American Journal of Clinical and Experimental Medicine
2022; 10(1): 23-37
http://www.sciencepublishinggroup.com/j/ajcem
doi: 10.11648/j.ajcem.20221001.14
ISSN: 2330-8125 (Print); ISSN: 2330-8133 (Online)

Review Article

New Hypothesis Unifies Previous Theories of Psychopathology and Identifies Core Biological Abnormality in Psychiatric Disorders

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To cite this article:
Michael Raymond Binder. New Hypothesis Unifies Previous Theories of Psychopathology and Identifies Core Biological Abnormality in Psychiatric Disorders. *American Journal of Clinical and Experimental Medicine.* Vol. 10, No. 1, 2022, pp. 23-37.
doi: 10.11648/j.ajcem.20221001.14

Received: January 4, 2022; **Accepted**: January 20, 2022; **Published**: January 28, 2022

Abstract: Despite millennia of philosophical debate and the enormous strides that have been made in neuroscience over the last century, the pathophysiology of psychiatric disorders remains unclear. Although the monoamine hypothesis has, for more than fifty years, provided a strong basis of support for the use of antidepressants in the treatment of depression, the overall success rate with antidepressants has been disappointingly low. Coincidingly, the monoamine hypothesis has come under increasing scrutiny for failing to explain all of the phenomena that characterize mood disorders. Consequently, mental health researchers, in an effort to find new molecular targets for treatment, have been searching for a more comprehensive explanation of the means by which psychiatric symptoms develop. Recently, several new models of depression have been proposed, including the immune, the endocrine, the glutamatergic, the GABAergic, the mitochondrial, and the neuroplastic; but none of them integrate the workings of the mind with the workings of the brain, and none of them explain how abnormalities in brain function actually translate into abnormalities in thought and emotion. However, an emerging hypothesis—one that reconceptualizes the anatomy of the cognitive-emotional system and unifies previous psychological and biological theories of psychopathology—posits that psychiatric symptoms are induced by a vicious cycle of mutual overstimulation between the mind and the brain. According to the Multi-Circuit Neuronal Hyperexcitability Hypothesis of Psychiatric Disorders, the mind, when under stress, overstimulates the associated neurons and circuits. The associated neurons and circuits, in turn, overstimulate the mind, particularly if the neurological system is inherently hyperexcitable. The result is an abnormal increase in the intensity and the duration of the associated thoughts and emotions, a change that distinguishes functionally abnormal thoughts and emotions from normal ones. A more detailed understanding of the mechanism by which psychiatric symptoms develop and perpetuate has important implications for treatment, as it would allow psychotherapists to better visualize what is happening in the cognitive-emotional system; it would allow psychiatrists to better visualize the target for medical interventions; and, by reducing the stigma of mental illness, it would allow patients to be more willing to seek and follow through with mental health care.

Keywords: Pathophysiology of Psychiatric Disorders, Biology of Mental Illness, Neuronal Hyperexcitability, Biomarkers of Disease, Objective Assessments, Anticonvulsants, Mood Stabilizers, Neuroregulators

1. Introduction

Despite millennia of philosophical debate and the enormous strides that have been made in neuroscience over the last century, the pathophysiology of psychiatric disorders remains unclear. Although the monoamine hypothesis has, for more than fifty years, provided a strong basis for the medical treatment of depression, the overall success rate with antidepressants has been disappointingly low [1]. Coincidingly, the monoamine hypothesis has come under increasing scrutiny for failing to fully explain the biology of mood disorders [2]. Consequently, mental health researchers, in an effort to find new molecular targets for treatment, have been searching for a more comprehensive explanation of the

means by which psychiatric symptoms develop. Acquiring a better understanding of the psychological and neurological mechanisms by which psychiatric symptoms begin and perpetuate has important implications for treatment, as it would allow psychotherapists to better visualize what is happening in the cognitive-emotional system; it would allow psychiatrists to better visualize the target for medical interventions; and, by reducing the stigma of mental illness, it would allow patients to be more willing to seek and follow through with mental health care.

This article will review the various beliefs that have been held and theories that have been proposed about mental illness and then proceed with a discussion of the most recent theories in relation to an emerging new hypothesis that unifies those theories and integrates, for the first time, brain structure, brain function, and mind-brain dynamics to illuminate what I believe to be the core physiological abnormality in psychiatric disorders. The article will then discuss how that core abnormality links psychiatric disorders to a wide range of chronic diseases and calls for psychiatric symptoms to be reconceptualized as the first subjective markers of a vulnerability trait that can hasten the onset and progression of any disease that can be precipitated or exacerbated by stress. It will also discuss how the new hypothesis guides the use of resting vital-sign measurements as the first *objective* markers of the vulnerability trait and opens the door to a whole new world of preventive medicine.

2. Historical Views of Psychopathology

2.1. Spiritual Beliefs About Psychopathology

The prevailing views from early history were that psychiatric disorders were spiritual in nature, the evidence that evil forces had taken hold of a person's soul. As a result, the mentally ill were both judged and feared by others, including the physicians of the time, who were primarily religious leaders. Primitive treatment practices included social isolation, threats of punishment, and invasive procedures such as blood-letting and trepanning in an effort to release the offending spirit [3]. These views persisted through the Dark and Middle Ages, and it was not until the turn of the twentieth century that modern theories about psychopathology began to emerge.

2.2. Psychological Theories of Psychopathology

Newly evolving theories about mental illness were broadly divided into two camps: the psychodynamic theory, introduced by Austrian neurologist Sigmund Freud (1856–1939), and the behaviorist theory, introduced by American psychologist John B. Watson (1878–1958) [4]. Freudian theory was based on the idea that intrapsychic conflict between unconscious drives and socially acceptable behavior created emotional and psychological distress. Hence, Freud believed that psychopathology could be treated by relieving that distress. In contrast, behavioral theory conceptualized psychopathology as the consequence of maladaptive behavioral conditioning. Accordingly, treatment involved the use of behavioral interventions, which were primarily based on the principles of classical conditioning elucidated by the Russian physiologist Ivan Pavlov (1849–1936) [4]. Later, other theorists, such as American psychologist Albert Ellis (1913–2007) and American psychiatrist Aaron Beck (b. 1921) began to adopt treatment strategies aimed at addressing the maladaptive cognitions and emotions that were believed to underlie mental disorders [5, 6]. The cognitive and behavioral schools of thinking were eventually combined to form cognitive-behavioral therapy (CBT), an approach that has become the gold standard in the treatment of anxiety disorders [7, 8]. Other psychological approaches that are commonly used today include cognitive-analytic therapy, dialectic behavioral therapy, interpersonal psychotherapy, supportive psychotherapy, and mindfulness therapy [9]. Although all of these approaches provide benefit to many patients, the psychophysiological mechanism (or mechanisms) by which they exert their therapeutic effects remain unclear.

3. More Recent Views of Psychopathology

3.1. The Genetic Hypothesis

Family, twin, and adoption studies provide solid evidence that all of the major psychiatric disorders are familial and that this familiality is mostly due to genetic factors [10]. This important finding suggests that parental influences and other early life experiences are not as important in the development of these disorders as previously thought. However, twin and adoption studies fail to show a 100% concordance of any of the major psychiatric disorders, and the data from genome-wide association studies suggest that multiple genes combine to differentially increase one's vulnerability to developing one psychiatric disorder or another. Still, a major limitation of these studies is the necessity to use symptom-based classification systems, which, being based on subjective observations and clinical outcomes rather than objective determinations, do not necessarily describe distinct pathophysiological processes and could instead be describing different manifestations of a shared vulnerability trait.

3.2. Psychosocial Stress Hypothesis

Psychosocial stress has long-been recognized to be an important factor in the development of psychiatric symptoms. For example, studies have found that depressive disorders are associated with a 2.5 times greater frequency of stressful life events during the period leading up to the onset of symptoms [11]. Stress has also been linked to treatment resistance [12], poorer prognosis [13], and higher rates of relapse [14, 15] of major depressive disorder. Although numerous theories have been proposed to explain these phenomena, such as stress-induced dysregulation of neurotransmitters [16], alterations in receptor sensitivity [17], overactivity of the amygdala [18], under-activity of the hippocampus [18], dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis [19, 20], dysruption of metabolic [21] and

immunologic function [22-24], mitochondrial dysfunction [25], stress-induced activation of the lateral habenula [26-30], decreased neurotrophic factors [21], blunted neurogenesis [21], disrupted synaptogenesis, diminished dendritic spines, and stress-induced apoptosis [19, 20, 25, 31], they fail to explain why stress causes psychiatric symptoms in some persons but not in others. They also fail to explain the cycling of symptoms that occurs in bipolar disorder, cyclothymia, and other disorders in the bipolar spectrum, and, most fundamentally, they fail to explain how the identified chemical and physiological abnormalities translate to the cognitive and emotional abnormalities that characterize clinical depression and other psychiatric disorders.

3.3. The Diathesis-Stress Hypothesis

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

3.4. The Monoamine Hypothesis of Depression

The monoamine hypothesis, which for more than fifty years has provided a biological basis for the use of antidepressants in the treatment of clinical depression, was formulated based on a number of key observations. The first was that the antihypertensive drug reserpine precipitated depressive symptoms in a subset of hypertensive patients [32]. Reserpine was noted to deplete intracellular stores of serotonin and to increase urinary output of the serotonin metabolite 5-hydroxyindoleacetic acid [33]. Further evidence for the role of serotonin (and subsequently of other monoamines) in the pathophysiology of depression came from the serendipitous discovery that iproniazid, an anti-tuberculin drug that was later found to increase the availability of monoamines in the synaptic cleft, improved mood in tuberculosis patients who were also suffering from depression. Although the aforementioned clinical and biochemical observations provided a basis of support for the idea that depression was caused by a deficiency of monoaminergic neurotransmission, there was a subsequent need to modify the hypothesis to account for the delay in therapeutic effect that was observed with antidepressants. However, even after modification of the hypothesis to include receptor downregulation, there were still several limitations of the hypothesis. First, the hypothesis could not explain the beneficial effects of antidepressants in the treatment of psychiatric disorders that seemed to have a different biological basis than depression, such as panic disorder, obsessive-compulsive disorder, and a number of other psychiatric disorders [34]. Second, it could not explain why antidepressants sometimes cause depressive symptoms to worsen, cycle back and forth, or just continue without any improvement. Third, it failed to explain why the depletion of serotonin precursors did not produce depressive symptoms in normal subjects [35]. Fourth, it could not explain how the putative abnormalities in the monoaminergic system translated to the abnormalities in thought, emotion, and behavior that characterize mood disorders.

4. Newer Models of Psychopathology

4.1. The Immunologic Hypothesis

In recent years, a bidirectional link has been found between psychiatric disorders and mediators of inflammation [36-43]. Psychological stress and negative emotions activate peripheral physiological mechanisms that stimulate the immune system. Conversely, peripheral mediators of inflammation signal cognitive, emotional, and behavioral changes that are consistent with major depressive disorder. Recent meta-analyses that bring together many thousands of patients have found that more than half of patients with major depressive disorder have elevated inflammatory markers [37], and one study found that nearly half of patients being therapeutically treated with the proinflammatory cytokine interferon-alpha developed symptoms of depression that resolved when the immunotherapy was discontinued [38]. Although the neurological system and the immunological system had long-been thought to function independently of each other, numerous points of interaction between the two systems have now been identified [39]. These links raise the question of whether mental illness is an immunological abnormality [37]. However, it was found that reducing inflammation failed to completely eliminate psychiatric symptoms [40, 41]. Also, it was later found that anti-inflammatory drugs are more helpful in those patients who have higher levels of pre-treatment inflammation [42, 43]. These observations suggest that while inflammatory markers can precipitate or exacerbated symptoms of depression, they are not the underlying cause of depression.

4.2. The Endocrine Hypothesis

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

4.3. The Glutamatergic Hypothesis

Several lines of evidence have linked major depressive disorder to a dysregulation of the excitatory neurotransmitter glutamate [46, 47]. The attention to glutamate was sparked by the rapid and robust antidepressant effects of ketamine, an antagonist of the N-methyl-D-aspartate (NMDA) receptor. Although the clinical use of ketamine for depression is limited by its potential for abuse, its speed of action and impressive ability to relieve symptoms deserve special attention in regard to elucidating the neurobiology of depression. Glutamate is

the primary excitatory neurotransmitter in the brain, and so the observation that blocking its activity can rapidly relieve depressive symptoms suggests that mental illness may somehow be related to pathologically-elevated excitation in the brain. Yet the idea that psychiatric symptoms are due to brain hyperactivity still leaves many questions unanswered, the most basic of which is the question of why antidepressants, many of which *increase* excitatory neurotransmission, can be so effective in relieving depression, anxiety, and other psychiatric symptoms.

4.4. The GABAergic Hypothesis

A series of magnetic resonance spectroscopy studies consistently showed reductions in total gamma-aminobutyric acid (GABA) concentrations in the prefrontal and occipital cortex in acutely depressed patients [48]. Since this abnormality was specific to GABA, it raised the question of whether depression could be the consequence of altered GABAergic transmission. However, the reduced GABAergic activity could simply be part of the natural response to stress, as acute stress generally does induce presynaptic down-regulation of GABAergic transmission in the prefrontal cortex [49]. In addition, chronic stress may reduce GABA-A receptor function, possibly through changes in neuroactive steroid synthesis [50]. Although it has been suggested that the depressed GABAergic activity could also reflect a reduction in the size and density of GABAergic interneurons [51], this idea is refuted by the observation that prefrontal GABA concentrations return to normal when depressive symptoms remit [52]. That being said, it appears that what the decreased GABAergic concentrations do reflect is that clinical depression is intimately tied to stress.

4.5. The Central Sensitivity Hypothesis

Another hypothesis—one that primarily emerged from the observation that biopsychosocial stress tends to initiate or exacerbate various physical systems for which no organic basis can be found—has been named "central sensitivity." According to the central sensitivity hypothesis, an inciting factor, such as an allergen, a toxin, a physical injury, or an emotionally traumatic event, increases the sensitivity of the central nervous system (CNS) to subsequent stressors, thereby leading to intermittent and, in some cases, chronic conditions, such as irritable bowel syndrome, fibromyalgia, migraine headache, temporomandibular joint syndrome, and other chronic pain syndromes [53]. Central sensitivity is also thought to explain the various psychiatric symptoms that are commonly observed in persons who present with the aforementioned conditions [54, 55]. A similar nosology, referred to as "body distress syndrome" likewise unifies a wide range of functional disorders under a single title [56]. What remains unexplained, however, is why some persons develop the aforementioned hypersensitivities and psychiatric symptoms, while others do not. It also fails to explain how, neurophysiologically, the hypersensitivities translate into psychiatric symptoms.

4.6. The Gut-Brain Hypothesis

In recent years, reciprocal interactions between the bowel and the brain have become an area of increasing focus, particularly in relation to mental health [57, 58]. The high co-morbidity between psychiatric disorders and gastrointestinal disorders is well-recognized [57, 59]. The brain and the bowel interact both directly and indirectly. The vagus nerve connects directly to the bowel via the celiac and superior mesenteric plexus [59]. Conversely, the bowel synthesizes GABA, monoamines, and other neurotransmitters, which can enter the peripheral circulation and cross the blood-brain barrier [59].

Top-down, there is some evidence that emotional stress and poor dietary habits can drive pathological changes in the gut microbiome [60]. Conversely, pathological changes in the gut microbiome can affect mental health. For example, subepithelial dendritic cells, a common cell-type of the intestinal immunological system, extend their dendrites past intestinal epithelial cells and collect bacteria and their metabolic products from the intestinal lumen [58]. These cellular products can then be presented to T cells in the lymphatic system, thus initiating an immune response. They can also circulate to the brain, where they can have the same effect. Another means by which pathogenic antigens can enter the bloodstream is via microdamage to the gut epithelium caused by pathological changes in gut microbiota [58]. This phenomenon, known as "leaky gut syndrome," provides another mechanism through which pathological changes in the flora of the intestine can stimulate an inflammatory response. The significance of this is that inflammatory cyctokines, such as interleukin-1-beta, tumor necrosis factor-alpha, and interleukin-6, which are secreted not only by peripheral immune cells but also by microglia, astrocytes, and neurons in the CNS, increase neuronal excitability by several mechanisms, including direct modification of neuronal membrane ion channels, upregulation of glutamate transmission, and downregulation of GABAergic transmission [22-24].

Although the reciprocal interactions between the brain and the bowel provide support for the gut-brain hypothesis of psychiatric disorders, it stills fails to explain why some persons are relatively resistant to mental illness regardless of their diet and exposure to stress, while others are highly vulnerable to both mental illness and physical illness irrespective of how much attention they pay to their bowel health and lifestyle. Also, like other hypotheses, the gut-brain hypothesis fails to explain how the proposed pathogenic effects actually translate into psychiatric symptomatology.

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

The MCNH hypothesis of psychiatric disorders is based on the simple premise that thoughts and emotions stimulate the corresponding brain circuits and, conversely, specific brain circuits stimulate the corresponding thoughts and emotions. That this mind-brain dialogue actually occurs has now been

demonstrated experimentally. Recording from single neurons in patients implanted with intracranial electrodes for clinical reasons, Cerf et al. [61] found that willful thoughts and emotions readily stimulated specific neurons when subjects were asked to perform specific mental tasks. Conversely, stimulation of different parts of the brain with an electrical probe was found to trigger different thoughts and emotions [62]. What this implies is that specific cognitive-emotional stressors could cause the activity of the associated neurons and circuits to become amplified accordingly [63]. Likewise, elevated activity in specific neurons and circuits could cause the related cognitions and emotions to become correspondingly amplified [64, 65]. According to the MCNH hypothesis, this mind-brain dialogue, in conjunction with the neuroplastic effects of primed burst potentiation [66], could explain how persistent stress could cause specific circuits in the brain to become increasingly active over time. It could also explain how manipulating the activity of specific circuits, as is currently done both pharmacologically [67] and magnetically [68] in the treatment of depression, can affect cognitive and emotional functioning. In other words, it could explain how psychological processes affect neurological processes, and neurological processes affect psychological process in the production of psychiatric symptoms.

Note that a mind-brain dialogue could also provide a psychophysiological explanation for the distinction between conscious, preconscious, and unconscious thoughts as originally proposed by Sigmund Freud [69]. According to the mind-brain hypothesis, conscious thoughts would be those that arise when neurological impulses synchronize with mental impulses; preconscious thoughts would be those that the brain could readily synchronize with if the mind were to turn its attention to them; and unconscious thoughts would be those that the brain, whether by the will of the mind or otherwise, is not synchronizing with.

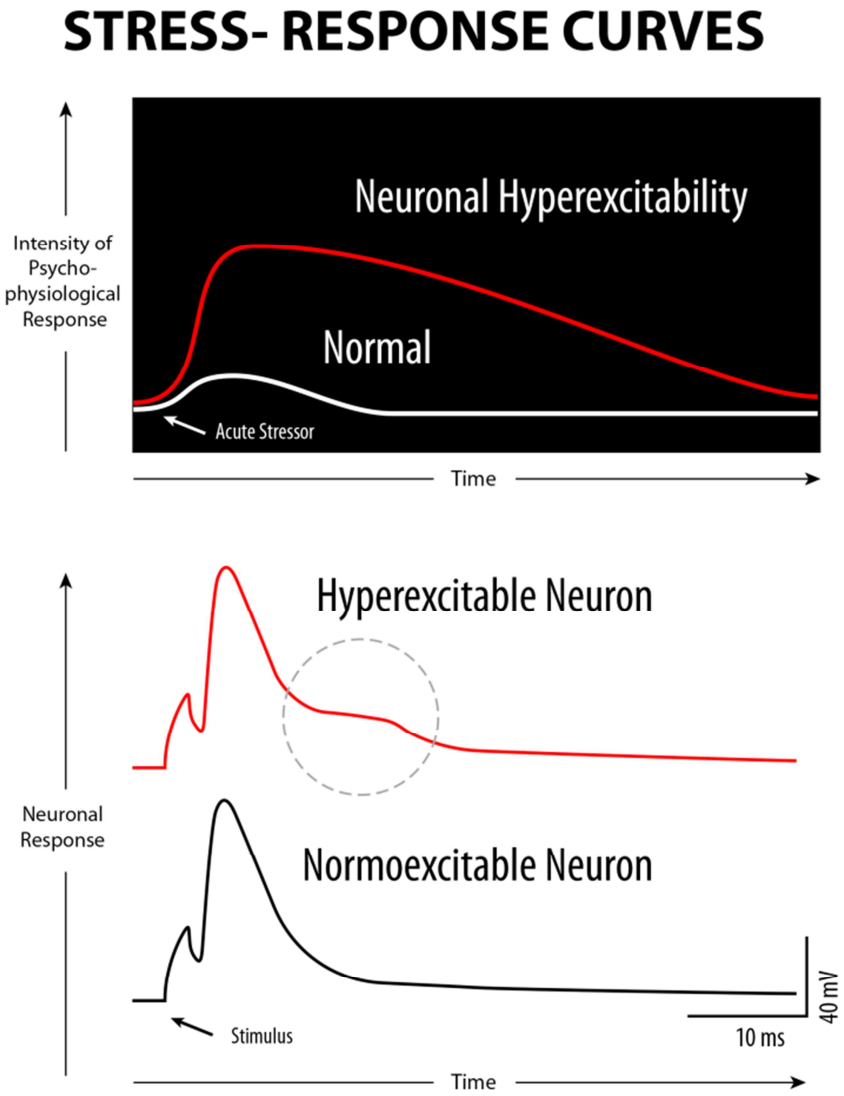

Figure 1. *Stress-response curves illustrating 1) pathological cognitive-emotional response in comparison to a normal response; 2) electrical response of a hyperexcitable neuron in comparison to a normal neuron. Note the striking similarity between the cognitive-emotional response curves and the neuronal response curves. Adapted from Lopez-Santiago LF, et al. "Neuronal hyperexcitability in a mouse model of SCN8A epileptic encephalopathy" [70].*

Still, a stress-induced escalation in the dialogue between the mind and the brain would not explain why some persons are more vulnerable to developing psychiatric symptoms than others. Strikingly, however, a number of large, multi-center gene association studies have found that the top candidate genes for bipolar disorder, major depressive disorder, and schizophrenia—disorders that together express all of the symptoms of the common psychiatric disorders, involve ionchannelopathies [71-82]. In other words, the protein products of the candidate genes fail to regulate the excitability of neurons. The inheritance of these genes would amp up the vicious cycle of mutual overstimulation between the mind and the brain that is proposed to occur under the influence of stress. Thus, the inheritance of ionchannelopathies would distinguish those patients who were more vulnerable to developing psychiatric symptoms from those who were less vulnerable. The unlikely connection between the gene research and the fundamental tenets of the MCNH hypothesis provides strong evidence that the hypothesis is valid. Additional evidence in support of the MCNH hypothesis includes but is not limited to the following observations:

1) That some psychological or biological stressor is always antecedent to the development or exacerbation of psychiatric symptoms.
2) That the same conditions and chemicals that increase the risk of seizures also increase the risk of psychiatric symptoms, and the same conditions and chemicals that decrease the risk of seizures also decrease the risk of psychiatric symptoms [83].
3) That there is a striking similarity between the electrical response of an individual hyperexcitable neuron and the stress-response of a person with mental illness (Figure 1). Note the delay in recovery of both curves in comparison to their reference curves. This delay is precisely what distinguishes, on a neuropsychiatric basis, an abnormal thought or emotion from a normal one. Of course, psychiatric symptoms are more intense and more persistent than illustrated by the response curve of an individual neuron; but that is hypothetically because psychiatric symptoms represent the collective and repetitive responses of populations of neurons rather than a single neuron.
4) That psychiatric symptoms, such as depression, can be alleviated by identifying and modulating the circuits in the brain that are uniquely associated the symptoms [68].
5) That an antidepressant can have a therapeutic effect at one point in time and a counter-therapeutic effect at another point in time, as exemplified by a bipolar switch [84]. The MCNH explanation for this is that pathologically hyperactive circuit loops fuel hyperactivity in collateral circuit loops while themselves waning in activity due to synaptic fatigue [85, 86].
6) That antidepressant drugs, which alter the activity of specific circuits relative to other circuits in unpredictable ways, likewise have unpredictable effects on psychiatric symptomatology [84].
7) That electroconvulsive therapy, which induces strong GABAergic activity and exerts a powerful postictal stabilizing effect on the neurological system, has for decades been the gold standard in the treatment of a wide range of psychiatric disorders [87].
8) That anticonvulsant drugs, which, like the postictal state, have powerful neuroinhibitory effects, rapidly reduce psychiatric symptoms and stabilize the cognitive-emotional system [88-90].
9) That the premenstrual period, the postpartum period, and the perimenopausal period, all of which are associated with a fall in the concentration of progesterone (a neurosteroid with powerful anticonvulsant effects), are commonly associated with the development of psychiatric symptoms [83].
10) That even in those psychiatric patients who do not formally qualify for a diagnosis of obsessive-compulsive disorder (OCD), obsessional tendencies, which represent a reverberation of hyperactive circuit loops, are common [91, 92].
11) That the MCNH hypothesis would offer the first psychophysiological explanation for the symptom of psychosis. 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, pathologically-elevated neurological activity in the auditory processing system would cause the patient to think that the auditory nerve were being stimulated. This would lead to the false perception that sound were coming from the environment. Likewise, pathologically-elevated neurological activity 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 [93].
12) A related phenomenon that could likewise be explained by the MCNH hypothesis is the odd separation or "schism" between thoughts and feelings after which the term "schizophrenia" was coined. What hypothetically causes this type of inappropriate affect is that cognitive functions that would normally activate the corresponding emotional circuitry are unable to do so because hotspots of neural activity are competing for dominance [94]. 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 very 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 [78, 95, 96].

13) That virtually every drug that has been used to treat psychiatric disorders—from potassium bromide to treat "hysterical epilepsy," to the barbiturates and benzodiazepines to treat insomnia and anxiety disorders, to chlorpromazine and haloperidol to treat hallucinations and delusions, to non-benzodiazepine anticonvulsants to treat bipolar spectrum disorders—the use of anticonvulsant and other brain-calming drugs have been the mainstay of psychiatric pharmacotherapy. Conversely, drugs with neurostimulatory effects, such as antidepressants and psychostimulants, have been found to have variable, mixed, and sometimes paradoxical effects, especially at higher doses [97].
14) That the two drugs that are most commonly used to self-medicate; namely alcohol and cannabis, likewise have brain-calming effects. However, strains of cannabis with high levels of THC, a stimulatory cannabinoid, can precipitate or worsen psychiatric symptoms in spite of the brain-calming effects of other constituents of the plant [97].
15) That ketamine, an anesthetic that reduces neuronal excitability [47, 98], and Zuranolone, an investigational drug that likewise reduces neuronal excitability [89], exert some of the most rapid and robust antidepressant effects yet to be observed clinically.
16) That inflammatory cytokines, which increase neuronal excitability [22-24], likewise increase psychiatric symptomatology [36, 40, 41], yet anti-inflammatory drugs do not completely alleviate psychiatric symptomatology [42, 43].
17) That Mazarati et al. [64], in their experiments on rats, found that when the level of neuronal excitability was experimentally increased by repeated subconvulsive stimulation of the brain, the laboratory animals began to demonstrate depressive-like behavior. This observation, taken together with the observation that depressive symptoms in susceptible individuals commonly develop in association with the circuit-specific stimulatory effects of severe or recurrent psychosocial stress [63], is compelling evidence that clinical depression is a manifestation of hyperactivity in depressive circuit loops. Lending further support to this hypothesis is the observation that the increased vulnerability to depression that is fueled by persistent psychosocial stress persists for about the same length of time as an experimentally-induced kindling effect [99]. Also, this observation suggests that stress-induced kindling, like experimentally-induced kindling, could be additive if there is too little time between stressful periods to allow the neurological system to return to baseline [100]. Conversely, a progressive growth in maturity tends to be increasingly protective against this effect, thus explaining why some affected persons seem to outgrow mental illness, whereas others become increasingly symptomatic as they age [101, 102].
18) That virtually any natural intervention that has a brain-calming effect, whether it be stress-reduction, establishing an early sleep schedule, engaging in moderate exercise, avoiding caffeine and other psychostimulants, minimizing refined sugar, or engaging in psychotherapy, tends to reduce psychiatric symptoms irrespective of the psychiatric diagnosis [103].
19) That stress-reduction alone, which allows the neurological system to calm down, can reduce psychiatric symptomatology to the point that there remains virtually no discernible evidence that there is an abnormality.

4.8. Neuroimaging and the MCNH Hypothesis

Although attempts to localize mental function have historically been unsuccessful, recent advances in neuroimaging technology have made it possible to observe changes in brain function in relation to specific tasks and cognitive-emotional states. One of the most notable findings of these studies is that, contrary to expectation, clinically depressed patients display *elevated* rather than depressed neurological activity in specific brain networks [104, 105]. Furthermore, Johnstone et al. [104], using fMRI, found that depressed subjects, unlike controls, were unable to consciously regulate activity in their emotional response centers despite intense activity in their regulatory centers as they attempted to turn off negative emotions when they arose. Similarly, Leuchter et al. [105] found that clinically depressed subjects showed increased synchronization across all frequencies of electrical activity, suggesting a general loss of selectivity in functional connections. According to Leuchter, the healthy brain must synchronize and then desynchronize activity from various brain areas in order to allow a person to analyze information, regulate mood, and control his or her actions. In persons with clinical depression, this ability appears to be lost due to the inability of electrical signals to shut off. The area of the brain that showed the most severe abnormalities was the prefrontal cortex, which works in conjunction with the limbic system to regulate mood and solve problems. From the perspective of the MCNH hypothesis, abnormally-elevated activity in the emotional centers causes the mind to withdraw from goal-directed activity as it becomes absorbed in negative emotion. Moreover, even when

the mind attempts to change this cognitive-emotional pattern, intense and persistent firing in default mode circuitry makes it difficult for the mind to do so. However, if the neurological system is inherently hyperexcitable, as it is hypothesized to be in most psychiatric disorders [85], the locus of hyperactivity can migrate spontaneously due to a combination of synaptic fatigue in the hot circuit and aberrant circuit induction, as previously stated. During this process, one cognitive-emotional state can morph into another as occurs in bipolar disorder, cyclothymia, and other disorders in the bipolar spectrum.

Another psychiatric disorder that shows hyperactivity in specific brain networks is obsessive-compulsive disorder (OCD). In OCD, the patient is not depressed but rather obsessed with trying to reduce the anxiety and other uncomfortable feelings that are driven by pathologically-elevated activity in the related brain circuitry. This idea is supported by the observation that the supplemental motor area and the orbitofrontal cortex of the brain, regions that are involved in the processing of thoughts and their translation into behaviors, are hyperactive in OCD [106, 107]. A number of limbic structures, including the amygdala and the hippocampus, are also thought to be involved [108]. OCD patients have also been found to have elevated concentrations of the excitatory neurotransmitter glutamate in their cerebral spinal fluid [109], a finding that further suggests that the brain is pathologically hyperactive in OCD. In addition to being hyperactive, the functional circuitry is further primed and reinforced each time the sufferer repeats the thoughts and actions that characterize the disorder. Hypothetically, disrupting this psychophysiological dynamic is what has made cognitive-behavioral therapy the gold standard in the treatment of OCD.

In summary, no other psychological or biological construct is as consistent with all of the clinical, experimental, and genetic evidence pertaining to mental illness as a genetically-based hyperexcitability of the neurological system in conjunction with a mind-brain duality of the cognitive-emotional system. However, that is not to say that previous theories of psychopathology are incorrect. On the contrary, they provide additional support for the MCNH hypothesis. For example, intrapsychic conflict, environmental stress, and biological stress, each of which is the focus of its own theory of depression, are merely different avenues through which the level of excitation in the brain can become pathologically increased. Freudian psychotherapy could help reduce symptoms by reducing the neuronal excitation that is driven by intrapsychic conflict; cognitive-behavioral therapy could help reduce symptoms by starving symptom-related circuits (which are usually maladaptive) and feeding more adaptive ones; and meditative psychotherapy could help reduce symptoms by quieting the brain as a whole.

On the biological side stands the monoamine hypothesis as the most widely accepted of the biologically-based explanations for depressive symptoms. The strength of the hypothesis is that it provides a biological basis for the use of antidepressants in the treatment of depression. The weakness of the hypothesis is that it assumes that depression is caused by a chemical imbalance. This idea is too simplistic because it fails to explain why antidepressant drugs, which boost the chemicals that are supposedly deficient in depression, can sometimes make symptoms worse. Moreover, this paradoxical effect can occur after an initial period of improvement. Antidepressants can also have acute mood-destabilizing effects, and the glutamate antagonist ketamine, which has pharmacological effects that should offset those of antidepressants, has some of the most immediate and robust antidepressant effects yet to be observed. Beyond these weaknesses, the monoamine hypothesis fails to explain how changes in neurotransmission actually translate into the symptoms of depression.

The MCNH explains all of these phenomena because it integrates brain structure, brain function, and mind-brain dynamics. It ascribes depression to an electrical imbalance between those circuits that are associated with a positive mood and those circuits that are associated with a negative mood. Hypothetically, antidepressants reduce symptoms by chemically boosting the activity in positive circuits more than in negative circuits. However, if, because it goes everywhere in the brain, an antidepressant boosts activity in negative circuits more than positive circuits, it could make symptoms worse. Also, by fueling cross-talk between incongruous circuit loops (a kind of neurological short-circuiting that is hypothesized to be facilitated by increasing the level of excitation in the brain) an antidepressant could induce symptom-cycling [110].

That is not to discount the usefulness of antidepressants in the treatment of depression. However, from the perspective of the MCNH hypothesis, which associates psychiatric symptoms with electrical imbalances rather than chemical imbalances, the only patients who would be appropriate for antidepressant monotherapy (i.e., without the coadministration of an effective mood stabilizer) would be those who have normoexcitable neurological systems [85, 100]. In such patients, depressive symptoms would not be driven by an inherent hyperexcitability of the neurological system, nor would they be driven by a chemical imbalance. Rather, they would be driven by an overstimulation of symptom-related neural circuits in association with a severe and persistent cognitive-emotional stressor. Over time, the associated circuits would become increasingly responsive to further stimulation. This kindling effect, which could more aptly be described as “primed burst potentiation” [66], is the MCNH explanation for how stress alone can fuel the development of psychiatric symptoms. It also explains why the onset of symptoms in such patients tends to be more gradual than in those who have hyperexcitable neurological systems and why they tend to have a lower risk of antidepressant-induced paradoxical effects. However, such patients would be relatively rare because, in the absence of a constitutional hyperexcitability of the neurological system, it would take an unusually intense and persistent stressor to induce enough kindling to drive the patient into treatment.

Another of the aforementioned theories that provides

support for MCNH hypothesis is the decrease in GABAergic activity that has been found in patients with major depressive disorder. As the primary inhibitory neurotransmitter of CNS, a fall in GABAergic transmission would leave the system in a hyperactive state, thus supporting the idea that clinical depression is a manifestation of hyperactive neural circuits. This idea is reinforced by the immune, the endocrine, and the gut-brain hypotheses, all of which link psychiatric symptoms to a hyperactivity of the neurological system.

Finally, the long-held diathesis-stress hypothesis and the central sensitivity hypothesis cite the existence of another factor, either a constitutional or an acquired tendency for the neurological system to overreact when perturbed by stress. Again, both of these hypotheses are consistent with the MCNH hypothesis in that the hypothesized neuronal hyperexcitability is posited to be both a constitutional trait and a trait that can be further inflamed if perturbed by a psychological, emotional, or biological stressor.

5. Many Disorders, One Mechanism

The question of why one person with a hyperexcitable brain becomes trapped in depression, another becomes trapped in mania, another becomes trapped in obsessional thinking, and other becomes trapped in some other cognitive-emotional state is hypothetically dependent upon several factors, most notably the person's psychosocial circumstances and willful choices. This idea is supported by the observation that the same person can become caught in various different cognitive-emotional states at different times in his or her life. The one thing that all affected persons have in common, however, is that they become prisoners of their cognitive-emotional state, at least temporarily. The hypothetical reason for this is three-fold. First, hyperactive neurons are slow to shut off, hence they tend to resist mental efforts to redirect thinking. Second, hyperactive circuits compete for dominance [111], thus creating a kind of winner-takes-all until there is enough synaptic fatigue to allow a change in circuit-specific activity. Third, the mind becomes obsessed with the corresponding pattern of thinking, thus tending to exclude other ways of thinking and behaving.

Although numerous biochemical, morphological, and structural abnormalities have been observed in the psychiatrically-disturbed brain, the ability of all of these abnormalities to resolve during an extended period of remission strongly suggests that they are not causal but rather natural consequences of the circuit-specific imbalances that hypothetically underlie psychiatric symptoms. That would include the "chemical imbalances" that form the basis of the monoamine hypothesis of depression.

6. Practical Importance of Identifying the Neuronal Hyperexcitability Trait

The practical importance of identifying the neuronal hyperexcitability trait is that it is highly modifiable. Hypothetically, any intervention, whether natural or biological, that would reduce the excitability of the neurological system would reduce psychiatric symptomatology. Moreover, the trait of neuronal hyperexcitability is easy to identify. Barring the existence of confounding factors, such as cardiorespiratory disease, cardiorespiratory medications, illicit drugs, or extreme athletic conditioning, a resting heart rate (RHR) above 75 beats/min or a resting respiratory rate (RRR) above 15 breaths/min would be indicative of the neuronal hyperexcitability trait [85, 112]. These subtle vital-sign elevations are thought to be the consequence of a tonic elevation in basal neurological activity in those persons who inherit the genes for neuronal hyperexcitability [100, 112].

That raises two important questions: 1) how common is the trait; and 2) how influential is the trait?

An analysis of the distribution of psychiatric disorders in affected families could help answer these two questions. As previously discussed, individual psychiatric disorders, as defined by symptom-based diagnostic systems, do not follow a clear Mendelian distribution. However, if one considers the varying degrees to which the trait for neuronal hyperexcitability can be expressed and the diversity of forms that its expression can take, one could not reasonably expect the same symptomatology to be passed from one generation to the next even if the same gene variants were inherited. If, with this in mind, we go back and reconstruct family pedigrees based not only on overt psychiatric symptoms but also on soft signs of neuronal hyperexcitability, such as hyper-emotionality, mood instability, sleep difficulties, attentional problems, functional somatic symptoms, and substance use disorders, a consistent pattern of distribution emerges; that pattern is strikingly autosomal dominant (Figure 2). This observation suggests that 1) the trait is extremely common; and 2) that among the many factors that contribute to the development of psychiatric symptomatology, the trait of neuronal hyperexcitability is the most important. A rough estimate of the percentage of the population that harbors the neuronal hyperexcitability trait can be determined by studying the distribution of RHRs and RRRs in the general population. Nearly 40% of the population has an RHR above 75 beats/min or an RRR above 15 breaths/min [113, 114]. In other words, nearly half the population is affected!

Moreover, the significance of this extends far beyond psychiatric disorders. In recent years, an explosion of studies has found that upper-end-of-normal resting vital signs are predictive of the development of a wide range of chronic diseases, such as diabetes mellitus, high blood pressure, cardiovascular disease, autoimmune disease, cancer, and dementia. These studies, in conjunction with the MCNH hypothesis, suggest that the same abnormality that is increasing the vital signs is also increasing the risk of developing these illnesses. This is not surprising given that an inherent hyperexcitability of the neurological system would dysregulate not only the cognitive-emotional and autonomic nervous systems but also the endocrine, the immune, the metabolic, the musculoskeletal, and various other systems of the body. What's more, the aforementioned studies suggest

that the degree to which the trait influences the onset of these diseases, like the degree to which it influences the onset of psychiatric symptoms, is not small. Multiple studies have found that having upper-end-of-normal resting vital signs can more than double the risk of developing any one of the aforementioned medical conditions [112, 115]. The shortened lifespans of the mentally ill, whose psychiatric symptoms and early-onset physical illnesses are hypothetically fueled by neuronal hyperexcitability, bear witness to the powerful influence that the neuronal hyperexcitability trait can have on the development of chronic disease. Figure 3 illustrates the vicious cycle of stress, illness, and more stress that underlies the link between mental illness and physical illness in persons who inherit the genes for neuronal hyperexcitability.

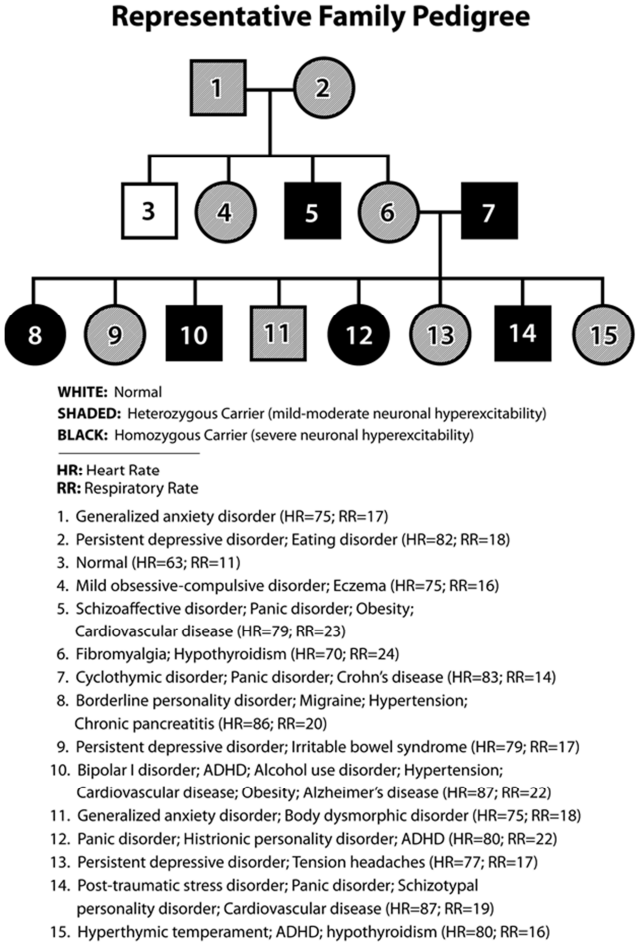

Figure 2. *Representative family pedigree illustrating the autosomal dominant inheritance pattern of the neuronal hyperexcitability trait. Also listed are the associated resting vital-sign measurements. Note that although individual disorders do not follow a classic Mendelian distribution, various disorders, when viewed as different manifestations of a shared vulnerability trait, do follow a classic Mendelian distribution; that distribution is strikingly autosomal dominant. Also note that some of the affected children (black symbols) are more severely affected than others (gray symbols). The sharp distinction in severity suggests that the trait of neuronal hyperexcitability is also additive. Representative illustration is based on more than 300 consecutive clinical interviews.*

Excitingly, this opens the door to a whole new world of preventive medicine: that of preventing disease by reducing the excitability of the neurological system. It suggests that both mental illness and physical illness can be prevented through the prophylactic use of Neuroregulators (i.e., anticonvulsants and other brain-calming drugs) [116]. This too is not surprising given that the health benefits of natural brain-calming interventions, such as stress-reduction, minimizing refined sugar, and regular exercise, have long-been recognized. However, for those with higher levels of neuronal excitability, these and other natural interventions would be unlikely to be sufficient. Such patients would likely need the additional brain-calming effects of Neuroregulators. Of course, the idea of treating asymptomatic children with anticonvulsant drugs may sound inappropriate, but the alternative is to continue to allow them to develop crippling and sometimes fatal psychiatric illnesses, such as mood disorders, eating disorders, psychotic disorders, and substance use disorders, as well as debilitating and often irreversible physical illnesses, such as type-1 diabetes, ulcerative colitis, rheumatoid arthritis, Hashimoto's thyroiditis, lupus erythematosis, multiple sclerosis, and other autoimmune diseases.

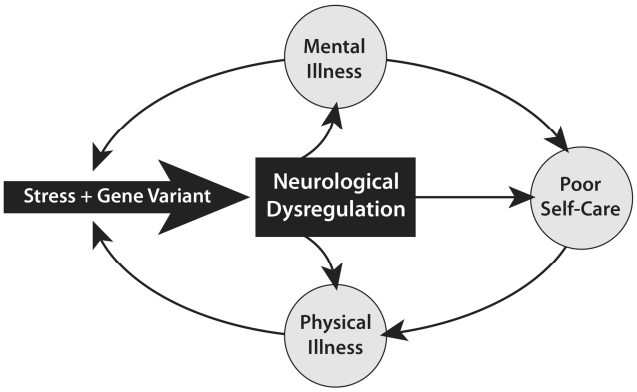

Figure 3. *Illustration of the vicious cycle of stress, mental illness, poor self-care, and physical illness in persons who inherit the neuronal hyperexcitability trait.*

Unlike the older anticonvulsant drugs, such as phenobarbital, phenytoin, and carbamazepine, the newer anticonvulsants, such as gabapentin, oxcarbazepine, and lamotrigine, have very few side effects and appear to be safe and effective in long-term use. The skyrocketing popularity of gabapentin in the treatment of an expanding range of ailments, from chronic cough to chronic pain and social anxiety to bipolar disorder, bears witness to the potential benefits of anticonvulsant prophylaxis in persons who inherit the neuronal hyperexcitability trait [117]. There is little doubt that this simple intervention could powerfully safeguard a young person's progress through life.

7. Recommendations for Future Research

Urgently needed are clinical studies aimed at assessing 1) the accuracy of resting vital signs in guiding the effective use of Neuroregulators in patients who might otherwise be treated with antidepressant drugs; 2) the effectiveness of

Neuroregulators in preventing the development of mental and physical illnesses in those who, based on resting vital-sign measurements, would be deemed to harbor the neuronal hyperexcitability trait; 3) the effectiveness of Neuroregulators in preventing the development of illicit substance use in those who, based on resting vital-sign measurements, would be deemed to harbor the neuronal hyperexcitability trait.

8. Discussion

Since antiquity, mental illness has been a topic of intense philosophical and spiritual debate. Yet even with the aid of modern advances in neuroscience, the psychophysiology of psychiatric disorders remains unclear. Though all of the most current conceptualizations, which include the psychodynamic and cognitive-behavioral theories of psychopathology, the genetic theories of psychopathology, the diathesis-stress model of psychopathology, the neurotransmitter theories, the immunological theories, the endocrinological theories, and the microbial theories of psychopathology, provide important clues to what could be causing psychiatric symptoms, none of them, neither individually nor collectively, answer all of the questions nor explain all of the observations that have been made in relation to psychiatric disorders. If we are to bring an end to the global mental health crisis, a more comprehensive explanation of the cause of mental illness is needed.

The MCNH hypothesis may be the first to do just that, to fully integrate mental function with neurological function to provide a complete psychophysiological explanation for the cause of mental illness. According to the hypothesis, psychiatric symptoms are the consequence of pathological hyperactivity in symptom-related circuits in the brain. The fundamental driver of that hyperactivity is the superimposition of a psychological or biological stressor upon a constitutional hyperexcitability of the neurological system. In addition to being consistent with the long-held diathesis-stress model of mental illness, the MCNH hypothesis offers a sound physiological explanation for all of the observations that have been made in relation to psychiatric disorders and unifies diverse conceptualizations of psychopathology to illuminate a precise biological target for treatment; namely, neuronal hyperexcitability.

In addition to guiding treatment, the MCNH hypothesis provides a physiologically-based explanation for the subtle vital-sign elevations that are now known to be predictive of the development of both psychiatric disorders and a wide range of general medical conditions. In so-doing, it provides a rationale for using resting vital-sign measurements to assess an individual's vulnerability to developing any illness, whether mental or physical, that could be precipitated or exacerbated by stress.

The recognition of this broadens the applicability of the MCNH hypothesis and resting vital-sign measurements to virtually all chronic diseases. The practical significance of this is immense, as it could allow resting vital-sign measurements to guide the use of Neuroregulators to prevent the vicious cycle of emotional, psychological, behavioral, social, academic, vocational, and biological deterioration that ultimately leads to the development of the many common illnesses that devastate individuals, disrupt families, and drive the skyrocketing cost of healthcare.

9. Conclusion

As the first comprehensive psychophysiologically-based explanation for the development of psychiatric symptoms, the MCNH hypothesis in conjunction with a mind-brain duality of the cognitive-emotional system unifies a range of different perspectives on the cause of mental illness and, quite unexpectedly, implicates psychiatric symptoms as the first subjective markers of a physiological abnormality that is hypothesized to be at the root of virtually every mental and physical illness that can be precipitated or exacerbated by stress. The practical significance of this is that the underlying physiological abnormality; namely, neuronal hyperexcitability, is both highly detectable and highly modifiable. The trait can be detected objectively through resting vital-sign measurements, and it can be modified therapeutically through any natural or medical intervention that has a calming effect on the brain. Beyond paving the way to the more accurate diagnosis and treatment of psychiatric disorders, the MCNH hypothesis in conjunction with neuroregulator therapy opens the door to the prevention of any illness, whether mental or physical, before the earliest signs of illness even begin. 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, and the availability of safe and effective ways to therapeutically modify the vulnerability trait, 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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