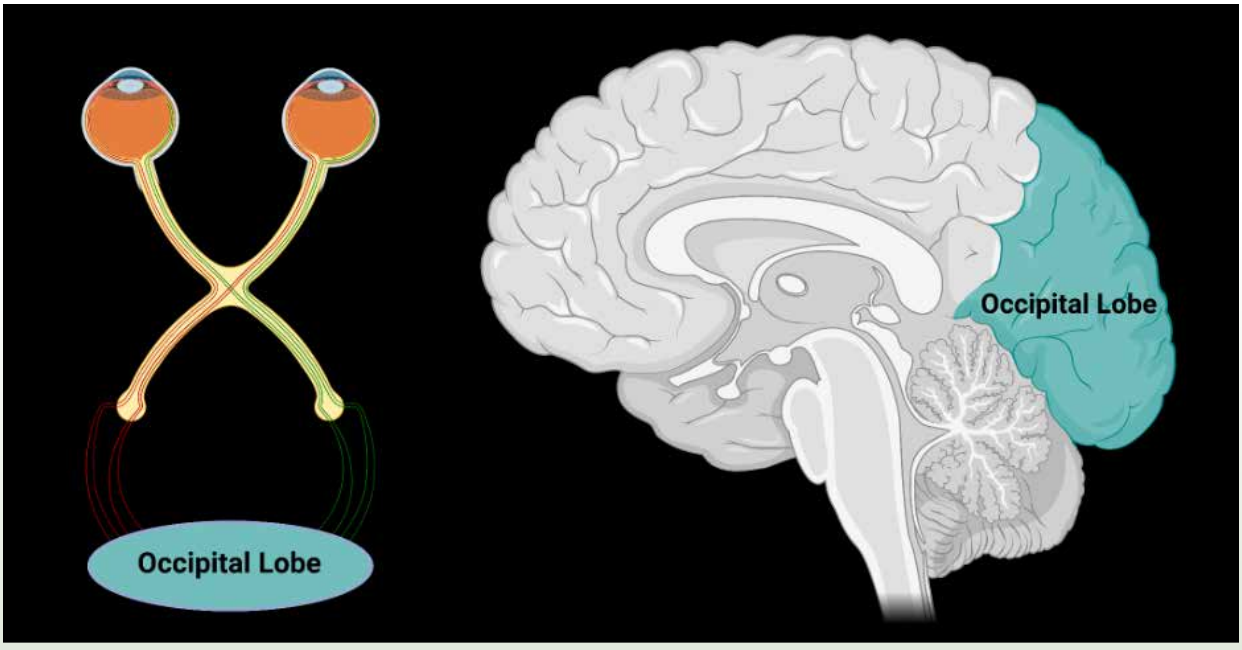


Figure 2: *Schematic of the brain showing the location of the occipital lobe, responsible for processing visual information from the eyes.*

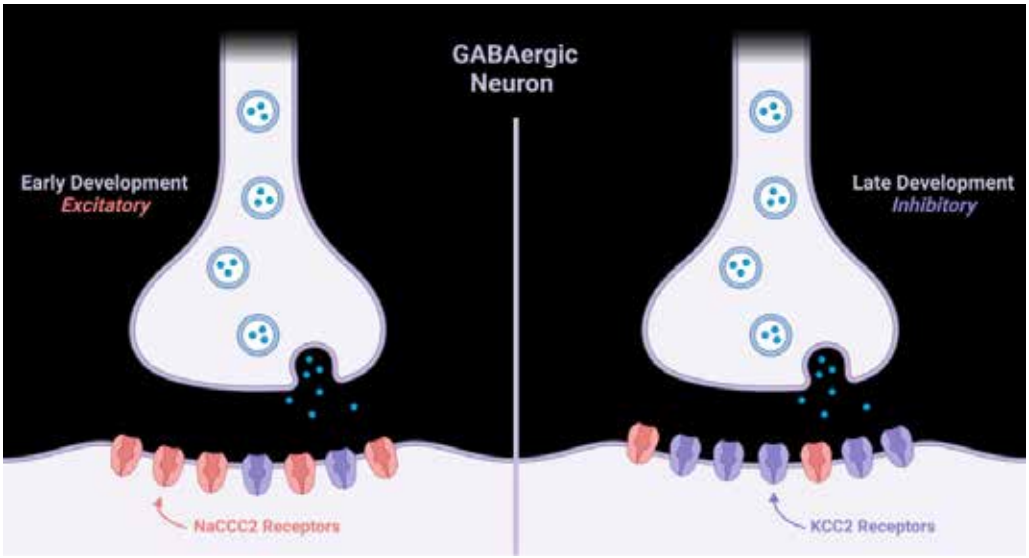


Figure 3: *Schematic showing the function of cation-chloride-cotransporters at the dendrites of postsynaptic neurons.*

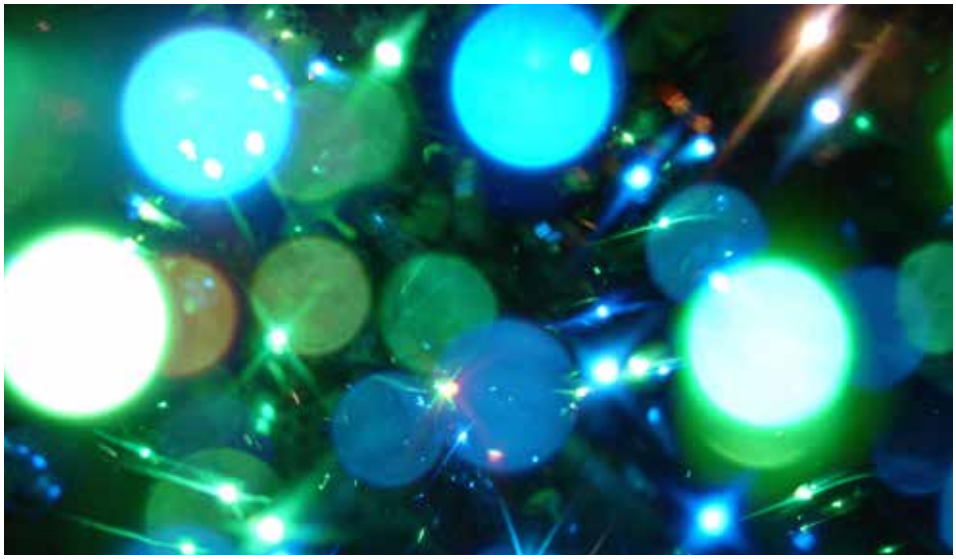
most common neurons in the brain and produce an inhibitory response. Recent literature has shown that epilepsy is more often the result of reduced GABA inhibition (which results in neuronal overexcitability). Too much glutamatergic activity and too little GABAergic activity both increase susceptibility to seizures, and increase the likelihood of being diagnosed with epilepsy [11]. One potential cause of excitatory-inhibitory imbalance are the overexpression or underexpression of transport proteins that are embedded at the dendrites (receive communications from other neurons) of postsynaptic neurons (the neuron that receives the neurotransmitter and thus excitatory/inhibitory signals). After receiving a neurotransmitter, these transport proteins can cause an influx of ions into the neuron that either increase or decrease the probability of an action potential occurring. One major group of such proteins are cation-chloride-cotransporters, which are responsible for transporting chloride, potassium, and or sodium ions across a membrane. There are two central nervous system specific cation-chloride-cotransporters called NKCC1 and KCC2 [12]. They are expressed at different levels as during the course of human development. NKCC1 brings chloride ions into the neuron, causing a hyperpolarization of the electrical gradient and decreasing the chance of an action potential (or signal) to propagate. On the other hand, KCC2 extruded chloride ions from the neuron, causing an effect that increases the chance that an action potential will propagate on the postsynaptic neuron (Figure 3). In newborn children, GABAergic neurons are thought to initially have a depolarizing effect. As an individual develops, however, a dramatic increase in the expression of KCC2 in GABAergic neurons occurs during the development [12]. As more and more KCC2 transporters line the postsynaptic neuron, more negatively charged chloride ions are extruded and the neuron becomes depolarized. Meanwhile, NKCC1 is also underexpressed causing the same depolarizing effect in the postsynaptic neurons. In other words, these changes in expression profiles cause the shift of GABAergic neurons from excitatory in newborns to inhibitory in the mature central nervous system [12]. Anything that impedes this process and stops the GABAergic neurons from reaching their desirable level of inhibitions can lead one to become much more prone to seizures; lack of inhibition makes the overexcitation of neurons more probable [12].

The best preventative measure for those with photosensitive epilepsy is to avoid provocative factors, but sadly this prevention is difficult for various reasons. Studies of the prevalence of photosensitive epilepsy showed the condition was most prominent amongst adolescents. Now, adolescents have more access to technology than ever before. We all know of an "iPad child": a 10 year old kid whose eyes are always glued to an iPad, watching what seems to be an endless array of media. On the other end of the spectrum, over 95% of adults 18-49 have access to a smart-phone [13]. With this smartphone comes endless forms of lightly regulated media suck at Tiktok, YouTube, and Instagram where users have an immense amount of freedom as to what they post. Thankfully, measures have been taken to accommodate those with photosensitive epilepsy. For example, Tiktok added a feature in 2020 where videos that

have many seizure promoting factors are hidden with a warning and such videos can be removed from the user's feed permanently [14]. Warnings like those mentioned prior precede many youtube videos (though not a process centralized by YouTube). The second best measure is antiepileptic medication.

Antiepileptic medication works to prevent the depolarization of excitatory neurons. Neurons have a negative charge compared to their environment. The more depolarized (the internal charge becoming more positive) a neuron becomes, the more likely it is to reach an action potential; in fact, once the internal charge reaches a certain level called a threshold, an action potential is inevitable. Antiepileptic medication often target the voltage-gated sodium channels of excitatory neurotransmitters. Sodium is a positive ion that is much more concentrated outside of the neuron than it is inside of the neuron. Sodium will enter the neuron at any chance it gets, thus depolarizing it. By blocking these voltage-gated sodium channels, antiepileptic drugs make sure sodium won't depolarize these excitatory neurons, regardless of the neuron's net charge. Antiepileptic drugs also target voltage-gated calcium channels [15]. These channels bring calcium into the neuron and are required for the release of neurotransmitters into the synapse. By blocking these channels, antiepileptic drugs inhibit neurons' ability to release excitatory neurotransmitters. While such medications are effective in most cases, about one third of epilepsy patients are not responsive to currently available medication [16].

While focal seizures affect a particular brain region and general seizures affect the entire brain, in neither model is every neuron overactive. Thus most of the current gene therapies that target neuronal excitability are ineffective because they are unable to discriminate between normal neurons and hyperactive ones in the epileptic model. However, a novel gene therapy model has been developed that can target overactive neurons in a closed loop: the gene therapy self-selects pathologically overactive neurons but doesn't target normal function [17]. In these overactive neurons, a gene called KCNA1 is modulated; KCNA1 encodes a potassium pump. When potassium pumps open, the electrochemical-gradient across the neuronal membrane thrusts positively charged potassium ions outside of the cell. This hyperpolarizes the neuron, greatly reducing the chance of an action potential occurring. Gene therapy adds a promoter gene that increases the expression of KCNA1 when a neuron becomes overactive [17]. The nature of a seizure means that the networks of neurons that are overactive during an episode can not be easily predicted. This targeted approach represents the rapidly developing field of antiepileptic treatments.



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Apart from physiological impacts, many adolescents suffering from epilepsy have difficulty transitioning to independence. Adults with childhood onset epilepsy were found to have less social participation, lower educational status, and more difficulty performing daily activities compared to non-afflicted adults [18]. In a study of this transition, a questionnaire was sent out to adults between the ages of 25-30 who experienced childhood onset epilepsy; 59 patients were asked about their functional level in three different domains: medical status, vocational status, and independence status [19]. The results found these individuals struggled to transition to independence compared to their healthy counterparts. Further, the patients had more social loneliness and less satisfaction with their independence from their parents [19]. These results reflect a chronic situation extending beyond the seizures experienced by those with epilepsy. Indeed, with such a large population affected by this condition, many Americans are unable to become completely self-sufficient.

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