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Probing The Link Between Substance Use and Psychiatric Disorders: Toward A New Paradigm in the Treatment and Prevention of These Intertwined Disorders

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ABSTRACT

Globally, the rates of substance use and psychiatric disorders continue to escalate, and in the U.S., both disorder-types have become a public health crisis. Concerningly, however, psychological, behavioral, and pharmacological interventions for both disorder-types are failing to keep up with the demands for treatment. Additionally, even with treatment, the long-term prognosis for both disorder-types is equally guarded, with each expected to reduce the lifespan of those affected by an average of 10 years. These observations raise the question of whether substance use disorders and psychiatric disorders share some unknown predisposing factor—one that, if identified and treated—would markedly increase the therapeutic success rate for both disorder-types. One such factor, and one that would be highly treatable, is neuronal hyperexcitability. According to the multi-circuit neuronal hyperexcitability (MCNH) hypothesis of psychiatric disorders, an inherent hyperexcitability of the neurological system causes normal thoughts and emotions to be abnormally amplified and persistent. This can lead to obsessive thoughts and behaviors, which are fundamental characteristics of addiction disorders and obsessive-compulsive disorder; it can lead to elevated levels of anxiety and depression, which are almost universal in substance use and psychiatric disorders; and it can lead to the use of illicit drugs in an effort to either reduce or offset the uncomfortable emotions that pathologically hyperactive neural circuits can create. This article will discuss the neuropsychiatric means by which an inherent hyperexcitability of the neurological system could be driving both substance use and its related psychiatric disorders. It will also discuss why this common neurophysiological abnormality has been so difficult to identify and provide a rationale for reducing neuronal excitability as a means of both treating and preventing a wide range of substance use and psychiatric disorders.

Keywords

Substance Abuse, Addiction, Psychiatric Disorders, Mental Illness, Neuronal Hyperexcitability, Anticonvulsants, Mood Stabilizers, Substance Abuse Prevention.

Introduction

Substance use disorders are pervasive in modern society. Worldwide, 61 million people aged 12 years and older reported using illicit drugs in 2020, and around half of those persons were reportedly addicted [1]. Even more alarmingly, upwards of 9 million of them (15%) reported misusing opioids, and more than 100,000 of those died of overdose [1]. In the U.S., an estimated 14.5 million people (5.3% of the population) are dependent on alcohol, and more than half of all American adults have a family history of either problem drinking or alcohol dependence [2]. Among youth, 62% have abused alcohol by the time they reach 12th grade, and 50% have misused an illicit drug at least once [3]. Notably, approximately the same percentage of U.S. adolescents (about 1 in 2) and a growing number of U.S. adults (about 1 in 5) have experienced a mental health disorder, the most common of which is some form of anxiety disorder [4]. The other alarming fact is that the long-term success rate of treatment for both substance use and psychiatric disorders is relatively low. Substance use disorders have a relapse rate of 40-60% (even higher with alcohol use disorders), and about

60% of patients treated for clinical depression will have another depressive episode within 5 years [5]. These statistics underscore the need to achieve a better understanding of what drives these disorders and to more carefully examine the basis of their close relationship with each other.

Theoretical Factors That Drive Substance Use Disorders

Poor Moral Choices

The moral view of substance abuse and addiction dates back to the Victorian era, when it was believed that a weakness of character could cause a person to make poor moral choices and start down a path of self-destruction. This perspective accuses substance users of making the poor choice of using chemicals to deal with their problems rather than internal fortitude and more constructive resources.

Psychological Theories of Substance Misuse

This view uses psychological theories of behavioral conditioning to explain why some persons choose to use illicit drugs and why they become addicted to illicit drugs. For example, the classical conditioning model would explain substance use as a behavior that is learned by the persistent pairing of specific environmental factors, such as friends, places, sounds, and smells, with the pleasant feelings that they experience when they use illicit drugs. These environmental factors then become "triggers" for repeated use. Similarly, operant conditioning invokes the idea of rewards and punishments as a means of explaining addiction. However, these psychological principles are equally applicable to everyone, and while they do help explain how one can become addicted to drugs, they do not explain why some persons become addicted, whereas others do not.

Social Theories of Substance Misuse

Human beings are social creatures, and so we tend to mimic the behavior of those around us. This includes our family members, friends, and others in the community. For many individuals, the first exposure to common substances of abuse, such as cigarettes and alcohol, begins in the home. For others, it begins with offers from friends or an intimate partner. In many cases, the use of the substance and the associated cognitive-emotional experiences then begin to define the relationship, thus making it difficult to stop using without breaking off the relationship. However, this still fails to explain why some persons become addicted to drugs, whereas others do not.

Biological Theories of Substance Misuse

The fundamental mechanism that is cited in all biological theories of substance misuse is that the drug of choice activates the reward system of the brain, thus causing the user to keep on using the drug. In addition, addictive drugs tend, over time, to lose their effectiveness in activating the reward system, thus leading to increased dosing and the potential for withdrawal. In addition, it is now believed that some individuals have a biological predisposition that either increases the pleasure that they experience from certain drugs or increases the tolerance and withdrawal that they experience with those drugs. These are unique characteristics that could begin to explain why some persons are more vulnerable to addiction than others.

Theoretical Factors That Drive Psychiatric Disorders

Spiritual Beliefs About Psychopathology

The earliest views of psychopathology, which date back to antiquity, were that emotional and behavioral disorders were evidence that evil spirits had taken hold of a person's soul. As a result, the mentally ill were often judged and ridiculed. Primitive treatment practices included social isolation, threats of punishment, and invasive procedures, such as blood-letting and trepanning, in an effort to release the offending spirits [6]. These views persisted through the Dark and Middle Ages, and it was not until the turn of the twentieth century that modern theories about psychopathology began to emerge.

Psychological Theories of Psychopathology

Psychological theories about psychopathology can be broadly divided into two camps: psychodynamic theory, introduced by Sigmund Freud, and behavioral theory, introduced by John B. Watson [7]. Freudian theory is based on the idea that intrapsychic conflict between unconscious drives and socially acceptable behavior creates emotional and psychological distress. Hence, Freud believed that psychopathology could be treated by relieving that distress. In contrast, behavioral theory conceptualizes psychopathology as the consequence of maladaptive behavioral conditioning. More recently, other theorists, such as American psychologist Albert Ellis and American psychiatrist Aaron Beck, began to adopt treatment strategies aimed at addressing the maladaptive cognitions and emotions that were believed to underlie mental disorders [8-10]. Other psychological approaches that are commonly employed today include cognitive-analytic therapy, dialectic behavioral therapy, interpersonal psychotherapy, supportive psychotherapy, and mindfulness therapy [11]. Although all of these approaches provide benefit to some patients, the psychophysiological mechanism (or mechanisms) by which they exert their therapeutic effects have heretofore remained unclear.

The Genetic Hypothesis of Psychiatric Disorders

Family, twin, and adoption studies provide clear evidence that all of the major psychiatric disorders are familial and that this familiality is mostly due to genetic factors [12]. This important finding suggests that parental influences and other early life experiences are not as important in the development of these disorders as previously thought. However, twin and adoption studies fail to show full concordance of any of the major psychiatric disorders, and the data from genome-wide association studies suggest that multiple genes combine to differentially increase one's vulnerability to developing one psychiatric disorder or another [13]. Still, a major limitation of these studies is that they use a symptom-based classification system, which, being based on subjective observations and clinical outcomes rather than objective measurements or tests, do not necessarily describe distinct pathophysiological processes and could instead be describing different manifestations of a shared vulnerability trait.

The Psychosocial Stress Hypothesis of Psychiatric Disorders

Psychosocial stress has long-been recognized as an important factor in the development of psychiatric symptoms. For example, studies have found that depressive disorders are associated with a 2.5 times greater frequency of stressful life events during the period leading up to the onset of symptoms [14]. Stress has also been linked to treatment resistance [15], poorer prognosis [16], and higher relapse rates [17,18] of major depressive disorder. Although numerous theories have been proposed to explain these phenomena, such as stress-induced dysregulation of neurotransmitters [19], alterations in receptor sensitivity [20], overactivity of the amygdala [21], under-activity of the hippocampus [21], dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis [22,23], disruption of metabolic [24] and immunologic function [25-27], mitochondrial dysfunction [28], stress-induced activation of the lateral habenula [29-33], decreased neurotrophic factors [24], blunted neurogenesis [24], disrupted synaptogenesis, diminished dendritic spines, and stress-induced apoptosis [22,23,28,34], none adequately explain why stress precipitates psychiatric symptoms in some persons but not in others. These theories also fail to explain the cycling of symptoms that occurs in bipolar disorder, cyclothymia, and other disorders in the bipolar spectrum. Even more fundamentally, they fail to explain how the putative chemical and physiological abnormalities actually translate to the cognitive and emotional abnormalities that characterize clinical depression and other psychiatric disorders.

The Diathesis-Stress Hypothesis of Psychiatric Disorders

This long-held hypothesis contends that it is neither stress alone nor an underlying predisposition or "diathesis" alone that drives psychiatric symptoms but rather a combination of the two. However, the diathesis-stress hypothesis does not identify what the underlying predisposition is, nor does it explain how the two factors combine to precipitate psychiatric symptoms.

The Monoamine Hypothesis of Depression

Though the monoamine hypothesis has, for more than fifty years, provided a biological basis for the use of antidepressants in the treatment of clinical depression, it falls short of explaining other common psychiatric disorders, such as panic disorder, obsessive-compulsive disorder, and bipolar spectrum disorders. Also, considering that it fails to explain why the depletion of serotonin precursors does not produce depressive symptoms in normal subjects [35], it even falls short of fully explaining major depressive disorder. Additionally, it fails to explain how a relative reduction in monamine neurotransmission actually translates into depressive mood states.

The Immunologic Hypothesis of Psychiatric Disorders

In recent years, a bidirectional link has been found between psychiatric disorders and mediators of inflammation [36-43]. Psychological stress and negative emotions activate peripheral physiological mechanisms that stimulate the immune system. Conversely, peripheral mediators of inflammation cause neurophysiological changes that lower the threshold for psychiatric symptoms. However, studies have found that reducing inflammation fails to completely eliminate psychiatric symptoms [40,41]. It has also been found that anti-inflammatory drugs are more helpful in those patients who have higher levels of pretreatment inflammation [42,43]. These observations suggest that while inflammation can precipitate or exacerbate psychiatric symptoms, it is not the primary vulnerability factor in mental illness.

The Endocrine Hypothesis of Psychiatric Disorders

Another burgeoning area of interest has been stress hormones and disruptions of the HPA axis, as many patients with depression have been found to have elevated levels of cortisol. However, most patients with clinical depression have no evidence of HPA dysfunction [44], and attempts to modulate the neuroendocrine system pharmacologically have met with limited therapeutic success [45].

The Glutamatergic Hypothesis of Depression

Several lines of evidence have linked major depressive disorder to a dysregulation of the excitatory neurotransmitter glutamate [46,47]. The attention to glutamate was sparked by the rapid and robust antidepressant effects of ketamine, an antagonist of the N-methyl-D-aspartate (NMDA) receptor. Although the clinical use of ketamine for depression is limited by its narrow therapeutic window and potential for abuse, its speed of action and impressive ability to relieve symptoms deserve special attention in regard to elucidating the neurobiology of depression. Glutamate is the primary excitatory neurotransmitter in the brain, and so the observation that blocking its activity can rapidly relieve symptoms of depression suggests that mental illness may somehow be related to abnormalities in neuronal excitation. Yet this still leaves many questions unanswered, the most basic of which is that of why antidepressants, many of which *increase* excitatory neurotransmission, can be so effective in relieving depression, anxiety, and other psychiatric symptoms.

The Central Sensitivity Hypothesis of Psychiatric Disorders

The central sensitivity hypothesis emerged from the observation that biopsychosocial stress tends to initiate or exacerbate various physical symptoms for which no organic basis can be found. According to the hypothesis, an inciting factor, such as a chemical toxin, a physical injury, or an emotionally traumatic event, can increase the sensitivity of the central nervous system to subsequent stressors, thereby leading to intermittent and, in some cases, chronic conditions, such as irritable bowel syndrome, fibromyalgia, migraine headache, temporomandibular joint disorder, and other chronic pain syndromes [48]. Central sensitivity is also thought to explain the various psychiatric symptoms that are commonly observed in persons who present with the aforementioned functional conditions [49,50]. A similar nosology, referred to as "body distress syndrome" likewise unifies a wide range of functional disorders under a single title [51]. What remains unexplained, however, is why some persons develop the aforementioned hypersensitivities, while others do not. The central sensitivity hypothesis also fails to explain how, neuropsychologically, the hypersensitivities translate into psychiatric symptomatology.

The Gut-Brain Hypothesis of Psychiatric Disorders

The high co-morbidity between psychiatric disorders and gastrointestinal disorders is well-recognized, and this association has, in recent years, caused gut-brain interactions to become an area of increasing focus in relation to mental illness [52,53]. The brain and the bowel interact both directly and indirectly. The vagus nerve connects directly to the bowel via the celiac and superior mesenteric plexus [53]. Conversely, the bowel synthesizes GABA, monoamines, and other neurotransmitters, which can enter the peripheral circulation and cross the blood-brain barrier [53]. Topdown, there is some evidence that emotional stress and poor diet can drive pathological changes in the gut microbiome [54], and, conversely, pathological changes in the gut microbiome can affect mental health. Although the reciprocal interactions between the brain and the bowel provide support for the gut-brain hypothesis of psychiatric disorders, they still fail to explain why some persons are relatively resistant to mental illness regardless of their diet and stress exposure, while others are highly vulnerable to both mental and physical illness irrespective of how much they control their diet and lifestyle. Also, like other hypotheses, the gut-brain hypothesis fails to explain how the proposed pathogenic effects actually translate into psychiatric symptomatology.

The Multi-Circuit Neuronal Hyperexcitability (MCNH) Hypothesis of Psychiatric Disorders

The MCNH hypothesis is based on the simple premise that thoughts and emotions stimulate the corresponding brain circuits and, conversely, specific brain circuits stimulate the corresponding thoughts and emotions [55]. That this mind-brain dialogue actually occurs has now been demonstrated experimentally. Recording from single neurons in patients implanted with intracranial electrodes for clinical reasons, Cerf et al. [56] found that willful thoughts and emotions readily stimulated specific neurons when subjects were asked to perform specific mental tasks. Conversely, stimulating different parts of the brain with an electrical probe has long-been known to trigger different thoughts and emotions [57]. Also, there is now irrefutable evidence from the rapidly expanding literature on near-death experiences that the mind and the brain are completely separate entities and that the mind has the ability to think, emote, and retrieve memories independent of brain function [58-64]. What this implies is that specific cognitive and emotional stressors could cause the activity of the associated neurons and circuits to become amplified accordingly [65]. Likewise, elevated activity in specific neurons and circuits could cause the corresponding cognitions and emotions to become amplified [66,67]. Thus, what we call "psychiatric symptoms" could reflect pathological imbalances in circuit-specific firing rather than chemical imbalances per se. At the same time, the dialogue between the mind and the brain, in conjunction with the neuroplastic effects of primed burst potentiation [68], could explain how persistent stress could cause specific circuits in the brain to become increasingly excitable over time. It could also explain how manipulating the activity of specific circuits, as is currently done recreationally using illicit drugs, pharmacologically using medicinal drugs, and magnetically using a skull-surface coil, could affect cognitive and emotional functioning. In other words, it could explain how psychological processes affect neurological processes, and neurological processes affect psychological process in both the production and alleviation of psychiatric symptoms. Note that persons with hyperexcitable neurological systems would also be more sensitive to the pleasurable effects, the sedating effects, and the withdrawal effects of illicit drugs, thus helping to explain their increased vulnerability to addiction.

Still, a stress-induced escalation in the dialogue between the mind and the brain would not explain why some persons are more vulnerable to developing various substance use and psychiatric disorders than others. Strikingly, however, a number of large, multi-center gene association studies have found that the top candidate genes for bipolar disorder, major depressive disorder, and schizophrenia—disorders that together express all of the symptoms of the common psychiatric disorders—involve ionchannelopathies [69-72]. In other words, the protein products of the candidate genes fail to adequately regulate the excitability of neurons. The inheritance of these genes would amplify the vicious cycle of mutual overstimulation between the mind and the brain that is proposed to occur under the influence of stress. Thus, the inheritance of ionchannelopathies would distinguish those patients who were more vulnerable to developing psychiatric symptoms from those who were less vulnerable. The unlikely connection between the gene research and the fundamental tenets of the MCNH hypothesis provides compelling evidence that the hypothesis is valid [73].

Explanatory Power of the MCNH Hypothesis

As one can see from the earlier sections of this article, many theories have been proposed to explain substance misuse, and many more have been proposed to explain psychiatric disorders. However, with the exception of the MCNH hypothesis, all of these theories fall short of explaining why, neurophysiologically, some persons are more vulnerable to becoming addicted to illicit drugs, and why, simultaneously, they are more vulnerable to developing various psychiatric disorders.

But even if we were to accept that the MCNH hypothesis has superior explanatory power, it would still leave the question of how influential the neuronal hyperexcitability trait is in comparison to the many other factors that influence the development of substance use and psychiatric disorders. The answer to that question lies in the pedigrees of families who are affected by substance use or psychiatric disorders or both. Although family, twin, and adoption studies have failed to identify a consistent pattern of inheritance for substance use or psychiatric disorders, a reconceptualization of these disorders as different manifestations of a shared neurophysiological abnormality (i.e., neuronal hyperexcitability) actually does reveal a consistent pattern of inheritance. That pattern is strikingly autosomal dominant! [74]. In other words, in those families who are affected, probands who misuse addictive drugs or develop psychiatric disorders almost always appear in a classic Mendelian distribution. Moreover, a predictable subset of children in these families are completely unaffected despite being

raised in the same households by the same parents. These so-called "survivors," who typically appear in an autosomal recessive distribution, are presumably those who did not inherit the genes for neuronal hyperexcitability. These observations combine to suggest that: 1) substance use disorders and psychiatric disorders are rooted in a shared biological abnormality; 2) many of the most common substance use and psychiatric disorders are driven by polymorphisms of a single gene locus; and 3) the hypothesized abnormality may be the most important predisposing factor in the development of substance use and psychiatric disorders. Though of seminal importance, these observations need to be interpreted with caution because they are based on informally-obtained family pedigrees (approximately 300 in a general outpatient psychiatric population) rather than tightly controlled studies. Importantly, however, they pave the way for such studies and reiterate the importance of reconceptualizing substance use and psychiatric disorders as different manifestations of a shared biological abnormality. They also underscore the importance of improving the ability to identify and treat neuronal hyperexcitability.

Although the relevance of the neuronal hyperexcitability trait to substance use and psychiatric disorders is not new [55,75], relatively little attention has been paid to the trait in the psychiatric literature. Concerningly, the emphasis on symptom-based treatment and the monoamine hypothesis of depression continues to overshadow other possible ways to explain and treat mental illness. However, that paradigm is beginning to change with the gradual recognition that the monoamine hypothesis of depression, as previously mentioned, fails to explain several key observations in the treatment of psychiatric disorders. First, it fails to explain the beneficial effects of antidepressants in the treatment of psychiatric disorders that are thought to have a different biological basis than clinical depression, such as panic disorder, obsessive-compulsive disorder, and a number of other psychiatric disorders [76]. Second, it fails to explain why antidepressants sometimes cause depressive symptoms to worsen, cycle back and forth, or just continue unabated. Third, it fails to explain why the depletion of serotonin precursors does not produce depressive symptoms in normal subjects [35]. Fourth, it fails to explain how the putative abnormalities in the monoaminergic system translate to the abnormalities in thought, emotion, and behavior that characterize mood disorders. Fifth, it fails to explain the tight link between substance misuse and a wide range of psychiatric disorders.

In contrast, all of these phenomena can readily be explained by the MCNH hypothesis. First, the broad utility of antidepressants in the treatment psychiatric disorders can be explained by the hypothesis that psychiatric symptoms, regardless of which symptom-based diagnosis they are grouped under, merely reflect firing imbalances in the associated neural circuits. Antidepressants attempt to correct these imbalances by modulating the activity of specific neurotransmitters. However, because these neurotransmitters affect the activity of many different circuits, treatment with antidepressants can also create new circuit-specific imbalances, accentuate existing ones, or have no net effect. Also, because pathologically hyperactive circuits have the potential to aberrantly fuel hyperactivity in relatively *hypo*active circuits while themselves quieting down due to synaptic fatigue [77,78], antidepressant can cause various symptoms to cycle back and forth and meld into one another, as in bipolar disorder, cyclothymia, and other disorders in the bipolar spectrum. The MCNH hypothesis can also help explain why the depletion of serotonin precursors does not produce depressive symptoms in normal subjects. Unlike patients with psychiatric symptoms, who, according to the MCNH hypothesis, would have hyperexcitable neurological systems, persons with no psychiatric history would be unlikely to have hyperexcitable neurological systems and, thus, have little risk of developing pathological circuit-specific imbalances even if they were relatively low on the predominantly inhibitory neurotransmitter, serotonin.

According to the MCNH hypothesis, psychiatric symptoms are simply normal thoughts and emotions that are abnormally intense and persistent due to an inherent hyperexcitability of the neurological system [55]. Pathologically hyperactive circuits overstimulate the mind, thereby causing the various cognitive and emotional symptoms that characterize psychiatric disorders. The natural desire to control these abnormally intense and prolonged cognitive-emotional states is what would drive affected persons to use sedatives, stimulants, and other illicit drugs. The observation that alcohol and cannabis, both of which have powerful brain-calming effects, have always been and continue to be the most commonly used and abused drugs bears witness to the validity of the MCNH hypothesis and readily explains the tight link between substance use and psychiatric disorders.

Over the past 25 years in clinical practice, I have not seen a single patient with a substance use disorder who did not have a hyperexcitable brain. However, I have seen many patients with hyperexcitable brains who did not have a substance use disorder. Thus, it appears that neuronal hyperexcitability is necessary but not sufficient to drive the development of a substance use disorder. It also appears, based on family pedigrees, to be the most important predisposing factor in the development of a substance use disorder. Accordingly, when the underlying neuronal hyperexcitability is effectively treated in those patients who do have a substance use disorder, most either spontaneously reduce or altogether stop using their drug or drugs of choice. They also experience a concomitant reduction or resolution of any co-occurring psychiatric symptoms.

Treatment

Fortuitously, neuronal hyperexcitability is highly responsive to treatment. There are now more than a dozen anticonvulsant drugs on the market, most of which are generic. Anticonvulsants such as gabapentin, oxcarbazepine, depakote, lamotrigine, topiramate, and the anticonvulsant-like drug lithium are relatively safe, nonaddictive, and fast-acting. Unlike antidepressants, they exert their therapeutic effects purely by reducing the activity of pathologically hyperactive neural circuits, thus helping to stabilize the system and minimize the risk of creating new circuit-specific imbalances; hence the term "mood stabilizers" [79]. Based on

data from large population studies, treatment with anticonvulsants increased the risk of suicidality from just 0.22 per thousand patients to 0.43 per thousand patients [80]. By comparison, treatment with antidepressant drugs has been found to increase the risk of suicidality between 2 [81] and 10-fold [82-84]. What appears to be increasing the risk of suicidality with antidepressant therapy is not so much the paradoxical effects of antidepressants but rather the failure to distinguish true unipolar depressives from those in the bipolar spectrum (i.e., those with hyperexcitable neurological systems). Among psychiatric patients, only an estimated 2% have normoexcitable neurological systems [77], yet the sale of antidepressants currently outnumbers the sale of anticonvulsants by more than 6 to 1 [85]. This suggests that the trait of neuronal hyperexcitability is either poorly recognized or poorly treated or both.

Indeed, the trait can be difficult to detect for several reasons. First, mood instability, which is one of the hallmarks of neuronal hyperexcitability, is often underreported or even denied by patients. Second, hyperexcitable neurons, like a hive of irritable bees, can become relatively quiescent during periods of low stress, when, metaphorically speaking, the hive is not being disturbed. Hence, symptoms can become subclinical during those times. Third, the symptoms of neuronal hyperexcitability, which can be limitless in their nature and magnitude, can mimic the symptoms of virtually any psychiatric or physical illness. Fourth, the trait tends to evade detection by neuroimaging studies both because the neuronal hyperactivity occurs in the brain's microcircuitry [86] and because it tends to migrate around the brain as neural circuits compete for dominance [87]. Fifth, the most common clinical manifestations of neuronal hyperexcitability are anxiety and depression, and mental health practitioners have been indoctrinated into associating these symptoms with the monoamine hypothesis and the use of antidepressants. Hence, when confronted with such symptoms, most clinicians are quick to prescribe an antidepressant or a combination of an antidepressant and a benzodiazepine. The problem with this approach is that antidepressants (including SSRIs) have mixed effects: they quiet some parts of the brain while stimulating others [88]. From the perspective of the MCNH hypothesis, they cary the risk of creating new circuit-specific imbalances or of counteracting their own therapeutic effects, depending upon how and where in the brain they affect the excitation/inhibition balance [86]. Worse yet, combining a benzodiazepine with an antidepressant can obscure the effects of the antidepressant, thus making the treatment even more imprecise. Another problem with antidepressants is that the excitatory effects tend to increasingly outweigh the inhibitory effects as the dosage is increased. This can increase the need to administer a neuroinhibitory drug, which, as previously stated, will likely be a benzodiazepine. Although patients generally do benefit from the anticonvulsant effects of benzodiazepines, the problem is that their long-term use can lead to tolerance, dependence, and withdrawal. All of these problems could be avoided by simply focusing efforts on reducing the excitability of the neurological system using non-benzodiazepine anticonvulsants. This approach, which could be called "focused neuroregulation," has been found anecdotally to yield unprecedented short and long-term results in the treatment of all of the most common substance use and psychiatric disorders. The only exceptions are the relatively rare patients who do *not* have hyperexcitable neurological systems but, due solely to the kindling effect of severe and prolonged cognitive-emotional stress, can develop a persistent pathological circuit-specific imbalance. Such imbalances usually begin in the depression circuitry because of the depressive nature of severe and persistent cognitive-emotional stress. However, they also tend to remain in the depressive circuitry because *normoexcitable* neurons are relatively resistant to aberrant circuit induction [77]. Such patients, who could appropriately be described as "true bipolar depressives," typically respond better to antidepressant therapy than anticonvulsant therapy because of the stability of their neurological systems. Such patients constitute the vast *minority* of psychiatric patients because, unlike in persons with hyperexcitable neurological systems, daily stressors are typically insufficient to precipitate psychiatric symptoms. The big challenge confronting psychiatry today is that of accurately distinguishing true unipolar depressives from the rest of the psychiatric patient population, which could appropriately be described as bipolar spectrum patients. The term "bipolar spectrum," which harkens back to the work of Akiskal [89] and Koukopoulos [90,91], is, in my opinion, just a symptom-based way of identifying the activating and mood-destabilizing trait of neuronal hyperexcitability.

Although the significance of neuronal hyperexcitability in relation to both substance use disorders and psychiatric disorders has been described previously [55,75], its degree of importance has heretofore been obscured by methodological difficulties in studying the therapeutic effects of anticonvulsant drugs in these disorders. As in the treatment of epilepsy, clinical experience has shown that combinations of anticonvulsants are often needed before their their full potential can be realized. In fact, when used this way in psychiatry, their potential benefit is actually greater than in neurology because the abnormality that is being treated is, hypothetically, entirely physiological, whereas in epilepsy there is, in most cases, a structural component that is not correctable with anticonvulsant drugs. However, most behavioral health studies of anticonvulsant therapy involve single agents at different dosages. The problem with this approach is that monotherapy often fails to reduce neuronal excitability enough to achieve the full potential of anticonvulsant therapy. Nonetheless, there is evidence that even when a single agent is used, clinically significant benefits can sometimes be achieved. For instance, the widely prescribed anticonvulsant gabapentin has been found to be effective in the treatment of alcoholism and the relapse-related symptoms of insomnia, dysphoria, and craving [92-94]. Gabapentin has also demonstrated benefits in the treatment of anxiety disorders [95,96] and as add-on therapy in the treatment of bipolar disorders [97].

Another factor that obscures the importance of neuronal hyperexcitability as a target for treatment in both substance use and psychiatric disorders is the traditional belief that these conditions are more psychological than biological in nature. Thus, if a biological abnormality is not suspected, a biological target is not sought. This long-held idea continues to guide the philosophy

of psychologists, psychotherapists, and chemical dependency specialists, including group leaders of Alcoholics Anonymous, Narcotics Anonymous, and other chemical dependency programs. Yet another factor that obscures the importance of neuronal hyperexcitability as a target for treatment is the symptom-based system of diagnosis in addictionology and psychiatry. Rather than targeting neuropathology, chemical dependency programs tend to focus on abstinence, and psychiatric programs tend to focus on symptom-reduction rather than addressing the underlying biological abnormality. This last factor—targeting symptoms rather than the underlying biological abnormality—leads to a host of other clinical oversights, which in turn prevent clinicians from recognizing the rapid, persistent, and highly therapeutic effects of anticonvulsant drugs. For example, if an anticonvulsant fails to demonstrate a therapeutic effect in a given patient, clinicians often make the false assumption that either the diagnosis is wrong or the drug is ineffective. However, if the target for treatment were more accurately visualized, clinical reasoning would be changed in a number of important ways. First, the clinician would be more tenacious in the use of anticonvulsant drugs, taking into consideration the possibility that the dosage might be too low, that a different anticonvulsant might be more effective, or that combining anticonvulsants might achieve greater symptom reduction than any single anticonvulsant alone. Second, when a clinician recognizes that a waxing and waning of symptoms, irrespective of the type of symptoms, is indicative of clinically significant neuronal hyperexcitability, a return of symptoms after starting an anticonvulsant that initially appeared to be effective would not necessarily be viewed as a treatment failure. Rather, consideration would be given to the possibility that the dosage might need to be further adjusted or that a second anticonvulsant might need to be added. Third, given that stress causes hyperexcitable neurons to become pathologically hyperactive [98], recognizing neuronal excitability as the therapeutic target would guide the timing of treatment. For example, anticonvulsants could be used more aggressively during high-stress periods, and less aggressively during low-stress periods. They could also be used prophylactically because stress has a kindling effect on the brain, and this effect develops over time. Recognizing this, an anticonvulsant that had previously been effective could be restarted when a period of high stress threatens to cause symptoms to re-emerge. Unfortunately, however, there has heretofore been no way to reliably identify the neuronal hyperexcitability trait clinically.

Toward an Objective Method of Identifying the Neuronal Hyperexcitability Trait

An objective aid in identifying the trait of neuronal hyperexcitability is now growing out of an explosion of recent studies that have uncovered an association between resting vital-sign measurements and the later development of various psychiatric and general medical conditions. In a longitudinal study involving more than one million men in Sweden, Latvala et al. [99] found that subtle elevations in resting heart rate (RHR) were predictive of the later development of generalized anxiety disorder, obsessive-compulsive disorder, and schizophrenia. Similarly, Blom et al. [100] found that adolescent girls with emotional disorders had increased resting respiratory rates (RRR) in comparison to healthy controls. Persons with higher resting heart and respiratory rates have also been found to be at increased risk of developing a wide range of physical illnesses, including diabetes, high blood pressure, cardiovascular disease, autoimmune diseases, and all-cause mortality [101]. The subtle vital-sign elevations with which these illnesses are associated are thought to be the consequence of a tonic elevation in basal neurological activity in those persons who inherit the genes for neuronal hyperexcitability [101]. This is the MCNH explanation for why the lifespan of persons with severe mental illness tends to be much shorter than the general population [101]. The reason that psychiatric and "functional" physical symptoms tend to precede the development of diagnosable physical abnormalities is that the cognitive-emotional system is more expressive of neuronal excitation than other organs and tissues of the body. The physical consequences tend to be delayed because they express the erosive effects of neuronal hyperexcitability, which take time to occur [101]. Thus, there is mounting evidence that what is proposed to be the underlying driver of both substance use and psychiatric disorders can be identified objectively [77,101]. It has been estimated that, in the absence of any significant cardiorespiratory disease, confounding drugs, or prescription medications, an RHR above 75 beats/min or an RRR above 15 breaths/min would be indicative of the neuronal hyperexcitability trait. It should be noted that in the more than 100 consecutive outpatients that have been studied thus far, this objective method has proven to be more sensitive in detecting the neuronal hyperexcitability trait than formal clinical assessments.

Discussion

The goal of this article was to examine the underpinnings of substance use and psychiatric disorders and to identify, if possible, some shared psychological or biological predisposing factor that could explain their high co-morbidity and serve as a guide to a more effective way to treat and, if possible, prevent these two commonly occurring and often co-occurring disorder-types. As discussed, none of the current theories of substance misuse or mental illness can adequately explain why some persons are more vulnerable to developing these illnesses, nor can they adequately explain the high level of co-morbidity between them. However, an emerging hypothesis proposes that a genetically-based neurophysiological abnormality may be the underlying driver of both disorder-types. That abnormality, which can be described as a tendency for the neurological system to overreact and fail to self-regulate, may provide the long-sought answer and begin to explain a long history of observations in regards to substance misuse and mental illness.

Historically and still today, the two most commonly used and abused drugs have been alcohol and marijuana. Both of these drugs have powerful anticonvulsant effects. Alcohol binds to GABA-A receptors, thereby increasing their responsively to GABA, the neurological system's primary inhibitory neurotransmitter [102]. Alcohol also inhibits the major excitatory neurotransmitter glutamate, particularly at the NMDA glutamate receptor [103]. Cannabis produces the same effect in a different way:

constituents of the cannabis plant bind to the transient receptor potential vanilloid (TRPV) channel, which likewise reduces neuronal excitability. Although most of the emphasis has been on cannabinoid receptors type 1 and 2, cannabinoids actually have low affinity for these receptors [104,105]. Also, with the exception of Δ9-tetrahydrocannabinol, cannabinoids have antagonistic effects at the type 1 receptor, thus predicting that they would increase rather than decrease neurotransmission via that receptor. In contrast, CBD has high affinity for the TRPV channel, which has a high Ca2+ permeability and is involved in the modulation of neuronal excitability [106,107]. When active, this channel promotes the release of the excitatory neurotransmitter glutamate and the movement of calcium ions into the cell, both of which increase neuronal excitability. CBD (in contrast to Δ9tetrahydrocannabinol, anandamide, and pro-inflammatory agents [107]) deactivates this channel, thereby reducing neuronal excitability [106]. Another ion channel with which CBD interacts is the T-type calcium channel. This channel, which normally destabilizes the neuron upon opening, is blocked by CBD, thus providing another mechanism by which CBD can reduce neuronal excitability [106]. In comparison to the brain-calming effects of alcohol and cannabis, stimulant-type drugs are actually less preferred by users despite the fact that they activate the reward system of the brain. In a recent survey conducted by the Substance Abuse and Mental Health Services Administration [108], only 25% of those who had used crack cocaine in the previous one to two-year period had reused one year later. In contrast, more than half of those who had used marijuana, and roughly three-quarters of those who had used alcohol, had reused during the same followup period. Hypothetically, what makes sedatives so attractive is that they reduce the excitability of the neurological system. Even when addicts do use stimulants, they generally prefer to combine them with sedatives in an effort to prevent the anxiety, irritability, and other psychiatric symptoms that are, according to the MCNH hypothesis, exacerbated by stimulant-induced hyperactivity in the associated circuit loops. A well-known class of drugs that helps reduce circuit-specific hyperactivity while at the same time activating the brain's reward system is the opium alkaloids. This could help explain why opioids are so highly addictive.

Consonant with the long history of anticonvulsant drug use socially and recreationally, there is a long history of anticonvulsant drug use medicinally. The oldest of these was again, alcohol, with evidence of alcohol's medicinal use mentioned in Sumerian, Egyptian, and Hebrew texts (Proverbs 31:7-7). The second oldest medicinal remedy was, once again, the cannabis plant, which continues to be exploited for its potent anticonvulsant effects [104-106]. This was followed by the opium poppy, which, like cannabis, has sedative and analgesic effects. Heading into the modern era, anticonvulsants and other brain-calming drugs continued to be used medicinally, beginning with bromine, an anticonvulsant that Sir Charles Locock used for "hysterical epilepsy" [109], followed in succession by barbiturates, benzodiazepines, and antipsychotic drugs, all of which have brain-calming effects. The notable exception to the use of sedative drugs was electroconvulsive therapy (ECT), which later became, and still is, the gold-standard in the treatment of clinical depression. Although the mechanism by which ECT relieves psychiatric symptoms remains unclear, it is evident that clinical improvement occurs not during the induced seizure but in the aftermath of the seizure. It is now recognized that seizures are brought to a halt by a host of neuroinhibitory changes that occur in response to the seizures themselves. Known inhibitory mechanisms include glutamate depletion, GABAergic recurrent inhibition, membrane shunting, depletion of energy stores, loss of ionic gradients, endogenous neuromodulator effects, and regulatory input from various brain regions [110]. Hypothetically, these same mechanisms are what also allow ECT to be used to treat status epilepticus [111,112]. That a remission of depression and other psychiatric symptoms occurs in conjunction with the aforementioned neuroinhibitory responses of the brain reiterates the idea that psychiatric symptoms are rooted in neuronal hyperexcitability.

Thus, what was happening historically was that the same drugs that were being used recreationally—namely, alcohol and marijuana—were being used medicinally until ECT and safer brain-calming drugs became available for medical use. In other words, the historical record of social drug use, recreational drug use, medicinal drug use, and ECT unequivocally point to the therapeutic value of calming the brain. Calming the brain reduces the excitability of the neurological system, thus corroborating the MCNH hypothesis.

However, what appears to have happened in more recent history was that the medical profession became side-tracked after the anti-tuberculin drugs isoniazid and iproniazid were serendipitously found to have potent antidepressant effects [113,114]. The powerful mood-elevating effects of these drugs in some patients were more dramatic than the mood-normalizing effects of the drugs that preceded them. An Associated Press release from Staten Island's Seaview Hospital, where the antidepressant effect was first discovered, captured a telling scene: patients dancing in celebratory mood; hence the term "anti-depressant" [115]. Some of these patients, who had been under quarantine for tuberculosis, were suddenly feeling so good emotionally that they wanted to leave the sanatorium against medical advise. In other words, the sense of well-being that they were experiencing was distorting their judgment. As previously discussed, this is the kind of thing that can occur when attempts are made to rebalance pathologically hyperactive neural circuits by modulating the activity of specific neurotransmitters. That is not to discount the benefits of antidepressants but only to say that they may not be the drugs of choice for every patient who presents with symptoms of anxiety and depression. According to the MCNH hypothesis, the overwhelming majority of persons who experience anxiety, depression, and other psychiatric symptoms have hyperexcitable neurological systems, thus explaining why anticonvulsant drugs had been the mainstay of treatment for these ailments until the antidepressant effect raised the expectation of patients (and clinicians) from achieving normalcy to achieving an elevated mood. Concerningly, the medical profession is now moving one step beyond that as evidenced by the steady rise in psychostimulant prescriptions. Yet this is not surprising because

psychostimulants, like many antidepressants, can increase firing in feel-good neural circuits. What's more, attentional difficulties, for which psychostimulants have traditionally been prescribed, are one of the most common manifestations of the neuronal hyperexcitability trait. Hypothetically, the hyperexcitable brain, in creating the symptoms of ADHD, spams the mind with an over-abundance of electrical signals, thus causing a triad of distractibility, hyperactivity, and impulsivity. Psychostimulants can help reduce these symptoms by stimulating inhibitory neurons in the reticular nucleus of the thalamus [98]. The problem is that they also stimulate the pleasure centers and other brain circuits, thereby exacerbating the underlying problem of neuronal hyperexcitability and creating the risk of abuse. From the perspective of the MCNH hypothesis, a healthier way to reduce the symptoms of ADHD (as well as any co-occurring psychiatric symptoms) would be to quiet the brain with anticonvulsant drugs in conjunction with natural brain-calming routines, such as stress reduction, establishment of an early sleep schedule, regular exercise, avoidance of caffeine, and minimization of refined sugar. If these interventions prove to be inadequate, a low dose of a psychostimulant could be added. However, the continued co-administration of an anticonvulsant would help ensure that 1) any co-occurring psychiatric symptoms would be controlled; 2) the overall balance between excitation and inhibition in the brain would be maintained; and 3) the necessary dosage of a psychostimulant would be minimized. In some cases, a single anticonvulsant or combination of anticonvulsants could be enough to fully correct the attentional problem and is often enough to reduce any co-occurring hyperactivity or impulsivity. However, clinical experience has shown that most patients with significant attentional difficulties will ultimately need a low dose of a psychostimulant added to an effective anticonvulsant.

As one can see from the forgoing discussion, clinical application of the MCNH hypothesis has benefits that go far beyond providing a biological basis for the tight link between substance use and psychiatric disorders. Also, the potential to use resting vital-sign measurements to objectively identify the neuronal hyperexcitability trait could allow at-risk persons to be educated and possibly even treated before any psychiatric symptoms or illicit drug experimentation begins. These interventions could also reduce the risk of developing any of the functional physical symptoms and medical conditions that untreated neuronal hyperexcitability can create [101]. This, in turn, could be yet another means by which the risk of both substance use and psychiatric disorders could be reduced.

Conclusion

Although it is well-recognized that a better understanding of the pathophysiology of substance use and psychiatric disorders is sorely needed, no unifying theory has yet been embraced by the medical community. In the meantime, morbidity and mortality rates from these disorders continue to climb, and both have been declared public health emergencies. However, an emerging hypothesis—one that has unprecedented explanatory power and is supported by the long history of both recreational and medicinal drug use—could revolutionize the treatment of substance use and psychiatric disorders. Although anticonvulsant drugs, which are instrumental to the MCNH hypothesis, have been widely available for decades, they have heretofore been like arrows shot in the dark. That is to say, they have been used sub-optimally or not at all due to a symptom-based rather than pathophysiologically-based approach to treatment [85]. By identifying the core physiological abnormality in substance use and psychiatric disorders, the MCNH hypothesis turns the lights on and illuminates the biological target for treatment; it guides an approach called "focused neuroregulation," in which anticonvulsants could be used alone or in combination with other anticonvulsants as first-line therapy. By staying focused on the biological target, treatment could be streamlined, and the use of antidepressants, psychostimulants, and other drugs that have conflicting and sometimes paradoxical effects could be minimized or completely avoided. Moreover, with the recent discovery that the neuronal hyperexcitability trait can be identified objectively via resting vital-sign measurements, the stage is also set to explore the possibility of using anticonvulsants prophylactically.

Directions for Future Research

Urgently needed are clinical studies in which anticonvulsant drugs are used either alone or in combination with other anticonvulsants (focused neuroregulation) to calm the brain in persons who are suspected, based on objective and subjective signs and symptoms, of having hyperexcitable neurological systems. Guided by the MCNH hypothesis, which conceptualizes substance misuse and related psychiatric disorders as different manifestations of a shared neurophysiological abnormality rather than different biological abnormalities, the experimental and control arms of these studies would not segregate participants based on DSM diagnosis but rather on symptoms and signs of neuronal hyperexcitability (i.e., substance misuse, psychiatric symptoms, and upper-end-of-normal resting vital signs). Given that most persons who have a history of substance misuse also have a history of various other psychiatric conditions, the MCNH-guided approach would circumvent the historical problem of diagnostic inclusion criteria. Any subject who was suspected of having a hyperexcitable neurological system could be included regardless of what combination of DSM diagnoses he or she had. In addition to overcoming the problem of overlapping and co-occurring diagnoses, this approach would allow researchers to get a better idea of which signs and symptoms would be responsive to focused neuroregulation. It would also create the potential to identify and treat prophylactically persons at high risk of developing a substance use or psychiatric disorder. The accuracy of using resting vital-sign measurements to identify such persons could be estimated indirectly by observing the protective effects of anticonvulsant prophylaxis. Of course, these studies would be based in-part upon the premise that the trait of neuronal hyperexcitability follows an autosomal dominant distribution. To verify this, whole-family diagnostic studies could be performed to determine the distribution of various substance use and psychiatric disorders. If confirmed, a classic Mendelian distribution of the neuronal hyperexcitability trait would not only add validity to the MCNH hypothesis but would also open the door to boundless possibilities through CRISPR-Cas 9 technology [116].

References

1. https://fherehab.com/addiction-statistics/
2. Facing addiction with NCADD. Facts about alcohol.
3. https://drugabusestatistics.org/teen-drug-use/.
4. https://www.nimh.nih.gov/health/statistics/mental-illness.
5. Pim cuijpers, Argyris Stringaris, Miranda Wolpert. Treatment outcomes for depression: challenges and opportunities - The Lancet Psychiatry. 2020; 20: 925-927.
6. Restak R. Mysteries of the mind. Washington, DC: National Geographic Society. 2000.
7. Butcher JN, Mineka S, Hooley JM, et al. Abnormal psychology, first Canadian edition. Toronto, ON: Pearson Education Canada. 2010.
8. Ellis A. Rational emotive behavior therapy. Corsini RJ, Wedding D, editors. Current psychotherapies. 8th ed. Belmont, CA: Thomson Brooks/Cole. 2008; 63-106.
9. Oatley K. Emotions: A brief history. Malden, MA: Blackwell Publishing; 2004.
10. Otte C. Cognitive behavioral therapy in anxiety disorders: Current state of the evidence. Dialogues Clin Neurosci. 2011; 13: 413-421.
11. Cook SC, Schwartz AC, Kaslow NJ. Evidence-based psychotherapy: Advantages and challenges. Neurotherapeutics. 2017; 14: 537-545.
12. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry. 2000; 157: 1552-1562.
13. Lee PH, Feng YA, Smoller JW. Pleiotropy and cross-disorder genetics among psychiatric disorders. Biol Psychiatry. 2021; 89: 20-31.
14. Hammen C. Stress and depression. Annu Rev Clin Psychol. 2005; 1: 293-319.
15. Amital D, Fostick L, Silberman A, et al. Serious life events among resistant and non-resistant MDD patients. J Affect Disord. 2008; 110: 260-264.
16. Gilman SE, Trinh NH, Smoller JW, et al. Psychosocial stressors and the prognosis of major depression: a test of Axis IV. Psychol Med. 2013; 43: 303-316.
17. Monroe SM, Harkness KL. Life stress, the "kindling" hypothesis, and the recurrence of depression: considerations from a life stress perspective. Psychol Rev. 2005; 112: 417-445.
18. Harkness KL, Theriault JE, Stewart JG, et al. Acute and chronic stress exposure predicts 1-year recurrence in adult outpatients with residual depression symptoms following response to treatment. Depress Anxiety. 2014; 31: 1-8.
19. Sanacora G, Treccani G, Popoli M. Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. Neuropharmacology. 2012; 62: 63-77.
20. Charney DS, Menkes DB, Heninger GR. Receptor sensitivity and the mechanism of action of antidepressant treatment. Implications for the etiology and therapy of depression. Arch Gen Psychiatry. 1981; 38: 1160-1180.
21. Andrade C, Rao NS. How antidepressant drugs act: A primer on neuroplasticity as the eventual mediator of antidepressant efficacy. Indian J Psychiatry. 2010; 52: 378-386.
22. Holsboer F, Barden N. Antidepressants and hypothalamic-pituitary-adrenocortical regulation. Endocr Rev. 1996; 17: 187-205.
23. Holsboer F. The corticosteroid receptor hypothesis of depression. Neuropsychopharmacology 2000; 23: 477-501.
24. Liu B, Liu J, Wang M, et al. From serotonin to neuroplasticity: evolvement of theories for major depressive disorder. Front Cell Neurosci. 2017; 11: 305.
25. Schäfers M, Sorkin L. Effect of cytokines on neuronal excitability. Neuroscience Letters. 2008; 437: 188-193.
26. Vezzani A, Viviani B. Neuromodulatory properties of inflammatory cytokines and their impact on neuronal excitability. Neuropharmacology. 2015; 96: 70-82.
27. Galic MA, Riazi K, Pittman QJ. Cytokines and brain excitability. Frontiers in Neuroendocrinology 2012; 33: 116-125.
28. Allen J, Romay-Tallon R, Brymer KJ, et al. Mitochondria and mood: Mitochondrial dysfunction as a key player in the manifestation of depression. Front Neurosci. 2018; 12: 386.
29. Gold PW, Kadriu B. A major role for the lateral habenula in depressive illness: physiologic and molecular mechanisms. Front Psychiatry. 2019; 10: 320.
30. Popovic J, Mestrovic A. Habenula – the role in depression. Gyrus. 2014; 3: 97-99.
31. Authement ME, Langlois LD, Shepard RD, et al. A role for corticotropin-releasing factor signaling in the lateral habenula and its modulation by early-life stress. Sci Signal. 2018; 11: 6480.
32. Aizawa H, Cui W, Tanaka K, et al. Hyperactivation of the habenula as a link between depression and sleep disturbance. Frontiers in Human Neuroscience. 2013; 7: 1-6.
33. Shepard RD, Langlois LD, Browne CA, et al. Ketamine reverses lateral habenula neuronal dysfunction and behavioral immobility in the forced swim test following maternal deprivation in late adolescent rats. Front Synaptic Neurosci. 2018; 10: 39.
34. De Kloet ER, Joëls M, Holsboer F. Stress and the brain: from adaptation to disease. Nat Rev Neurosci. 2005; 6: 463-475.
35. Neumeister A, Nugent AC, Waldeck T, et al. Neural and behavioral responses to tryptophan depletion in unmedicated patients with remitted major depressive disorder and controls. Arch Gen Psychiatry. 2004; 61: 765-773.
36. Messay B, Lim A, Marsland AL. Current understanding of the bi-directional relationship of major depression with inflammation. Biol Mood Anxiety Disord. 2012; 2: 4.
37. Pariante CM. Increased inflammation in depression: A little in all, or a lot in a few? Am J Psychiatry. 2021; 178: 1077-1079.

38. Quan N, Banks WA. Brain-immune communication pathways. Brain Behav Immun. 2007; 21: 727-735.

39. Leonard BE. The concept of depression as a dysfunction of the immune system. Cure Immunol Rev. 2010; 6: 205-212.

40. Osimo EF, Pillinger T, Rodriguez IM, et al. Inflammatory markers in depression: a meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. Brain Behav Immun. 2020; 87: 901-909.

41. Osimo EF, Baxter LJ, Lewis G, et al. Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. Psychol Med. 2019; 49: 1958-1970.

42. Bowcut JC, Weiser M. Inflammation and schizophrenia. Psychiatric Annals. 2018; 48: 237-243.

43. Boorman E, Romano GF, Russell A, et al. Are mood and anxiety disorders inflammatory diseases? Psychiatric Annals. 2015; 45: 240-248.

44. Belmaker RH, Agam G. Major depressive disorder. N Engl J Med. 2008; 358: 55-68.

45. Hasler G. Pathophysiology of depression: Do we have any solid evidence of interest to clinicians? World Psychiatry. 2010; 9: 165-161.

46. Zarate CA Jr, Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D- aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry. 2006; 63: 856-864.

47. Newport DJ, Carpenter LL, McDonald WM, et al. APA Council of Research Task Force on Novel Biomarkers and Treatments. Ketamine and other NMDA antagonists: Early clinical trials and possible mechanisms in depression. Am J Psychiatry. 2015; 172: 950-966.

48. Fleming KC, Volcheck MM. Central sensitization syndrome and the initial evaluation of a patient with fibromyalgia: a review. Rambam Maimonides Med J. 2015; 6: e0020.

49. Yunus MB. Central sensitivity syndromes: A new paradigm and group nosology for fibromyalgia and overlapping conditions, and the related issue of disease versus illness. Semin Arthritis Rheum. 2008; 37: 339-352.

50. Yunus MB. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. Semin Arthritis Rheum. 2007; 36: 339-356.

51. Fink P, Rosendal M, Dam ML, et al. Ny faelles diagnose for de funktionelle sygdomme [New unifying diagnosis of functional diseases]. Ugeskr Laeger. 2010; 172: 1835-1838.

52. Carabotti M, Scirocco A, Maselli MA, et al. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol. 2015; 28: 203-209.

53. Mittal R, Debs LH, Liu XZ, et al. Neurotransmitters: The critical modulators regulating gut-brain axis. J Cell Physiol. 2017; 232: 2359-2372.

54. Karl JP, Hatch AM, Arcidiacono SM, et al. Effects of psychological, environmental and physical stressors on the gut microbiota. Front Microbiol. 2018; 9: 2013.

55. Binder MR. The multi-circuit neuronal hyperexcitability hypothesis of psychiatric disorders. AJCEM. 2019; 7: 12-30.

56. Cerf M, Thiruvengadam N, Mormann F, et al. On-line, voluntary control of human temporal lobe neurons. Nature. 2010; 467: 1104-1108.

57. Penfield W. Epilepsy and surgical therapy. Archives of Neurology and Psychiatry. 1936; 36: 449-484.

58. Parnia S, Spearpoint K, de Vos G, et al. AWARE — AWAreness during Resuscitation — [2] A prospective study. Resuscitation. 2014; 85: 1799-1805.

59. Greyson B. After: A doctor explores what near-death experiences reveal about life and beyond. St. Martin's Essentials. New York. 2021.

60. Van Lommel P. Consciousness beyond life: The science of the near-death experience. Harper-Collins Publishers. New York. 2010.

61. Moody RA. Life after life. Mockingbird Books. 1975.

62. Fenwick P, Fenwick E. The art of dying. Continuum Books, New York. 2008.

63. Greyson B, Kelly EF, Dunseath WJR. Surge of neurophysiological activity in the dying brain. Proceedings of the National Academy of Sciences. 2013; 110: E4405.

64. Parnia S, Post SG, Lee MT, et al. Guidelines and standards for the study of death and recalled experiences of death—a multidisciplinary consensus statement and proposed future directions. Annals of the New York Academy of Sciences. 2022; 1511: 5-21.

65. Al-Shargie F, Kiguchi M, Badruddin N, et al. Mental stress assessment using simultaneous measurement of EEG and fNIRS. Biomedical Optics Express. 2016; 7: 3882-3898.

66. Mazarati A, Shin D, Auvin S, et al. Kindling epileptogenesis in immature rats leads to persistent depressive behavior. Epilepsy Behav. 2007; 10: 377-383.

67. Van der Gaag M. A neuropsychiatric model of biological and psychological processes in the remission of delusions and auditory hallucinations. Schizophr Bull. 2006; 32: S113-S122.

68. Rose GM, Diamond DM, Pang K, et al. Primed burst potentiation: lasting synaptic plasticity invoked by physiologically patterned stimulation. In: Haas HL, Buzsàki G. (eds) Synaptic plasticity in the hippocampus. Springer, Berlin, Heidelberg. 1988.

69. Ferreira MAR, O'Donovan MC, Sklar P. Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. Nat Genet. 2008; 40: 1056-1058.

70. Yuan A, Yi Z, Wang Q, et al. ANK3 as a risk gene for schizophrenia: new data in Han Chinese and meta analysis. Am J Med Genet B Neuropsychiatr Genet. 2012; 159: 997-1005.

71. Green EK, Grozeva D, Jones I, et al. Wellcome Trust Case Control Consortium, Holmans PA, Owen MJ, O'Donovan MC, Craddock N. The bipolar disorder risk allele at

CACNA1C also confers risk of recurrent major depression and of schizophrenia. Mol Psychiatry. 2010; 15: 1016-1022.

72. Lopez AY, Wang X, Xu M, et al. Ankyrin-G isoform imbalance and interneuronopathy link epilepsy and bipolar disorder. Mol Psychiatry. 2017; 22: 1464-1472.
73. Binder MR. New hypothesis unifies previous theories of psychopathology and identifies core biological abnormality in psychiatric disorders. AJCEM. 2022; 10: 23-37.
74. Binder MR. Neuronal hyperexcitability: The elusive but modifiable instigator of disease. AJCEM 2022; 10: 1-7.
75. Grunze HCR. The effectiveness of anticonvulsants in psychiatric disorders. Dialogues Clin Neurosci. 2008; 10: 77-89.
76. Hirschfeld RM. History and evolution of the monoamine hypothesis of depression. J Clin Psychiatry. 2000; 61: 4-6.
77. Binder MR. The neuronal excitability spectrum: A new paradigm in the diagnosis, treatment, and prevention of mental illness and its relation to chronic disease. AJCEM. 2021; 9: 187-203.
78. Henkel AW, Welzel O, Groemer TW, et al. Fluoxetine prevents stimulation- dependent fatigue of synaptic vesicle exocytosis in hippocampal neurons. Journal of Neurochemistry. 2010; 114: 697-705.
79. El-Mallakh RS, Vöhringer PA, Ostacher MM, et al. Antidepressants worsen rapid- cycling course in bipolar depression: A STEP-BD randomized clinical trial. Journal of Affective Disorders. 2015; 184: 318-321.
80. Britton JW, Shih JJ. Antiepileptic drugs and suicidality. Drug, Healthcare and Patient Safety. 2010; 2: 181-189.
81. Fergusson D, Doucette S, Glass KC, et al. Association between suicide attempts and selective serotonin reuptake inhibitors: Systematic review of randomised controlled trials. BMJ. 2005; 330: 396-402.
82. Braun C, Bschor T, Franklin J, et al. Suicides and suicide attempts during long-term treatment with antidepressants: A meta-analysis of 29 placebo-controlled studies including 6,934 patients with major depressive disorder. Psychother Psychosom. 2016; 85: 171-179.
83. Juurlink DN, Mamdani MM, Kopp A, et al. The risk of suicide with selective serotonin reuptake inhibitors in the elderly. Am J Psychiatry. 2006; 163: 813-821.
84. Healy D. Let Them Eat Prozac: The unhealthy relationship between the pharmaceutical industry and depression. New York: University Press. 2004.
85. Binder MR. A pathophysiolgically-based approach to the treatment and prevention of mental illness and its related disorders. AJCEM. 2021; 9: 223-232.
86. Yizhar O, Fenno LE, Deisseroth K. Neocortical excitation/inhibition balance in information processing and social dysfunction. Nature. 2011; 477: 171-178.
87. http://hargreaves.swong.webfactional.com/kindle.html
88. Khedr EM, Elserogy Y, Fawzy M. Effect of psychotropic drugs on cortical excitability of patients with major depressive disorders: A transcranial magnetic stimulation study. Psychiatry Research. 2020; 291: 113287.
89. Akiskal HS. The bipolar spectrum: new concepts in classification and diagnosis. In: Grinspoon L, editor. Psychiatry Update; The American Psychiatric Association Annual Review. Washington DC: American Psychiatric Press. 1983; 2: 271-292.
90. Koukopulos A, Reginaldi P, Laddomada G, et al. Course of the manic-depressive cycle and changes caused by treatment. Pharmakopsychiatr Neuropsychopharmakol. 1980; 13: 156-167.
91. Koukopoulos A, Tundo A. A mixed depressive syndrome. Clin Neuropharmacol. 1992; 15: 626A-627A.
92. Mason BJ, Quello S, Begovic A. Gabapentin treatment for alcohol dependence: A randomized controlled trial. JAMA Intern Med. 2014; 174: 70-77.
93. Kranzler HR, Feinn R, Morris P, et al. A meta-analysis of the efficacy of gabapentin for treating alcohol use disorder. Addiction. 2019; 114: 1547-1555.
94. Anton RF, Latham P, Voronin K, et al. Efficacy of gabapentin for the treatment of alcohol use disorder in patients with alcohol withdrawal symptoms: A randomized clinical trial. JAMA Intern Med. 2020; 180: 728-736.
95. Pande AC, Davidson JR, Jefferson JW, et al. Treatment of social phobia with gabapentin: a placebo-controlled study. J Clin Psychopharmacol. 1999; 19: 341-348.
96. Pande AC, Pollack MH, Crockatt J, et al. Placebo-controlled study of gabapentin treatment of panic disorder. J Clin Psychopharmacol. 2000; 20: 467-471.
97. Sokolski KN, Green C, Maris DE, et al. Gabapentin as an adjunct to standard mood stabilizers in outpatients with mixed bipolar symptomatology. Ann Clin Psychiatry. 1999; 11: 217-222.
98. Binder MR. Mind-brain dynamics in the pathophysiology of psychiatric disorders. Am J Psychiatry and Neurosci. 2022; 10: 48-62.
99. Latvala A, Kuja-Halkola R, Rick C, et al. Association of resting heart rate and blood pressure in late adolescence with subsequent mental disorders: A longitudinal population study of more than 1 million men in Sweden. JAMA Psychiatry. 2016; 73: 1268-1275.
100. Blom EH, Serlachius E, Chesney MA, et al. Adolescent girls with emotional disorders have a lower end-tidal CO2 and increased respiratory rate compared with healthy controls. Psychophysiology. 2014; 51: 412-418.
101. Binder MR. FLASH Syndrome: tapping into the root of chronic illness. AJCEM. 2020; 8: 101-109.
102. Davies M. The role of GABAA receptors in mediating the effects of alcohol in the central nervous system. J of Psychiatry Neurosci. 2003; 28: 263-274.

103. Hoffman PL, Rabe CS, Moses F, et al. N-methyl-D-aspartate receptors and ethanol: inhibition of calcium flux and cyclic GMP production. J Neurochem. 1989; 52: 1037-1940.

104. Rosenberg EC, Tsien RW, Whalley BJ, et al. Cannabinoids and epilepsy. Neurotherapeutics. 2015; 12: 747-768.

105. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ9-tetrahydrocannabinol, cannabidiol and Δ9-tetrahydrocannabivarin. British Journal of Pharmacology. 2008; 153: 199-215.

106. Silvestro S, Mammana S, Cavalli E, et al. Use of cannabidiol in the treatment of epilepsy: Efficacy and security in clinical trials. Molecules. 2019; 24: 1459.

107. Du Q, Liao Q, Chen C, et al. The Role of transient receptor potential vanilloid 1 in common diseases of the digestive tract and the cardiovascular and respiratory system. Front Physiol. 2019; 10: 1064.

108. Substance Abuse and Mental Health Services Administration, Office of Applied Studies, Rockville, MD. The NSDUH Report: Substance use and dependence following initiation of alcohol or illicit drug use. 2008.

109. Pearce JMS. Bromide, the first effective antiepileptic agent. Journal of Neurology, Neurosurgery & Psychiatry. 2001; 72.

110. Lado FA, Moshé SL. How do seizures stop? Epilepsia. 2008; 49: 1651-1654.

111. Lambrecq V, Villég F, Marchal C, et al. Refractory status epilepticus: electroconvulsive therapy as a possible therapeutic strategy. Seizure. 2012; 21: 661-664.

112. Kamel H, Cornes SB, Hegde M, et al. Electroconvulsive therapy for refractory status epilepticus: a case series. Neurocritical Care. 2010; 12: 204-210.

113. Hillhouse TM, Porter JH. A brief history of the development of antidepressant drugs: from monoamines to glutamate. Exp Clin Psychopharmacol. 2015; 23: 1-21.

114. Ramachandraih CT, Subramanyam N, Bar KJ, et al. Antidepressants: from MAOIs to SSRIs and more. Indian Journal of Psychiatry. 2011; 53: 180-182.

115. Kreston R. The psychic energizer! The serendipitous discovery of the first antidepressant - Body Horrors. 2016.

116. Binder MR. Exploring the potential of preventing human disease by genetically altering the excitability of the neurological system. Am J Psychiatry and Neurosci. 2023; 11: 22-29.

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