

## Review Article

# New Hypothesis on the Pathophysiology of Psychiatric Disorders Illuminates Shared Mechanism of Past and Emergent Treatment Strategies

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**Abstract:** Although psychotherapy and pharmacotherapy continue to be first-line treatments for a wide range of mental and emotional disorders, a high percentage of patients are ultimately considered to be treatment-resistant. For more than half a century, electroconvulsive therapy had been the gold-standard for such patients. However, in recent years a variety of alternative treatment modalities have been developed for these patients, including deep brain stimulation, vagus nerve stimulation, repetitive transcranial magnetic stimulation, stellate ganglion block, and sub-anesthetic doses of the dissociative drug ketamine. Although these alternative treatments have offered new hope for many patients, there is a great deal of individual variability in their degree of effectiveness, and their mechanisms of action, like standard treatments, remain unclear. However, 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, 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... The aim of this review is twofold: the first is to discuss the new hypothesis in relation to the aforementioned treatment strategies; and the second is to tease out the shared neurophysiological effects of past and present treatment strategies to determine whether they support or refute the new hypothesis. Clarifying the cause of mental illness is of critical importance to curbing the escalating mental health crisis, as new medications and emergent treatment strategies are failing to keep up with the steady rise in domestic disputes, suicides, homicides, and mass shootings that are driving the disintegration of individuals, families, and communities.

**Keywords:** Pathophysiology of Psychiatric Disorders, Neuronal Excitability Spectrum, Anticonvulsants, Neuroregulators, ECT, VNS, rTMS, Ketamine

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## 1. Introduction

Although psychotherapy and pharmacotherapy continue to be first-line treatments for a wide range of mental and emotional disorders, a high percentage of patients are ultimately considered to be treatment-resistant [1-3]. For more than half a century, electroconvulsive therapy (ECT) had been the gold-standard for such patients [4]. However, in recent years, a variety of alternative treatment modalities have been developed for these patients, including deep brain stimulation

(DBS), vagus nerve stimulation (VNS), repetitive transcranial magnetic stimulation (rTMS), stellate ganglion block (SGB), and sub-anesthetic doses of the dissociative drug ketamine. Although these alternative treatments have offered new hope for many patients, there is a great deal of individual variability in their degree of effectiveness, and their mechanisms of action, like standard treatments, remain unclear [5-9]. However, 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, 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... [10]. Based on this hypothesis, any intervention, whether medical or non-medical, that has a calming effect on the brain should help reduce psychiatric symptoms irrespective of the symptom-based diagnosis. This could help explain why natural interventions, such as stress-reduction, maintaining an early sleep schedule, avoiding caffeine and other psychostimulants, minimizing refined sugar, regular exercise, and meditative practices, are well-known to help reduce and prevent the recurrence of psychiatric symptoms. Still, a continued lack of clarity about the cause of mental illness has left psychotherapists in the dark about the psychophysiological effects of psychotherapy; it has left prescribers continuing to treat symptoms rather than pathophysiological processes; and it has left patients pursuing various psychological, pharmacological, and somatic treatments without a clear understanding of what is really wrong with them or how the treatments work.

The aim of this review is twofold: the first is to discuss the MCNH hypothesis in relation to the aforementioned treatment strategies; and the second is to tease out the shared neurophysiological effects of past and present treatment strategies to determine whether they support or refute the new hypothesis. Clarifying the cause of mental illness is of critical importance to curbing the escalating mental health crisis, as new medications and emergent treatment strategies are failing to keep up with the steady rise in domestic disputes, suicides, homicides, and mass shootings that are driving the disintegration of individuals, families, and communities.

## 2. The MCNH Hypothesis

To date, numerous theories of psychopathology have been proposed and much has been learned about the chemical, physiological, and morphological correlates of psychopathology. However, a precise understanding of how those pathological changes translate into psychiatric symptoms and why some persons are more vulnerable than others to developing symptoms remains an enigma. Fortuitously, all that may be about to change with the recent introduction of the first comprehensive psychophysiological hypothesis of psychiatric disorders. According to the MCNH hypothesis, psychiatric symptoms are the consequence of a pathological elevation in the activity of symptom-related circuits in the brain. The hyperactive circuits, in turn, overstimulate the related thoughts and emotions, thus creating a vicious cycle of mutual overstimulation between the mind and the brain [11-13].

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. [14] found that willful thoughts 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 has long been recognized to trigger different thoughts and emotions [15]. What this implies is that specific cognitive-emotional stressors could cause the activity of the associated neurons and circuits to become amplified accordingly [16]. Likewise, elevated activity in specific neurons and circuits could cause the related thoughts and emotions to be correspondingly amplified [17, 18]. According to the MCNH hypothesis, this mind-brain dialogue could cause specific neurons and circuits to become increasingly active over time, thus explaining why persistent stress is such a ubiquitous precipitant of psychiatric symptomatology. It could also explain why manipulating the activity of specific circuits, as is currently done both pharmacologically [19] and magnetically [20], can affect cognitive-emotional functioning. In other words, it could explain how psychiatric symptoms develop and how various treatment strategies work to reduce or, paradoxically, exacerbate symptoms.

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. 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 [21-23]. Specifically, the protein products of the candidate genes fail to regulate the excitability of neurons. The inheritance of these gene variants would amp up the vicious cycle of mutual overstimulation between the mind and the brain that is hypothesized 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. A wealth of additional evidence in support of the MCNH hypothesis has been presented in a set of peer-reviewed scientific articles published between 2019 and the present [10-13, 24-28].

## 3. An Historical Perspective

The most common approach to psychopathology, and the oldest, is psychotherapy. Consistent with the tenets of the MCNH hypothesis, psychotherapy involves efforts to reduce cognitive-emotional distress through a combination of emotional support and constructive analysis of the way a person thinks, feels, and behaves. Though many different forms of psychotherapy have emerged over the years, most have been at least somewhat helpful to patients. According to the MCNH hypothesis, the benefits of psychotherapy are mediated through three synergistic mechanisms. The first is emotional support, as this helps calm the emotional system; the second is conflict resolution, as reducing intrapsychic tension has a calming effect on the mind and the brain; and the

third is a reduction of symptom-related neural signaling as the patient adopts new ways of thinking and behaving. All of these mechanisms help break the vicious cycle of mutual overstimulation between the mind and the brain that, according to the MCNH hypothesis, tends to perpetuate psychiatric symptoms.

Also consistent with the tenets of the MCNH hypothesis is the observation that virtually every drug that, throughout history, has been used to treat mental and emotional disturbances has brain-calming effects. From Sir Charles Locock's use of potassium bromide to treat "hysterical epilepsy," to the use of barbiturates and benzodiazepines to treat insomnia and anxiety disorders, to the use of anticonvulsants and antipsychotics to treat bipolar disorder and schizophrenia, efforts to reduce brain-signaling had, until recent history, been the mainstay of psychiatric treatment [28]. Similarly, the most commonly used drugs to self-medicate, both historically and still today, have been anticonvulsant drugs; namely, alcohol and marijuana. It was not until the early and middle parts of the last century that the medical profession began to taut the use of stimulant-type drugs such as amphetamines and antidepressants for psychiatric purposes [29-31]. However, the current mental health crisis and the continued search for new and improved treatment strategies bear witness to the failure of both psychotherapy and stimulant-type drugs to effectively treat mental illness. Interestingly, however, the various alternative treatment strategies that have been developed over the last several decades, beginning with the introduction of electroconvulsive therapy (ECT) in the 1940s, followed by the development of various neurostimulator techniques closer to the turn of the century, followed most recently by the use of the neuroinhibitory drugs ketamine [32] and bruxanolone [33, 34], have varied and sometimes opposing effects on the brain. Reviewing these approaches from the perspective of the MCNH hypothesis and their shared neurophysiological effects will, hopefully, better illuminate the core abnormality in psychiatric disorders and, thus, help streamline treatment.

## 4. Alternative Treatment Approaches

### 4.1. *Electroconvulsive Therapy (ECT)*

Although ECT has, for more than half a century, been the gold-standard for treatment-resistant depression as well as a number of other psychiatric disorders [35], the precise mechanism by which it works remains poorly understood. One theory posits that ECT exerts its rapid and robust therapeutic effects by modulating the activity of neurotransmitters, particularly serotonin and dopamine [36]. Another theory, which relates to the immunological hypothesis of depression, posits that ECT works by down-regulating the immunological system [37]. Yet another theory posits that ECT's therapeutic effects are mediated by some combination of epigenetic and neuroplastic changes [38, 39]. While each of these theories identifies some aspect of the biochemical, physiological, and morphological changes that

occur during a series of ECT treatments, all fall short of explaining how the observed changes actually translate into a reduction of psychiatric symptoms.

An important clue to the central mechanism through which ECT exerts its therapeutic effects is the sharp contrast between ECT's acute effects and its after-effects. During the acute phase of treatment, psychiatric symptoms become more severe; in fact, there is a complete loss of consciousness. This happens in conjunction with a surge of electrical activity that characterizes an epileptic seizure. However, the brain's compensatory mechanisms drive a reduction of neurological activity to a level lower than the pre-treatment level. It is during this phase of treatment that the therapeutic effects of ECT begin to occur. This suggests that a reduction in neuronal excitation may be at least partially responsible for ECT's therapeutic effects. Known inhibitory mechanisms in response to seizure activity include glutamate depletion, GABAergic recurrent inhibition, membrane shunting, depletion of energy stores, loss of ionic gradients, endogenous neuromodulator effects, and regulatory input from various brain regions [40]. Notably, these effects mimic the neuroinhibitory effects of insulin coma, which Polish neuropsychiatrist Manfred Sakel, just prior to the development of ECT, had found to be remarkably effective in treating otherwise intractable mental disorders [41]. They also mimic the effects of the long line of neuroinhibitory drugs that, as previously discussed, had been the mainstay of psychiatric treatment until the latter part of the twentieth century. Finally, a neuroinhibitory effect would be consistent with the MCNH hypothesis, which, taken together with the gene research, contends that psychiatric symptoms are driven by an inherent hyperexcitability of the neurological system [10]. Although ECT also mimics the effects of antidepressant drugs in that it drives a sharp rise in the release of the same neurotransmitters as antidepressants do, this effect is unlikely to play a significant role in ECT's therapeutic effects because clinical improvement occurs at a time when the release of these neurotransmitters is actually diminished (i.e., during the neuroinhibitory phase of treatment). Taken together, these observations implicate neuroinhibition in ECT's mechanism of action.

Hypothetically, the reason that multiple treatments and, even after a successful course of ECT, maintenance treatments are needed is that the after-effects of ECT (i.e., the neuroinhibitory effects) are relatively short-lived. However, a cumulative effect can be achieved by administering a series of treatments in rapid succession. Hypothetically, the generally required course of 6-12 treatments administered on alternate days keeps the nervous system in a relatively inhibitory state for a long enough period of time to break the vicious of mutual overstimulation between the mind and the brain that, according to the MCNH hypothesis, keeps the patient locked into his or her pathological cognitive-emotional state. However, because the neuronal hyperexcitability trait is constitutional, the therapeutic effects of ECT would be expected to start diminishing following the completion of a series of treatments. Indeed, studies have found that 15–20% of ECT responders relapse within one week of the last

treatment [4], and 50–80% relapse within six months of the last treatment [4, 42]. According to the MCNH hypothesis, the rare exceptions (which would hypothetically be included in the remaining 20% of patients) would be those patients whose depression was not rooted in neuronal hyperexcitability but rather a stressor that was so severe and persistent that it drove the development of psychiatric symptoms through kindling alone. First observed by Graham Goddard in his experiments on rats [43], kindling describes the natural tendency for neurons to become increasingly responsive with repeated stimulation. This adaptive process, which under normal physiological conditions could more aptly be described as “primed burst potentiation” [44], is the MCNH explanation for why the onset of psychiatric symptoms tends to be delayed relative to the onset of a triggering stressor. Patients with normoexcitable neurological systems would be few in comparison to those with hyperexcitable neurological systems because, neurophysiologically, they would be more resistant to stress [12]. Moreover, even when such patients did become clinically depressed, they would be more likely to respond to antidepressant pharmacotherapy than those with hyperexcitable neurological systems because they would be less vulnerable to symptom-cycling and other antidepressant-induced paradoxical effects [12].

Clearly, the more conservative way to reduce neuronal hyperexcitability would be to administer neuroinhibitory drugs (i.e., anticonvulsants and antipsychotics), which could more aptly be called “Neuroregulators” because of their proposed mechanism of action [45]. However, short of a clear understanding of what drives psychiatric symptoms or how ECT exerts its therapeutic effects, patients who are resistant to antidepressant therapy are often referred for ECT or one of the other more costly and cumbersome treatments that will be discussed next.

#### **4.2. Deep Brain Stimulation (DBS)**

Deep Brain Stimulation, also known as “brain pacemaker,” involves the selective stimulation of specific brain areas via an implanted electronic device. The primary aim of the treatment is to rebalance the activity of neural circuits that are believed to be damaged or associated with the patient’s symptomatology. Thus, for example, in a patient with severe intractable depression, symptoms are thought to be relieved by stimulating circuits that would normally be more active when the patient was not depressed. This mimics the effects of antidepressants in that it involves stimulating activity in specific circuits.

#### **4.3. Vagus Nerve Stimulation (VNS)**

Vagus nerve stimulation is another “pacemaker” technique that involves the surgical implantation of electrodes, in this case into the chest, to stimulate specific circuits in the brain. It is used in the treatment of epilepsy, depression, and chronic pain that are resistant to pharmacotherapy. After the VNS device is placed under the skin, a wire is connected to the vagus nerve in the neck. Through this connection, the

stimulator delivers thirty-second pulses of electricity to the vagus nerve, which feeds into the solitary tract nucleus. Affarrents of the solitary tract increase the activity of the inhibitory neurotransmitter GABA while at the same time reducing activity of the excitatory neurotransmitter glutamate. They also promote epinephrine signaling via projections to the locus coeruleus and the amygdala [46]. This combination of effects is thought to be responsible for the therapeutic effects of VNS in the treatment of depression.

#### **4.4. Repetitive Transcranial Magnetic Stimulation (rTMS)**

One of the newest techniques for treatment-resistant depression uses electromagnetic induction to non-invasively depolarize or hyperpolarize neurons in the brain. The goal of this technique, known as rTMS, is to relieve symptoms by modulating the activity of specific neural circuits. Because rTMS can be used to either increase or decrease the activity of specific circuits, it too could be considered a mixed neurostimulatory and neuroinhibitory technique [47].

#### **4.5. Stellate Ganglion Block (SGB)**

SGB is now being used to treat a number of conditions, including complex regional pain syndrome, high blood pressure, and some psychiatric disorders, particularly post-traumatic stress disorder [48]. The stellate ganglion is present in approximately 80% of the general population and is composed of the inferior cervical ganglion and the first thoracic ganglion fusion. It is located posteriorly in the neck at the level of the seventh cervical vertebra. The treatment involves anesthetizing the ganglion so as to reduce the sympathetic outflow that is relayed through it. As with ECT, the rapid improvement that is achieved through this technique highlights the importance of neuroinhibition in reducing psychiatric symptoms.

#### **4.6. Ketamine**

Most recently, ketamine, an antagonist of the excitatory neurotransmitter glutamate, has been found to exert some of the most rapid and robust antidepressant effects yet to be observed [49]. Though its effects are relatively short-lived, the therapeutic success of ketamine in otherwise treatment-resistant patients has sparked interest in the possible role of glutamate in the pathogenesis of depression and other psychiatric disorders. While no definite conclusions have yet been drawn about the means by which glutamate transmission might be related to psychiatric symptomatology, the rapid therapeutic effects of inhibiting the principle excitatory neurotransmitter in the nervous system clearly implicates neuronal excitation in the pathogenesis of psychiatric disorders.

#### **4.7. Neuroactive Steroid Pharmacotherapy**

Recognizing that the postpartum period is a time of both increased vulnerability to depression and acute deficiency of neurosteroids, brexanolone, a positive allosteric modulator of the GABA-A receptor, was tested in women with postpartum

depression. At just 60 hours post-injection, brexanolone yielded significant and clinically meaningful reductions in HAM-D total score compared to placebo [33, 34]. Subsequently, zuranolone (SAGE-217), a structurally-related neuroactive steroid but one that can be administered orally [50], showed similar benefits in the treatment of postpartum depression [50], unipolar depression [51], and bipolar disorder [50]. Though both of these drugs are still in the early stages of development, the rapid and robust effectiveness they have thus far demonstrated in the treatment of depression has attracted increased attention to their mechanism of action. Brexanolone and zuranolone appear to exert their therapeutic effects by reducing neuronal excitability.

Although their effects appear to be short-lived, the aforementioned results deserve close attention because they are yielding clinical improvement in hours rather than weeks. Then again, many other drugs that reduce neuronal excitability (i.e., benzodiazepine and non-benzodiazepine anticonvulsants) likewise have rapid and robust therapeutic effects in the treatment of mood disorders.

#### 4.8. Bright Light Therapy

Also known as “phototherapy,” bright light therapy has been used since antiquity for a variety of ailments, including rickets, skin diseases, and sleep disorders. The modern science of light therapy was inaugurated at the turn of the twentieth century by Nobel Prize laureate Niels Finsen, who pioneered the medical use of artificial light sources as a substitute for natural sunlight. Following the discovery of seasonal affective disorder in the 1980s, Dr. A. J. Lewy at the National Institutes of Mental Health identified a connection between decreased light exposure during the winter months and feelings of depression. Since that time, artificial light has been used as an alternative treatment for depression.

Neurophysiological support for bright light therapy comes from the fact that the pineal gland, which regulates circadian rhythm, receives signals from the suprachiasmatic nucleus, which is sensitive to sunlight. Circadian rhythms are known to be important in regulating sleep-wake cycles, the release of hormones, core body temperature, and a variety of other physical functions. It has been hypothesized that the decrease in light intensity that occurs in the fall and winter months triggers psychiatric symptoms in susceptible individuals by disrupting these rhythms [52].

However, not all patients experience seasonal depression in the fall; some experience it in the spring [53]. Also, some of those who experience seasonal depression sometimes experience manic symptoms rather than depressive symptoms. There are also some years in which patients with seasonal affective disorder do not experience any flare-ups at all [54]. Thus, the so-called “seasonal effect” is not a consistent phenomenon even in those who do have a propensity to develop psychiatric symptoms during the change of season. The DSM-5 allows for this variability based on the following criteria: 1) depression that begins during a specific season for two consecutive years; and 2) many more seasons of depression than seasons without depression over the

long-term course of the illness. The variability in the nature of the flare-ups, the timing of the flare-ups, and the duration of the flare-ups suggests that the correlation between the time of year and the onset of symptoms does not specify a distinct disorder but rather acts as a marker of some seasonally recurring factor or combination of factors that some patients with mood disorders are especially vulnerable to.

From the perspective of the MCNH hypothesis, the observed benefits of light-box therapy in some patients with SAD and non-SAD [55] could be attributed to the same effects that antidepressants have in the treatment of clinical depression; namely, that they stimulate activity in positive (feel-good) neural circuits [10]. Bright light therapy is also known to carry the same risks as antidepressants; namely, that it can cause an abnormal elevation in mood, energy, and other hypomanic symptoms [56, 57]. It also has the potential to worsen depressive symptoms [56]. As with antidepressants, this would hypothetically be caused by a disproportionate stimulation of negative (feel-bad) circuits in the brain or by a cycling of symptoms into the depressive range.

## 5. Discussion

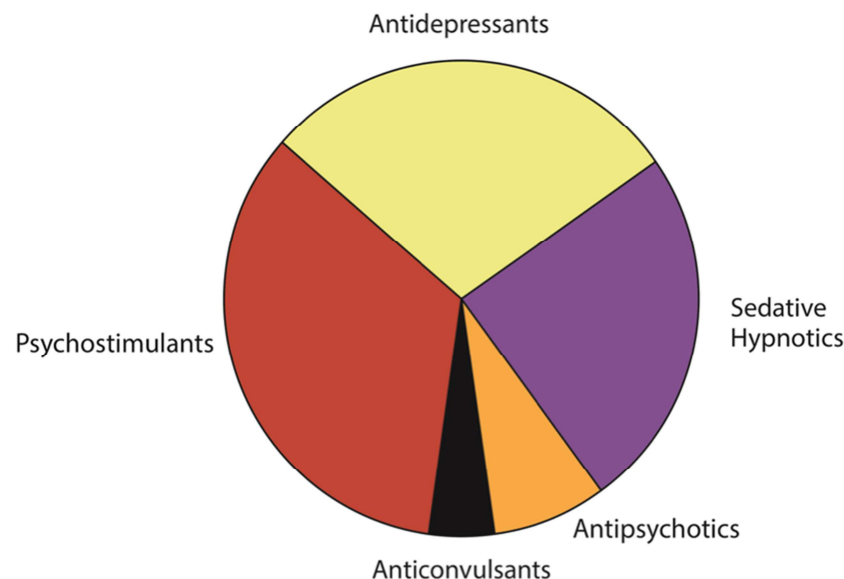
The goal of this review was to probe the pathophysiology of mental illness by studying past and emerging treatment strategies in relation each other and the MCNH hypothesis of psychiatric disorders. Upon comparing all of these treatment strategies together with their observed neurophysiological effects, it becomes apparent that two fundamentally different effects are working to relieve symptoms: 1) inhibition of neurological activity; and 2) stimulation of neurological activity. If one includes the long history of brain-calming pharmacotherapy, the vast majority of the treatment approaches reduce neurological activity, whereas the remaining approaches either stimulate or modulate neurological activity. Although this observations highlights the importance of neuronal excitability in the pathogenesis of psychiatric disorders, it begs the question: how can opposing neurophysiological effects have similar therapeutic effects?

The MCNH hypothesis offers an answer to that question. According to the hypothesis, psychiatric symptoms are driven by pathologically-elevated activity in symptom-related circuits in the brain. Hence, the most obvious way to reduce symptoms would be to reduce that excessive activity. Indeed, that is what most treatments do; psychotherapy, anticonvulsants, antipsychotics, ECT, VNS, SGB, Ketamine, and neuroactive steroids all work to reduce neurological activity. As mentioned earlier, there are also a variety of natural ways to reduce neurological activity, and these too are well-known to reduce psychiatric symptomatology.

In contrast, antidepressants [58], psychostimulants, DBS, rTMS, and bright light therapy either stimulate or modulate excitation in the brain. According to the MCNH hypothesis, the increase in neurological activity that these interventions generate can potentially reduce psychiatric symptoms by bolstering activity in those circuits that are relatively *hypo*-active. For example, in clinical depression, the right

dorsolateral prefrontal cortex (DLPFC), which is associated with emotional judgement, is relatively *hyper*-active, whereas the left DLPFC, which is associated with planning and executive function, is relatively *hypo*-active. Repeated stimulation of the left DLPFC, as is done with rTMS, leads to clinical improvement [10]. Note, however, that stimulating the neurological system is antithetical to the long-recognized benefits of calming it. That could explain why rTMS, like other neurostimulatory techniques, poses a higher risk of paradoxical effects and bipolar switching than neuroinhibitory techniques [56, 59-63]. The hypothetical means by which neurostimulatory treatments can cause paradoxical effects is that they can inadvertently increase activity in negative circuitry more than positive circuitry [10, 13]. For example, if the treatment increases the activity in the anxiety circuitry or the irritability circuitry more than in the reward circuitry, the patient will report paradoxical effects. Similarly, the hypothetical means by which bipolar switching occurs is that pathologically hyperactive circuits, through their collateral connections, cause inappropriate circuits to become hyperactive whilst themselves quieting down due to synaptic

fatigue [11, 27, 64]. The risk of this aberrant circuit induction increases as the overall level of excitation in the brain increases [11, 57]. Moreover, the persons who are the most vulnerable to this phenomenon are those with psychiatric symptoms, as they are the ones who are most likely to harbor the trait of neuronal hyperexcitability. Hypothetically, the reason that persons with hyperexcitable neurological systems are more vulnerable to bipolar switching is two-fold. The first is that the level of activity in their cognitive-emotionally active circuits tends to be pathologically-elevated; and the second is that the circuits that these feeder circuits aberrantly activate are themselves hyperexcitable [10, 13]. What this implies is that the safest way to alleviate psychiatric symptoms is to *decrease* rather than increase the level of excitation in the brain. Note, however, that this idea does not square up with the sales of neurostimulatory-type drugs in comparison to neuroinhibitory-type drugs (Figure 1) [65-68]. The large disparity between the combined sales of antidepressants and psychostimulants in comparison to anticonvulsants and antipsychotics could help explain why the mental health crisis is spinning out of control.



**Figure 1.** Pie chart illustrating the sales of antidepressants and psychostimulants relative to other psychotropic drugs.

Concerningly, what seems to be happening is that the robust mood-elevating and energy-enhancing effects of stimulant-type drugs is leading prescribers to dispense them with increasing frequency relative to brain-calming drugs. Subsequently, patients who experience an abnormal elevation in mood and energy, a paradoxical worsening of symptoms, or a loss of beneficial effects may not report the change to their prescribers. Some of the possible obstacles to reporting include: 1) patient misattribution of changes in medication effect to changes in life circumstances; 2) patient reluctance to risk losing a prescription drug that originally had emotional-enhancing or energy-boosting effects even if those effects were abnormally exaggerated; 3) discontinuation of the medication or transfer of care to another prescriber; 4) diversion of prescribed medication for social or monetary

reasons; and 5) fear of withdrawal effects were the doctor to recommend a medication change. There are also prescriber-side reasons that paradoxical drug effects can go unrecognized. These include: 1) prescriber misattribution of paradoxical drug effects to a change in the patient's psychosocial stressors; and 2) prescriber misattribution of paradoxical prescription drug effects to the effects of illicit drugs their patients might be using. Also, due to the lack of a physiologically-based understanding of how psychotropic drugs exert their therapeutic effects, prescribers can mismanage paradoxical effects even when they are recognized. For example, the prescriber might respond to subtle or vaguely-reported paradoxical effects by increasing the dosage of an antidepressant or psychostimulant. Alternatively, the prescriber might change the prescription to another drug in the

same class or even add another drug in the same class. If these efforts repeatedly fail, the prescriber might conclude that the patient is treatment-resistant and recommend one of the alternative therapies described earlier. Yet, as previously discussed, each of those modalities exert their therapeutic effects by either or both of two mechanisms: they either increase neurological activity or decrease neurological activity. And although decreasing neurological activity would be the better choice for the vast majority of patients, prescribers do not at this time have a reliable way of determining which patients have hyperexcitable neurological systems. The ability to identify those patients is of critical importance because, according to the MCNH hypothesis, the only patients who would be well-tolerant of neurostimulatory interventions would be those with normoexcitable neurons (i.e., those who are outside the bipolar spectrum) [11]. Another concern is that some of these interventions, such as DBS and rTMS, are being guided by neuroimaging, and that can be misleading. For example, in rTMS it is assumed that because clinical depression is associated with an hypo-active left DLPFC, stimulation of that area could be an effective way to lift the depression [20]. However, this reasoning may be too simplistic because it fails to identify the underlying cause of the prefrontal hypoactivity. According to the MCNH hypothesis, which recognizes a mind-brain duality of the cognitive-emotional system, the cause of the hypoactivity is cognitive paralysis; the mind is so caught up in negative emotion that there is neither enough desire nor ability to formulate plans and engage in goal-directed activities. In the vast majority of cases, the excessive emotionality is driven by intrapsychic stress superimposed upon an inherent hyperexcitability of the neurological system. As the mind continues to be absorbed in negative emotion, it continues to fuel activity in the corresponding limbic circuitry and, conversely, the corresponding limbic circuitry continues to fuel activity in the mind. Although this vicious cycle of mutual overstimulation between the mind and the brain is usually initiated by cognitive-emotional stress, it is usually perpetuated by a hyperexcitability of the neurological system. Hence, if the excitability of the system could be reduced, the activity in the left DLPFC (and other brain areas that are affected by this pathological mind-brain dialogue) would tend to normalize. The concern about stimulating the brain would not necessarily apply to the minority of patients who have *normoexcitable* neurons because, as previously discussed, such patients are more tolerant of neurostimulatory interventions. This reasoning is supported by the observation that rTMS has been more effective in the treatment of unipolar disorders than bipolar disorders [62]. It also underscores the importance of determining which patients have hyperexcitable neurons and which ones have normoexcitable neurons [11].

The problem is that not all patients who have hyperexcitable neurons have clinically-recognizable symptom instability. Hence, such patients are frequently misdiagnosed as unipolar depressives [69-71]. This again is where the MCNH hypothesis becomes highly useful. Unlike current diagnostic systems, which rely on symptoms to guide

diagnosis and treatment, the newly-introduced “neuronal excitability spectrum” [11] relies on the identification of the underlying driver of the symptoms; namely, neuronal hyperexcitability. Although clinical symptoms can and should be used to help assess the excitability of a patient’s neurological system, there is emerging evidence that the determination can also be made objectively based resting vital-sign measurements [11, 25]. Assuming that there are no significant confounding factors, such as severe cardiopulmonary disease, cardiopulmonary medications, illicit drug effects, or extreme athletic conditioning, a resting heart rate above 75 beats/min or a resting respiratory rate above 15 breaths/min would be indicative of the neuronal hyperexcitability trait. Such patients would be prime candidates for anticonvulsant pharmacotherapy because anticonvulsants address the underlying problem of neuronal hyperexcitability.

What makes the neuronal hyperexcitability trait so important to identify is that it appears to be the fundamental driver of mental illness [25]. It also appears to be what drives the chronicity and vulnerability to recurrences that persons with mental illness have. Although most persons with higher levels of neuronal hyperexcitability will need ongoing Neuroregulator therapy, there is rarely any loss of effect with Neuroregulators, nor is there much risk of paradoxical switching or withdrawal effects. In addition to these benefits, Neuroregulator therapy helps prevent the plethora of chronic diseases that, like psychiatric disorders, have been linked to upper-end-of-normal resting vital signs and the neuronal hyperexcitability trait [25]. These include diabetes, high blood pressure, cardiovascular disease, autoimmune diseases, cancer, dementia, and many other chronic diseases. The shared association between these disorders, psychiatric disorders, and neuronal hyperexcitability is the MCNH explanation for why the lifespans of persons with severe mental illness are so short in comparison to the general population [25]. Hence, early treatment with Neuroregulators can be as important medically as it is psychiatrically.

Another advantage of Neuroregulators is their speed of action. Unlike antidepressant drugs, which take weeks to work, Neuroregulators exert their therapeutic effects within minutes of achieving the correct dosage. That’s because once they are absorbed into the bloodstream and cross the blood-brain barrier (a process that takes only about 30-45 minutes) they have a direct stabilizing effect on neuronal membranes.

Importantly, however, the therapeutic effects of Neuroregulators are highly dependent upon accurate dosing. Too low of a dose won’t work, and too high of a dose can cause intolerable side effects. The potential for inaccurate dosing is increased by the fact that the recommended dosage of anticonvulsant Neuroregulators is based primarily on experience with seizure disorders. However, seizure disorders, though being more likely to occur in persons with neuronal hyperexcitability, are typically not caused by neuronal hyperexcitability alone. In most cases, another abnormality is present, thus facilitating the hypersynchronous neurological activity that hypothetically distinguishes a seizure disorder



from a psychiatric disorder [27]. Hence, for most patients with seizure disorders, anticonvulsants have to quiet the brain enough to overcome this other abnormality. Psychiatrists are faced with the lesser challenge of having only to quiet the brain. For them, any reduction in neuronal excitability could reduce the patient's symptoms. Fittingly, it has been said that anticonvulsants may be more effective in the treatment of psychiatric disorders than seizure disorders [72]. A failure of prescribers to recognize the dosing implications of this could cause psychiatric patients to incur unnecessarily severe side effects...and possibly to reject the treatment altogether. Hypothetically, it could even cause them to experience a paradoxical worsening of symptoms if the firing of inhibitory neurons were reduced more than excitatory neurons.

One final note specifically pertains to the use of *anticonvulsant* Neuroregulators. Unlike other classes of psychotropic drugs, anticonvulsants can readily be combined with one another without throwing the neurological system out of balance; hence the term "mood stabilizer." As in the treatment of epilepsy, there is often added benefit to combining anticonvulsants because there are many mechanisms (and receptors) through which the excitability of the neurological system can be reduced. Therefore, if one anticonvulsant fails to alleviate all of the patient's symptoms, another one can be added, and so forth. This is important to recognize because focusing treatment on reducing neuronal excitability would not be targeting specific symptoms but rather the underlying driver of the symptoms.

## 6. Recommendations for Future Research

Urgently needed are clinical studies aimed at assessing: 1) the accuracy of resisting vital signs in helping to distinguish bipolar spectrum disorders from "true" unipolar disorders; 2) the comparative benefits of combining anticonvulsants rather than combining antidepressants with anticonvulsants in poorly responsive bipolar spectrum patients; and 3) the psychiatric and medically-protective effects of using anticonvulsant drugs prophylactically in young persons who, based on family history and resting vital-sign measurements, would be deemed to be at increased risk of developing various mental and physical illnesses.

## 7. Conclusion

Although the pathophysiology of psychiatric disorders has heretofore remained elusive, a comprehensive review of the various treatment modalities that have been used over the centuries has brought into focus two divergent mechanisms of action: 1) inhibition of neurological activity; and 2) stimulation of neurological activity. Although this paradox would in itself be difficult to explain, it is entirely consistent with the MCNH hypothesis of psychiatric disorders and can readily be explained by the MCNH hypothesis. According to the new hypothesis, psychiatric symptoms are the consequence of an imbalance between the activity of "feel-good" circuits and "feel-bad" circuits.

Hence, clinical improvement can be achieved by either stimulating activity in feel-good circuits or inhibiting activity in feel-bad circuits. Although neurostimulatory interventions are becoming increasingly popular, the evidence base, which includes evolving therapies, points to neuroinhibitory interventions as the treatment of choice for the vast majority of patients. This is not surprising because, as suggested by the gene research, the primary vulnerability trait for the development of psychiatric symptoms is an inherent hyperexcitability of the neurological system. In contrast to neurostimulatory interventions, neuroinhibitory interventions reduce this excitability, thereby helping to correct the underlying abnormality rather than chasing after symptoms. This is important to recognize because reducing symptoms without addressing the underlying driver of the symptoms leaves patients at an increased risk of relapse and can even lead to a chronic cycling of symptoms. Hypothetically, the only patients who would be well-tolerant of neurostimulatory interventions would be the small percentage of patients who develop psychiatric symptoms in the absence of neuronal hyperexcitability. Because such patients have a natural resistance to symptom-cycling, they have classically been described as having "true" unipolar depression. The problem is that they can be very difficult to distinguish from bipolar spectrum patients. The MCNH hypothesis, in conjunction with resting vital-sign measurements, can potentially allow clinicians to side-step this problem because the neuronal excitability spectrum is not based on symptoms but on the underlying driver of the symptoms [11, 25]. It also streamlines treatment because it illuminates a biological target for treatment.

Beyond these benefits, attention to the neuronal hyperexcitability trait has the potential to reduce the risk of any illness that can be precipitated or exacerbated by neuronal hyperexcitability. 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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