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Review Article

A Pathophysiologically-Based Approach to the Treatment and Prevention of Mental Illness and Its Related Disorders

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Abstract: Medication, psychotherapy, or both are the most common approaches to the treatment of psychiatric disorders. However, due to the high incidence, early onset, and chronicity of psychiatric symptoms, both medication and psychotherapy can be resource-intensive, yet there is little consensus about which should be applied to which clinical syndromes. This is a matter of increasing concern in light of the growing mental health crisis. Much of the problem stems from the lack of a precise psychophysiological explanation for psychiatric symptomatology, as it leaves clinicians without a clear target for treatment. However, an emerging hypothesis—one that identifies the fundamental vulnerability trait in psychiatric disorders—has the potential to help solve these problems. According to the Multi-Circuit Neuronal Hyperexcitability (MCNH) Hypothesis, psychiatric symptoms are driven by an abnormal elevation in the activity of the neural circuits with which they are associated. Particularly under the influence of stress, too many neurons fire for too long, resulting in circuit-specific symptoms, such as anxiety, depression, irritability, insomnia, inattention, apathy, and obsessional thinking. What hypothetically determines which circuits will be pathologically hyperactive at any point in time are the aberrant neuronal discharges that tend to occur spontaneously or in conjunction with willful cognitions and emotions when the neurological system is hyperexcitable. Clinical application of this hypothesis has the potential to guide which form of treatment would be most effective for which patient and to streamline the use of medications and other medical interventions because it illuminates a specific target for treatment. It also has the potential, for the first time in history, to prevent the development of psychiatric symptoms because the trait of neuronal hyperexcitability is highly modifiable and can be identified objectively by simply measuring one's resting vital signs. Moreover, because the trait of neuronal hyperexcitability also appears to be at the root of a wide range of general medical conditions, such as diabetes, high blood pressure, cardiovascular disease, and cancer, the early detection and management of the trait could usher in history's greatest campaign in the first against sickness and disease.

Keywords: Pathophysiology of Psychiatric Disorders, Neuronal Hyperexcitability, Biomarkers of Disease, Preventive Medicine, Anticonvulsants, Mood Stabilizers, Neuroregulators, Antidepressants

1. Introduction

Short of a clearly-defined medical explanation for psychiatric symptoms, the treatment of psychiatric disorders continues to be divided into two fundamentally different philosophical approaches: psychological therapy and biological therapy. Also, within these two camps, there continues to be a great deal of debate about which treatment modality is best for which patient and what the duration of that treatment should be. These uncertainties are the result of 1) a lack of clarity about what abnormality is being treated in psychiatric disorders; and 2) the observation that many different modalities seem to be helpful for a wide range of psychiatric disorders. Yet the mere use of the word "disorders" is questionable because, in the absence of a clearly defined explanation for symptoms, there is uncertainty about whether various combinations of psychiatric symptoms reflect different pathological processes or a shared underlying

abnormality [1]. However, the mere fact that so many different psychological and biological treatment approaches can be effective for the same syndromes suggests that many or all of the syndromes are rooted in a shared abnormality. Be that as it may, there is a major difference between the psychological and the biological schools of thinking. The psychological school believes that psychopathology arises in the mind and, therefore, can be treated by correcting the psychological abnormalities that drive the symptoms. In contrast, the biological school believes that psychopathology arises in the brain and, therefore, can be treated by correcting the neurological abnormalities that drive the symptoms.

Though these two schools of thinking have yet to be reconciled conceptually, the evidence base, which shows similar benefits from both approaches to treatment [2], suggests that both are correct; that psychopathology is a mental illness but that it is also neurologically-driven. This idea is reinforced by the observation that psychotherapy and medical therapy tend to have synergistic effects [3]. That begs the question: how is it possible that these two modalities, though distinctly different, can have complementary effects?

Seemingly, the answer would lie in the functional anatomy; the mind and the brain must differ in essence yet be mutually influential. Based on this hypothesis, psychotherapy would target the mind, and biological therapy would target the brain. Since the mind and the brain would influence each other, treating both would have complementary and additive effects. However, this would lead to two more questions: 1) what goes on in the mind; and 2) what goes on in the brain?

2. Distinction Between Mental Function and Neurological Function

The answer to the first question would seem fairly simple. The inner workings of the human mind have been discussed, debated, and documented since antiquity. Particularly over the last several hundred years, numerous theories have been proposed and many forms of psychological therapy have been applied to abnormalities of thought and behavior. This was taken to a whole new level when, at the turn of the 20th Century, the Austrian psychiatrist Sigmund Freud divided the mind into functionally different compartments that he referred to as the "conscious" (what one is aware of), the "preconscious" (what one could become aware of through selective attention), and the "unconscious" (what one is unaware of though processing at a deeper level) [4]. Freud related these three levels of mental function to the three parts of the mind that he called the "id," the "ego," and the "superego" [5]. Here, the id was regarded as entirely unconscious whilst the ego and superego had conscious, preconscious, and unconscious aspects. However, Freud's structural characterization of the mind said nothing about the brain or its function. It was not until the 1950s, when David Ricoh began to integrate neuroscience with clinical psychiatry, that a thorough inquiry into the brain's function in relation to the mind began.

Today, after nearly 70 years of integrative research, the relationship between the mind and the brain continues to be a mystery. The delay in solving this mystery primarily stems from the false notion that mental function can be understood by analyzing brain function. To do so would be like trying to analyze the workings of a person's brain by analyzing the workings of his computer. The person uses his computer to process information, send messages, and search the internet, but his computer is not him. Similarly, the mind uses the brain to think, speak, and receive input from the environment, but the mind is as different from the brain as the brain is from a computer.

3. Pathophysiology of Mental Illness

Based on the premise that the mind and the brain are distinctly different entities, it follows that they process information in parallel. The mind processes information intrapsychically, and the brain processes the same information neurologically. That could explain why learning and memory require repetition. The mind has to train the brain to synchronize with it on demand. In other words, the mind, acting as a computer programmer, has to train the brain, acting as a computer, to activate the relevant neural circuits when it decides to bring a preconscious thought into conscious awareness. That the mind, using its own energy and will, is able to activate specific circuits in the brain has now been demonstrated experimentally. Using cutting-edge technology, it has been shown that willful effort can cause intention-specific neurons to turn on and, simultaneously, competing neurons to turn off [6]. Conversely, the activation of specific neurons can induce changes in specific thoughts and emotions. This has been demonstrated using an advanced technology called "optogenetics" The technique allows specific neurons to be turned on and off using photic energy [7]. The manipulation of these genetically-engineered, light-sensitive neurons has been observed to cause immediate changes in behavior, such as switching from passivity to aggression, or curiosity to withdrawal. Taken together, these experiments demonstrate that the mind can influence the brain, and the brain can influence the mind.

The bidirectional influence between the mind and the brain could hold the key to solving the mystery of mental illness. Recall that most of the common psychiatric disorders, such as major depressive disorder, bipolar disorder, and obsessive-compulsive disorder, consist of symptoms that are really just aberrations of normal thoughts and emotions. Irrespective of the specific disorder, the nature of these aberrations is always the same: it involves an abnormal elevation in the intensity and duration of the related thoughts and emotions. The most logical explanation for this is that the symptom-related circuits in the brain keep reverberating, thus causing circuit-related thoughts and emotions to keep repeating [8, 9]. Hypothetically, these pathologically hyperactive circuits could also cause other circuits, through their collateral connections, to become hyperactive while themselves quieting down due to synaptic fatigue [10]. This

could explain the emotional instability and cycling of symptoms that characterizes most psychiatric disorders [11-13].

The firing of neurons is regulated by the movement of ions across neuronal membranes. Too much positive charge passing into the cell or too much negative charge passing out of the cell would reduce neuronal membrane stability, thereby increasing the excitability of the neurological system. Hence, it would not be unreasonable to think that psychiatric symptoms could be rooted in ionchannelopathies. The neuronal hyperexcitability would abnormally amplify various thoughts and emotions and delay their return to baseline [8, 9, 12]. It could also cause racing thoughts and distractibility as the mind was bombarded by neurologically-induced impulses, and it could cause impulsivity if the mind attempted to respond to the related thoughts and feelings before it had a chance to think things through in conjunction with the brain.

This conceptualization, which is the basis of the Multi-Circuit Neuronal Hyperexcitability (MCNH) Hypothesis of Psychiatric Disorders, is corroborated by gene associations studies that link the major psychiatric disorders to ionchannelopathies [14-25]. More specifically, the research suggests that the protein products of the susceptibility genes for psychiatric disorders fail to properly regulate the movement of calcium and sodium ions through their respective channels [14-16, 18, 19]. The delay that this creates as neurons attempt to reestablish and maintain their resting potential is thought to be at the root of virtually every psychiatric symptom and disorder [8, 9].

That is not to say that every person who has hyperexcitable neurons will develop psychiatric symptoms, nor is it to say that every person who does not have hyperexcitable neurons will be completely immune to developing psychiatric symptoms. Rather, it is only to say that persons with hyperexcitable neurons would be more vulnerable to developing psychiatric symptoms because their neurons would abnormally amplify the neural-activating effects of intrapsychic stress [8]. This observation, in conjunction with the mind-brain duality of the cognitive-emotional system, provides a logical explanation for the shared beneficial effects of psychological and biological treatment approaches. It also illuminates two targets at which to aim treatment: the mind and the brain. By reducing mental tension, psychotherapy would prevent the mind from overstimulating the brain, and by reducing the excitability of the brain, anticonvulsant drugs, which could more aptly be called Neuroregulators because of their putative mechanism of action [26], would prevent the brain from overstimulating the mind.

4. How to Identify the Neuronal Hyperexcitability Trait

In the past, identifying the trait of neuronal hyperexcitability would have depended upon a physician's clinical assessment and inquiries about a patient's behavior, lifestyle, and relationships. Through rapidly advancing technology, one could also envision the use of neuroimaging and electroencephalography to assist in this process. Fortuitously, however, there is growing evidence that the trait of neuronal hyperexcitability can be detected by simply measuring one's resting vital signs [27]. This is suggested by the observation that upper-end-of-normal resting vital signs are predictive of the same disorders that are believed to be rooted in neuronal hyperexcitability. For example, in a longitudinal study involving more than 1 million men in Sweden, Latvala et al. [28] 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. [29] 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 [27]. Strikingly, these are the same illnesses that shorten the lives of the mentally ill. These unlikely connections suggest that neuronal hyperexcitability is at the root of both the vital-sign elevations and the plethora of mental and physical illnesses of which they are predictive. The link between neuronal hyperexcitability, resting vital-sign elevations, and the aforementioned mental and physical illnesses is thought to be the consequence of a chronic hyperactivation of the autonomic nervous system, the cognitive-emotional system, the hypothalamic-pituitary system, the immunologic system, the metabolic system, and various other systems of the body consequent to neuronal hyperexcitability [27]. 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 gradual erosive effects of neuronal hyperexcitability [27]. Based on the foregoing connections, which are rapidly being replicated [30-53], it has been hypothesized that a RHR above 75 beats/min or a RRR above 15 breaths/min is indicative of the neuronal hyperexcitability trait [27].

5. Benefits of Identifying the Neuronal Hyperexcitability Trait

Recognizing the connection between psychiatric symptoms, neuronal hyperexcitability, and upper-end-of-normal resting vital signs has led to a new paradigm in the diagnosis and treatment of psychiatric disorders. The new paradigm, called the "neuronal excitability spectrum" [12], is based on the hypothesis that an inherent hyperexcitability of the neurological system is the biological driver of psychiatric symptoms irrespective of the manner in which they are expressed. As such, the new paradigm could be

conceptualized as the neurophysiological basis of the "bipolar spectrum," which many experts believe to be the most accurate of the symptom-based diagnostic systems [13]. Among the many advantages of the neuronal excitability spectrum over symptom-based diagnostic systems are that it 1) circumvents the need for stigmatizing diagnoses; 2) includes an objective basis for diagnosis and possibly also treatment-response monitoring (i.e., resting vital-sign measurements); 3) illuminates a precise biological target for treatment (i.e., neuronal hyperexcitability); and 4) is more comprehensive than the bipolar spectrum in that it would include those patients who, having normoexcitable or hypo-excitable neurons, would fall outside the bipolar spectrum. For example, using the bipolar spectrum construct, a patient with a good pre-morbid adjustment, no previous psychiatric history, and slowly developing psychiatric symptoms in the face of a severe and persistent emotional stressor would fall outside the bipolar spectrum [54]. However, there would be no way to confirm this because the bipolar spectrum, like all previous classification systems, is based on symptoms, which are subjective. In contrast, the neuronal excitability spectrum could use the patient's resting vital-sign measurements to confirm, both objectively and quantitatively, that the patient was outside the bipolar spectrum *neurophysiologically*. In so-doing, it would express the patient's potential to respond to various types of treatment without the need for diagnostic labels. Assuming that there were no confounding factors, such as cardiopulmonary disease, cardiopulmonary medications, illicit drugs, extreme athletic conditioning, or recent food intake, an RHR below 75 beats/min and an RRR below 15 breaths/min would suggest that the patient's neurological system was NOT hyperexcitable [12, 27]. The certainty that the patient was outside the bipolar spectrum would correspond to the numerical value of the vital-sign measurements; the lower the numbers, the greater the certainty [12]. According to the MCNH hypothesis, the primary cause of symptoms in such patients is an over-stimulation of stress-related circuits in the brain rather than a stress-induced exacerbation of an inherent neurophysiological abnormality. From a mind-brain perspective, persistent cognitive-emotional stress in such patients causes the mind to keep stimulating the brain. Over time, the repeated stimulation of the associated brain circuits causes them to become increasingly responsive to further stimulation. This effect, which is known as "primed burst potentiation" [55], is the MCNH explanation for how stress alone can fuel the development of psychiatric symptoms and why the onset of symptoms tends to be delayed relative to the onset of an inciting stressor. Hypothetically, this process could be aborted in several ways. One would be a resolution of the inciting stressor. Another would be a cognitive reframing of the stressor so as to reduce the amount of intrapsychic tension that it was causing. Yet another would be a medical rebalancing of the neurological system (as opposed to a medical stabilization of the system). Hence, such a patient, as demonstrated by numerous clinical studies [3], would be expected to respond best to a combination of psychotherapy and antidepressant therapy. Again, antidepressant-induced paradoxical effects would be unlikely in such a patient because the neurological system is not inherently hyperexcitable [12].

In contrast, the patient with a history of chronic or recurrent psychiatric symptoms who presents with a stress-induced exacerbation of symptoms would most likely have a neurological system that was inherently hyperexcitable. In dimensional terms, the patient would fall into the bipolar spectrum [12, 54]. A resting heart rate above 75 beats/min or a resting respiratory rate above 15 breaths/min would confirm this categorization [11]. According to the MCNH hypothesis (and current recommendations), such a patient would best be treated with Neuroregulators (i.e., anticonvulsants and other brain-calming drugs) [56-59]. Although antidepressant therapy might reduce some of the patient's symptoms, it would fail to address the underlying problem of neuronal hyperexcitability [60, 61]. For the same reason, it would also incur the risk of bipolar switching and other paradoxical effects [62]. Moreover, the risk of paradoxical effects would tend to increase in conjunction with the numerical value of the patient's resting heart and respiratory rate measurements. Although psychotherapy would be another possible way to reduce this patient's symptoms, it too would fail to manage the underlying problem of neuronal hyperexcitability. It would also run the risk of increasing the patient's distress by attempting to address issues that have entered into consciousness not so much in relation to the current stressor but in relation to a pathological elevation in neurological activity consequent to the underlying neuronal hyperexcitability. These issues could include an over-dramatization of the presenting symptoms, a distortion of the inciting stressor, and possibly even the dredging up of issues that have long-since been resolved. These neurologically-based distortions could hinder or even completely thwart progress in therapy. In some cases, they could even cause the patient to regress. Consequently, the treatment of such patients, who are hypothesized to constitute the vast majority of mental health referrals [12], should begin with supportive psychotherapy and natural brain-calming interventions, such as stress reduction, establishment of an early sleep schedule, avoidance of caffeine and other psychostimulants, minimization of refined sugar, and, if not medically contraindicated, the initiation of a moderate exercise program [63]. Due to the severity of their symptoms, most of these patients will also need Neuroregulator therapy…at least until the precipitating stressor has passed or they are able to achieve adequate protection through the aforementioned natural interventions. The potent brain-calming effects and rapid onset of action of an effective anticonvulsant can quickly allow such patients to regain perspective and, if still needed, utilize psychotherapy more effectively. Also, because anticonvulsant therapy addresses the underlying problem of neuronal hyperexcitability, it could bring the patient to a higher level of functioning than before the inciting stressor began. It could also reduce the risk of relapse because the underlying vulnerability trait has been therapeutically modified. Thus, application of the MCNH hypothesis in conjunction with

resting vital-sign measurements could, by more accurately guiding treatment, reduce both the time to recovery and the risk of relapse.

Another, more challenging group of patients whose treatment could be improved by application of the MCNH hypothesis is personality-disordered patients. Although the chronic psychiatric symptoms that are experienced by such patients are commonly attributed to early life trauma and dysfunctional family dynamics, they too, according to the MCNH hypothesis, are rooted in neuronal hyperexcitability [8, 12]. Hypothetically, it is the extreme hypersensitivity of their emotional systems that causes them to develop the primitive defense mechanisms and extreme coping mechanisms that characterize a personality disorder. This is corroborated by the observation that many of these patients have siblings who, despite being raised by the same parents in the same households, are relatively unaffected by the dysfunction in their families [12]. Other siblings, though not developing a personality disorder, may develop some other kind of psychiatric disorder [64]. Based on the autosomal dominant and additive pattern of this distribution [8, 12], it is thought that the unaffected siblings inherit normal genes, whereas the less severely affected siblings inherit one rather than two of the alleles for neuronal hyperexcitability [8]. The classic Mendelian distribution of psychopathology in these families also suggests that, among the many variables that contribute to the development of a psychiatric disorder, the trait of neuronal hyperexcitability is the most important.

Under the contention that severe neuronal hyperexcitability is at the root of personality disorders and that family dysfunction, in the face of severe neuronal hyperexcitability, is what precipitates the severe psychological problems that complicate the treatment of personality-disordered patients, the MCNH hypothesis would advocate the use of Neuroregulators prior to initiating any exploratory forms of psychotherapy. The historic failure to recognize that personality disorders are rooted in neuronal hyperexcitability could help explain why personality-disordered patients have notoriously been so difficult to treat. According to the MCNH hypothesis, antidepressant therapy should be avoided in such patients because their emotional systems, being hyperexcitable, are too unstable to tolerate the stimulating effects of antidepressants [60, 61]. The hyperexcitability of their neurological systems can be confirmed by resting vital-sign measurements [12]. In the absence of potential confounding factors, nearly all personality-disordered patients would be expected to have upper-end-of-normal resting heart and/or respiratory rates [12]. The single exception would be the subgroup of antisocial personality disorder known as "primary psychopathy." These individuals, who have been characterized as having callous and unemotional traits [65], do not have an emotional disturbance but rather an emotional deficit [66]. Hypothetically, their neurological systems are *hypo*-excitable [12]. As would be predicted by the MCNH hypothesis, their resting vital signs have been found to be on the lower end of normal [67]. That is not to say that every person who has hypo-excitable neurons will become a psychopath, as there are many other factors that contribute to the development of a personality disorder. However, the diminished emotional sensitivity that the trait of neuronal hypo-excitability confers would seem to increase the risk of developing a hedonistic disregard for others. Then again, that alone would not qualify as a psychiatric disorder.

The hypothetical reason that persons with hypo-excitable and normoexcitable neurological systems are so resistant to developing psychiatric symptoms is that their neurons, when stimulated, are less likely to react and faster to re-establish their resting potentials, thereby tending to prevent enough neuronal recruitment and temporal summation to precipitate symptoms (Figure 1, white curve). In contrast, the neurons of persons with hyperexcitable neurological systems are more likely to react and slower recover, thus permitting enough neuronal recruitment and temporal summation to precipitate psychiatric symptoms even under conditions of only mild-to-moderate stress (Figure 1, red curve). Now then, given that mild-to-moderate stressors are encountered much more frequently than the severe and persistent stressors that would be required to precipitate psychiatric symptoms in persons with normoexcitable neurons, the MCNH hypothesis would predict that the vast majority of persons who seek mental health care have hyperexcitable neurological systems (Figure 2).

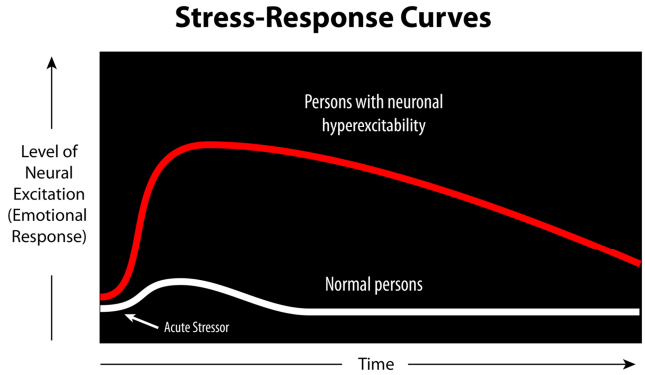

Figure 1. *Conceptual illustration of the stress response in a person with neuronal hyperexcitability (red curve) in comparison to a normal response (white curve). The relatively large magnitude of the neuronal hyperexcitability curve is hypothetically due to the tendency for more hyperexcitable neurons to be recruited and for their responses to summate due to the extra time that they take to return to baseline.*

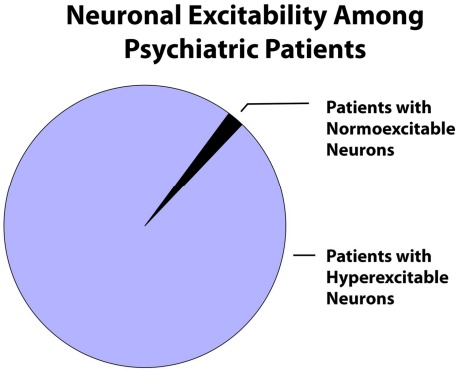

Figure 2. *Pie chart estimating the proportion of patients seeking mental health services who have hyperexcitable neurons (purple area) in comparison to those who have normoexcitable neurons (black area).*

Note, however, that this does not align with the fact that the vast majority of psychiatric patients are treated with antidepressants rather than anticonvulsants (Figure 3). In fact the sales of antidepressants outnumber the sales of anticonvulsants by more than six-to-one [68-71]. This could help explain why the success rate with antidepressants, which would be more appropriate for persons with normoexcitable neurons, is so low [72]. The discrepancy highlights the weakness of symptom-based diagnostic systems. The other problem with symptom-based treatment is that it fails to guide the duration of pharmacotherapy in an operationally-precise way. Instead, it relies on a patient's illness history and population outcome measures to guide treatment duration—informatics that are subjective, sometimes incomplete, and often unavailable. The MCNH hypothesis guides the duration of treatment more accurately because it divides the risk of relapse into three identifiable factors: 1) the excitability of the neurological system; 2) the level of psychosocial stress; and 3) the strength of the patient's coping skills and social support. Thus, for example, a patient with mild-to-moderate neuronal hyperexcitability and strong psychosocial support may need a Neuroregulator only during high-stress periods, particularly if combined with natural brain-calming interventions. This conservative approach is facilitated by the fact that Neuroregulators exert their therapeutic effects almost immediately and generally lack any withdrawal effects. A patient with a higher level of neuronal hyperexcitability would be more likely to need continuous Neuroregulator therapy, especially if his or her support systems were weak. Finally, a patient with a very high level of neuronal hyperexcitability, such as one with schizophrenia, bipolar disorder, or a severe personality disorder, would be expected to experience psychiatric symptoms even when environmental stressors were low and sometimes even when treated continuously with Neuroregulators. Moreover, there is increasing evidence that, beyond leaving such a patient at considerable risk for chronic psychiatric symptoms, the disruptive effects that very high levels of neuronal excitability have on the endocrine, the metabolic, the cardiovascular, the muscular, and the immunologic systems increase the patient's vulnerability to developing any of a wide range of general medical conditions, such as diabetes, high blood pressure, cardiovascular disease, chronic pain, autoimmune disease, cancer, and dementia [12, 27, 73].

In addition to its ability to improve diagnostic accuracy, optimize treatment, and minimize the risk of relapse, the MCNH hypothesis, in conjunction with resting vital-sign measurements, could help overcome the barriers to treatment that are created by the broad overlap between psychiatric symptoms and normal cognitions and emotions. Because psychiatric symptoms such as anxiety, depression, fear, and irritability, differ from normal emotions only in their intensity and duration, and because these and other psychiatric symptoms, such as euphoria, excitement, repetitive thoughts, and trouble sleeping, can easily be rationalized as situationally-induced, many patients are unaware that their symptoms are abnormal. This, together with the stigma of mental illness, prevents many patients from seeking psychiatric evaluation. Moreover, it can even prevent trained clinicians from recognizing the pathological nature of the symptoms. For example, a patient who becomes depressed after being diagnosed with a serious illness or losing a close family member can easily be perceived as reacting appropriately under the circumstances. Moreover, even if a psychiatric diagnosis is made, it is often delayed because normal cognitions and emotions tend to grow into abnormal cognitions and emotions insidiously rather than abruptly. Additional delays in diagnosis and treatment can be caused by a reluctance on the part of the patient and possibly members of the patient's family to admit that a treatable psychiatric condition is developing. Alternatively, many patients, due fears of being ostracized, unconsciously "convert" their psychiatric symptoms into physical symptoms. Both of these barriers to treatment could be circumvented by objectively identifying what is hypothesized to be the subtle but pernicious instigator of nearly all psychiatric disorders; namely, neuronal hyperexcitability. The neuronal hyperexcitability trait, its genetic mode of transmission, it psychiatric manifestations, and its effects on the autonomic nervous system can aptly be expressed by the non-stigmatizing but fittingly-descriptive acronym "Familial Limbic Autonomic System Hyperexcitability" or FLASH [27]. Moreover, because the trait of neuronal hyperexcitability is also thought to underlie a wide range of general medical conditions, the use of the term "FLASH syndrome" would not necessarily specify the presence of psychiatric symptomatology. This would help prevent it from becoming stigmatized while at the same time broadening its applicability.

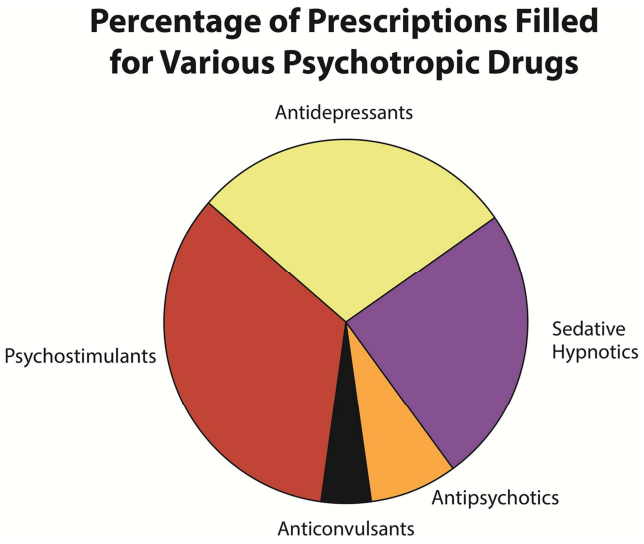

Figure 3. *Pie chart illustrating the sales of antidepressants relative to various other psychotropic drugs. Note the large discrepancy between the proportion of patients who are prescribed antidepressants and the small number of patients who, having normoexcitable neurons (Figure 2), would be appropriate to receive antidepressants. This discrepancy highlights the weakness of the current diagnostic system.*

6. Discussion

Throughout history, the understanding of mental, emotional, and behavioral abnormalities has been hampered by a limited understanding of brain structure and function. Yet despite the enormous strides that have been made in neuroscience over the last century, the relationship between psychopathology and neuropathology has remained unclear. Consequently, psychiatric disorders continue to be treated with various forms of psychological and biological therapy without a clear guide to which modality is most appropriate for which patients.

Although the monoamine hypothesis has, for more than fifty years, offered a biological basis for using antidepressants in the treatment of depression, the hypothesis is incomplete and is increasingly becoming viewed as too simplistic to explain all of the phenomena that are observed in the psychophysiology of mood disorders [74]. Other proposals, such as the immune [75, 76], the endocrine [77], the mitochondrial [78], the glutamatergic [77], and the neuroplastic [77] models of depression are likewise incomplete in that they too fail to explain how the related changes in brain structure and function cause the symptoms that characterize clinical depression and other psychiatric disorders.

As the first comprehensive psychophysiologically-based explanation for the development of psychiatric symptoms, the MCNH hypothesis, in conjunction with resting vital-sign measurements and the mind-brain duality of the cognitive-emotional system, is the first to integrate the psychological and biological schools of thinking about mental illness into one cohesive psychophysiological framework. Beyond reconciling the fields of psychology and psychiatry, the new conceptualization of mental illness traces all chronic illnesses, whether mental or physical, to a shared, highly influential, vulnerability trait; namely, neuronal hyperexcitability.

The following seven observations testify to the importance of identifying the neuronal hyperexcitability trait. First, the trait is highly common, affecting an estimated 40% of the population. Second, the trait is highly influential, as demonstrated by the autosomal dominant distribution of those who inherit the genes for neuronal hyperexcitability. Third, the trait is highly recognizable, making its presence known through a wide range of psychiatric symptomatology, functional physical symptoms, and objective physical measurements. Fourth, the trait is highly modifiable, as there are many ways, both natural and medical, to reduce the excitability of the neurological system. Fifth, the trait is highly descriptive, thus allowing patients to conceptualize and more readily accept the treatment that it guides. Sixth, the trait is highly resistant to becoming stigmatized, as it is proposed to underlie both mental and physical illness. Seventh, the trait is highly preventable through education, family planning, and, if necessary, the prophylactic use of anticonvulsants and other Neuroregulators. For all of these reasons, attention to the neuronal hyperexcitability trait may usher in history's greatest campaign in the fight against sickness and disease.

7. Directions for Future Research

Urgently needed are clinical studies comparing the effectiveness of Neuroregulator therapy (specifically anticonvulsants either alone or in combination with other anticonvulsants) to standard pharmacotherapy for a variety of psychiatric disorders. Also needed are studies comparing the effectiveness of Neuroregulators to psychotherapy alone and to psychotherapy in combination with other psychotropic medications.

8. Conclusion

Although treatment with medication and psychotherapy are the mainstays of mental health care, there are few guidelines regarding which to use, for how long, and for which patients. At best, this can cause resources to be squandered, and at worst, it can cause patients to become more symptomatic than before they started treatment. As the first comprehensive psychophysiologically-based explanation for the development of psychiatric symptoms, the MCNH hypothesis, in conjunction with the mind-brain duality of the cognitive-emotional system, offers a more precise framework through which to organize and implement treatment. It also offers an easily-accessible, objective means by which to determine the presence of the neuronal hyperexcitability trait, thereby making its use practical for both patients and clinicians. Because neuronal hyperexcitability is also thought to be the underlying driver of chronic disease, the MCNH hypothesis offers opportunities for illness prevention that are unprecedented in the history of medicine. Clinical and experimental confirmation of the hypothesis could revolutionize the diagnosis, treatment, and prevention of disease.

Conflicts of Interest

The author declares that he has no competing interests.

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