American Journal of Clinical and Experimental Medicine
2021; 9(5): 157-167
http://www.sciencepublishinggroup.com/j/ajcem
doi: 10.11648/j.ajcem.20210905.16
ISSN: 2330-8125 (Print); ISSN: 2330-8133 (Online)

Review Article

Neuronal Hyperexcitability: Significance, Cause, and Diversity of Clinical Expression

Michael Raymond Binder

Department of Psychiatry, North Shore University Health System, Highland Park, USA

Email address:
mbinder@drmichaelbinder.com

To cite this article:
Michael Raymond Binder. Neuronal Hyperexcitability: Significance, Cause, and Diversity of Clinical Expression. *American Journal of Clinical and Experimental Medicine.* Vol. 9, No. 5, 2021, pp. 157-167. doi: 10.11648/j.ajcem.20210905.16

Received: September 8, 2021; **Accepted**: September 30, 2021; **Published**: October 15, 2021

Abstract: Although the pathophysiology of psychiatric disorders remains unclear, an emerging hypothesis contends that most of the common psychiatric disorders are rooted in an inherent hyperexcitability of the neurological system. Particularly under the influence of stress, too many neurons fire for too long, resulting in pathologically severe and persistent symptoms such as anxiety, depression, irritability, insomnia, inattention, and obsessional thinking. However, these symptoms are just a small sampling of the many ways that neuronal hyperexcitability can be expressed. According to the Multi-Circuit Neuronal (MCNH) Hypothesis of Psychiatric Disorders, the trait can also be expressed as overly aggressive behavior, disruptive behavior, risky behavior, promiscuous behavior, avoidant behavior, self-injurious behavior, deviant behavior, addictive behavior, and criminal behavior. In essence, any behavioral extreme is likely to be rooted in an inherent hyperexcitability of the neurological system. The importance of recognizing this is that the abnormality, though highly treatable, is commonly overlooked and either mismanaged or poorly managed. Also, there is emerging evidence that the neuronal hyperexcitability trait, which appears to be heritable as a single nucleotide polymorphism, may be detectable by simply measuring one's resting vital signs. If proven to be correct, these findings could incentivize carriers to develop prophylactic strategies early in life. The importance of this is immense, not only because it could reduce the risk of developing psychiatric and substance use disorders but also because it could have a protective effect against developing any of a wide range of general medical conditions, such as diabetes, high blood pressure, heart disease, cancer, and dementia. This article explores the many faces of neuronal hyperexcitability in an effort to increase awareness of this highly prevalent but elusive neurophysiological abnormality.

Keywords: Neuronal Hyperexcitability, Clinical Manifestations, Pathophysiology of Psychiatric Disorders, Bipolar Spectrum Disorders, Psychotic Disorders, Anticonvulsants, Neuroregulators

1. Introduction

The quest to understand abnormal behavior dates back to early civilization, as psychological and behavioral abnormalities have always been and continue to be a leading cause of human morbidity and mortality. From personal suffering and domestic violence to civil unrest and world wars, the emotional and behavioral extremes of specific individuals has led to more emotional pain and physical suffering than the dying process itself. Yet despite numerous psychological and behavioral theories, none have been able to fully explain why some persons deviate from acceptable norms and develop psychiatric and behavior pathology.

However, an emerging hypothesis contends that a subtle physiological abnormality, described as "neuronal hyperexcitability," may be the underlying driver of nearly all psychological and behavioral pathology [1, 2]. According to the Multi-Circuit Neuronal Hyperexcitability (MCNH) Hypothesis of Psychiatric Disorders [1], an inherent hyperexcitability of the neurological system causes psychological and emotional responses to be abnormally intense and persistent, thus creating a natural tendency for the individual's psychological and behavioral responses to be equally extreme (Figure 1). It also appears that over time, the abnormality drives the development of attitudes and defense mechanisms that are geared more toward emotional self-defense than practical benefit, thus increasing the risk of

personality disorders. Of course, there are numerous other factors that can contribute to the development of abnormal thinking and behavior; however, the trait of neuronal hyperexcitability appears to be the most important of them as demonstrated by the observation that a predictable proportion of the descendants of affected individuals develop psychological and behavioral pathology, whereas a predictable proportion of their other children do not [1, 3]. Based on a careful clinical assessment of hundreds of affected families, the neuronal hyperexcitability trait appears to be autosomal dominant and additive, as descendants with various psychological, emotional, and behavioral disturbances consistently appear in a classic autosomal dominant distribution whereas both unaffected and more seriously affected descendants appear in a classic autosomal recessive distribution (Figure 2). Then again, the relative degree of influence of the neuronal hyperexcitability trait would depend on the degree of genetic loading: those who inherit an allele from both parents would be more highly influenced by the trait than those who inherit only one allele (Figure 2). Practically speaking, this variability is what seems to obscure the autosomal dominant nature of the neuronal hyperexcitability trait and the high prevalence that it has in the general population. The goal of this article is to describe the diversity of ways that the neuronal hyperexcitability trait can manifest clinically and to discuss the practical importance of recognizing its many faces.

2. Many Disorders; Few Symptoms

Although psychiatric disorders are said to be many in number, the array of symptoms that characterize them is actually quite small. Most psychiatric disorders involve some combination of anxiety, depression, irritability, difficulty concentrating, loss of insight, and abnormal sleep. Moreover, none of these symptoms are inherently abnormal; they are said to be pathological only when they become severe and persistent.

To understand what causes the aforementioned symptoms to escalate to pathological levels, let us recall that every thought and emotion is processed by neurons of the brain. It follows, therefore, that cognitive-emotional hyper-reactivity would involve a hyper-reactivity of the associated neurons and circuits (Figure 1). That the neurological systems of some persons, as described by the MCNH hypothesis, are inherently prone to this hyper-reactivity is suggested by the link between constitutionally-elevated vital signs and an increased vulnerability to mental illness [4]. Just as those who are more vulnerable to mental illness tend, even in the absence of specific stressors, to be preoccupied with abstract worries and fears [5, 6], their sympathetic nervous systems, which are tightly integrated with the cognitive-emotional system [7], are chronically activated above what would be considered normal basal activity [5, 8]. Thus, it is hypothesized that the same physiological abnormality that drives the vital-sign elevations drives the psychiatric symptoms of which they are predictive [4]. This conceptualization, which is consistent with the long-held diathesis-stress model of mental illness, could be used to explain virtually every psychiatric disorder. Note, however, that the underlying neurophysiological abnormality, like the letters of the alphabet, could be expressed in an almost limitless number of ways. That is presumably because there are many other factors that help shape the phenotypic expression of the trait. Such factors include, among others, the unique architecture of an individual's brain, one's internal and external environmental influences, and the willful choices of the individual. The most important of these, however, appears to be the trait of neuronal hyperexcitability because the related cognitive-emotional abnormalities, when conceptualized as different expressions of the same neurophysiological abnormality, appear in a classic autosomal distribution [1, 3].

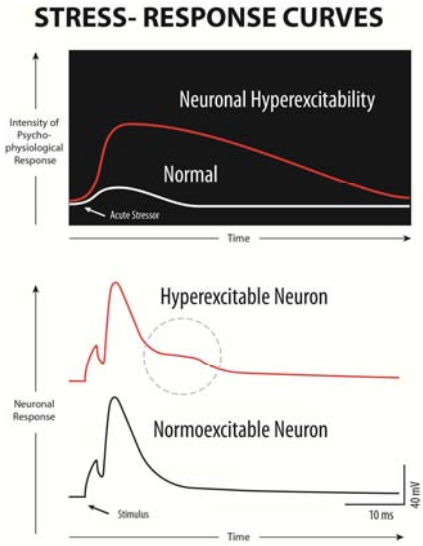

Figure 1. *Stress-response curves illustrating 1) pathological cognitive-emotional response in comparison to a normal response; 2) electrical response of a hyperexcitable neuron in comparison to a normal neuron. Note the striking similarity between the cognitive-emotional response curves and the neuronal response curves. Adapted from Lopez-Santiago LF, et al. "Neuronal Hyperexcitability in a Mouse Model of SCN8A Epileptic Encephalopathy." [9].*

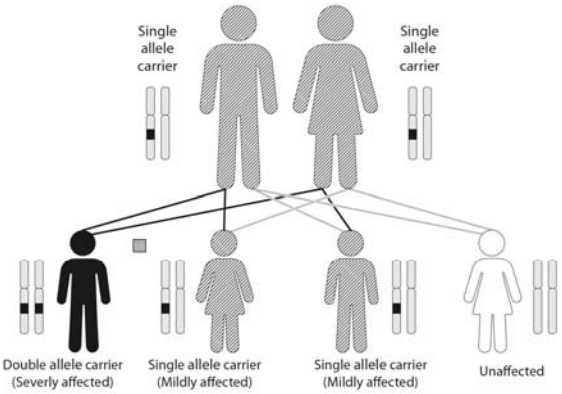

Figure 2. *Family pedigree illustrating the autosomal dominant and additive nature of the neuronal hyperexcitability trait. The grey silhouettes depict heterozygous carriers, the black silhouette depicts a homozygous carrier, and the white silhouette depicts no inheritance of the trait.*

3. The Many Faces of Neuronal Hyperexcitability

3.1. Mood Disorders

Among the most common ways that the trait of neuronal hyperexcitability is thought to be expressed is the spectrum of mood disorders from unipolar depression to bipolar disorder [1, 2]. In most cases, depressive symptoms are initiated by the mind. A major loss, a personal failure, or a sense of rejection can cause the mind to start ruminating. This, in turn, repeatedly activates the neurons and circuits that are associated with those thoughts and emotions [10]. As this occurs, the involved neurons and circuits repeatedly stimulate the same thoughts and emotions, thus creating a depressive dialogue between the mind and the brain. Normally, this dialogue continues only until the mind resolves the issue or, for whatever reason, decides to move on to thinking about something else. For some persons, however, the ruminating continues, even to the point of continuing against the person's will. From the perspective of the MCNH hypothesis, this is driven by two factors. The first is that hyperexcitable neurons are unable to self-regulate. Consequently, the involved circuitry remains active despite the reduction in cognitive and mood-specific mental drive that normally accompanies a desire to move on to thinking about something else [11, 12]. The second factor that tends to perpetuate the ruminating is that the hyperactive cognitive and mood-specific neurons, rather than becoming refractory to further activation, become increasingly active the more they are stimulated. As a result of this process, known as "primed burst potentiation" [13], the hyperactive circuitry drives the mind to continue to ruminate, and, over time, the escalating dialogue between the mind and the brain could begin to spin out of control. This is presumably what can lead to suicidality, homocidality, and other behavioral extremes. In some cases, the inherent excitability of the neurological system may be so high that select populations of neurons cause the individual to ruminate spontaneously [5]. This is the MCNH explanation for persistent depression, frequently recurring episodes of depression, spontaneous hypomanic or manic episodes, and other persistent or recurrent cognitive-emotional symptoms. Another possibility is that hyperactivity in one circuit could aberrantly fuel hyperactivity in a circuit that would normally be hypoactive in a given cognitive-emotional state [14]. This process, which is akin to a short-circuit in a wired electrical system, is the MCNH explanation for the rapid and sometimes dramatic changes in mood and other symptoms that characterize disorders in the bipolar spectrum [14].

3.2. Anxiety Disorders

3.2.1. Generalized Anxiety and Panic Attacks

Just as persistent hyperactivity in depressive circuits can cause clinical depression, persistent hyperactivity in anxiety circuits can cause persistent anxiety. Periodically, hyperactive feeder circuits, particularly if fueled by an anxiety-provoking cue or stimulant-retype drug, could drive a surge of activity in the hypothalamic-pituitary axis, thus causing a flood of epinephrine and cortisol to be released from the adrenal glands. This is the MCNH explanation for panic attacks.

3.2.2. Obsessions and Compulsions

Although obsessive ruminations can be driven by the need to make an important decision under complex circumstances, the abnormal persistence of such ruminations, particularly if ego-dystonic and unrelated to any extraordinary circumstances, are indicative of neuronal hyperexcitability [15]. As in mood disorders, what is hypothetically happening is that persistent activity in specific brain circuits or networks of circuits is causing the individual to keep dwelling on the associated thoughts and feelings [16, 17]. In an effort to resolve the matter, the individual may begin seeking ways to undo the disturbing thought content, such as repeated hand-washing, lock-checking, or second-guessing one's self. Unfortunately, however, the tendency for the hyperexcitable circuits to keep firing prevents the mind from resolving the issue, and so the individual keeps washing, checking, or second-guessing.

3.2.3. Post-Traumatic Stress Disorder (PTSD)

PTSD is characterized by a complex of recurrent memories about a traumatic event; recurrent flashbacks about the event; recurrent distressing dreams about the event; marked psychological reactions to cues about the event; and avoidance behavior pertaining to the event. Taken together, these symptoms can be viewed as psychophysiologically-driven cognitive-emotional reverberations of an intense psychophysiological experience. Hypothetically, the intensity and duration of this phenomenon would be dictated, in part, by the excitability of the neurological system, thus suggesting that persons with higher baseline levels of neuronal excitability would be more vulnerable to developing PTSD. They would also be more vulnerable to developing other symptoms that are hypothesized to be rooted in neuronal hyperexcitability, such as anxiety, depression, and insomnia, thus explaining why patients with PTSD commonly have preexisting psychiatric symptoms or disorders [18].

3.4. Hormonally-Related Psychiatric Disorders

Premenstrual and postpartum psychiatric symptoms, which include premenstrual syndrome, premenstrual dysphoric disorder, and postpartum depression, are hypothetically different manifestations of the rapid loss of progesterone's anticonvulsant effects during the premenstrual and postpartum periods [1, 19]. As the progesterone level falls, the brain becomes increasingly excitable, thus increasing the potential for psychiatric symptoms to emerge [19]. These effects would tend to be most clinically apparent in women whose neurological systems were inherently hyperexcitable, thus explaining why women with pre-pregnancy psychiatric symptoms are at an increased risk of developing postpartum depression, postpartum psychosis, and other postpartum psychiatric symptoms [1].

3.5. Inflammation-Related Psychiatric Disorders

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and other psychiatric manifestations of the inflammatory response are hypothetically the consequence of the increased neuronal excitability that is conferred by inflammatory cytokines [20, 21] in combination with the increase in neuronal activity that is driven by the psychological, emotional, and physical stress of being ill. This idea is supported by a large study in which a group of researchers from the University of Copenhagen in Denmark found that among children who had one or more positive streptococcal tests, the risk was increased not only for developing OCD and tic disorders but any psychiatric disorder [22].

3.6. Chronic Illnesses

Although psychiatric symptoms, by virtue of their exquisite sensitivity to neuronal excitation, are typically the first subjective markers of the neuronal hyperexcitability trait [4], neuronal hyperexcitability can, via its disruptive effects on immune and metabolic processes, drive the development of any of a wide range of chronic illnesses [4].

Because the nervous system can influence the immunological system through both neural and non-neural pathways [23], hyperexcitability of the neurological system can drive hyperactivity in the immunological system. The resulting increase in cytokine production can then make the neurological system even more hyperexcitable [24-26], thus leading to a vicious cycle of mutual overstimulation between the two systems. Aside from being pro-inflammatory, this vicious cycle can complicate recovery from infection and, in more severe cases, drive the development of autoimmune diseases, such as type-1 diabetes, Hashimoto's thyroiditis, and rheumatoid arthritis [3].

Similarly, the disruptive effects of neuronal hyperexcitability on metabolic function [27, 28] can drive the development "metabolic syndrome," a cluster of physiological abnormalities that include hypertension, obesity, insulin resistance, and dyslipidemia [27, 28]. These abnormalities have been linked to the development of serious chronic illnesses, such as high blood pressure, cardiovascular disease, cancer, and dementia [29, 30]. The idea that neuronal hyperexcitability tends to hasten the onset and progression of these illnesses helps explain why persons with severe mental illness tend to die at a much earlier age than the general population [31]. The tendency for neuronal hyperexcitability to drive a subtle elevation in resting heart and respiratory rates also helps explain why these vital sign-elevations tend to be predictive of the aforementioned health conditions [4].

3.7. Impulse Control Disorders

3.7.1. Pyromania, Pathological Gambling, Kleptomania, Trichotillomania

From the perspective of the MCNH hypothesis, impulse control disorders are the consequence of two fundamental factors. One is the desire to either increase the emotional pleasure (as in pyromania and pathological gambling) or decrease the emotional pain (as in kleptomania and trichotillomania) that is driven by pathologically elevated firing in euphoria-related or dysphoria-related circuits in the brain, respectively. The other is the inability to fully assess the potential consequences of the actions being contemplated because the mind, being bombarded by too many distracting (and often extraneous) signals from the hyperexcitable brain, is unable to adequately think things through before taking action.

3.7.2. Hyperactivity, Inattention, and Impulsivity (ADHD)

Because neuronal hyperexcitability drives neuronal hyperactivity, the mind of the affected individual tends to be bombarded by too many neurological signals at once. This has a natural tendency to cause physical *hyperactivity*, although it can also cause physical paralysis if the mind is unable to take action before it becomes distracted by another thought. The overabundance of mental stimulation can also cause the mind to be easily distracted or *inattentive*, and it can interfere with the ability to fully think things through before taking action, thus explaining the *impulsivity* that completes the triad of attention deficit hyperactivity disorder (ADHD).

3.7.3. Tourette's Syndrome

The semi-voluntary movements and vocalizations that characterize Gilles de la Tourette syndrome hypothetically represent repeated impulses that are initiated by the hyperexcitable brain but permitted by the unconscious mind in an effort to discharge some of the nervous tension that is created by pathologically hyperactive neural circuits [17]. This conceptualization is supported by functional imaging studies, which show that in patients with Tourette's, several areas of the brain are chronically hyperactive in comparison to healthy controls [32]. This hyperactivity would tend to be even more prominent if the mind were under stress, thus explaining the link between Tourette's syndrome, emotional stress, and other psychiatric disorders. Nearly 80% of patients with Tourette's have been diagnosed with another mental illness or developmental disability [33].

3.8. Psychotic and Delusional Thinking

Healthy reality testing is dependent on the ability to distinguish between internally-driven thoughts and emotions and externally driven thoughts and emotions. Hypothetically, what makes this possible is that input from the eyes, ears, integument, and other sensory organs carries a stronger neurological signal than internally-generated thoughts and emotions. Thus, if the level of electrical activity in specific sensory processing systems of the brain were to increase to the level that would normally be stimulated by sensory input, the distinction between internal and external reality could become blurred. For example, aberrant discharges from neurons in the auditory processing system could cause the person to think that the auditory nerve were being stimulated, thus leading to auditory hallucinations (Figure 3). Likewise, aberrant discharges from neurons in the visual processing system could

cause the person to think that the optic nerve were being stimulated, thus leading to visual hallucinations, etc… Although such aberrant signaling could potentially occur in anyone, it would be more likely to occur in persons whose neurological systems were hyperexcitable. This conceptualization is supported by a recent study that found that auditory hallucinations in schizophrenia were exaggerated versions of perceptual distortions that are occasionally experienced by persons who do not have schizophrenia [34]. The researchers found that the perceptual distortions were more pronounced in those participants whose neurons were releasing more dopamine, a neurotransmitter that helps modulate the processing of auditory signals [35]. From the perspective of the MCNH hypothesis [1], the excess dopamine release would be driven by hyperactivity in dopaminergic circuitry. Similarly, other forms of psychosis, such as paranoia and delusional thinking, could occur when the intensity of internally-generated, circuit-specific signaling began to approach the intensity of signaling that would normally be driven by the higher processing of visual, auditory, tactile, and other sensory input. In other words, the hyperexcitable brain could amplify purely internal processes to the point that the mind, believing that the impetuses were coming from the environmental, began to weave the content into narratives to explain what it believed to reflect external reality. The risk of such aberrant signaling would be increased by intrapsychic stress, stimulant-type drugs, and any factor that increased excitation in the brain, thus explaining why psychotic symptoms are more likely to develop under such circumstances.

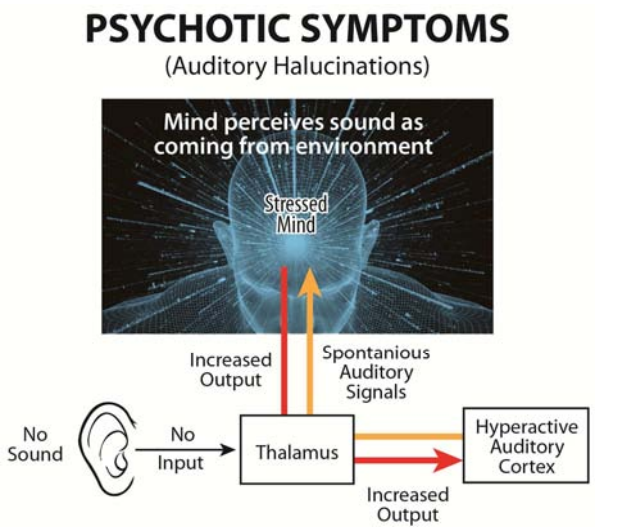

Figure 3. *Illustration of the hypothetical means by which auditory hallucinations occur. In the diagram, pathological hyperactivity in auditory circuits is mistakenly perceived as sound coming from the environment, Because intrapsychic stress activates brain circuits, psychotic symptoms are more likely to occur during times of stress, particularly if the brain is inherently hyperexcitable.*

A related phenomenon that could likewise be reflective of neuronal hyperexcitability is the odd separation or "schism" between thoughts and feelings from which the term "schizophrenia" was derived. What hypothetically could cause this type of inappropriate affect is that cognitive functions that would normally activate the corresponding emotional circuitry would fail to do so because scattered hotspots of neural activity were competing for dominance [1, 36]. As a result, the person's emotions, rather than being dictated by the thought content, would be dictated by aberrant firing in limbic circuitry. It is also possible that the thought content, rather than being dictated by the emotions, could be dictated by aberrant firing in cognitive circuitry. In some cases, the willful intentions of the individual could be completely usurped by this abnormally intensive, spontaneous, electrical activity. Such chaotic brain signaling would be more likely to occur in persons with very high levels of neuronal excitability, such as those with schizophrenia, bipolar disorder, and other severe mental disorders. That such patients have exceptionally high levels of neuronal excitability is corroborated by the elevated risk of seizures that they have in comparison to those with less debilitating psychiatric disorders [37-39].

3.9. Functional Disorders

3.9.1. Functional Physical Symptoms

Functional physical symptoms are, by definition, devoid of any demonstrable physical abnormality that could sufficiently explain them. Though very common and sometimes highly disabling, functional symptoms had traditionally been viewed as being purely psychological in nature. In recent years, however, it has become increasingly apparent that functional symptoms, which tend to be exacerbated by stress, may be explained by a phenomenon called "central sensitivity." According to the central sensitivity hypothesis, an inciting factor, such as an allergen, a toxin, a physical injury, or an emotionally traumatic event, increases the sensitivity of the central nervous system to subsequent stressors, thereby leading to intermittent and, in some cases, chronic conditions, such as migraine headache, temporomandibular joint syndrome, myofacial pain syndrome, irritable bowel syndrome, fibromyalgia, and other chronic pain syndromes [40]. It is also believed to explain a wide range of psychiatric conditions, such as generalized anxiety disorder, major depressive disorder, bipolar disorder, panic disorder, and post-traumatic stress disorder [41, 42]. A similar nosology, referred to as "body distress syndrome" likewise unifies a wide range of functional disorders under a single title [43]. What remains unexplained, however, is why some persons are more vulnerable to developing these syndromes. According to the MCNH hypothesis, the sensitizing event or illness is not the causal factor but rather an exacerbation of a more fundamental abnormality. That abnormality is a genetically-based hyperexcitability of the neurological system. The observation that all of the aforementioned functional symptoms tend to run in families, that they can completely remit during low-stress periods, and that they can readily be explained by the MCNH hypothesis adds validity to this explanation.

3.9.2. Somatoform Disorders

Because neuronal hyperexcitability causes the mind to keep

thinking, various worries and preoccupations can easily develop. In some cases, this can involve somatic preoccupations, resulting in obsessive concerns about the physical functioning of the body. The risk of this is increased by the possibility that excess electrical output by the hyperexcitable brain could overstimulate various organs and, likewise, that the sensory feedback from those organs could be abnormally amplified by the hyperexcitable neurological system. Thus, in addition to causing various worries and preoccupations, neuronal hyperexcitability could drive physiological changes that become actual physical symptoms. This could help explain why such patients have so much difficulty accepting reassurance, even from a qualified healthcare professional.

3.9.3. Chronic Pain Disorders

Although chronic pain can sometimes be rooted in an identifiable physical abnormality, an inherent hyperexcitability of the neurological system could, as discussed in regard to somatoform disorders, abnormally amplify the sensory signals, thus increasing the perceived level of pain [40, 44] (Figure 4). In addition, hyperexcitability of limbic and cortical neurons could abnormally amplify negative emotions and recurrent thoughts about the pain and its implications. This could help explain why injury-related pain is often difficult to distinguish from functional pain and suffering. In the case of chronic musculoskeletal pain, which is the most common form of chronic pain [40, 44], neuronal hyperexcitability could also be contributing to the development of the pain (i.e., by hastening the development of hypertonic spasm) [45, 46]. In such cases, neuronal hyperexcitability could be both initiating the pain and compounding the pain, thus helping to explain why chronic pain can be such a medical-psychiatric conundrum.

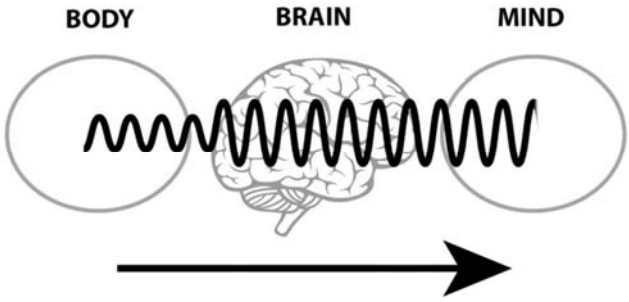

Figure 4. *Schematic illustration of the abnormal amplification of pain (and other sensory input) by the hyperexcitable brain.*

3.9.4. Conversion Disorders

In a conversion disorder, the patient displays a deficit in voluntary motor or sensory function in an effort to avoid the experience of intensely distressing emotions. Although the choice of symptoms has a rational basis, the logical remains unconscious in order to protect the individual from having to face the fact that he or she is being deceptive. Like other primitive defense mechanisms, such as denial, regression, and acting out, conversion reactions would be more likely to occur in persons who were more emotionally sensitive or who had experienced severe emotional trauma prior to developing more mature coping mechanisms. This would help explain why conversion disorders are commonly associated with child abuse and personality disorders (most notably histrionic personality disorder). They are also commonly associated with seizure disorders [47] in the form of non-epileptic psychogenic seizures, also known as "pseudoseizures" [48]. Their association with severe emotional trauma and other disorders that are themselves thought to be promoted by neuronal hyperexcitability suggests that conversion disorders are another manifestation of the neuronal hyperexcitability trait.

3.10. Other Disorders

3.10.1. Chronic Insomnia

Sleep depends on the ability of the brain to shut off, or at least partially reduce the extent to which the mind can process thoughts and feelings neurologically. Hypothetically, the relevant neuroregulatory mechanism tends to be overridden as hyperactive circuits keep firing despite the mind's desire to stop thinking and fall asleep.

3.10.2 Substance Use Disorders

Although there are many factors that contribute to the development of a substance use disorder, two consistent observations combine to suggest that an inherent hyperexcitability of the neurological system is the most important of them. The first is that alcohol and marijuana, the two most popular abusive substances, have potent anticonvulsant effects. Stimulant-type drugs are actually less preferred 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 [49], only 25% of those who had used crack cocaine in the previous one-to-two-year period had reused one year later, whereas roughly three quarters of those who had used alcohol, and more than one-half of those who had used marijuana, had reused during the same follow-up period. The second observation is the high comorbidity between substance use disorders and psychiatric disorders. According to reports published in the Journal of the American Medical Association [50], 37% of those who abuse alcohol, and 53% of those who abuse other drugs have at least one serious mental health condition. The emphasis here is on the word "serious." Assuming that those with serious mental health conditions are just the tip of the iceberg, then many more must have mild to moderate mental health conditions. This suggests that virtually all persons who abuse alcohol or other drugs have some type of mental health condition.

Historically, the drugs that have been used most commonly to treat these conditions—phenobarbital, diazepam, alprazolam, lorazepam, depakote, lithium, chlorpromazine, haloperidol, and, more recently, the atypical antipsychotics and serotonin reuptake inhibitors, likewise have brain-calming effects. Thus, the drugs that users prefer and the drugs that are most commonly prescribed to treat their substance misuse all have this one thing in common—they calm the brain. In other

words, they combat neuronal hyperexcitability. Hypothetically, the primary reason that substance use disorders are so difficult to treat is that neuronal hyperexcitability is a biological trait rather than a temporary state. Hence, the key to treating substance use disorders would be to identify and reverse the vulnerability trait. This could help explain why gabapentin, a well-tolerated and inexpensive anticonvulsant drug, is skyrocketing in popularity both as a prescription drug and as an illicit drug [3].

3.10.3. Feeding Disorders of Infancy and Early Childhood

Although there are a variety of medical conditions that could potentially prevent an infant or child from maintaining adequate food intake, the most common among them, based on the relatively high frequency of psychiatric conditions in comparison to other medical conditions [51], is likely to be an inherent hyperexcitability of the neurological system. The link between neuronal hyperexcitability and feeding disorders tends to be obscured by the fact that one or both of the parents are themselves carriers of the neuronal hyperexcitability trait. When the associated psychiatric disturbances prevent them from being effectual caregivers, the assumption is that the parental neglect is the cause of the infant's fussiness and failure to thrive when in fact the problem is usually much more complex. The child's natural fussiness can make caregiving more challenging for the parent, and the parent's inappropriate responses can make the child even more fussy, particularly if the child inherited the neuronal hyperexcitability trait. Added to this are the physiological effects that neuronal hyperexcitability can have on the child's digestive system, beginning with taste hypersensitivity and possibly including the stomach and intestines secondary to an overabundance of neurological output from the hyperexcitable brain to those organs. Added to this would be the overabundance of neurological feedback from those organs to the brain and the further amplification of that feedback by the hyperexcitable brain before it is interpreted by the mind.

3.10.4. Eating Disorders in Adolescents and Adults

In an effort to control their obsessive thoughts and unpredictable emotions, some persons with neuronal hyperexcitability, most commonly young women under the influence of cultural expectations, hypothetically learn to manipulate food as a proxy to manipulating the reverberating and migrating loci of hyperactivity in their hyperexcitable brains. That the neurological systems of such persons are inherently hyperexcitable is suggested by the high comorbidity between eating disorders and other psychiatric disorders. In one study, 97% of female eating disorder inpatients were found to have one or more co-morbid psychiatric disorders [52], and twin studies have found that eating disordered patients have a strong genetic diathesis that typically begins to manifest around the time of adolescence [53]. However, the psychological and emotional relief that such persons achieve by manipulating food are only temporary, as they do not correct the underlying problem of neuronal hyperexcitability. Consequently, the behavior continues. Moreover, even when eating-disordered behavior is reduced through cognitive and behavioral techniques, these individuals commonly continue to manifest other psychiatric abnormalities, such as clinical depression and obsessional thinking [52]. Then again, it is also possible that over time, progressive maturation and improved coping skills could reduce intrapsychic tension enough to keep the brain calmer. As this occurs, neural circuits that had previously been hyperactive could become less active, thus reducing psychiatric symptomatology more comprehensively.

3.10.5. Personality Disorders

Personality can be defined as the unique set of temperamental, social, and behavioral characteristics that shape the way a person expresses him or her self under ordinary circumstances. A personality disorder is defined as an enduring pattern of maladaptive thoughts and behaviors exhibited in many contexts and deviating markedly from accepted cultural norms. Disordered personality traits, such as denial, splitting, projection, and other primitive defense mechanisms typically develop early in life and likely represent desperate attempts to relieve the painful emotions that are driven by hyperexcitable neurons [1]. In the majority of cases, the hyperexcitable nature of the neurological system evades clinical detection until mounting stress, like stones thrown at a beehive in which the bees are abnormally temperamental, causes the neurons to become pathologically hyperactive. However, because personality disorders tend to begin early in life—a time that, ordinarily, is relatively stress-free—the development of a personality disorder would suggest that either the neurological system were very hyperexcitable or that stress levels during childhood were unusually high, or both. This supposition is supported by the well-known link between personality disorder-development and childhood abuse [54] and by the high degree of disability that is associated with personality disorders (no psychiatric disorder other than schizophrenia ranks as high) [55].

3.10.6. Type A and Type D Personalities

In the 1950s, a longitudinal study found that specific personality traits, defined as the "Type A Personality," more than doubled the risk of coronary heart disease [56]. First described by cardiologists Meyer Friedman and Ray Rosenman after an upholsterer called to their attention the peculiar fact that the chairs in their waiting rooms were only worn out on the front edge, the Type A Personality was characterized as over-ambitious, competitive, domineering, impatient, and fast-talking [56]. Also predictive of cardiac events, independently, were depression, anxiety, or both [57]. The latter pair of symptoms, to which gloominess, indecisiveness, irritability, lack of ambition, and low self-esteem were subsequently added, are now described as the "Type D Personality." Both the Type A and Type D personalities are variable expressions of the neuronal hyperexcitability trait [1, 3, 4]. The association of these so-called "personality types" with an increased risk of cardiovascular disease hypothetically stems from the increased sensitivity to stress and consequent metabolic dysfunction that are conferred by the neuronal

hyperexcitability trait [4].

3.10.7. Child Sexual Abuse and Neglect

Because neuronal hyperexcitability tends to cause so many cognitive and emotional difficulties, affected persons often have as much difficulty taking care of their children as they do themselves. Just as they neglect their own health and well-being by eating fast-food, using illicit drugs, and engaging in high-risk behavior, they tend to neglect the health and well-being of their children. In addition, neuronal hyperexcitability in the reward circuitry of the brain can drive addictive behavior from within due to the unusually high intensity of the pleasurable emotions that become linked to specific behaviors and activities. The abnormally intense pleasure can also occur in relation to the use of illicit drugs, making it that much more difficult for such persons to stop using them. In some cases, the drug "high" can be so intense that the affected person is willing to do anything necessary, even if immoral or illegal, to re-experience the pleasurable feelings.

3.10.8. Paraphillias

As discussed in regards to child sexual abuse, hyperactivity in the reward circuitry can fuel addictive behavior endogenously, thus causing the affected person to form abnormally intense attachments to whatever (or whoever) the feelings of pleasure and excitement become linked. In some cases, this includes sexually deviant behaviors such as fetishes, sexual perversions, or pedophilia. That is not to say that such persons should be excused from any of the illegal acts they may commit, but only that the hyperexcitability of their brains can make it more difficult for them to control their behavior.

3.10.9. Sociopathy

As discussed in regards to both child sexual abuse and paraphillias, sociopathy is likely fueled by the endogenously addictive effect of neuronal hyperexcitability. Although such individuals have been stereotyped as unemotional and non-empathic, some of them may actually be so emotionally sensitive (and perhaps so traumatized by their own experiences as victims) that they have built a psychic wall that prevents them from experiencing any uncomfortable feelings, including feelings of sympathy, compassion, shame or guilt [58]. This is suggested by the hidden rage that drives the antisocial behavior of many sociopaths. Conversely, there is emerging evidence that other sociopaths may actually have hypo-excitable neurological systems, which might then drive them to behavioral extremes in an effort to experience satisfactory levels of pleasure, excitement, and, possibly, vindication of their own victimization [59].

3.10.10. Criminality

Recent statistics have shown that up to one-half of all prison inmates have at least one diagnosable mental disorder [60, 61], and the correctional system currently holds more psychiatric patients than all the public and private mental healthcare facilities combined [62]. Moreover, the lack of a diagnosable mental disorder does not exclude the possibility that a person experiences neuropsychiatric symptomatology. The possibility of subclinical symptomatology is even greater for prison inmates, who often lack insight or may be unwilling to communicate their psychiatric struggles. Such persons may silently experience intermittent or persistent racing thoughts, insomnia, paranoia, delusional thinking, restlessness, irritability, impulsivity, substance misuse, and other symptoms of neuronal hyperexcitability. Consistent with this hypothesis, approximately 40% of inmates *admittedly* have symptoms of ADHD, and other psychiatric symptoms may be obscured or misattributed to the use of alcohol, marijuana, cocaine, or other psychoactive substances [60, 63]. Considering the high frequency of psychiatric symptomatology, particularly ADHD, and the money that affected persons require to maintain their drug habits, it is easily to see why they commit so many impulsive and illegal acts.

4. Discussion

The foregoing are just some of the many faces of the neuronal hyperexcitability trait. When these disorders and abnormal behavioral patterns are identified on family pedigrees as different manifestations of a shared neurophysiological abnormality, the distribution is strikingly autosomal dominant! That suggests not only that all of these disorders and conditions, which affect close to half the population, are rooted in the same physiological abnormality but also that most of the candidate genes that have been linked to psychiatric, functional, and general medical illnesses make small contributions in comparison to a few genes that make large contributions and may, by themselves, be enough to markedly increase one's vulnerability to developing any of a wide range psychological, behavioral, and physical symptoms.

The practical importance of this is that neuronal hyperexcitability is a highly modifiable risk factor, and so recognition of its genetic etiology can incentivize carriers to develop prophylactic strategies early in life and, if symptomatic, seek treatment with less hesitation. Any habit or activity that quiets the brain can potentially prevent or reduce the symptoms of any of the related psychological, behavior, or physical abnormalities. Some of these habits and activities include proper stress management, maintaining an early sleep schedule, regular exercise, avoidance of caffeine and other psychostimulants, and minimizing refined sugar. If these habits are either insufficient to reduce symptoms or too difficult to implement, then medical therapy aimed at reducing neuronal excitability (i.e., anticonvulsants and other Neuroregulators [64]) may be necessary. Also of potential benefit would be psychotherapy, meditation, and other interventions that take strain off the brain.

Future directions for research in this area include studies comparing the psychiatrically and medically-protective effects of Neuroregulators to the long-recognized benefits of the aforementioned natural interventions both alone and in combination with Neuroregulators. Also needed are studies to verify the autosomal dominant distribution of the neuronal

hyperexcitability trait and prospective studies involving carriers of the single nucleotide polymorphism CACNA1C [65] and other risk genes for neuronal hyperexcitability [39, 66-77].

5. Conclusion

Despite more than a century of scientific study and a rich history of religious and philosophical debate, the psychophysiology of cognitive, emotional, and behavioral abnormalities continues to be an enigma. Now, for the first time, comes a hypothesis that integrates psychology and biology—the mind and the brain—to explain nearly every known mental, emotional, behavioral, and general medical abnormality. According to the MCNH hypothesis of psychiatric disorders, an inherent hyperexcitability of the neurological system fuels the development of mental illness by abnormally amplifying one's sensitivity to stress. It can also fuel the early development of the wide range of functional physical symptoms that have historically been viewed as purely psychological in nature, and the later development of various degenerative diseases that had previously been thought to be completely separate from mental illness. Based on the hypothesis that 1) the neuronal hyperexcitability trait is autosomal dominant; 2) the associated gene polymorphisms are highly prevalent; and 3) the abnormality, even in its heterozygous form, tends to be the most important determinant of both mental and physical illness, it is imperative to raise clinician awareness of this subtle but highly disruptive neurophysiological abnormality. Fortuitously, there is also emerging evidence that the abnormality may be detectable by simply measuring one's resting vital signs, a finding that would make it the first objective measure of one's vulnerability to illness in general. If demonstrated to be true, the combination of diagnostic simplicity and ease of treatment could usher in history's greatest campaign in the fight against sickness and disease.

Disclosure Statement

The author declares that this article was conceived and written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

[1] Binder MR. The multi-circuit neuronal hyperexcitability hypothesis of psychiatric disorders. AJCEM 2019; 7 (1): 12-30.

[2] Grunze HCR. The effectiveness of anticonvulsants in psychiatric disorders. Dialogues Clin Neurosci 2008; 10 (1): 77-89.

[3] Binder MR. Gabapentin — The Popular but Controversial Anticonvulsant Drug May Be Zeroing in on the Pathophysiology of Disease. AJCEM 2021; 9 (4): 122-134.

[4] Binder MR. FLASH Syndrome: tapping into the root of chronic illness. AJCEM 2020; 8 (6): 101-109.

[5] Larsen BA, Christenfeld NJS. Cardiovascular disease and psychiatric comorbidity: the potential role of preservative cognition. Cardiovascular Psychiatry and Neurology 2009; Article ID: 791017.

[6] Brainstorm Consortium; Anttila V, Bulik-Sullivan B, Finucane HK, et al. Analysis of shared heritability in common disorders of the brain. Science 2018; 360 (6395): eaap8757.

[7] Beissner F, Meissner K, Bär KJ, Napadow V. The autonomic brain: an activation likelihood estimation meta-analysis for central processing of autonomic function. J Neurosci 2013; 33 (25): 10503-10511.

[8] McEwen BA. Stress, adaptation, and disease allostasis and allostatic load. Annals of the New York Academy of Sciences 1998; 840 (1): 33-44.

[9] Lopez-Santiago LF, Yuan Y, Wagnon JL, et al. Neuronal hyperexcitability in a mouse model of SCN8A epileptic encephalopathy. PNAS 2017; 144 (9): 2383-2388.

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

[11] Leuchter AF, Cook IA, Hunter AM, Cai C, Horvath S. (2012) Resting-state quantitative electroencephalography reveals increased neurophysiologic connectivity in depression. 7 (2): 1-13. e32508.

[12] Johnstone T, van Reekum CM, Urry HL, Kalin NH, Davidson, RJ. Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. J. Neuroscience 2007; 27 (33): 8877-8884.

[13] Rose GM, Diamond DM, Pang K, Dunwiddie TV. Primed Burst Potentiation: lasting synaptic plasticity invoked by physiologically patterned stimulation. In: Haas HL and Buzsàki G. (eds) Synaptic Plasticity in the Hippocampus. Springer, Berlin, Heidelberg, 1988.

[14] Binder MR. Electrophysiology of seizure disorders may hold key to the pathophysiology of psychiatric disorders. AJCEM 2019; 7 (5): 103-110.

[15] Greenberg BD, Ziemann U, Cora-Locatelli G et al. Altered cortical excitability in obsessive-compulsive disorder. Neurology 2000; 54: 142–147.

[16] Ting JT Feng G. Neurobiology of obsessive-compulsive disorder: insights into neural circuitry dysfunction through mouse genetics. Curr Opin Neurobiol 2011; 21 (6): 842-848.

[17] Lindgren KA, Larson CL, Schaefer SM, et al. Thalamic metabolic rate predicts EEG alpha power in healthy control subjects but not in depressed patients. Biological Psychiatry 1999; 45: 943-952.

[18] Lassemo E, Sandanger I, Nygard JF, Sorgaard KW. The epidemiology of post-traumatic stress disorder in Norway: trauma characteristics and pre-existing psychiatric disorders. Soc Psychiatry Psychiatr Epidemiol 2017; 52 (1): 11-19.

[19] Finocchi C, Ferrari M. Female reproductive steroids and neuronal excitability. Neurol Sci. 2011; 32 (Suppl 1): S31-5.

[20] Bowcut JC, Weiser M. Inflammation and schizophrenia. Psychiatric Annals 2018; 48 (5): 237-243.

[21] Boorman E, Romano GF, Russell A, Mondelli V, Pariante CM. Are mood and anxiety disorders inflammatory diseases? Psychiatric Annals 2015; 45 (5): 240-248.

[22] Orlovska S, Vestergaard CH, Bech BH, et al. Association of streptococcal throat infection with mental disorders: testing key aspects of the PANDAS hypothesis in a nationwide study. JAMA Psychiatry 2017; 74 (7): 740-746.

[23] Kenney MJ, Ganta CK. Autonomic Nervous System and Immune System Interactions. Compr Physiol 2014; 4 (3): 1177-1200.

[24] Schäfers M, Sorkin L. Effect of cytokines on neuronal excitability. Neuroscience Letters 2008; 437 (3): 188-193.

[25] Vezzani A, Viviani B. Neuromodulatory properties of inflammatory cytokines and their impact on neuronal excitability. Neuropharmacology 2015; 96 (Part A): 70-82.

[26] Galic MA, Riazi K, Pittman QJ. Cytokines and brain excitability. Frontiers in Neuroendocrinology 2012; 33 (1): 116-125.

[27] Meyers Jr MG, Olson DP. Central nervous system control of metabolism. Nature 2012; 491: 357-363.

[28] Han C, Rice MW, Cai D. Neuroinflammatory and autonomic mechanisms in diabetes and hypertension. Am J Physiol Endocrinol Metab 2016; 311 (1): E32-E41.

[29] Kassi E, Pervanidou P, Kaltsas G, Chrousos G. Metabolic syndrome: definitions and controversies. BMC Medicine 2011; 9 (48).

[30] Murphy R, Carroll RW, Krebs JD. Pathogenesis of the metabolic syndrome: Insights from monogenic disorders. Mediators of Inflammation 2013; 2013.

[31] Alvares GA, Quintana DS, Hickie IB, Guastella AJ. Autonomic nervous system dysfunction in psychiatric disorders and the impact of psychotropic medications: a systematic review and meta-analysis. J Psychiatry Neurosci 2016; 41 (2): 89-104.

[32] Hershey T, Black KJ, Hartlein JM, et al. Cognitive-pharmacologic functional magnetic resonance Imaging in Tourette syndrome: a pilot study. Biol Psychiatry 2014; 55: 916–925.

[33] Scahill L. Prevalence of Diagnosed Tourette Syndrome in Persons Aged 6--17 Years --- United States, 2007. Yale Univ Child Study Center and School of Nursing. Bitsko, RH and Visser, SN. Div of Human Development and Disability, National Center on Birth Defects and Developmental Disabilities. Blumberg, SJ. Div of Health Interview Statistics, National Center for Health Statistics, CDC.

[34] Cassidy CM, Balsam PE, Weinstein JJ, et al. A perceptual inference mechanism for hallucinations linked to striatal dopamine. Current Biology 2018; 28 (4): 503-514. e4.

[35] Gittelman JX, Perke DJ, Portfors CV. Dopamine modulates auditory responses in the inferior colliculus in a heterogeneous manner. J Assoc Res Otolaryngol 2013; 14 (5): 719-729.

[36] Hargreave E. (2006) The neuroplasticity phenomenon of kindling. http://hargreaves.swong.webfactional.com/kindle.htm. (Accessed 5/19/18).

[37] Begh M, Beghi E, Cornaggia CM. Epilepsy in psychiatric disorders. In: Mula M. (eds) Neuropsychiatric Symptoms of Epilepsy. Neuropsychiatric symptoms of neurological disease. pp. 289-302. Springer, Cham Publishing Company, 2016. ISBN: 978-3-319-22158-8.

[38] Josephson CB, Lowerison M, Vallerand I, et al. Association of depression and treated depression with epilepsy and seizure outcomes: a multicohort analysis. JAMA Neurol 2017; 74 (5): 533-539.

[39] Lopez AY, Wang X, Xu M, et al. Ankyrin-G isoform imbalance and interneuronopathy link epilepsy and bipolar disorder. Molecular Psychiatry 2017; 22: 1464–1472.

[40] Fleming KC, Volcheck MM. Central sensitization syndrome and the initial evaluation of a patient with fibromyalgia: a review. Rambam Maimonides Med J 2015; 6 (2): e0020.

[41] 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 Jun; 37 (6): 339-352.

[42] Yunus MB. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. Semin Arthritis Rheum 2007; 36 (6): 339-356.

[43] Fink P, Rosendal M, Dam ML, Schröder A. Ny faelles diagnose for de funktionelle sygdomme [New unifying diagnosis of functional diseases]. Ugeskr Laeger 2010; 14; 172 (24): 1835-1838.

[44] Aurora SK, Wilkinson F. The brain is hyperexcitable in migraine. Cephalalgia 2007; 27 (12) 1442-1453.

[45] Griner T. What's really wrong with you? A revolutionary look at how muscles affect your health. Avery Publishing. New York, NY, 1995.

[46] Binder M. The golden Book of muscle health and restoration. Lightningsource Publishing, 2016.

[47] Harden CL. Pseudoseizures and dissociative disorders: a common mechanism involving traumatic experiences. Seizure 1997; 6 (2): 151-155.

[48] El-Naggar H, Moloney P, Widdess-Walsh P, Kilbride R, Delanty N. Simultaneous occurrence of nonepileptic and epileptic seizures during a single period of in-patient video-electroencephalographic monitoring. Epilepsia Open 2017; 2 (4): 467-471.

[49] 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.

[50] Saisan J, Smith M, Robinson L, Segal J. Substance abuse and mental health issues: dealing with drug or alcohol addiction and co-occurring mental health problems. https://www.helpguide.org/articles/addictions/substance-abuse-and-mental-health.htm. (Accessed 9/25/18).

[51] Cherry D, Albert M, McCaig LF. Mental health-related physician office visits by adults aged 18 and over: United States, 2012-2014. NCHS Data Brief 2018; 311.

[52] Blinder BJ, Cumella EJ, Sanathara VA. Psychiatric comorbidities of female inpatients with eating disorders. Psychosom Med 2006; 68 (3): 454-462.

[53] Klump KL, Burt SA, McGue M, Lacono WG. Changes in Genetic and Environmental Influences on Disordered Eating Across Adolescence A Longitudinal Twin Study. Arch Gen Psychiatry 2007; 64 (12): 1409-1415.

[54] Keyes KM, Eaton NR, Hasin DS. Childhood maltreatment and the structure of common psychiatric disorders. British Journal of Psychiatry 2012; 200 (2): 107-115.

[55] Weye N, Santomauro DF, Agerbo E, et al. Register-based metrics of years lived with disability associated with mental and substance use disorders: a register-based cohort study in Denmark. Lancet Psychiatry 2021; 8 (4): 310-319.

[56] Friedman M, Rosenman R. Association of specific overt behaviour pattern with blood and cardiovascular findings. Journal of the American Medical Association 1959; 169 (12): 1286–1296.

[57] Friedman HS, Booth-Kewley S. Personality, Type A behavior, and coronary heart disease: the role of emotional expression. Journal of Personality and Social Psychology 1987; 53 (4): 783-792.

[58] Levy KN, Johnson BN, Clouthier TL, Scala JW, Temes CM. An attachment theoretical framework for personality disorders. Canadian Psychology 2015; 56 (2): 197–207.

[59] 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 (12): 1268-1275.

[60] Ginsberg Y, Hirvikoski T, Lindefors N. Attention deficit hyperactivity disorder (ADHD) among longer-term prison inmates is a prevalent, persistent and disabling disorder. BMC Psychiatry 2010; 10: 112.

[61] Bronson J, Berzofsky M. U.S. Department of Justice Special Report: Indicators of mental health problems reported by prisoners and jail inmates, 2011-2012.

[62] Ill-equipped: US prisons and offenders with mental illness. Human Rights Watch. October 2003.

[63] Jen Karberg JC, James DJ. Bureau of Statistics Special Report. Substance Dependence, Abuse, and Treatment of Jail Inmates, 2002.

[64] Binder MR. Introducing the term "Neuroregulator" in Psychiatry. AJCEM 2019; 7 (3): 66-70.

[65] Nieratschker V, Brückmann C, Plewnia C. CACNA1C risk variant affects facial emotion recognition in healthy individuals. Sci Rep 2015; 5: 17349.

[66] Ferreira, MAR, O'Donovan MC, Sklar P. (2008) Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. Nat Genet 2008; 40 (9): 1056-1058.

[67] 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; 159B (8): 997-1005.

[68] 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 (10): 1016-1022.

[69] Liu Y, Blackwood DH, Caesar S, et al. Meta-analysis of genome-wide association data of bipolar disorder and major depressive disorder. Mol Psychiatry 2011; 16 (1).

[70] Iqbal Z, Vandeweyer G, van der Voet M, et al. Homozygous and heterozygous disruptions of ANK3: at the crossroads of neurodevelopmental and psychiatric disorders. Human Molecular Genetics 2013; 22: 1960-1970.

[71] Subramanian J, Dye L, and Morozov, A. Rap1 signaling prevents L-type calcium channel-dependent neurotransmitter release. Journal of Neuroscience 2013; 33 (17): 7245.

[72] Santos M, D'Amico D, Spadoni O, et al. Hippocampal hyperexcitability underlies enhanced fear memories in TgNTRK3, a panic disorder mouse model. Journal of Neuroscience 2013; 33 (38): 15259-15271.

[73] Contractor A, Klyachko VA, Portera-Cailliau C. Altered neuronal and circuit excitability in Fragile X syndrome. Neuron 2015; 87 (4): 699-715.

[74] O'Brien NL, Way MJ, Kandaswamy R, et al. The functional GRM3 Kozak sequence variant rs148754219 affects the risk of schizophrenia and alcohol dependence as well as bipolar disorder. Psychiatric Genetics 2014; 24: 277–278.

[75] Schizophrenia Working Group of the Psychiatric Genomics Consortium: Ripke S, Neale BM, O'Donovan MC. Biological insights from 108 schizophrenia-associated genetic loci. Nature 2014; 511 (7510): 421-427.

[76] Freedman R, Coon H, Myles-Worsley M, et al. Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. PNAS 1997; 94 (2): 587–592.

[77] Pizzarelli R, Cherubini E. Alterations of GABAergic signaling in autism spectrum disorders. Neural Plast 2011; 1011: 157193.