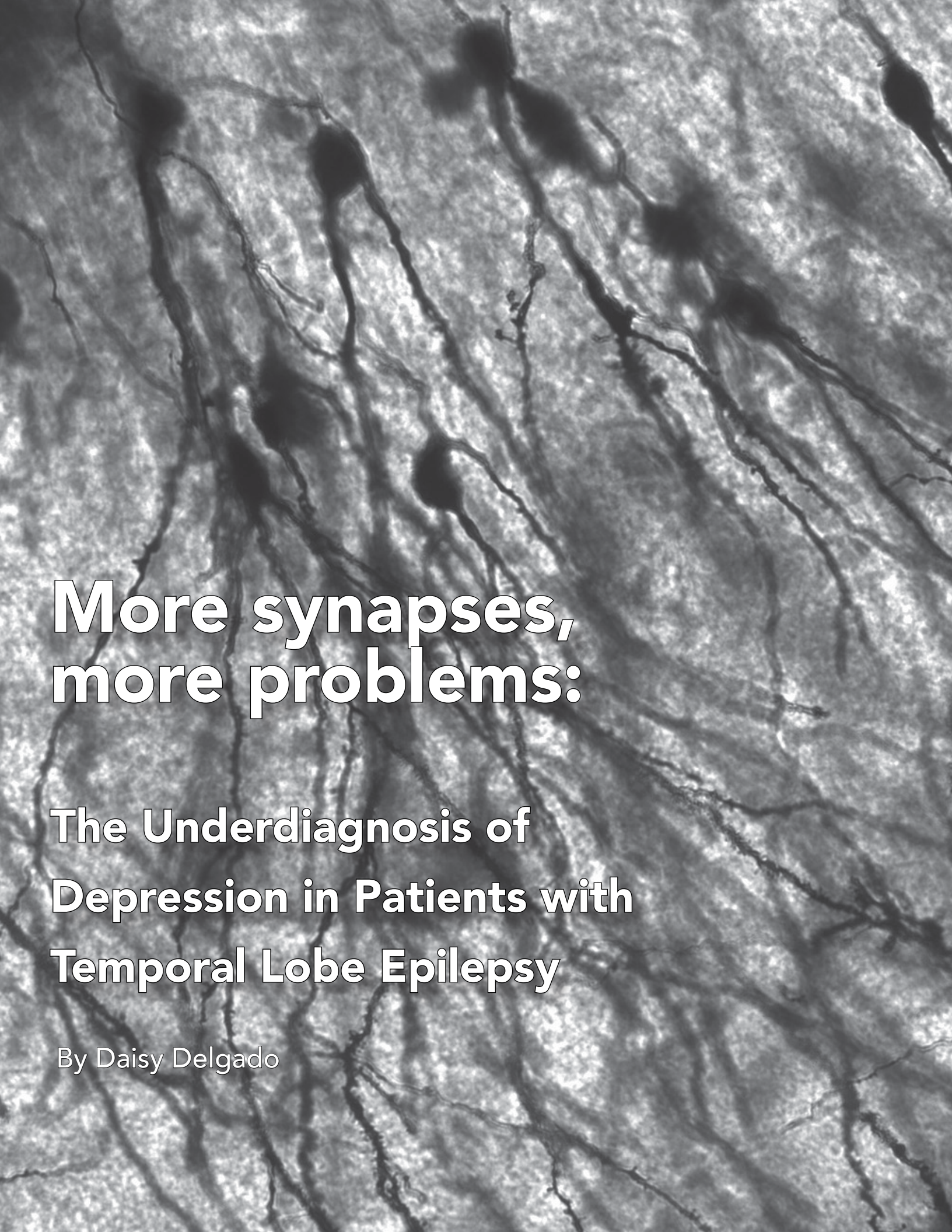


More synapses, more problems:

The Underdiagnosis of Depression in Patients with Temporal Lobe Epilepsy

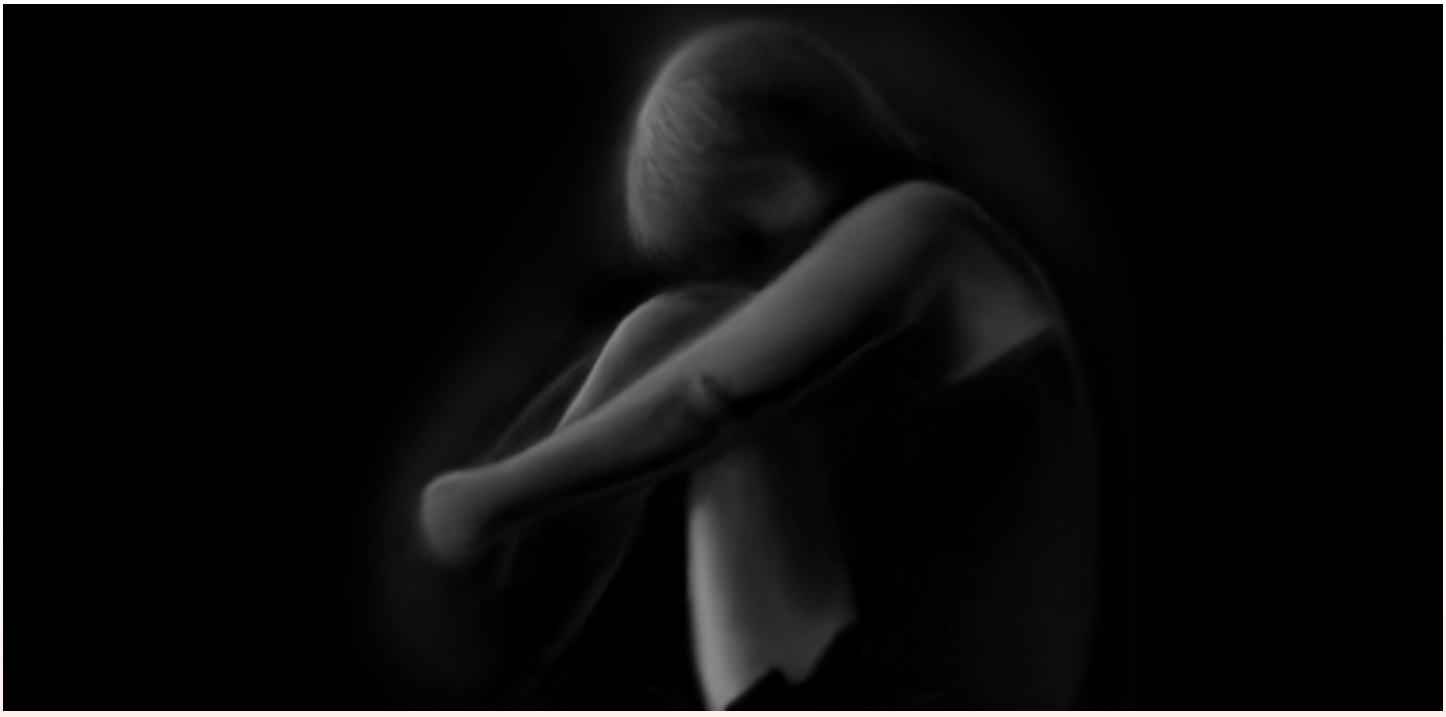
By Daisy Delgado

Susie, a 59 year old woman, presented no previous history of depression and seizures [1]. In recent months, Susie had experienced a drastic increase in her depressive moods, along with other symptoms such as loss of appetite, insomnia, fatigue, and a loss of interest in activities she used to previously enjoy. After visiting her doctor, Susie was diagnosed with depression and was treated with antidepressants, keeping her hopes that she would revert back to the happy woman she once considered herself to be. A month later, Susie went back to the hospital as she felt the antidepressants had worsened her symptoms. She also developed additional symptoms, such as sleeplessness, pollakiuria (frequent, abnormal urination), and dysuria (painful urination). Susie also described to her doctor that she felt a discomforting sensation in her mouth and throat, almost like an object was stuck between the walls of her chest. Since the antidepressants had not improved her symptoms, it had become harder as each day passed for Susie to get out of bed, suggesting that her psychological state was deteriorating [1].

Although Susie had no previous history of seizures, she began to present complex partial seizures (CPS) [1]. CPS are focal seizures that begin in one hemisphere of the brain accompanied by a loss of consciousness [9]. In Susie's case, her display of CPS was associated with a range of abnormal oral movements, such as lip smacking and abnormal swallowing, and an inability to vocalize. With these symptoms in mind, Susie was diagnosed with temporal lobe epilepsy (TLE), a neurological disorder which affects both children and adults, that started in the right hemisphere of her brain. She was provided anti-epileptic medication, which significantly improved her symptoms. Suzie was able to gain her appetite again and showed drastic improvement with her depressive disorder [1].

Recently, mental health has been increasingly recognized for its importance, which has facilitated the fight for destigmatizing mental health disorder diagnoses. The current emphasis society is starting to place on caring for mental health, especially when referring to younger generations. This has manufactured a movement that demands a call to action from schools, governments, families, and jobs.

This recent popularization of actively caring for one's mental health is supported by scientific findings, which emphasize the importance of mental health as it is essential for preserving an overall physiological balance. Even with the increasing social awareness of mental health, it's alarming that the prevalence of underdiagnosing psychiatric comorbid disorders is still a recurring issue. Specifically, in patients diagnosed with TLE, the incidence of depression is significantly underdiagnosed, affecting patient quality of life [2], [3]. The tragic effects of depression in patients with TLE will further be elucidated to advocate for a proper diagnosis that could drastically change the lives of the pediatric and adult patients with TLE, such as Susie's.



"Grieving shadow" by Flickr user shattered.art66. Licensed under CC BY-SA 4.0.

Temporal Lobe Epilepsy: What is it?

Temporal Lobe Epilepsy, one of the most common forms of Refractory Focal Epilepsy, is defined as a cyclical occurrence of seizures in those diagnosed with this disorder [3]. Due to the continuous occurrence of seizures, the strength and duration of each epileptic episode varies from patient to patient, causing physical and psychological difficulty in diagnosed patients. The occurrence of seizures is due to a significant increase in excitability and synchronicity of neurons [2]. There are two types of temporal lobe epilepsy: mesial temporal lobe epilepsy (mTLE) and lateral temporal lobe epilepsy (nTLE). The most significant difference between these two types of TLE are the areas which are affected. In mTLE, there is a higher involvement of the hippocampus and the amygdala. In nTLE, however, their associated structures include different areas of the temporal lobe such as the neocortex, the occipital junctions, and parietal junctions. Depression is increasingly associated with mTLE due to commonly exhibiting rejection of anti-epileptic medication compared to nTLE.

In individuals diagnosed with mesial temporal lobe epilepsy, the epileptic episodes affect areas such as the hippocampus and the amygdala. Since these regions of the brain are essential for memory, identifying danger, and sensory processing, patients diagnosed with TLE experience a decline in language, memory, and analytical problem solving [3]. Although the molecular mechanism that could possibly explain the damage to these regions has not been yet fully elucidated, studies have shown that neurodegeneration as a result of hippocampal sclerosis may serve as an explanation [2],[8],[10]. Specifically, hippocampal sclerosis is associated with changes in the populations of several types of brain cells. This includes degeneration of pyramidal neurons (cells that produce the neurotransmitter glutamate), the formation of glial cells (support cells that are not electrically active), and the dispersion of granule cells (another type of glutamate cell). This all occurs in the hippocampus [2],[10].

Although this is one of the most common neurological disorders to affect both adults and children, the disorder becomes increasingly complex as it may also be resistant to drug treatment, defining TLE as pharmacoresistant disorder. Patients with hippocampal sclerosis are drug resistant [10]. In fact, about a third of patients diagnosed with this form of epilepsy are considered to be pharmacoresistant. This pharmacoresistance makes it difficult for specialists to treat the disorder in patients diagnosed with TLE [2].

In regards to treatment, patients with temporal lobe epilepsy are typically administered antiseizure medication to assist with the duration and frequency of their experienced epileptic episodes [2],[3],[4]. In the patients that are diagnosed with pharmacoresistant TLE, their course of treatment revolves around different surgical approaches, some more invasive than others. For example, some of the most common surgical procedures are temporal lobe resections and amygdalohippocampectomy [11]. When performing temporal lobe resections, part of the temporal lobe is surgically removed [11]. On the other hand, for an amygdalohippocampectomy, patients undergo the removal of both their temporal lobe and their amygdala. Both of these surgical approaches are applied to pharmacoresistant patients in an attempt to decrease or terminate the occurrence of focal epileptic seizures in patients with TLE. Less invasive approaches are currently being investigated for individuals diagnosed with temporal lobe epilepsy [12].

It's a sensitivity

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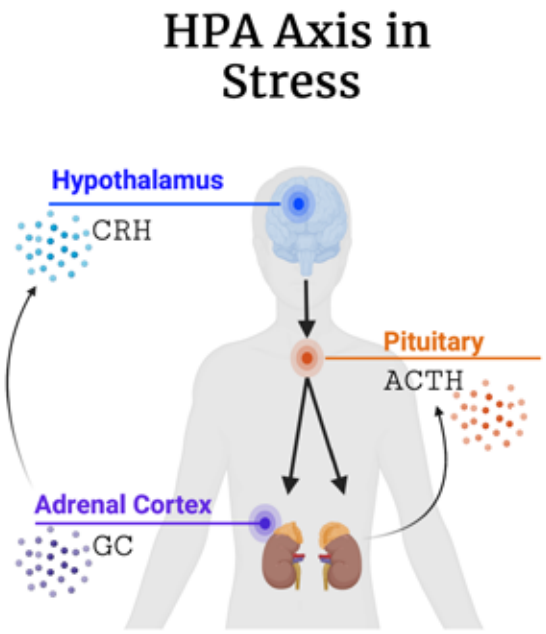


Figure 1. *Stress stimulates the function of the Hypothalamic-Pituitary-Adrenal (HPA) Axis, leading to the secretion of multiple hormones from different organ structures. A negative feedback occurs to regulate the longevity and occurrence of the activation stimulated by stress. Created in BioRender by Daisy Delgado. Figure adapted from: Gulyeva, N.V. "Stress-Associated Molecular and Cellular Hippocampal Mechanisms Common for Epilepsy and Comorbid Depressive Disorders." Biochemistry (Mosco). 2021; 86(6). doi: 10.1134/S0006297921060031.*

thing: TLE and Stress

As mTLE heavily involves the hippocampus, it is important to discuss how the hippocampus is essential for the functioning of the Hypothalamic-Pituitary-Adrenal (HPA) axis. The HPA axis is in charge of mediating a stress response to allow the body to cope with the stressful event at hand. When exposed to stress, the neurons that are located in the paraventricular nucleus, which is part of the hypothalamus and essential for the response to threat/stress, stimulate the release of the corticotropin-releasing hormone (CRH). The CRH, As the CRH hormone is released by the hypothalamus, the hormone travels and stimulates the release of adrenocorticotrophic hormone (ACTH) [13]. The ACTH hormone is released by the pituitary gland and once released, is able to activate the production and secretion of glucocorticoids [13]. The glucocorticoids are then released by the adrenal cortex [13],[14]. This process is depicted in Figure 1, but the story does not end there.

Once released, the glucocorticoids bind onto mineralocorticoid receptors (MR) or glucocorticoid receptors (GR) [13]. Importantly, binding to the GR is what influences physiological effects in response to the HPA axis in stress [13].

The release and binding of glucocorticoids onto glucocorticoid receptors leads to a negative feedback inhibition [13]. Through this negative feedback loop, the activity of the HPA axis is mediated, determining how long the HPA axis will be activated for and whether or not it will remain active [13]. This negative feedback loop is depicted on Figure 1, through the black arrows that contain negative signs to indicate how the activation of GR regulates the HPA axis.

Additionally, the hippocampus is sensitive to glucocorticoids which can interact with progenitor cells. Progenitor cells are cells that can specialize in particular functions and can interact with glucocorticoids to become a specific type of specialized cell [15]. Thus, the release of the glucocorticoid hormone is also essential for the activity of progenitor cells in the hippocampus, allowing for the hormone to affect memory and mood.

Why Depression?

Temporal lobe epilepsy has been associated with a wide range of comorbid disorders that significantly affect patient quality of life, making it increasingly difficult for the patient to cope with its subsequent effects. Overall, the most common comorbidity that occurs in patients with TLE is psychiatric disorders [6] of which the most common were depression and anxiety [4]. Initially, researchers believed that the occurrence of psychiatric disorders in patients diagnosed with TLE were associated with the occurrence of seizures. Specifically, the constant occurrence of focal epileptic seizures. Patients diagnosed with temporal lobe epilepsy tend to develop depression due to their uncontrollable epileptic episodes and increase of focal epileptic seizures. Instead, researchers now believe that the development of depression in patients with TLE is associated with a bidirectional relationship that exists between depression and seizure occurrence (Figure 2) [3],[4],[5],[6]. The stressful factors in an individual's life have been linked to the occurrence of depression. It has further been determined that the devel-

opment of depressive disorders increases the risk of developing epilepsy, and that epilepsy places individuals at a higher risk of developing depression [3]-[6].

Make it make sense: Relating TLE and Depression

Given this bidirectional relationship, you might ask yourself: "How could this be possible if one is a neurological disorder and the other is a psychiatric disorder?" Well, this is the beauty about neurobiology—it allows us to explore the connectivity between things we didn't think could possibly be related.

Previous studies have explored how stress aggravates the development of epilepsy. Individuals who experience higher levels of stress were more likely to exhibit epileptic episodes, therefore, stress was associated with increasing seizure activity. Additionally, it was also discovered that the experience of chronic stress exacerbated the manifestation of epilepsy. Patients who self-report stress as a possible inducer for seizure activity have a significant history of anxiety, depression, and childhood trauma[2]. These findings were then compared to individuals who were diagnosed with epilepsy, but did not consider stress to be essential for the onset of epileptic attacks. The patients who felt as if stress was an important component for the onset of their epileptic attacks then began using stress reduction techniques, reported a decrease in the frequency of their seizures [2].

Although the pathogenetic mechanism of TLE and the development of comorbid depression remains unknown, the mechanism that has been the most associated with this bi-directionality has been the malfunction of the HPA axis. As previously discussed, the HPA axis is regulated by a negative feedback mechanism which maintains its functionality even during stressful conditions. Through signaling pathways, the axis is informed when it is time to close and how long it should remain open [13],[14]. Instead of carrying out the normal regulatory functions, the HPA axis dysfunction occurs due to the detection of an excessive amount of glucocorticoid hormones [2,14]. This significant abnormal presence of glucocorticoid hormones confuses the axis as this hormone is what establishes the negative feedback loop to regulate the HPA axis [13]. Its abnormality of glucocorticoid levels leads to a hyperactivation of the HPA axis, meaning that the axis remains open for too long and continues to be open causing the axis to be overly active [2],[14].

The malfunction of the HPA axis then causes a rearrangement of synaptic connections that is essential for epileptogenesis, the development of neural tissue that makes it possible to generate a seizure [2]. Additionally, the hyperactivity of the HPA axis significantly damages the structures in the temporal lobe, making it difficult for the temporal lobe to carry out its regular functions [15]. Although the temporal lobe has a wide-array of functions, it is heavily involved in the processing of emotions and short-term memory. Therefore, the damage that is caused by the dysfunction of the HPA axis is heavily involved in the pathophysiology of both depression and TLE.

The hippocampus has a heightened sensitivity to glucocorticoid hormones because it is a lot easier for the hormones to cross into the hippocampus due to the basal membrane only covering less than 30% of the hippocampus'

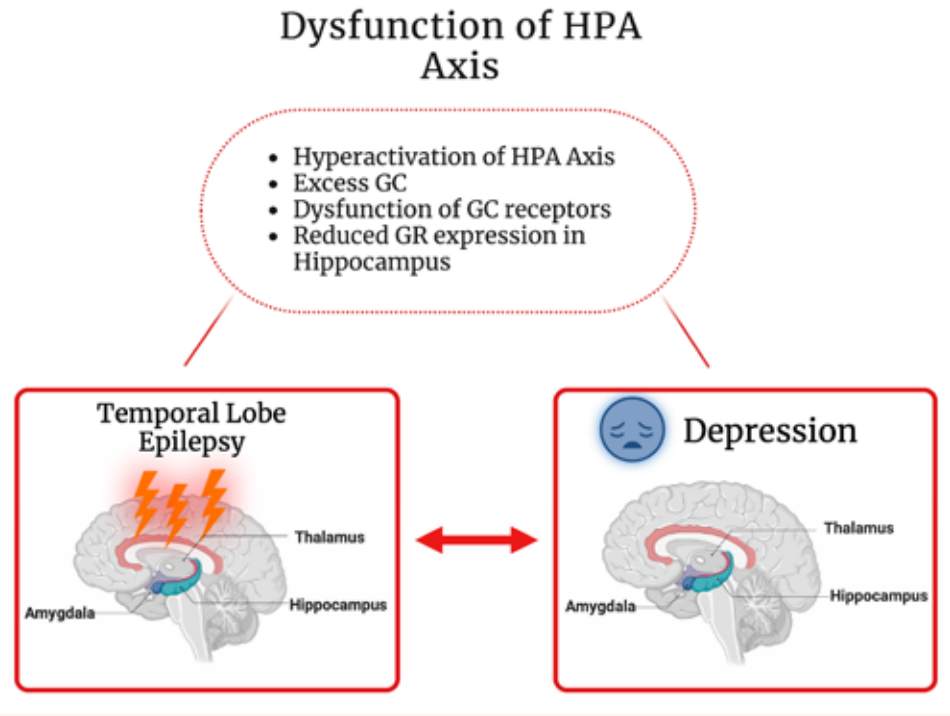


Figure 2. *Temporal Lobe Epilepsy (TLE) shares a common pathogenic mechanism with Depression through the dysfunction of the Hypothalamic-Pituitary-Adrenal (HPA) Axis. Created in BioRender by Daisy Delgado. Figure adapted from: Gulyeva, N.V. "Stress-Associated Molecular and Cellular Hippocampal Mechanisms Common for Epilepsy and Comorbid Depressive Disorders." Biochemistry (Mosco). 2021; 86(6). doi: 10.1134/S0006297921060031.*

vascular surface [2]. Therefore, the dysfunction of the HPA axis significantly affects the hippocampus as this dysfunction is characterized by an abnormal accumulation of the glucocorticoid hormone. Previous studies have shown that in the hippocampus, where there is usually the highest density of glucocorticoid receptors, there is a decrease in the density of glucocorticoid receptors in patients with TLE [2],[14]. This decrease is even more significantly evident in patients that are diagnosed with both TLE and depression [14].

Weighing down the mind: the socioeconomic detrimental aspect of TLE

For an individual to be diagnosed with epilepsy, it is required for the patient to be admitted into an in-patient center to be monitored. Additionally, epilepsy is associated with sudden spikes in the brain's electrical activity, therefore, patients are examined through an electroencephalogram (EEG). An EEG allows for the electrical activity of the brain to be measured, but it is a very expensive examination procedure. Once the individual is diagnosed, additional costs associated with medications and surgical procedures begin to weigh down even more upon the financial circumstances of the patients and their families [16].

These circumstances are experienced at an incredibly worse magnitude for low-income patients diagnosed with epilepsy. As low-income individuals do not have the ability to afford medical insurance, they are left to rely on social welfare programs such as Medicaid [16],[18]. Often, these social welfare programs do not provide proper coverage, making it increasingly difficult for patients to receive a proper diagnosis or be provided with the appropriate course of treatment [18]. This leaves individuals in financial catastrophe after attempting to be treated for an illness that affects their physiological and mental well-being.

At times, in an attempt to avoid such financial chaos, patients feel as if they are left with no other option but to discontinue their course of treatment that helps manage their epileptic episodes [16],[17],[18]. Discontinuing treatment then places the patient at a further risk of developing other comorbid disorders associated with TLE. This is accompanied with a high possibility for TLE to develop into an increasingly aggressive pathology [16],[17],[18].

Although direct costs are heavily associated with a diagnosis of epileptic disorders such as temporal lobe epilepsy, it is important to also discuss the indirect costs associated with such a heavy diagnosis. The occurrence of epileptic episodes specifically related to TLE are defined by a loss of consciousness with verbal and hearing impairments [5]. This manifestation of TLE makes it difficult for patients to engage in social settings. Specifically, living with epilepsy would make it for individuals to hold a job, as it could make any job incredibly dangerous and difficult to carry out [16]. This could then place the patient at risk of additional financial catastrophe that would not only affect their course of treatment, but would impact their living circumstances.

Therefore, both the direct and indirect costs associated with the diagnosis of TLE or any form of epilepsy leads to an overwhelming financial burden that is felt by the patient and their family. Such a heavy financial burden associated with the illness further contributes to a negative stigma that could encourage many to avoid or wait to seek out a medical consultation to receive a diagnosis and treatment.

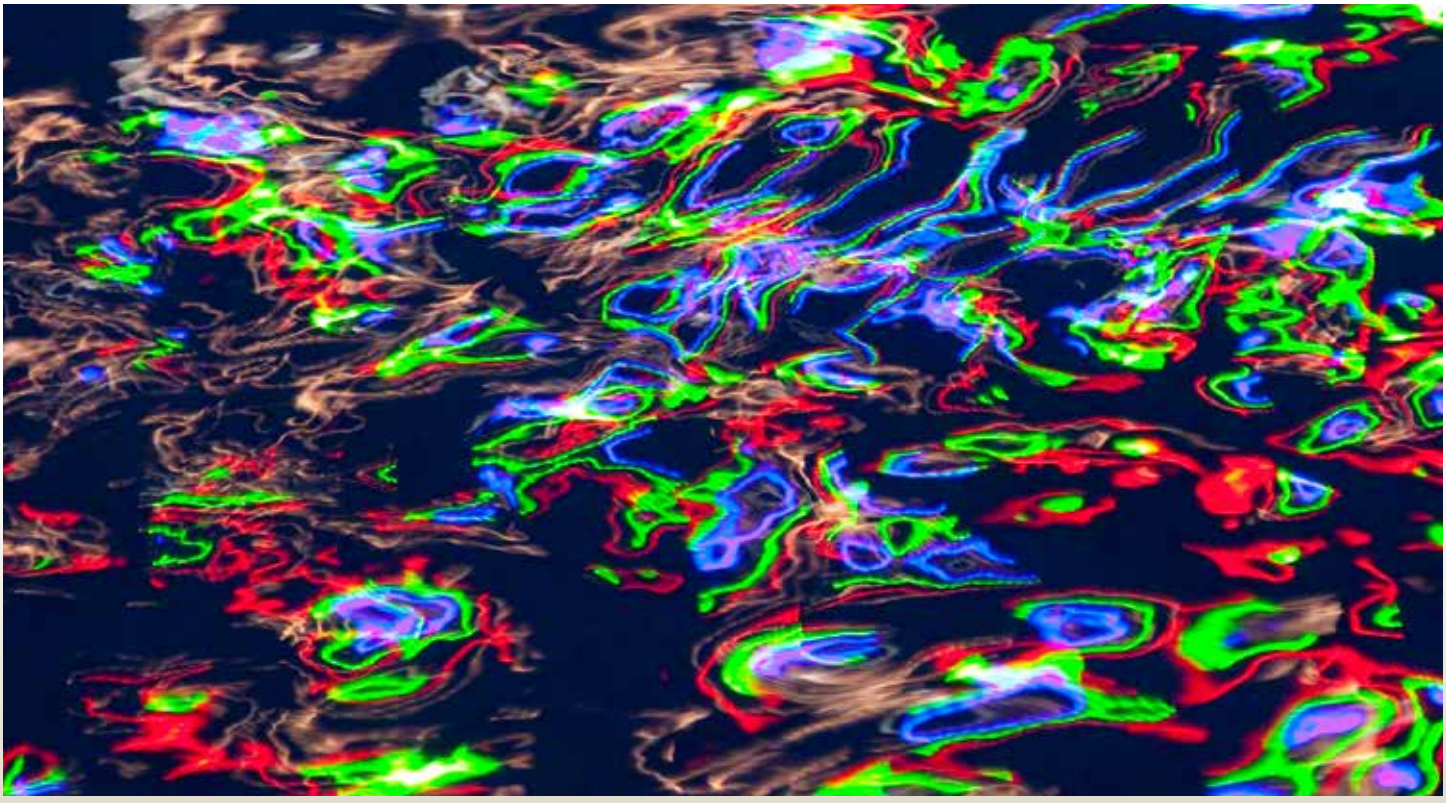
Underdiagnosis of Depression in TLE

The diagnosis of epilepsy can lead to significant unexpected financial burdens, which can be detrimental to the patient and place them at a higher risk for developing depression. Yet, findings in the field have demonstrated that there is a significant underdiagnosis of depression in patients with TLE [17]. Although the specific reasons for an underdiagnosis of depression remains unknown, it is essential to advocate for a thorough assessment of psychiatric comorbid conditions associated with TLE.

The bi-directional relationship between depression and TLE significantly affects the progression of TLE, along with the occurrence of epileptic episodes [7]. Although the designated treatment for patients with TLE focuses on addressing the epileptic episodes, there is a significant subset of patients that are pharmacoresistant, leaving them unable to use medications to treat their epileptic episodes. The patients that are diagnosed with pharmacoresistant TLE are the ones at a greater risk of suicide and major depressive disorder since it is more difficult for them to manage the occurrence of their seizures.

Overall, it is important to recognize that although our society has begun to progress towards weighing mental health at the same magnitude of importance as our physiological health, there are still several ongoing issues with the diagnosis of psychiatric disorders. Epilepsy is one of the most common neurological disorders in both adults and children, predisposing a large demographic to a high risk of developing depression. Specifically, as we focused on the depth to which depression is involved in the progression of temporal lobe epilepsy, it became apparent that the diagnosis of this illness severely affects every aspect of the lives of the patient and their families. Therefore, it is essential to focus on managing every possible factor, including the associated comorbid disorders, to avoid TLE from becoming an extremely aggressive disorder and ending in death [5].

The prevalence of epileptic disorders in a wide-range of distinct demographics also provides further commentary on the medical insurance institution in America as it significantly contributes to the financial ruin of many individuals suffering from epileptic disorders [16],[17],[18]. Specifically, it is important to understand that lower-socioeconomic patients are not provided proper access to the care required for the chronic issues that make up illnesses such as TLE. Advocating for a proper diagnosis in comorbid disorders associated with TLE, such as depression, is also a way of advocating for those in lower socioeconomic situations, as they are the ones that suffer the greatest economic displacements.



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efits and hopefully they will motivate you to fulfill your goal of elevating the power of your brain.