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Review Article

The Neuronal Excitability Spectrum: A New Paradigm in the Diagnosis, Treatment, and Prevention of Mental Illness and Its Relation to Chronic Disease

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Abstract: Short of a clear understanding of the pathophysiology of psychiatric disorders, treatment continues to be symptom-based rather than pathology-based. In an effort to improve the accuracy of diagnosis and treatment, a variety of symptom-based diagnostic classification systems have been utilized and numerous others have been proposed, but none have been able to satisfactorily compensate for the lack of a clearly-defined biological target for treatment. Based on the first comprehensive neurophysiological hypothesis of psychiatric disorders and mounting evidence that a subtle elevation in resting vital signs is predictive of a wide range of psychiatric and general medical conditions, this article will present an entirely new way of diagnosing and treating mental illness. It will also discuss how these vital-sign elevations increase one's vulnerability to developing any of a wide range of general medical conditions, such as diabetes mellitus, high blood pressure, cardiovascular disease, autoimmune disease, cancer, and dementia. The shared pathophysiological trait, known as "neuronal hyperexcitability," combines with life stressors to fuel a plethora of psychiatric, metabolic, and immunologic disturbances that have both immediate and long-term mental, emotional, and physical consequences. The identification of a single diathesis that unifies seemingly diverse mental and physical illnesses has enormous implications for healthcare. First, it revolutionizes the diagnosis and treatment of psychiatric disorders. Second, it unifies mental and physical illnesses, thereby reducing the long-held stigma of mental illness. Third, it provides an easy-to-measure, objective way to assess one's vulnerability to developing any illness, whether mental or physical. Fourth, it guides the use of a number of different natural and pharmacological methods of reducing one's risk of illness long before any clinical signs or symptoms appear. Fifth, it encourages patient participation by allowing those at risk to assess their own vulnerability to illness. Never could these insights be more timely than in an era in which the number of persons committing suicide is steadily increasing; the number of persons claiming disability is dramatically rising; and healthcare costs are spinning out of control.

Keywords: Bipolar Spectrum Disorders, Bipolar Switching, Paradoxical Effects of Antidepressants, Mood Stabilizers, Pathophysiology of Psychiatric Disorders, Neuronal Hyperexcitability, Biomarkers, Neuroregulators

1. Introduction

Since antiquity, the extremes of thought, emotion, and behavior that characterize mental illness have been studied, debated, and grouped into various classification systems in an effort to better define and treat them. From the time of Hippocrates until the latter part of the 19th century, symptoms on the high end of the emotional scale were categorized as "mania," and symptoms on the low end of the scale were categorized as "melancholia" [1]. These extremes, as well as another category that could be described as "psychotic states," were thought to be completely different abnormalities, though all were thought to have a biological origin. However, before the turn of the 20th century, German psychiatrist Emil Kraepelin, known as the "father of modern psychiatry,"

challenged this thinking with a new formulation of mental illness. Under the contention that psychotic states and the entire range of non-dementing psychiatric symptoms, from depression to mania, were different manifestations of a shared biological abnormality, Kraepelin grouped all of them under the title "manic-depressive insanity" [2]. According to Kraepelin, the core features of this condition were symptom-severity and symptom-persistence; much less important was the exact nature of the symptoms.

However, based on accepted validators of psychiatric diagnoses introduced by Washington University researchers prior to the publication of DSM-III [3], a decision was made to divide manic-depressive illness into "bipolar disorder" and "major depressive disorder." Subsequently, many of the other symptoms within the manic-depressive spectrum, such as chronic or waxing and waning anxiety, panic attacks, motor restlessness, inattentiveness, impulsivity, obsessive-compulsiveness, and various psychotic states, were singled out and given their own diagnostic labels in an effort to better study and more accurately treat them.

The problem with dividing manic-depressive illness into bipolar disorder and major depressive disorder is that the symptoms of one disorder tend to overlap with the symptoms of the other disorder. This would not be so much of a problem if the treatment for both disorders was the same. However, the recommended treatment of each differs markedly. The recommended treatment for major depressive disorder is antidepressant therapy, whereas the recommended treatment for bipolar disorder is mood stabilizer therapy [4-6]. What's more, treating a bipolar patient with an antidepressant drug can make the symptoms worse, even life-threatening, thus accentuating the liability of misdiagnosis [4, 7, 8]. Yet, for several reasons, misdiagnosis is virtually inevitable. First, because manic and hypomanic episodes are, by definition, euphoric rather than dysphoric, they can easily be under-reported by patients. Second, because they tend to vary in their nature, severity, and duration, they can easily be overlooked by the clinician. Third, because bipolar disorder commonly begins with a depressive episode, the clinician, at least early on, has no basis upon which to rule out the possibility of bipolar disorder. Fourth, assessing specific risk factors, such as family history, episodic course, and age of onset, though helpful, is not consistently reliable both because of the subjective nature of the risk factors and because of the many exceptions that occur.

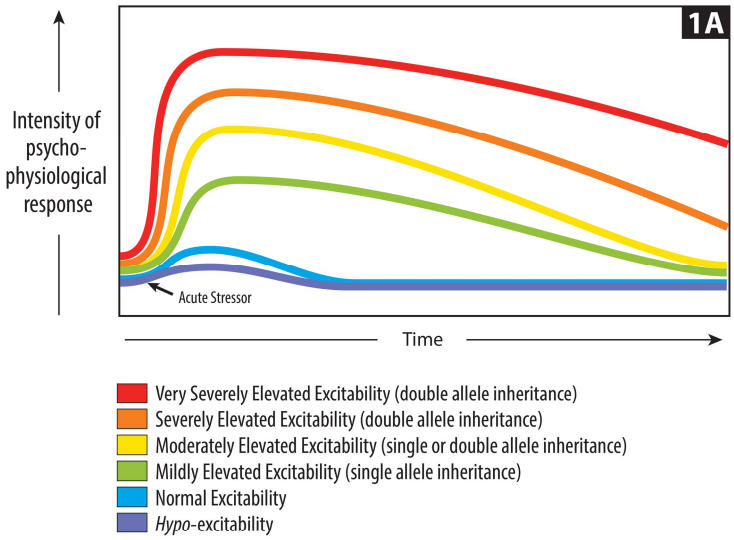
In an effort to help mitigate these problems, the more phenomenology-based concept of "bipolar spectrum" disorder has been advocated by some experts, most notably Hagop Akiskal in the U.S. [9] and Athanasios Koukopoulos in Europe [10, 11]. The bipolar spectrum concept harkens back to Kraepelin's manic-depressive classification in that it focuses more on symptom chronicity than symptom-type. However, there are opponents to the concept of bipolar spectrum disorder [12], and although several new diagnostic instruments have been introduced to help distinguish between bipolar spectrum disorder and unipolar depression, the frequency of misdiagnosing bipolar disorders as unipolar depressive disorders remains unacceptably high. According to recent studies, the average delay to the proper diagnosis of bipolar I disorder is approximately six years [13, 14], and given that Bipolar I is the easiest to identify of the cyclic mood disorders, one can only imagine the length of the delay to the proper diagnosis of the more subtle disorders in the bipolar spectrum. Then again, even if a clear distinction between bipolar spectrum disorder and major depressive disorder could be made, there continues to be a lack of clarity about what is being treated or even if the underlying abnormality is a medical disease [8].

2. Getting to the Root of Mental Illness

Ultimately, what is needed is a better understanding of the pathophysiology of psychiatric disorders. If that could be ascertained, treatments could be applied with far more precision, and the need for a cumbersome, symptom-based classification system could potentially be eliminated. Fortuitously, that advance might already be here. An emerging hypothesis contends that psychiatric symptoms are driven by pathological hyperactivity in symptom-related circuits in the brain. According to the Multi-Circuit Neuronal Hyperexcitability (MCNH) Hypothesis of Psychiatric Disorders [15], persistent firing in anxiety circuits causes persistent feelings of anxiety; persistent firing in depressive circuits causes persistent feelings of depression; persistent firing in cognitive circuits causes ruminative and obsessive thoughts; etc… This pathological circuit-specific hyperactivity is hypothetically caused by an inherent failure of the neurological system to self-regulate when perturbed by a psychological, emotional, or biological stressor. Neuropsychologically, symptoms are induced not by chemical changes in the brain but by the electrical changes that can either precede or follow them [15]. Although the MCNH hypothesis has yet to be validated through rigorous scientific studies, there is biological, observational, pharmacological, neuropsychiatric, behavioral, medical, psychophysiological, experimental, radiological, and explanatory evidence that nearly all psychiatric disorders and their functional comorbidities are rooted in this single, shared, neurophysiological abnormality [15]. The MCNH hypothesis is also corroborated by gene associations studies that link the major psychiatric disorders to ionchannelopathies [16-27]. These multi-center collaborative studies suggest 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 [16-23]. The delay in repolarization that this creates as neurons attempt to reestablish their resting potentials is thought to be at the root of virtually every psychiatric symptom and disorder [15].

In addition to the large body of evidence supporting it, the MCNH hypothesis has tremendous explanatory power. At the most fundamental level, the hypothesis explains why some persons are more vulnerable to developing psychiatric symptoms than others. This vulnerability is not an all-or nothing phenomenon but rather a *spectrum* of

vulnerability that is hypothetically determined by the level of excitability of the neurological system. Those with the lowest levels of neuronal excitability are thought to be the most resistant to developing psychiatric symptomatology because their neurological systems, when perturbed by stress, are slow to react and quick to recover, thus tending to prevent the pathological elevations in neurological activity that drive psychiatric symptoms (Figure 1A, purple and blue curves). At the other end of the spectrum are those with the highest levels of neuronal excitability. Their neurological systems are so reactive to stress and so slow to recover that psychiatric symptoms are experienced continuously (Figure 1A, red curve). In between these two extremes are those with mildly elevated neuronal excitability (Figure 1A, green curve); moderately elevated neuronal excitability (Figure 1A, yellow curve); and severely elevated neuronal excitability (Figure 1A, orange curve). All such persons are at an increased risk of developing psychiatric symptomatology because their neurological systems, when perturbed by stress, react more briskly and recover more slowly than normal [28]. The varying degrees of neuronal hyperexcitability are thought to correspond to the inheritance of either one or two of the additive and severity-specific gene polymorphisms that have been linked to the major psychiatric disorders [15]. Figure 1B provides an estimate of the percentage distribution of the different degrees of neuronal excitability in 1) the general population and 2) the psychiatric patient population.



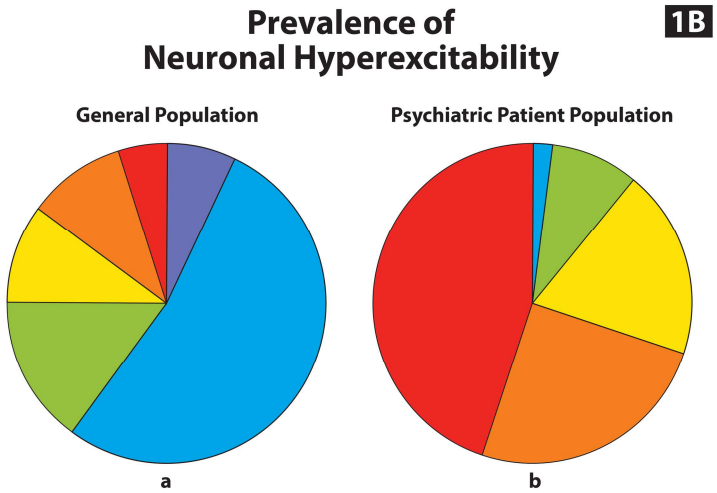


Figure 1. *1A) Conceptual illustration of the stress-response curves in persons with hypo-excitable neurons (purple curve); normoexcitable neurons (blue curve); mildly hyperexcitable neurons (green curve); moderately hyperexcitable neurons (yellow curve); severely hyperexcitable neurons (orange curve); and very severely hyperexcitable neurons (red curve). Note the differences that each of these groups express in their psychophysiological response and speed of recovery when challenged with a stressor. 1B) Approximate distribution of the spectrum of neuronal excitability in a) the general population and b) the psychiatric patient population. Note that an estimated 40% of the general population has some degree of neuronal hyperexcitability (green, yellow, orange, and red sections) and that among the psychiatric patient population nearly all have some degree of neuronal hyperexcitability and, thus, would fall into the bipolar spectrum. Also note that among psychiatric patients, only an estimated 2% do not have neuronal hyperexcitability (blue section). This is the small subgroup of patients that would be neurophysiologically-defined as having "true" unipolar depression.*

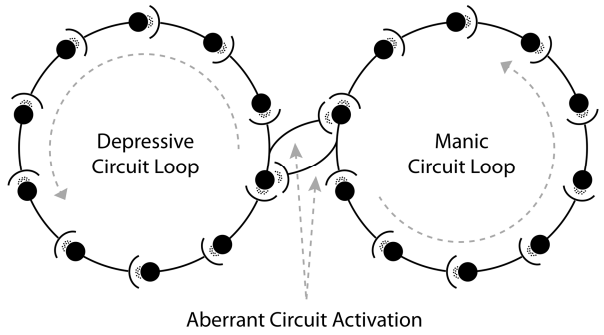


Figure 2. *Schematic illustration of aberrant circuit induction. In the example above, the depressive circuit-loop inappropriately excites the manic circuit-loop. This is more apt to occur in persons with neuronal hyperexcitability both because the neurological system tends to be more active and because aberrant receiver circuits, themselves being hyperexcitable, are more easily activated by aberrant feeder circuits. Note that in this example, the manic circuit loop could also excite the depressive circuit loop.*

In his original observations, Kraepelin noted that various different psychiatric symptoms could co-exist, wax and wane in severity, or alternate with one another [1]. It was this observation that led him to believe that all such symptoms were rooted in a shared biological abnormality [2]. The MCNH hypothesis provides the first comprehensive neurophysiological basis of support for this belief. According to the hypothesis, symptoms can co-exist because they are driven by pathological hyperactivity in symptom-related circuits in the brain, and more than one circuit can be pathologically hyperactive at the same time. More commonly, however, symptoms wax and wane in severity and alternate with one another because, in addition to competing for dominance [29], hyperactive circuits have the potential to aberrantly fuel hyperactivity in circuits that would normally be less active. The proposed mechanism by which this occurs is that hyperactive feeder circuits, typically in response to a psychological, emotional, or biological stressor [30], spontaneously stimulate hypo-active circuits via aberrant neuron-to-neuron connections [30]. Aberrant neuron-to-neuron connections are hypothesized to involve electrical and chemical connections between neurons that allow neural signaling to deviate from its intended path [30]. It is hypothesized that this aberrant electrical flow is encouraged by synaptic fatigue in hyperactive circuit loops [31] and further encouraged by a concomitant shift in attention, cognition, and emotion that then progressively feeds the bipolar switch. What is thought to make the involved connections aberrant is not their structure but their number; there are just too many of them, and the more of them there are, the greater the risk of aberrant circuit induction. The prototypical example of this neurological "short-circuiting" would be the inappropriate stimulation of a manic circuit loop by a depressive circuit loop or vice-versa (Figure 2). However, the same process could potentially involve a manic circuit and an anxiety circuit; an anxiety circuit and an irritability circuit; or an irritability circuit and a depressive circuit. Hypothetically, it could also involve the aberrant activation of limbic circuits by cognitive circuits and vice-versa.

The idea that symptom-cycling is at least partly related to the number of neuron-to-neuron connections is supported by the observation that although symptom-cycling is a highly dynamic process, each person with a bipolar-type disorder tends to have his or her own characteristic cycling frequency. It is also supported by computerized simulations of brain architecture, which suggest that the path taken by axons and dendrites as they sprout is much more random than previously thought, relying mostly on accidental collisions to determine which neurons connect with one another [32]. The randomness of these connections would, therefore, argue more for an abnormality in the number of connections than in a preprogrammed abnormality in their special architecture. This idea is also supported by the large variability in the total number of neurons in the brain. Using advanced counting techniques, the human brain has been estimated to have 81.6 billion (+/- 8.1 billion) neurons [33], and with each neuron forming connections with up to 15,000 other neurons [34], there is a lot of room for variance in the number of neuron-to-neuron connections the brain can have. Hypothetically, each extra connection would increase the risk of aberrant circuit induction, as would anything that increased the level of circuit-specific neurological activity. The latter could explain why bipolar patients tend to cycle during periods of high stress but stabilize during periods of low stress.

Although the number and location of aberrant neuron-to-neuron connections could, due to plasticity, change over time [35], they would clearly be more stable than the circuit-specific dynamics that are associated with changing thoughts and emotions. Those with more aberrant neuron-to-neuron connections would tend to cycle more rapidly and at lower excitation levels than those with fewer aberrant connections [30]. This, taken together with the fact that higher levels of neuronal hyperexcitability would, due to the additive nature of the alleles for neuronal hyperexcitability [15], be less common than lower levels of neuronal hyperexcitability, could explain why bipolar I disorder is less common than other disorders in the bipolar spectrum. It could also explain why the highs and lows in bipolar I disorder tend to be of greater amplitude than the highs and lows in bipolar II or cyclothymia. Having fewer neuron-to-neuron connections, patients with bipolar I disorder would tend to be more resistant to aberrant circuit induction and, thus, have more time to build momentum in a given cognitive-emotional state before the locus of hyperactivity was able to migrate to another cognitive-emotional circuit loop. Conversely, persons with more neuron-to-neuron connections would experience less time in one cognitive-emotional state or another and, thus, cycle more rapidly. Patients with an intermediate number of aberrant neuron-to-neuron connections would tend to develop cycles within cycles; that is, miniature or "ultra-rapid" cycles within more lengthy cycles of larger amplitude (Figure 3). Lending further support to this hypothesis of

symptom-cycling is the observation that patients with bipolar I disorder, who would necessarily have higher levels of neuronal excitability, are at greater risk of seizures than patients with other disorders in the bipolar spectrum [35-37].

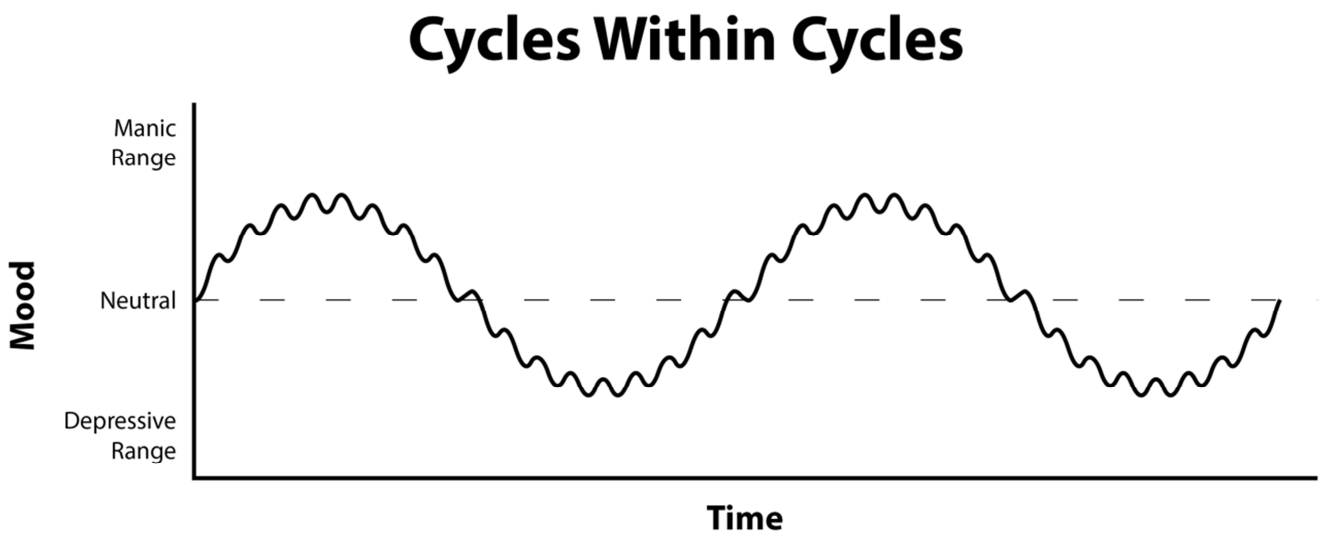


Figure 3. *Schematic illustration of cycles within cycles. Hypothetically, this pattern is reflective of an intermediate number of aberrant neuron-to-neuron connections.*

3. Neuronal Hyperexcitability: An Allusive Trait

Although neuronal hyperexcitability would, in itself, increase the risk of aberrant circuit induction, not all patients with neuronal hyperexcitability could be expected to display a cycling of symptoms. There are at least six possible reasons for this. The first is that the person's level of stress might not be high enough to directly stimulate any aberrant circuit induction. The second is that the inciting stressor might not persist for long enough to *kindle* aberrant circuit induction. First observed by Graham Goddard in his experiments on rats [38], kindling describes the natural tendency for neurons to become increasingly responsive with repeated stimulation. This adaptive process, which under normal physiological conditions is more aptly described as "primed burst potentiation" [39], is induced by stress [15, 29]. Kindling is the MCNH explanation for why the onset of psychiatric symptoms tends to be delayed relative to the onset of an inciting stressor. The third reason that neuronal hyperexcitability might not manifest as symptom-cycling is that the basal level of neuronal excitability might not be high enough to allow hyperactive feeder circuits to fuel hyperactivity in hypoactive receiver circuits. The fourth reason is that the mind could become so rigidly entrenched in one particular cognitive-emotional state, such as grief, anger, or fear, that it prevents aberrant circuit induction despite its natural potential to occur. The fifth reason is that there might not be enough aberrant neuron-to-neuron connections to support any recognizable cycling of symptoms. The sixth reason is that, conversely, the neurological system might be so tightly connected that the cycling of symptoms is too rapid to be detected by either the patient or the clinician. Also note that in such cases, the neurological system would convey a structural neuronal hyperactivity above and beyond any physiological neuronal hyperexcitability the person might have. This would further increase the risk of sensory hypersensitivity, sensory overload, and cognitive-emotional processing difficulties. The validity of this is supported by the unusually severe cognitive, emotional, and behavioral abnormalities that characterize autism spectrum disorder, a subgroup of patients that has been found to have an exceptionally large number of neurons and neuron-to-neuron connections [40, 41].

What makes the neuronal hyperexcitability trait even more elusive is that psychiatric symptoms might not develop until the hyperexcitable brain, like a hive of irritable bees, becomes adequately perturbed by some kind of mental, emotional, or biological stressor. That would explain why persons with low-to-moderate levels of neuronal hyperexcitability can enjoy relatively long periods of remission. However, the complete resolution of symptoms in such patients, especially if in the absence of medication, can lead both the patient and the clinician to erroneously conclude that symptomatic periods are purely psychological.

Another factor that makes neuronal hyperexcitability so elusive is that there is typically a time-lag between the onset of an inciting stressor and the onset of symptoms. This delay, which is the time required to generate enough stress-induced kindling to precipitate symptoms, can make it difficult for both the patient and the clinician to accurately identify the precipitating stressor or stressors. The problem is compounded by the fact that some patients, perhaps due to embarrassment or the associated emotional pain, may not reveal what is stressing them. Also, they might fail to report other common inducers of neuronal excitability, such as the illicit use of a stimulatory-type drug, the addition of a dietary supplement, the occurrence of an infection, or a significant

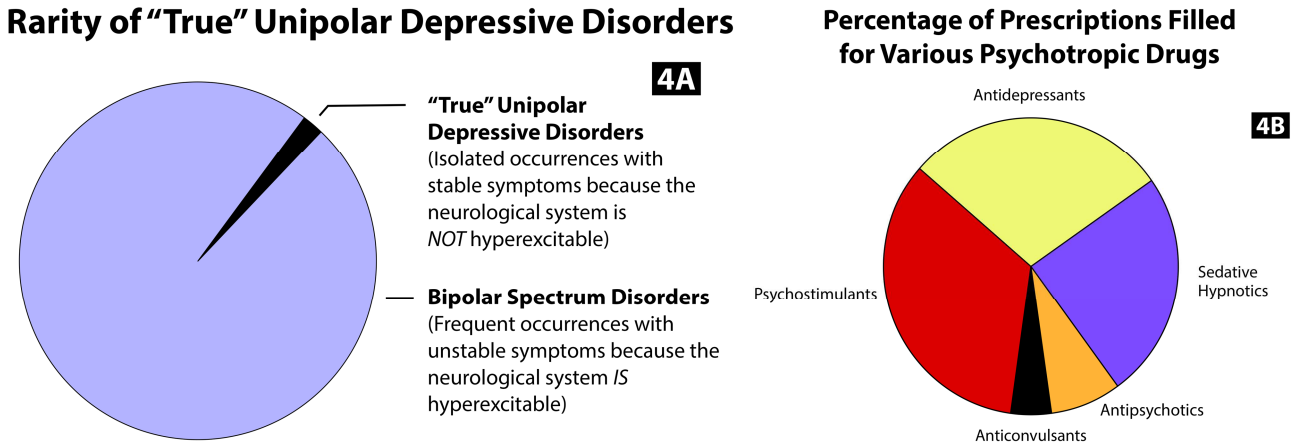
change in sleep schedule. These barriers to identifying the precipitating stressor have caused some clinicians to conclude that a psychiatric episode can begin spontaneously. However, unless the neurological system is so inherently hyperexcitable that symptoms are continuous, the onset or exacerbation of symptoms is always preceded by some kind of psychological or biological stressor.

Yet another reason that the neuronal hyperexcitability trait is so elusive is that the neurological hyperactivity that it fuels does not involve the brain as a whole, nor does it involve specific areas of the brain. Rather, it involves the brain's microcircuitry [42], both stimulating and being stimulated by the associated thoughts and feelings [43-47]. Because these microcircuits typically involve relatively small numbers of neurons communicating across distant parts of the brain, they are difficult to detect on scans that are more sensitive to regional changes in metabolic activity.

4. Discriminatory Power of the MCNH Hypothesis

Despite its subtlety, the recognition of neuronal hyperexcitability as the instigator of disease has opened up new vistas in the diagnosis and treatment of mental illness. The new conceptualization is embodied in the MCNH hypothesis, which states that psychiatric symptoms are the consequence of pathological hyperactivity in symptom-related circuits in the brain. Although this pathological hyperactivity is usually rooted in an inherent hyperexcitability of the neurological system, it can, in rare cases, be driven solely by an usually severe and persistent stressor. Hypothetically, the means by which this occurs is that the mind, in response to the stressor, becomes caught up in a specific cognitive-emotional state. As the involved circuits, under the influence of primed burst potentiation, become increasingly excitable, a vicious cycle of mutual overstimulation develops between the mind and the brain. In some cases, this psychophysiological dynamic can escalate to the point of continuing even against the willful intentions of the individual. This is the essence of clinical depression. Yet because such high levels of stress are relatively uncommon in comparison to low-to-moderate levels of stress, and because even low-to-moderate levels of stress could precipitate psychiatric symptoms in persons with hyperexcitable neurological systems, the MCNH hypothesis would predict that the vast majority of persons who present for psychiatric evaluation have some degree of neuronal hyperexcitability. In other words, they fall into the bipolar spectrum. By comparison, only a small minority of those with normoexcitable neurons would ever develop enough psychiatric symptomatology to present for psychiatric evaluation. Note, however, that such persons would in fact be different than Kraepelin's manic-depressive patients in that their neurons would not be inherently hyperexcitable. Also, when treated with antidepressants, such patients, because their neurons would lack enough excitability to permit aberrant circuit induction, would be relatively resistant to bipolar switching. They would also be relatively resistant to anticonvulsant therapy because their fundamental abnormality would not be neuronal hyperexcitability but rather a stress-related persistent circuit-specific imbalance. Isolated circuit-specific imbalances of this sort could potentially be corrected by bolstering activity in serotonergic, dopaminergic, and noradrenergic pathways, all of which tend to be inhibited by a stress-induced activation of the lateral habenula [48-52]. This is the MCNH explanation for the robust therapeutic effects that antidepressants can have in some patients. Hypothetically, the reason these patients are relatively resistant to mania is that, in the absence of neuronal hyperexcitability, pleasurable experiences are rarely capable of generating enough intrapsychic tension to drive a persistently pathological circuit-specific imbalance. The lack of sufficient neuronal excitability also prevents depression and other dysphoric emotional states from switching into mania. This is in contrast to patients with hyperexcitable neurons, who, because their neurological systems are so volatile, can rapidly shift in any direction, although, for the reasons discussed, they would be more likely to spiral into depression and other dysphoric states. Indeed, depressive episodes among patients with bipolar disorder are three times more common than manic episodes [53]. What makes antidepressant therapy in such patients so risky is that antidepressants, including serotonin reuptake inhibitors, have stimulatory effects on some parts of the brain [54, 55]. These effects can accentuate pre-existing circuit-specific imbalances [56]. They can also increase the risk of aberrant circuit induction [30]. On account of the instability of their neurological systems, patients with hyperexcitable neurons would more appropriately be treated with anticonvulsants, antipsychotics, and other drugs that help reduce excitation in the brain [8].

Thus, according to the MCNH hypothesis, Kraepelin's manic-depressive and Akiskal's bipolar spectrum nosologies are highly valuable in that they incorporate the vast majority of psychiatric patients. However, the MCNH hypothesis also supports the position of the DSM-3 working group and proponents of the bipolar-unipolar dichotomy in that it allows for the possibility that some patients could become clinically depressed though they do not, from a neurophysiological standpoint, fit into the bipolar spectrum. However, it should be re-emphasized that these patients would comprise only a tiny fraction of the psychiatric patient population (Figure 4A). Yet the sales of antidepressants out-stripe the sales of anticonvulsants by more than six-to-one (Figure 4B). What this implies, at least from the standpoint of the MCNH hypothesis, is that an alarming number of bipolar spectrum patients are being misdiagnosed with unipolar depressive disorders. This again underscores the weakness of symptom-based classification systems.



Figures 4. *Pie charts illustrating the approximate distribution of A) "true" unipolar depression in comparison to bipolar spectrum disorder; and B) sales of antidepressants relative to various other psychotropic drugs. Note the large discrepancy between the proportion of patients with bipolar spectrum disorder and the sales of the drugs that are the most appropriate for these patients; namely, anticonvulsants and antipsychotics. Also note the large discrepancy between the proportion patients with "true" unipolar depression and the number of prescriptions written for antidepressant drugs. These discrepancies reflect on the weakness of the current diagnostic system.*

A similar problem is created by the nosology of psychotic symptoms. Because psychosis can be a part of both bipolar disorder and schizophrenia, the presence of psychotic symptoms can blur the boundary between these two disorders. Kraepelin himself struggled with this, having assigned some psychotic patients to "manic-depressive insanity" and others to "dementia praecox" (roughly equivalent to modern-day schizophrenia) [2]. Yet the ability to distinguish between bipolar disorder and schizophrenia is important because one is treated primarily with anticonvulsant drugs and the other is treated primarily with antipsychotic drugs. Fortuitously, the MCNH hypothesis could, by illuminating the underlying cause of both disorders, be offering a biologically-based alternative to distinguishing between them. According to the MCNH hypothesis, psychotic symptoms develop when the level of electrical activity in the sensory processing system of the brain becomes as high as the level of activity that would normally be driven by input from the body's sensory organs. For example, aberrant discharges from neurons in the auditory processing system would cause the patient to think that the auditory nerve were being stimulated. This would lead to the misperception that sound was coming from the environment. Aberrant discharges from neurons in the visual processing system would cause the patient to think that the optic nerve were being stimulated. This would lead to visual hallucinations, etc… Although such aberrant signaling could potentially occur in anyone, it would be more likely to occur in persons with hyperexcitable neurons. This conceptualization is supported by a recent study that found that auditory hallucinations in schizophrenia were exaggerated versions of perceptual distortions that are not uncommonly experienced by persons who do not have schizophrenia [57]. 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 [58]. From the perspective of the MCNH hypothesis, the excess dopaminergic transmission would be the result of pathological hyperactivity in dopaminergic circuitry. Similarly, other forms of psychosis, such as paranoia and delusional thinking, would 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, olfactory, 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, or any factor that increases excitation in the brain, thus explaining why psychotic symptoms are more likely to develop under the influence of such factors.

A related phenomenon that can likewise be explained by the MCNH hypothesis is the odd separation or "schism" between thoughts and feelings that define the term "schizophrenia." Hypothetically, what causes this type of inappropriate affect is that cognitive activity that would normally activate the corresponding limbic circuitry is unable to do so because various hotspots of neural activity are competing for dominance [29]. As a result, the patient's emotions, rather than being dictated by the thought content, are dictated by inappropriate firing in limbic circuitry. It is also possible that the thought content, rather than being dictated by the emotions, could be dictated by inappropriate firing in cognitive circuitry. In extreme cases, the willful intentions of the individual could be completely usurped by this intensive, spontaneous, electrical activity. Such chaotic brain signaling would be more likely to occur in patients with extremely high levels of neuronal excitability, such as those with schizophrenia, bipolar disorder, borderline personality disorder, and other severe psychiatric 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 [23, 35, 36, 59].

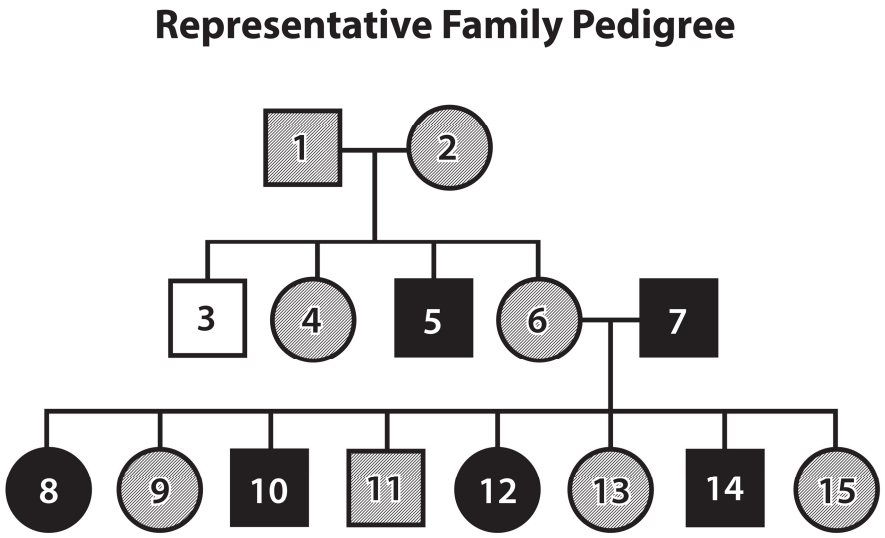
According to the MCNH hypothesis, antidopaminergic drugs exert their antipsychotic effects both by correcting circuit-specific imbalances in the dopaminergic system and by reducing neuronal excitability in general. The later is accomplished not only by blocking dopamine, which is an excitatory neurotransmitter, but also by blocking the excitatory neurotransmitters norepinephrine and histamine and by modulating a variety of serotonin receptors [60]. Note that this effect could be potentiated by other drugs that quiet the brain, thus explaining the well-known utility of combining benzodiazepines with antihistamines and antipsychotic drugs in the management of acutely agitated psychotic patients. Consistent with these observations, the neuronal hyperexcitability hypothesis would guide the additional use of non-benzodiazepine anticonvulsants and other brain-calming drugs in the treatment of psychotic disorders, as this would have the potential to reduce both positive *and* negative symptoms and with fewer side effects than when treatment is focused exclusively on blocking dopamine transmission.

The current classification system precludes this logic because a combination of psychotic symptoms and functional deterioration tends to trigger a diagnosis of schizophrenia. This is a matter of grave concern not only because of the adverse effects of, and poor patient compliance with, antipsychotic drugs, but also because of the negative effects that diagnostic labels can have on patients and their families. Particularly because psychiatric disorders tend to be chronic in nature, receiving a diagnosis like schizophrenia or bipolar disorder can be psychologically and emotionally devastating. Patients view doctors as authority figures, and so when a doctor hands down a stigmatizing diagnosis, it can feel to the patient as though a parent were saying that he or she were dumb, ugly, and would never amount to anything. Moreover, because psychiatric symptoms are so sensitive to intrapsychic tension, the associated stress could actually worsen the symptoms, thus leading to a kind of self-fulfilling prophesy. The other problem with diagnostic labels is that they generally dictate treatment…sometimes for the rest of a patient's life. They also dictate the labeling of the drugs that are used to treat the associated symptoms. Thus, if a patient is diagnosed with a psychotic disorder, the treatment is likely to be an antipsychotic drug. If a patient is diagnosed with a depressive disorder, the treatment is likely to be an antidepressant drug. As a result, antipsychotics, antidepressants, and other psychotropic drugs, both in name and in use, have become synonymous with the disorders they are used to treat. It follows then that the symptom-based diagnostic system can be damaging to patients even if the prescriber avoids using diagnostic terminology. The MCNH hypothesis circumvents these problems by offering a pathophysiologically-based, non-stigmatizing explanation for psychiatric symptoms together with a descriptive, user-friendly term for the tranquilizing drugs that could hypothetically be used to treat a wide range of psychiatric symptoms, including psychotic symptoms; namely "Neuroregulators" [61]. The validity of the MCNH hypothesis is supported by the observation that brain-calming drugs, from the early use of plant alkaloids and bromides, to phenothiazines and benzodiazepines, to the anticonvulsant and antipsychotic drugs of today, have always been the most rapidly-acting and continuously effective pharmacological agents for a wide range of psychiatric disorders [56, 61-63].

Another group of psychiatric disorders that has been distorted by the labeling of symptom clusters is the so-called "personality disorders." This poorly-defined categorization describes enduring patterns of maladaptive thoughts, emotions, and behaviors that develop early in life, deviate markedly from accepted cultural norms, and interfere with the development of normal healthy relationships. Because these abnormalities have traditionally been thought to be rooted in childhood emotional trauma and dysfunctional family dynamics, such patients are typically referred for psychotherapy with relatively little consideration given to the possibility their psychological, emotional, and behavior abnormalities could be rooted in a reversible neurophysiological abnormality. However, the observation that many of these patients have siblings who are relatively unaffected by the dysfunction in their families suggests that those who become more severely traumatized are inherently more vulnerable to stress. Moreover, the observation that such children, some of whom may not develop a personality disorder but rather some other kind of psychiatric disorder, tend to appear in a classic autosomal dominant distribution suggests that they may be the ones who inherit the genes for neuronal hyperexcitability [15] (Figure 5). The classic Mendelian distribution of psychopathology also suggests that among the many variables that contribute to the development of psychiatric disorders, including personality disorders, the inherited trait of neuronal hyperexcitability is the most influential.

Hypothetically, the reason that some of the children who inherit the genes for neuronal hyperexcitability develop personality disorders is that severe environmental stress, particularly caregiver stress, superimposed on an inherent hyperexcitability of the neurological system, creates the need for the child to develop the extreme coping strategies and primitive defense mechanisms that characterize personality disorders. Though these desperate efforts to protect the self may have been helpful in the chaotic households in which these children grew up, they tend to be relatively ineffective or even self-defeating later in life. Such children are likely to have very high levels of neuronal excitability, although some could have moderately elevated levels of neuronal excitability but a home life that was so dysfunctional and emotionally traumatic that they still developed a personality disorder. Hypothetically, those with moderately elevated neuronal excitability (or those being treated with Neuroregulators) would tend to make better progress in psychotherapy because the biological driver of the psychopathology is of lesser severity. Unfortunately, however, high levels of neuronal excitability and high levels of childhood trauma tend to co-occur because the trait that the children inherit tends to similarly impair the psychological, emotional, and behavioral functioning of their parents (Figure 5). This underscores the

importance of identifying the trait of neuronal hyperexcitability early in life and of reducing the level of neuronal excitability before initiating psychotherapy with personality-disordered patients. The failure to do so could help explain why, historically, personality disorders have been so treatment-resistant.



WHITE: Normal
SHADED: Heterozygous Carrier (mild-moderate neuronal hyperexcitability)
BLACK: Homozygous Carrier (severe neuronal hyperexcitability)

1. Generalized anxiety disorder; ADHD; Alcohol dependence;
2. Cyclothymia; ADHD; Alcohol dependence
3. Normal
4. Gereralized anxiety disorder; ADHD, Alcoholism
5. Borderline personality disorder
6. Persistent depressive disorder; Fibromyalgia
7. Cyclothymia; Narcissistic personality disorder
8. Borderline personality disorder; Migraine; Irritable bowel syndrome
9. Persistent depressive disorder
10. Bipolar Disorder; Panic disorder; ADHD; Alcohol dependence
11. Generalized anxiety disorder; Body dysmorphic disorder
12. Panic disorder; Histrionic personality disorder
13. Tourette's syndrome; Obsessive-compulsive disorder
14. Cyclothymia; Schizotypal personality disorder
15. Hyperthymic temperament; ADHD

Figure 5. *Representative family pedigree illustrating the autosomal dominant inheritance pattern of the neuronal hyperexcitability trait. Note that although individual psychiatric disorders do not follow a classic Mendelian distribution, various disorders, when viewed as different manifestations of a shared vulnerability trait, do follow a classic Mendelian distribution. Also note that personality disorders are more likely to occur in those children who inherent two alleles rather than only one allele for neuronal hyperexcitability. Representative illustration is based on more than 300 consecutive clinical interviews.*

The single exception would be a subtype of antisocial personality disorder known as "primary psychopathy" [64]. According to Skeem [65], primary psychopathy is associated with low emotional sensitivity, sub-normal levels of anxiety, and normal executive function. This is in contrast to "secondary psychopathy," (also referred to as "sociopathy" [66]), which is associated with high emotional sensitivity, high levels of anxiety, and impulsivity. Although both subtypes of antisocial personality disorder are characterized by antisocial behavior, such as defiance of authority, deceitfulness, and physical aggression, the behavior of the primary psychopath is cool and calculated, whereas the behavior of the secondary psychopath is volatile and impulsive [65]. From the perspective of the MCNH hypothesis, these two subtypes would be at opposite ends of the neuronal excitability spectrum. The primary psychopath would have *hypo*-excitable neurons, whereas the secondary psychopath would have *hyper*-excitable neurons (Figure 1A). The former could be considered "primary" in that neuronal *hypo*-excitability is an ipso facto trait; that is, its expression is a direct consequence of its presence. This is in contrast to neuronal *hyper*-excitability, which tends to be quiescent until the hyperexcitable brain, like a hive of irritable bees, is perturbed by stress. This difference could help explain why the

characteristics of primary psychopathy tend to develop earlier in life and somewhat independently of childhood adversity in comparison to secondary psychopathy, which tends to be more environmentally-influenced [65, 67]. Hypothetically, the lack emotional sensitivity in persons with *hypo*-excitable brains increases the potential for a hedonistic disregard for others, whereas the high emotional sensitivity of persons with *hyper*-excitable neurons increases the potential for a self-defensive disregard for others. The idea that primary psychopaths have *hypo*-excitable neurons is supported by functional imaging studies that reveal a widespread paucity of limbic activity in the brains of primary psychopaths [64, 68-70]. These individuals also tend to have lower HPA-axis activity, lower cortisol levels [70], lower resting heart rates, and lower systolic blood pressures [71-73]. Taken together, these observations suggest that the neurological systems of primary psychopaths are diffusely *hypo*-excitable. The early appearance and remarkable stability of these and other aspects of primary psychopathy across the lifespan provide strong support for the idea that primary psychopathy is genetically-based [74-76]. Likewise, the stability and persistence of the traits that characterize secondary psychopathy, though relatively delayed in onset, suggest that it too is genetically-based. That is not to say that every person who is genetically predisposed will develop some form of psychopathy, as there are many other factors that contribute to the development of a personality disorder. What it does suggest, however, is that psychopathy can be divided into two distinctly different neurophysiological subtypes: one that is an affective deficit, and one that is an affective disturbance. It suggests that the notorious resistance of primary psychopathy to therapeutic intervention is not the consequence of a failure to treat the underlying biological abnormality but rather the absence of a treatable biological target. This is in contrast to secondary psychopathy, which, like other psychiatric disorders, would be driven by a highly treatable neurophysiological abnormality. Moreover, the high level of neuronal excitability in which secondary psychopathy is likely to be rooted would be expected to drive relatively severe and persistent psychiatric symptoms, thus reiterating the importance of pharmacological intervention in such patients rather than psychotherapy alone. Appropriately educating such persons about the vulnerability trait that may underlie their emotional and behavioral problems could markedly increase the likelihood that they would participate in and benefit from treatment with medication and psychotherapy.

The same reasoning could be applied to any person who seeks psychotherapy as a first-line intervention. Clearly, what drives most persons to seek psychotherapy is a need to better manage their uncomfortable thoughts and emotions. With few exceptions, the underlying driver of these thoughts and emotions would be neuronal hyperexcitability: the hyperexcitable brain causes the mind to keep replaying things like a broken record. It causes the mind to keep rethinking things, holding on to anger, ruminating about the past, second-guessing one's self, and, in anticipation of the next emotionally traumatic experience, maintaining an overly defensive posture. From the perspective of the MCNH hypothesis, psychotherapy attempts to reduce this distressing mental and emotional activity by reducing intrapsychic tension. As the mind relaxes, the brain relaxes, and the neurological hyperactivity that drives the symptoms begins to diminish. In some cases, this can be extremely effective. However, there are several facets of psychotherapy that can potentially offset some of its benefits. First, the subject matter being discussed is itself processed by the hyperactive brain. Consequently, the information has the potential of being distorted. In other words, the patient can potentially present for discussion thoughts and feelings that are related more to aberrant discharges from the brain than to what is truly driving the intrapsychic tension. Also, some of these thoughts and emotions can actually increase intrapsychic tension, thus *increasing* rather than decreasing the neurological activity that is fueling the symptoms. Hypothetically, the reason that Freudian psychotherapy primarily targeted neurotic-range psychopathology was that neuroses, which, according to the MCNH hypothesis, would be driven by mild-to-moderate levels of neuronal hyperexcitability, would be less subject to neuropsychological distortion than more severe psychopathology, which would be driven by higher levels of neuronal excitability. Patients with neuroses would also have better processing ability and more room for tolerating the transient increases in neuronal activity that would be stimulated as one attempted to work through mentally and emotionally challenging issues. Another limitation of psychotherapy is that it fails to correct the biological abnormality that increases one's vulnerability to developing psychiatric symptoms in the first place. Consequently, most of the benefits of psychotherapy are short-lived, although some of them, through learning, plasticity, and, over longer periods of time, changes in attitude, can be more enduring, thus helping the patient to handle future stressors without allowing them to stress the mind, and in turn the brain, to such an extent. Still, this process takes time and is labor-intensive.

A more direct way to treat psychopathology, and one that would lay the groundwork for more effective psychotherapy, would be to address the root of the problem first. As alluded to earlier, that means reducing the excitability of the neurological system. This can be accomplished through a number of natural and medicinal interventions, which include establishing an early sleep schedule, engaging in moderate exercise, avoiding caffeine and other psychostimulants, minimizing refined sugar, and, in more severe cases, prescribing anticonvulsant drugs. By reducing the cognitive and emotional chatter that would otherwise interfere with the implementation psychological interventions, these interventions facilitate the use of psychotherapy, meditation, and other indirect methods of reducing psychiatric symptoms. Quieting the brain would also give the patient a greater ability to tolerate the emotionally distressing content that he or she may need to address in order to achieve satisfactory resolution of issues that would otherwise perpetuate a continuous cycle of mutual overstimulation between the mind and the brain.

Unfortunately, however, the availability of this targeted treatment modality has been eclipsed by distorted and incomplete theories of psychopathology, such as the belief that mental illness is purely psychological in nature; that psychiatric symptoms are driven entirely by stress; and that each of the common psychiatric disorders is a different biological abnormality requiring a different form of treatment. These beliefs can forestall or even prevent treatment by preventing affected persons from recognizing that most cases of severe mental and emotional distress are far more neurological in origin than they are psychological. Moreover, even when a patient attempts to address the presumed biological abnormality, the tendency of clinicians, due to their continued reliance upon symptom-based diagnostics, to mis-prescribe and over prescribe psychotropic drugs creates yet another barrier to successful treatment.

Another common psychiatric disorder that could be treated more effectively under the guidance of the MCNH hypothesis is attention deficit hyperactivity disorder (ADHD). According to the hypothesis, the primary symptom of ADHD—inattention—is the consequence of too many electrical signals bombarding the mind simultaneously. This causes the affected person to become distracted and, in some cases, speak and act impulsively as the mind shifts attention from one thought to another before it has a chance to fully process the previous thought psychophysiologically. The underlying neuronal hyperexcitability could also cause physical hyperactivity, although this would be expected to decline as the child became cognizant of behavioral and social norms. Lending further support to the idea that ADHD is rooted in neuronal hyperexcitability is the observation that attentional difficulties, like other psychiatric symptoms, tend to oscillate in severity for no logical reason. Yet, because the architecture of each person's brain is different and because neural circuits compete for dominance, not every person with a hyperexcitable brain would be expected to express the full triad of ADHD, and it is conceivable that some would not express any symptoms at all. Also, there is evidence that some persons, due to an inherent lack of dopamine sensitivity, may not be able to adequately modulate the abundance of electrical traffic coming into the thalamus [15, 77-79]. This finding is consistent with the observation that level of interest, which modulates dopamine release, also modulates the ease with which the mind can maintain focus. Although neuronal hyperexcitability and dopamine insensitivity are not mutually exclusive, attentional difficulties caused by dopamine insensitivity alone are, in my clinical experience, rare in comparison to attentional difficulties caused by neuronal hyperexcitability alone or a combination of neuronal hyperexcitability and dopamine insensitivity. Based on detailed clinical observations, it appears that more than 99% of patients with attentional difficulties have neuronal hyperexcitability, whereas attentional difficulties in the absence of neuronal hyperexcitability seem to occur in less than 1% of patients. The determination of whether a patient has both neuronal hyperexcitability and dopamine insensitivity as opposed to neuronal hyperexcitability alone can usually be made by analyzing the longitudinal course of the patient's symptoms. Attentional difficulties that date back to infancy and early childhood are suggestive of dopamine insensitivity with or without neuronal hyperexcitability, whereas attentional difficulties that begin to manifest in association with increasing stress (typically during the adolescent years) are hypothesized to be driven by neuronal hyperexcitability alone. The importance of making this distinction is that patients with neuronal hyperexcitability alone could hypothetically be treated with Neuroregulators alone. However, because neuronal hyperexcitability, which is estimated to affect at least 40% of the population, is so common among persons seeking mental health services, the vast majority of persons with dopamine insensitivity are likely to have neuronal hyperexcitability as well. Then again, neither neuronal hyperexcitability nor dopamine insensitivity is an all-or-nothing phenomenon, thus making it difficult to determine which patients with neuronal hyperexcitability also have dopamine insensitivity. However, recognizing that psychostimulants can exacerbate neuronal hyperexcitability and that reducing neuronal excitability could help alleviate the symptoms of ADHD, the MCNH hypothesis would suggest that in treating ADHD, any co-morbid psychiatric symptomatology be fully treated before adding a stimulant-type drug. Even better would be the ability to identify the trait that underlies the co-morbid symptoms and which can increase the risk of developing co-morbid symptoms.

No less consequential than the aforementioned short-comings of symptom-based diagnoses are the problems of patient-awareness and patient-acceptance of their own condition. Because psychiatric symptoms such as anxiety, depression, irritability, fear, and worry 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 being situationally-induced, many patients are unaware that their symptoms are abnormal. This, together with the stigma of mental illness, prevents many persons from seeking psychiatric treatment. 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 loved one 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 to admit that a treatable psychiatric condition is developing. All of these problems could be avoided by identifying the vulnerability trait in psychiatric disorders. The identification of such a trait could open the door to more timely treatment and, if the vulnerability trait could be therapeutically modified, symptom prevention.

5. Other Psychiatric Disorders

Although nearly all psychiatric disorders are thought to be rooted in an inherent hyperexcitability of the neurological system, the discussion of how the trait drives the symptoms of each disorder is beyond the scope of this article. However, much of this has been detailed in the article "Neuronal Hyperexcitability: Significance, Cause, and Diversity of Clinical Expression" [28].

6. How to Identify the Vulnerability Trait

All of this leads to a diagnostically critical question: is there an objective way to identify the neuronal hyperexcitability trait?

The answer is a resounding YES. It comes from a rapidly growing body of evidence that links subtle elevations in resting vital signs to the later development of various psychiatric and general medical conditions. For example, in a longitudinal study involving more than one million men in Sweden, Latvala et al. [80] 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. [81] 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 [82]. The subtle vital-sign elevations with which these illnesses are associated are thought to be the consequence of a tonic elevation in basal neurological activity in those persons who inherit the genes for neuronal hyperexcitability [82]. This is the MCNH explanation for why the lifespan of persons with severe mental illness tends to be much shorter than the general population [82]. The reason that psychiatric and "functional" physical symptoms tend to precede the development of diagnosable physical abnormalities is that the cognitive-emotional system is more expressive of neuronal excitation than other organs and tissues of the body. The physical consequences tend to be delayed because they express the erosive effects of neuronal hyperexcitability, which take time to occur [82].

From a treatment perspective, the biggest challenge in psychiatry today continues to be that of distinguishing bipolar spectrum disorders from unipolar depressive disorders. What makes this distinction so crucial is that, as previously discussed, the primary treatment for unipolar depression (i.e., antidepressant drugs) can make bipolar spectrum disorders worse [83-87]. Resting vital-sign measurements can make this distinction quantitatively because neuronal hyperexcitability, which is hypothetically at the root of bipolar spectrum disorders but not unipolar depressive disorders, drives a subtle but conspicuous elevation in resting heart and respiratory rates. 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. Hence, any patient with resting vital signs above these cut-offs would most likely have a bipolar spectrum disorder rather than a true unipolar depressive disorder (Figure 6).

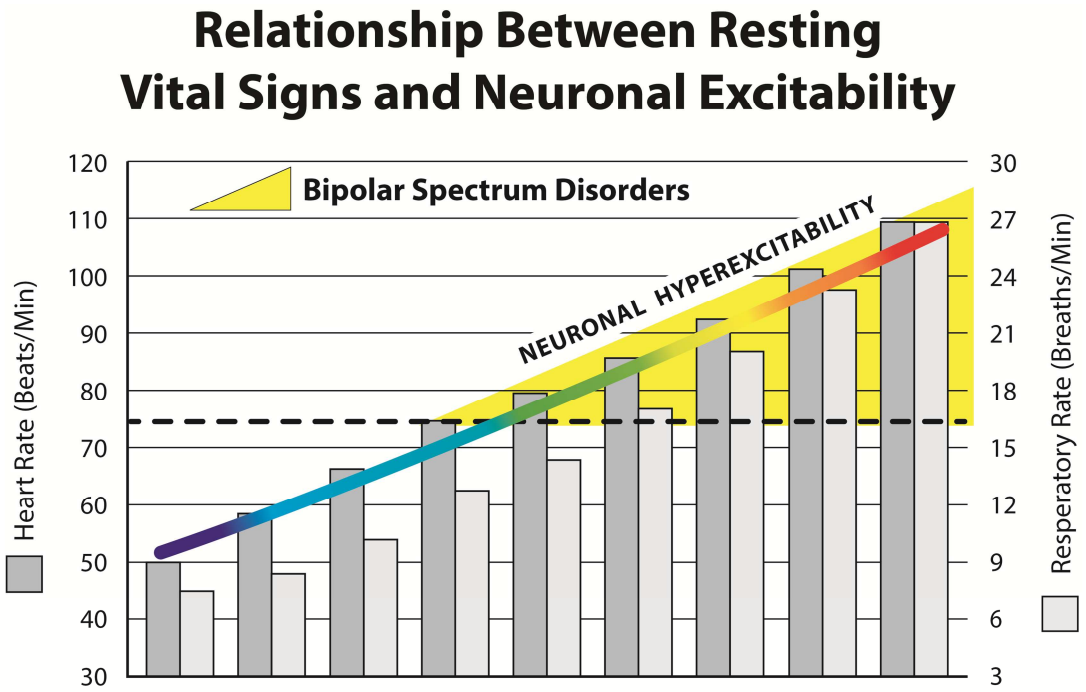


Figure 6. *Histogram illustrating the relationship between resting vital signs and neuronal excitability. As resting heart rate (dark grey bars) and resting respiratory rate (light grey bars) increase in numerical value, so too does the level of neuronal excitability (depicted by the changing colors of the multi-colored line). Because all patients on the right side of the graph (yellow zone) would have hyperexcitable neurons, all would fall into the bipolar spectrum and, therefore, would most appropriately be treated with Neuroregulators regardless of the nature of their psychiatric symptoms.*

Beyond having the potential to streamline the diagnosis of psychiatric disorders, the MCNH hypothesis provides a precise biological target for treatment; namely, neuronal excitability. Thus, by simply reducing the excitability of the neurological system, anticonvulsant drugs could, hypothetically, directly and rapidly alleviate psychiatric symptoms. Although the use of anticonvulsants in psychiatry is not new, what is new is the identification of the means by which they have been reducing psychiatric symptoms since antiquity. The practical advantage of recognizing this is that if one anticonvulsant fails to reduce symptoms, a different anticonvulsant could be tried rather than turning to a less targeted class of drugs. This approach, which could be called "Focussed Neuroregulation," is clinically valid because each anticonvulsant is structurally different, and there are multiple mechanisms (and receptors) through which the neurological system can be therapeutically regulated. Also, multiple anticonvulsants can be used in combination because they, unlike other classes of psychotropic drugs, carry little risk of further upsetting the excitatory/inhibitory imbalance in the brain; hence the name "mood-stabilizers."

Yet another advantage of the MCNH hypothesis is that it could replace socially-stigmatizing labels, such as "schizophrenia," "bipolar," and "borderline," with the more pathophysiologically-appropriate term "FLASH syndrome" [82]. FLASH is an acronym that stands for Familial Limbic Autonomic System Hyperexcitability. It describes what is hypothesized to be the fundamental abnormality in psychiatric disorders; namely, an inherent hyperexcitability of the neurological system that over-activates the limbic and autonomic nervous systems, thus elevating the affected person's temperament, vital signs, and emotional responses to stress. In addition to psychiatric disorders, FLASH is hypothesized to be the fundamental driver of violence, criminality, and substance use disorders [28]. As previously discussed, it is also thought to be the underlying driver of a wide range of chronic physical illnesses, thus giving it broad applicability.

7. Discussion

Since antiquity, psychiatric symptoms have been observed, studied, and debated. However, short of a clear understanding of their biological underpinnings, psychiatric symptoms have historically been segregated, somewhat arbitrarily [82], into various categories and treated accordingly. Not surprisingly, the symptom-based treatment of psychiatric disorders has led to unacceptably high levels of inappropriate psychological and pharmacological interventions. Long overdue is the need to elucidate the pathophysiology of psychiatric disorders so that diagnostics can be simplified and treatment can be directed squarely at the biological target.

That time may have arrived. According to the MCNH hypothesis, nearly all psychiatric disorders are driven by an inherent hyperexcitability of the neurological system. The hyper-responsively of the system to stress causes the affected person to over-react psychologically, emotionally, and behaviorally. What's more, a growing body of literature suggests that neuronal hyperexcitability also causes the autonomic, metabolic, and immunological systems of the body to over-react, thus increasing the risk of developing stress-related medical conditions, such as high blood pressure, diabetes, cardiovascular disease, autoimmune diseases, cancer, and dementia. It is hypothesized that even at rest, neuronal hyperexcitability drives a subtle elevation in basal neurological activity, thus allowing upper-end-of-normal vital signs to serve as objective markers of the neuronal hyperexcitability trait. This offers an enormous practical advantage to both mental health and primary care practitioners. For mental health practitioners, resting vital-sign measurements offer three important advantages. First, they offer the opportunity to assess mental illness objectively rather than having to rely solely on symptoms that, being subjective, are subject to interpretation by both the patient and the clinician. Second, they can be used to determine which patients would be more appropriately treated with Neuroregulator therapy than antidepressant therapy. Third, they can be used to determine which patients are at an elevated risk of developing psychiatric symptoms, thus opening the door to the possibility of using Neuroregulators prophylactically. For primary care practitioners, resting vital-sign measurements can be used to determine which patients are at an increased risk of developing any of wide range of general medical conditions. That opens the door to the possibility of using Neuroregulators to reduce the risk of physical illness as well.

The idea of being able to objectively measure one's vulnerability to developing almost any illness has the potential to initiate a major paradigm shift in healthcare. At present, the healthcare system is primarily reactive; a person develops symptoms, and the system responds by offering various treatment options. However, the final frontier of healthcare is to head-off illness before it even begins. The ability to assess illness vulnerability objectively and from an early age has the potential to make that possible. Also, because resting vital-sign measurements can be performed by almost anyone anywhere, and because the trait of neuronal hyperexcitability is highly modifiable, it has the potential to fully engage the public. That makes the measurement of resting vital-signs a simple, practical, and cost-effective way to prevent both acute and chronic illness.

8. Recommendations for Future Research

Throughout history, psychiatric symptoms have been observed, studied, and debated. However, short of a clear understanding of their biological underpinnings, psychiatric symptoms have historically been segregated, somewhat arbitrarily [88], into various categories and treated accordingly. Not surprisingly, the symptom-based treatment of psychiatric disorders has led to unacceptably high levels of errant psychological and pharmacological interventions. Long

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9. Recommendations for Future Research

Urgently needed are clinical studies aimed at better assessing the validity of the MCNH hypothesis and the ability of resting vital-sign measurements to predict the development, clinical course, and response of psychiatric disorders to various psychotropic drugs. One such study could involve assigning anticonvulsant therapy vs. antidepressant therapy to a cohort of clinically depressed patients based on resting vital-sign measurements as opposed to symptom-based methods of distinguishing bipolar spectrum disorders from unipolar depressive disorders. Another study could compare resting vital-sign measurements to symptom-based assessments as predictors of paradoxical antidepressant effects in depressed patients assigned to receive antidepressant therapy. Yet another study could examine the protective effects of anticonvulsant prophylaxis vs. natural interventions in a cohort of subjects that, based on resting vital-sign measurements, was deemed to be at an increased risk of developing a psychiatric disorder, substance use disorder, or general medical disorder.

10. Conclusion

The identification of neuronal hyperexcitability as the underlying driver of both mental and physical illness has enormous implications. First, it has the potential to simplify and strengthen the psychiatric diagnostic system by providing an easy-to-measure, pathophysiologically-based, objective means of determining which type of treatment would be best for which patient. Second, it helps engage the mentally ill by replacing stigmatizing diagnostic labels with a user-friendly acronym—"FLASH"—that recapitulates the fundamental abnormality that is being treated; namely, scattered electrical storms in the brain. Also, because the FLASH trait is thought to underlie both mental and physical illness, it has a natural resistance to becoming stigmatized. Third, it shows that attention to mental health is fundamental to optimizing physical health. Fourth, it provides the first biologically-based target for the treatment of a wide range of psychiatric disorders. Fifth, by introducing the possibility of preventing both mental illness and physical illness through the same natural and medicinal interventions (i.e., calming the brain) it paves the way to curtailing discriminatory practices that limit insurance coverage for mental health services. Sixth, it encourages health-awareness by providing a simple, objective means by which to self-assess one's vulnerability to any type of illness, mental or physical.

In an era of smartphones, wearable devices, and a growing public desire to prevent rather than react to illness, the ability to use resting vital signs to identify the fundamental driver of both mental and physical illness could usher in history's greatest campaign in the fight against sickness and disease.

Conflicts of Interest

The author declares that he has no competing interests.

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