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The *N*-Methyl-D-Aspartate Receptor: Memory, Madness, and More

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What else had I forgotten? What else would come back, knocking me off balance
and reminding me how tenuous my grip on reality was?

—Susannah Cahalan, *Brain on Fire: My Month of Madness*

In her book *Brain on Fire*, Susannah Cahalan recounts the terrifying experience of agitation, paranoia, psychosis, aggression, and memory loss (1). Her illness resembled a classic presentation of schizophrenia and ordinarily would have been treated with antidopaminergic agents and perhaps psychiatric hospitalization. Unfortunately, for many patients these treatments are far from ideal. These medications can have substantial side effects both in the short term (e.g., with dystonic reactions) and when used long-term (e.g., with metabolic syndrome). More significantly, they have inadequate efficacy, and many patients will fail to respond. An important reason for this may be that our diagnostic category of schizophrenia may encompass a broad range of underlying disorders rather than reflecting a single pathophysiologic entity.

Susannah Cahalan would not have responded to standard-of-care treatments. Although her symptoms resembled a classic phenotypic presentation she did not in fact have schizophrenia: instead, she had *N*-methyl-D-aspartate receptor (NMDAR) encephalitis, a rare autoimmune disease where one's own antibodies attack the NMDAR in the brain (1). Today, the disorder is both diagnosable and treatable, though even a decade ago it is estimated that more than 90% of patients with the same illness were misdiagnosed as having schizophrenia or another psychiatric condition (1). How do we think about this striking clinical scenario? How should it inform treatment today? And, at a more basic level, what can it teach us about the underlying biology of psychotic disorders?

Like much in the history of psychiatry and neuroscience, our first clinical exposure to the NMDAR was by accident. In the 1950s a compound known as phencyclidine (PCP) was developed as an anesthetic agent but then was quickly taken from the market after it was noted to cause dissociative hallucinations in patients. However, by the time it was removed the street value of PCP had already been established and people continued to use PCP (also

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known as angel dust) recreationally. In 1978, Allen and Young (2) published an article noting the similarity between PCP-induced psychosis and the symptoms of schizophrenia. Wondering if PCP psychosis could be used as a model for schizophrenia, David Lodge's lab at the University of Bristol began studying the mechanism of action of PCP and in 1983 identified PCP as a noncompetitive antagonist of the NMDAR, thus establishing the hypothetical link between the NMDAR and schizophrenia (3). This also helped develop the glutamate hypothesis of schizophrenia, challenging the prevailing dogma that excessive dopamine was the causative agent of schizophrenia.

The NMDAR, along with the alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor, is one of two major ionotropic receptors for the excitatory neurotransmitter glutamate. As such, the NMDAR plays a vital role in depolarizing synapses and propagating electrical signals from one neuron to the next. Moreover, it turns out that NMDARs located on dendritic spines have unique properties that make them essential for the establishment of long-term memories [reviewed in (4)]. Meanwhile, NMDARs located on the neuron cell bodies have been implicated in triggering cell death and neuronal degeneration after strokes and seizures—a phenomenon known as glutamate excitotoxicity. So how can the same receptor have such different and seemingly opposing functions as memory formation and cell death?

The NMDAR is an extraordinarily complex yet highly versatile receptor (Figure 1). The receptor itself is assembled from four subunits that can be combined in different ways to form unique NMDAR isoforms. We know that different NMDAR subtypes are functionally significant because they are differentially expressed based on stages of neural development, anatomic brain region, and neuronal compartment.

To form a functional NMDAR, each NMDAR channel must have two NR1 subunits bound with any combination of two NR2 receptor subunits (5). The NR1 subunit is essential for channel formation and is the binding site for the co-agonists glycine and D-serine. Meanwhile, the NR2 subunit is the binding site for glutamate, the main excitatory neurotransmitter required for activation of NMDARs. Both glutamate and its co-agonist (glycine or D-serine) must be simultaneously present at the synapse for an NMDAR to be activated. Additionally, magnesium usually blocks the channel pore and must be displaced prior to activation (typically occurring via depolarization of the cell following AMPA activation).

Different NMDAR isoforms—formed by diverse combinations of NR2 subunits—serve unique roles in the brain. For instance, NR2A/B subunits are better suited than NR2C/D subunits for long-term potentiation. Unsurprisingly, NR2A/B subunits are found in the hippocampus, the brain region most distinctly tied to memory. This unique, complex structure–function relationship of the NMDAR provides a vast substrate for pharmacologic treatment. For example, one can theoretically modulate NMDAR function by targeting different NR2 subunits, manipulating levels of glycine or D-serine, or altering the availability of glutamate at the synapse.

Given the many different roles that the NMDAR plays in both healthy and diseased brains, one can see why it has become an attractive target for treating a diverse range of conditions. For instance, given the role of somatic NMDARs in mediating cell death, memantine—an NMDAR antagonist—is being used for Alzheimer's disease to try to slow this process of neurodegeneration and cell death. Another NMDAR antagonist, ketamine, is being explored in phase II clinical trials as a potentially powerful medication to treat depression, the effects of which are thought to be mediated more by secondary increases in AMPA receptor activity than by decreased NMDAR activity (6). And D-cycloserine, a drug formerly used to treat tuberculosis and later discovered to be an NMDAR agonist, is being tested as a memory-enhancing agent with therapeutic application to post-traumatic stress disorder, exposure therapy, and anxiety disorder (7). While many puzzles and apparent paradoxes regarding the therapeutic mechanisms of NMDAR modulators are yet to be resolved, their clinical utility is undeniable. Perhaps where the NMDAR shows the most promise for psychiatry is in the future investigation and treatment of schizophrenia (3).

Standard antipsychotic treatments for schizophrenia have historically been motivated by the dopamine hypothesis and tend primarily to work by antagonizing dopamine receptors. While these medications are effective at treating positive symptoms (such as hallucinations, disorganized thought process, and agitation), they have notoriously been ineffective at treating negative symptoms of schizophrenia—including alogia, apathy, anhedonia, and asociality. Interestingly, the NMDAR antagonist PCP can reproduce not only the positive symptoms of psychosis—such as hallucinations—but also the negative symptoms. This implicates NMDAR as a possible target for treatment of negative symptoms of schizophrenia. If true, this breakthrough would transform treatment of psychotic disorders, as the persistence of negative symptoms is a crucial determinant of a patient's social and occupational reintegration, and consequently their long-term prognosis.

In lieu of targeting the NMDAR itself, one recent experimental treatment approach has been to identify agents that can enhance receptor function indirectly by increasing the availability of co-agonists. Bitopertin is one such agent. It acts by binding to glycine transporters at the synapse and interfering with reuptake, thus increasing the concentration of glycine available at the synapse. In one proof-of-concept phase II trial, bitopertin was found to reduce negative symptoms of schizophrenia by 25%, as measured by the Positive and Negative Syndrome Scale assessment tool (8). These results were met with widespread enthusiasm and rushed bitopertin into phase III clinical trials. However, three recent phase III clinical trials—FlashLyte, DayLyte, and SunLyte (terminated early)—reviewed in this issue of *Biological Psychiatry* by Bugarski-Kirola et al. (9) failed to show efficacy over placebo for treatment of negative symptoms.

Despite the null outcomes of these three trials, the silver lining is that after so many years of the dopamine theory of schizophrenia prevailing as the only credible scientific theory of schizophrenia, new models are offering both a new understanding of psychosis and a pathway for rigorous scientific inquiry into new treatments (10). There will undoubtedly be setbacks along the way—but it is inspiring to move from a passive, serendipitous process of drug discovery toward more active, hypothesis-driven inquiries.

The field of medicine has a long way to go when it comes to the diagnosis and treatment of psychiatric disorders. The story of Susannah Cahalan highlights both these points. Schizophrenia and many other diagnoses currently defined by the DSM are likely a heterogeneous group of diseases. Understanding the relevant underlying neurobiology will help us to better parse—and thereby treat—the assorted collection of syndromes we presently label as schizophrenia, depression, and anxiety. Studies aimed at the NMDAR are among many burgeoning areas of research that show promise toward achieving this goal.

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Figure 1.

Structure of the *N*-methyl-D-aspartate (NMDA) receptor. On the left is a schematic of neuron A making synaptic contact with the dendrites of neuron B. Illustrated in the blue circles are NMDA receptors, demonstrating the distinct compartmental localization of somatic vs. dendritic NMDA receptors. Magnified on the right is the tetrameric structure of an NMDA receptor on the postsynaptic membrane of a synapse, along with the multiple agonists, co-agonists, and various targets for pharmacologic modulation. PCP, phencyclidine.