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Electrophysiology of Seizure Disorders May Hold Key to the Pathophysiology of Psychiatric Disorders

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Abstract: Despite the increasing burden of mental illness, social stigma and fears that psychological and emotional problems are a sign of character weakness prevent most sufferers from seeking treatment. These barriers are reinforced by diagnostic ambiguity, frequent drug side effects, variable treatment success, and a lack of clarity about the cause of mental illness. Much more progress has been made with epilepsy, a closely related group of disorders for which the pathophysiology is better understood. Although psychiatric disorders and seizure disorders are known to be distinctly different conditions, they have many shared features including their disruptive effects on mentation, their migratory nature, and their responsiveness to anticonvulsant drugs. In addition, a comparative analysis of the two disorder-types strongly suggests that they have shared mechanisms of symptom production, symptom progression, and symptom prevention. In this side-by-side comparison of the two disorder-types, I will discuss how the electrophysiological patterns that underlie seizure initiation and migration help explain how psychiatric symptoms develop and morph into one another, thus providing important insights into the pathophysiology of mental illness and potentially serving as a guide to the development of more effective treatments.

Keywords: Neuronal Hyperexcitability, Pathophysiology of Psychiatric Disorders, Bipolar Spectrum, Mood Cycling, Electrophysiology of Seizures, Kindling, Therapeutic Mechanism of ECT

1. Introduction

Despite the increasing burden of mental illness, social stigma and fears that mental and emotional problems are a sign of character weakness prevent most sufferers from seeking treatment. These barriers are reinforced by diagnostic ambiguity, frequent drug side effects, variable treatment success, and a lack of clarity about the cause of mental illness. Much more progress has been made with epilepsy, a closely related group of disorders for which the pathophysiology is better understood. Although psychiatric disorders and seizure disorders are known to be distinctly different abnormalities, they have many shared features including their disruptive effects on mentation, their migratory nature, and their responsiveness to anticonvulsant drugs. In addition, a comparative analysis of the two disorder-types strongly suggests that they have shared mechanisms of symptom production, symptom progression, and symptom prevention. This leads to the question: what can the study of epilepsy teach us about the elusive pathophysiology of mental illness? Could the same electrophysiological processes that underlie epileptiform activity be at work in psychiatric disorders? If so, the connection could shed new light on the biological underpinnings of history's most perplexing and stigmatizing group of disorders.

2. Comparison of the Two Disorder-Types

The idea that psychiatric disorders and seizure disorders are related dates back to around 400 B.C., when Hippocrates wrote: "Melancholics ordinarily become epileptics, and epileptics, melancholics: what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy." Closer to the modern era, Polish neuropsychiatrist Manfred Sakel recognized that a metabolically-induced quieting of the brain known as "insulin coma" was remarkably effective in treating otherwise intractable mental disorders [1]. It is

likewise known that quieting the brain can prevent seizure activity, thus explaining why anticonvulsant drugs are effective for both seizure disorders and psychiatric disorders. Both disorder-types are also responsive to electroconvulsive therapy (ECT) [2, 3], though the seizures themselves promote the symptoms of both [4-7]. These observations strongly suggest that psychiatric disorders and seizure disorders are closely related. But what is the common ground between them?

Seizures develop when clusters of neurons begin to fire hypersynchronously [8]. The associated surge in magnetic field strength and chemically-mediated neurotransmission cause other neurons nearby or throughout the tissue to become engulfed in a spreading wave of depolarization [9]. Because the risk of hypersynchrony increases as the level of excitation in the brain increases, the catalyst for a seizure is any condition or chemical that increases the excitability of the neurological system, such as emotional stress, an inflammatory process, a metabolic disturbance, or a stimulant-type drug. An important clue to the pathophysiology of psychiatric disorders, which can be clinically indistinguishable from seizure disorders [4-7], is that the same conditions and chemicals that *increase* the potential for seizures also *increase* the potential for psychiatric symptoms, and the same conditions and chemicals that *decrease* the potential for seizures also *decrease* the potential for psychiatric symptoms (Table 1). The unwavering consistency of these associations strongly suggests that neuronal hyperexcitability is a catalyst for psychiatric symptoms, just as it is for epileptic seizures.

Table 1. *Directionally Shared Impact of Various Conditions and Chemicals on Seizure and Psychiatric Symptom Potential.*

CONDITIONS AND CHEMICALS THAT *INCREASE* SEIZURE AND PSYCHIATRIC SYMPTOM POTENTIAL
Cognitive-emotional stress [10-13]
Sleep deprivation [11, 12, 14]
Psychostimulants (caffeine, methamphetamine, phencyclidine) [15, 16]
Sedative withdrawal (benzodiazepines, barbiturates, hypnotics, alcohol)
Inflammation [17-19]
Corticosteroids [20, 21]
Dietary sugar (especially refined sugar) [22, 23]
Oxygen deprivation (living at altitude) [24, 25]
Experimentally induced kindling of the brain [26, 27]

CONDITIONS AND CHEMICALS THAT *DECREASE* SEIZURE AND PSYCHIATRIC SYMPTOM POTENTIAL
Stress reduction [10-13]
Normal sleep [11, 12, 14]
Progesterone [28-31]
Anticonvulsant drugs
Sedatives (benzodiazepines, barbiturates, hypnotics, alcohol, some cannabinoids) [32-34]
Centrally-acting alpha-2 agonists (clonidine, guanfacine) [35, 36]
Acamprosate [37-41]
Riluzole [42, 43]
N-acetyl cysteine [44]
Magnesium [45, 46]
Taurine [47, 48]
Low carbohydrate (Ketogenic) diet [22, 23]
Omega-3 fatty acids [49, 50]
Plant-based oils and alkaloids [51-56]
ECT [2, 3]
Vagus Nerve Stimulation [57, 58]
Deep Bran Stimulation [59, 60]

+ Itemization of the various conditions and chemicals that have a directionally shared impact on seizure and psychiatric symptom potential. Note that all of the items on the list affect the excitability of neurons. It should also be noted that the first two items on the list (stress and sleep deprivation) are the two most commonly associated triggers of both seizures and psychiatric symptoms [11, 12, 14].

As previously stated, epileptic seizures can, via ECT, be used to treat both seizures and psychiatric symptoms. Although the mechanism by which ECT relieves symptoms remains unclear, it is evident that clinical improvement occurs not during the seizure but in the aftermath of the seizure. It is now recognized that seizures are brought to a halt by a host of neuroinhibitory changes that occur in response to the seizures themselves. Known mechanisms 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 [61]. That a remission of depression and other psychiatric symptoms occurs in conjunction with this robust inhibitory activity is further evidence that psychiatric symptoms, like epileptic seizures, are driven by neuronal hyperactivity. Moreover, high resolution neuroimaging studies have found that in major psychiatric disorders, such as clinical depression, bipolar disorder, and obsessive-compulsive disorder, the neurons won't shut off [62-65].

The connection between neuronal hyperactivity and psychiatric symptoms leads to the hypothesis that psychiatric disorders are a manifestation of persistent, non-hypersynchronous hyperactivity in symptom-related circuits

[66]. Pathological elevations in circuit-specific firing would cause the associated thoughts and feelings to become abnormally intense and prolonged. For example, if depressive circuits became persistently hyperactive, the person would experience persistent feelings of depression (Figure 1a). If anxiety circuits became persistently hyperactive, the person would experience persistent feelings of anxiety (Figure 1b). If irritability circuits became persistently hyperactive, the person would experience persistent feelings of irritability (Figure 1c). The same would apply to cognitive circuits. If they became persistently hyperactive, the person would experience repetitive or racing thoughts (Figure 1d). In other words, the persistence of pathological levels of hyperactivity in specific circuits would create the symptoms that have been grouped into the various psychiatric disorders.

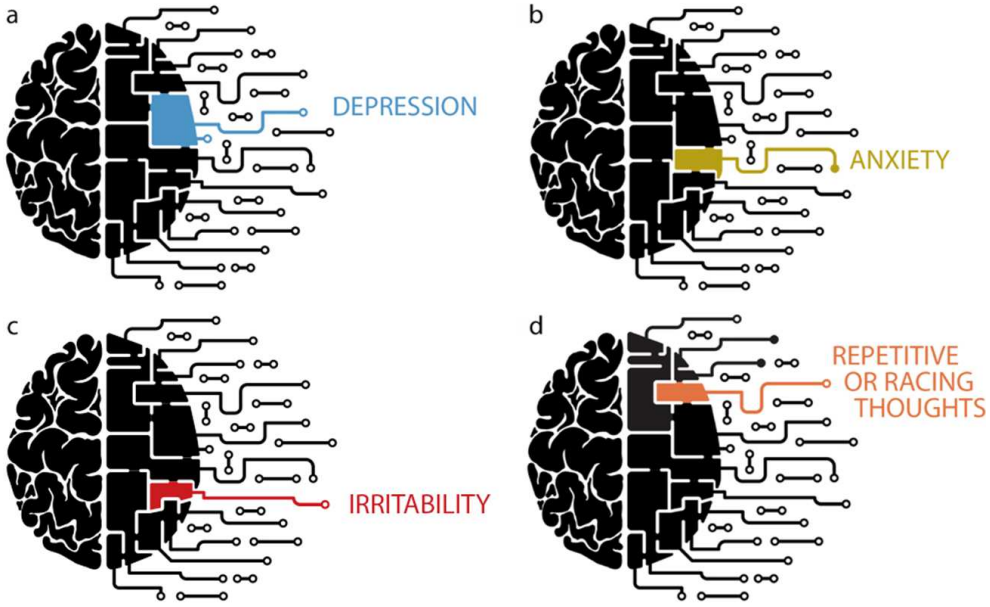

Figure 1. *Conceptual illustration of hyperactivity in specific brain circuits and their related emotional and cognitive expressions. (1a) hyperactivity in depressive circuits; (1b) hyperactivity in anxiety circuits; (1c) hyperactivity in irritability circuits; (1d) hyperactivity in cognitive circuits. Note: color codes are intended to represent hyperactivity in the brain's microcircuitry, not necessarily whole or specific brain regions.*

The idea that psychiatric symptoms could be produced by neuronal hyperactivity has been demonstrated experimentally by Mazarati et al, who found that when the excitability of the brain was experimentally increased by repeated subconvulsive stimulation, the kindled animals began to demonstrate depressive-like behavior [26]. The effect was the psychiatric equivalent of the seizure activity that was elicited by the pioneering neuroscientist Graham Goddard as he repeatedly stimulated the brains of rats during his original experiments on learning [27]. This observation, taken together with the observation that depressive symptoms in susceptible individuals commonly develop in association with the neurostimulatory effects of severe or recurrent psychosocial stress [67], is compelling evidence that clinical depression is a manifestation of hyperactivity in depressive circuit loops [66]. Lending further support to this hypothesis is the striking observation that the increased vulnerability to depression (and other psychiatric symptoms) that is fueled by persistent psychosocial stress persists for about the same length of time as an experimentally-induced kindling effect [68]. These observations strongly imply that neuronal hyperactivity is the common ground between seizures and psychiatric symptoms. What theoretically distinguishes the one disorder-type from the other is the degree of synchrony of the neuronal discharges; if they are highly synchronous, seizures occur; if they are less synchronous, psychiatric symptoms occur.

Of course, the duration of a psychiatric episode is much longer than that of an epileptic seizure. That is theoretically because the number of neurons involved in the induction of psychiatric symptoms is too small and unsynchronized to stimulate the neuroinhibitory changes that bring seizures to a halt (that is, unless it is bolstered by ECT). It is also too small and unsynchronized to induce enough magnetic field strength to cause the rapid migration of symptoms, disruption of consciousness, and electroencephalographic (EEG) changes that characterize seizure activity [9]. Then again, when consciousness *is* preserved during a seizure, the symptoms often resemble those of a psychiatric disorder. In simple partial seizures, for example, psychotic symptoms can be misdiagnosed as schizophrenia, mood symptoms can be misdiagnosed as major depressive disorder, anxiety symptoms can be misdiagnosed as panic disorder, dissociative states can be misdiagnosed as dissociative disorders, and impaired cognition can be misdiagnosed as an executive function disorder [6]. In one study, nearly half of the patients with seizure-related psychotic symptoms could easily have been misdiagnosed with schizophrenia [7].

At the same time, the most ubiquitous trigger of psychiatric symptomatology, like that of epileptiform activity, is cognitive-emotional stress, which has a graded and robust excitatory effect on the neurological system [10, 69, 70].

Excluding those cases in which there is a complicating biological stressor, a careful analysis of the illness history of psychiatric patients consistently reveals a close, though somewhat delayed, temporal relationship between the onset of a psychosocial stressor and the development of symptoms. With few exceptions, the onset of symptoms will occur within days, weeks, or months of the rise in stress, which is presumably the time needed for the stressed mind to induce enough kindling in the brain to precipitate symptoms.

Pathological levels of neuronal excitation are associated with another feature that is shared by seizure and psychiatric disorders—the migration of symptoms. From the study of epilepsy, it is known that focal areas of hyperactivity do not necessarily remain focal; instead, they tend to migrate from one group of neurons to another, and from one group of circuits to another. This is what underlies the classic "Jacksonian march" of convulsive activity. A similar process may be occurring in psychiatric disorders. What theoretically allows symptoms such as anxiety, depression, and irritability to oscillate back and forth and morph into one another is that the circuit-specific hyperactivity that is driving the symptoms fuels hyperactivity in various circuit loops that would be resistant to such aberrant activation were they not themselves hyperexcitable (Figure 2a). The process is akin to a short-circuit in a wired electrical system (Figure 2b). So common is the cycling of symptoms in psychiatric disorders that the dimensional term "bipolar spectrum" has, for some time now, been used to describe the phenomenon.

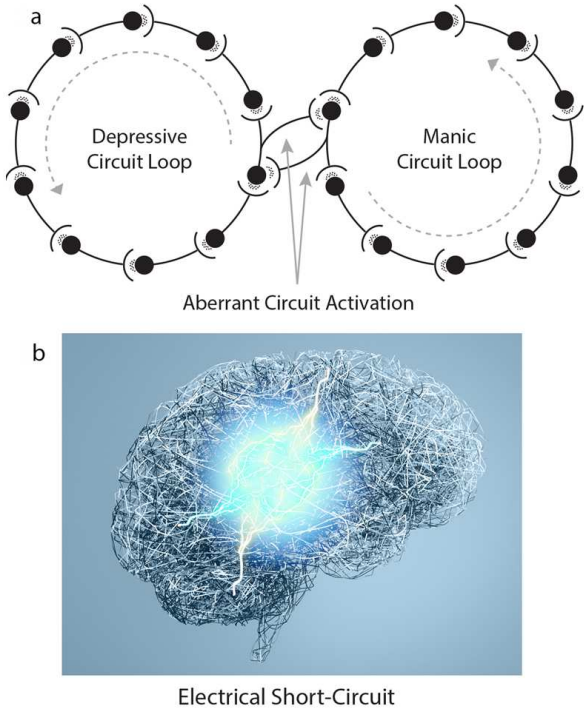

Figure 2. *Conceptual illustration of how the locus of hyperactivity in psychiatric disorders is theorized to activate inappropriate brain circuits, causing various thoughts and feelings to arise spontaneously and various symptoms to morph into one another (2a). The process is akin to a short-circuit in a wired electrical system (2b). Figure 2a is adapted from Binder MR:"The Multi-Circuit Neuronal Hyperexcitability Hypothesis of Psychiatric Disorders" [62].*

3. Electrophysiology of Kindling as a Guide to the Neurophysiology of Psychiatric Disorders

The most fundamental element of kindling is the phenomenon of *afterdischarges,* in which populations of neurons continue to fire in bursts after the driving stimulus is removed; hence the term "afterdischarge" [71]. As part of this hyperactivation phenomenon, the persistent electrical activity smoothly increases and decreases and increases again over a period of several seconds. Afterdischarge activity produces the "spike and wave" pattern that, on an EEG, is characteristic of epileptic seizures. After this activity dies out, the EEG flattens and subsequently normalizes again. When Dr. Goddard first observed this phenomenon, he recognized that the brain was changing in response to a constant stimulus and that this "plasticity" could be helpful in understanding the mechanisms that underlie seizure production [27, 71]. Today, this phenomenon is likewise thought to help explain why repeated psychiatric episodes increase the likelihood of future recurrences [67].

Related to the phenomenon of afterdischarges are what are known as "hyperspikes." These can occur when more than one area of epileptiform activity competes for dominance [71]. Typically, one area of activity will ultimately suppress the non-dominant areas of activity for a period of time. In relation to psychiatric disorders, this could help explain why a person can become locked into a particular emotional state, such as anxiety or depression, for a sustained period of time. Of course, the duration of a pathological emotional state is typically much longer than an epileptiform state, but once locked in, the persistence of hyperactivity in one cognitive or emotional circuit would keep fueling the same negative thoughts and feelings, thereby perpetuating the hyperactivity in those circuits loops.

At times, afterdischarge activity can wax and wane until it subsides, only to return seconds later in what are known as "secondary afterdischarges." Secondary afterdischarges are indicative of the spread of seizure activity to other populations of neurons and are another characteristic of the kindling phenomenon [71]. In relation to psychiatric disorders, this could help explain why pathological emotional states tend to wax and wane in severity. It could also help explain why more than one emotional state can develop and persist simultaneously and why intrapsychically conflictual states, such as mania and depression, can sometimes coexist.

In contrast to hyperspike activity, wherein multiple structures are recruited simultaneously by the epileptiform activity, the locus of hyperactivity that is driven by secondary afterdischarges can migrate from one structure (or neural network) to another [71]. This could help explain the cycling of divergent symptoms in bipolar disorder, cyclothymia, and other psychiatric disorders in which the symptoms have a cyclic pattern (Figure 2). What would theoretically determine the cycling frequency would be a dynamic interplay between the degree of cognitive-emotional stress, the inherent

excitability of the neurons, the choices of the individual, and the physical connectedness of the neurological system. Those whose neurons were more extensively connected would be expected to cycle more rapidly because of the increased likelihood that hyperactive feeder circuits would stimulate firing in collateral circuits. That would also mean that in those whose brains were more densely wired, the aberrant circuit activation would tend to start at lower levels of excitation and migrate to and fro more easily. This could explain why both the amplitude and duration of the cycles is typically lower in rapid-cycling disorders. Conversely, those whose brains were less densely wired would be expected to have longer cycles of higher amplitude. Their neural circuits would also have to become more hyperactive before any discernible cycling could begin. This could explain why non-rapid cycling, as in bipolar I disorder, is correlated with larger peaks and troughs than in rapid cycling disorders and why the clinical states in bipolar I disorder tend to be easier to recognize than in rapid cycling disorders. Additional support for the idea that cycling frequency could be related to the number of neuron-to-neuron connections comes from the observation that the large waves that characterize bipolar I disorder are relatively rare in patients with autism spectrum disorder [72], a condition that is believed to be rooted in an overabundance of neurons and neuron-to-neuron connections [73, 74].

4. Discussion

Although psychiatric disorders generally do not evidence either the ictal or interictal EEG activity that is observed in seizure disorders [75], multiple lines of evidence, including high resolution imaging studies, indicate that psychiatric disorders, like seizure disorders, are fueled by neuronal hyperexcitability [62-67, 76]. In addition, the same treatment techniques, including anticonvulsant drugs, ECT, vagus nerve stimulation, and deep brain stimulation, are effective for both disorder-types [2, 3, 57, 59, 66, 76]. In recognition of this, it is reasonable to think that the same electrophysiological phenomena that underlie the electrical storms of a seizure also underlie the acute phase of a psychiatric illness, when symptom-related circuits are the most pathologically hyperactive [62-66, 76]. Additional support for this hypothesis comes from the observation that the symptoms of most psychiatric disorders *migrate* just as they do in most seizure disorders [66]. What's more, the tendency for the symptoms to migrate increases in conjunction with the severity of psychosocial stress, which is the most ubiquitous driver of neuronal hyperactivity. Together, these observations provide a strong basis of support for the idea that psychiatric disorders, like seizure disorders, are fueled by neuronal hyperexcitability. In conjunction with this, they also provide important insights into the electrophysiological mechanisms by which psychiatric symptoms wax and wane in severity and meld into one another.

5. Conclusion

The large overlap in phenomenology between seizure disorders and psychiatric disorders strongly suggests that neuronal hyperexcitability is a catalyst for both disorder-types and that the electrophysiological phenomena that underlie seizure activity also underlie the emotional extremes and symptom instability that characterize psychiatric disorders. In addition, the latest gene research links the top candidate genes for psychiatric disorders to neuronal hyperexcitability, thus providing a genetic basis of support for the idea that psychiatric symptoms are driven by hyperactivity in the brain [77-89]. This in turn suggests the possibility that a genetically-determined hyperexcitability of the neurological system could be the chief predisposing factor in the development of psychiatric disorders. This has important clinical implications, as confirmatory studies could shift the treatment of psychiatric disorders from a symptom-based strategy to a pathology-based one—a change that would, for the first time, allow clinicians to precisely target what has been called "the world's largest single health problem."

Competing Interests

The author declares that this article was conceived and written in the absence of any competing interests.

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