Glutamate and Schizophrenia: From Theory to Treatment Implications

Glutamatergic models have led to greater understanding of the causes of social and occupational disability in schizophrenia, and thus have provided new targets for remediation and compensation strategies.

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This activity offers CE credits for:
1. Physicians (CME)
2. Other

ACTIVITY GOAL
This article reviews the mechanisms by which NMDA receptor dysfunction might lead to the complex patterns of symptoms and neurocognitive deficits seen in schizophrenia and on methods by which glutamate-based theories can be used to develop new treatment methodologies.

LEARNING OBJECTIVES
At the end of this CE activity, participants should be able to:
1. Discuss the role of glutamate in the pathology of schizophrenia.
2. Explain the possible mechanisms by which glutamatergic dysfunction leads to dopamine hyperactivity.
3. Describe the treatment implications based on new understanding of possible causes of disease onset and progression.

TARGET AUDIENCE
This continuing medical education activity is intended for psychiatrists, psychologists, primary care physicians, physician assistants, nurse practitioners, and other health care professionals who seek to improve their care for patients with mental health disorders.

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By Daniel C. Javitt, MD, PhD [4]
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Decrease NMDA receptors by, say, 40%, and you might get psychosis; decrease them by 70%, and you have catatonia. In “knockout mice” without NMDA receptors at all, even the most basic life functions are impossible. . . .

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

Schizophrenia was first described over 100 years ago. Sixty years ago, the first effective medication for schizophrenia, chlorpromazine, was discovered by fortunate clinical observation. Shortly thereafter, the antipsychotic effects of chlorpromazine were attributed to its ability to block dopamine D2 receptors, and the dopamine model of schizophrenia was born. For the past 60 years, compounds developed based on dopamine models, such as chlorpromazine, haloperidol, risperidone, and olanzapine, have been invaluable in the management of schizophrenia and remain the only available FDA-approved treatments.

Since the discovery of chlorpromazine, treatment options for schizophrenia remain limited. Even among patients who respond to medication, negative symptoms and cognitive deficits frequently persist and contribute to long-term disability. Only a small minority of patients with first-onset schizophrenia return to their former level of functioning. Further muddying the waters is the increasing disconnect between dopamine models, which suggests that cognitive deficits in schizophrenia should be restricted to specific brain regions, while neuropsychological studies show impairments across a range of neurocognitive functions.

An alternative conceptual approach for schizophrenia focuses on dysfunction of brain glutamate systems, particularly involving N-methyl-D-aspartate (NMDA)-type glutamate receptors. NMDA receptor–based theories originated more than 20 years ago. Since then, these models have led to new approaches to the conceptualization of schizophrenia, along with potential new measures for assessing risk in individuals who show early symptoms. Attempts to translate glutamate theories into effective pharmacological treatments are ongoing and may require new techniques, such as neuromodulation, in addition to more conventional neuropharmacological approaches.

Glutamate-based models of schizophrenia

Similar to the dopamine theory, glutamate-based theories of schizophrenia are also based on a chance clinical event. Unfortunately, however, in the case of glutamate, the event did not involve discovery of a new treatment but instead the discovery of two closely related compounds—phencyclidine (PCP) and ketamine—that produced symptoms and cognitive deficits in healthy volunteers that closely resembled those of schizophrenia. Such symptoms, including negative as well as positive symptoms, resolved following elimination of the compounds. Approximately 25 years ago, it was shown that these compounds produce their effects by blocking neurotransmission at NMDA-type glutamate receptors (Figure 1), giving rise to current glutamatergic theories. Since the discovery of the relationship between PCP-induced psychosis and NMDA receptors, scientists have been attempting to determine causes of NMDA receptor dysfunction in schizophrenia—and causes most likely vary among individuals. For example, many of the candidate genes for schizophrenia affect glutamatergic neurotransmission. NMDA receptors are also regulated by brain levels of glycine, d-serine, and glutathione. Disturbances in brain concentrations of these compounds and of genes related to their synthesis may therefore all contribute to schizophrenia. It appears that there is more than a single cause of NMDA receptor dysfunction among individuals. Instead, threshold models may be critical, such that for each individual the sum of genetic and environmental factors determines whether NMDA receptor function will fall below a critical level. In Parkinson disease, symptoms are thought to emerge once brain dopamine levels fall by approximately 80%. In schizophrenia, psychosis may emerge once the level of NMDA receptor
function drops by about 20%, with increasing symptom severity thereafter.\textsuperscript{4}

**Dopamine-glutamate interaction**

In addition to providing an overall theoretical framework for negative as well as positive symptoms, a specific contribution of the NMDA model is to help explain why dopaminergic hyperactivity develops in schizophrenia and why some patients fail to show improvement of positive symptoms even when treated with antipsychotics. Dopamine levels in the brain can be detected by positron emission tomography and, as predicted by dopamine models, elevations in brain dopamine levels correlate with response to antipsychotics.\textsuperscript{8} Nevertheless, the reasons for the increased dopamine synthesis and release in schizophrenia remain unknown.

In some individuals, dopaminergic dysfunction may be due to genetically determined abnormalities of dopamine synthesis or degradation enzymes. However, an alternative possibility is that NMDA receptor dysfunction leads to failures in the regulation of the dopamine system within the striatum. In support of this possibility, dopamine abnormalities similar to those observed in schizophrenia can also be induced by NMDA blockers such as ketamine, both in healthy volunteers and in rodent models.\textsuperscript{9,10} More recently, it has been suggested that patients who fail to respond to antipsychotic treatment have baseline disturbances in glutamatergic, but not dopaminergic, function.\textsuperscript{11} Thus, in those patients, there is no dopaminergic excess that can be reversed. Nevertheless, such patients still show psychotic symptoms, which suggests that disturbances in both the glutamate and dopamine systems may contribute to the development of positive symptoms, both in schizophrenia and in other psychotic disorders.

**Where in the brain is schizophrenia?**

A second major difference between glutamate and dopamine models relates to what parts of the brain are likely affected. As first proposed by Kraepelin more than 100 years ago, the “core” of schizophrenia continues to be a severe impairment in cognitive function that persists even when psychotic symptoms are controlled. Dopamine is found only in limited brain regions, such as the frontostriatal and limbic regions. Therefore, an exclusive focus on dopamine forces clinicians to try to attribute all aspects of cognitive deficits in schizophrenia to failure in some regions of the brain. For this reason, relatively little schizophrenia research has been conducted on other brain regions, such as the auditory and visual cortices, and much of the brain remains unexplored.

In contrast to dopamine, glutamate and NMDA receptors are widely distributed throughout the brain, leading to a concept of “whole brain” dysfunction that involves not only the prefrontal and limbic brain regions but also nontraditional regions, such as the auditory and visual cortices. As predicted by glutamate models, not only are severe deficits associated with these regions but, thinking “glutamatergically,” also specific types of deficits that would not be suspected on the basis of dopamine theories have been identified.

**Mismatch negativity and auditory system dysfunction**

The differences between glutamate and dopamine models are most clear-cut with regard to sensory brain regions, such as the primary auditory and visual cortices. These regions contain relatively little dopamine and so were rarely studied before the advent of glutamatergic models. This concept began to change, however, in the early 1990s with the advent of glutamate models and, in particular, with the study of mismatch negativity (MMN) in brain response.

MMN is the response of nerve cells in the auditory cortex to changes in the pattern of ongoing auditory stimulation. Unlike later brain responses, MMN occurs even in the absence of consciousness to stimuli. An important function of MMN is to “alert” the rest of the brain that a potentially important event has occurred. Parallel studies performed in the early 1990s demonstrated that NMDA receptor function was critical in generating MMN and that patients showed severe deficits in generating this simple auditory response.\textsuperscript{12,13}

Since that time, MMN has become one of the best-established biomarkers in schizophrenia research, and it appears to predict the likelihood that individuals who show early schizophrenia-like symptoms will progress to schizophrenia.\textsuperscript{14,15} Whereas NMDA receptor antagonists such as ketamine induce MMN deficits in healthy volunteers, agents that influence dopamine neither induce nor reverse impairments in MMN, reinforcing the concept that the strongest predictors of schizophrenia may reside outside the dopamine system.

**Paths from basic auditory dysfunction to clinical outcome**

Although the initial studies of MMN focused on its role as a marker of NMDA receptor function, it turned out that MMN is an unexpectedly strong predictor of function, even in healthy volunteers. For example, in a recent study, amplitude of MMN in adulthood was strongly correlated with the level of education.\textsuperscript{15} To understand this relationship, parallel studies have been conducted using behavioral measures of auditory function.
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MMN is most associated with the ability to match tone following a brief delay. As with studies of MMN, studies of tone matching in schizophrenia were first conducted in the mid-1990s. Consistent with MMN results, the tone matching findings showed dramatic deficits in patients with schizophrenia. Specifically, healthy individuals have the ability to detect about a 3% difference between tones presented about a second apart—approximately corresponding to the difference between a white and black note on a piano. In contrast, individuals with schizophrenia and especially with poor-outcome forms of the illness required about a 20% difference—roughly the difference between a C and an E; some patients required differences of an octave (100%) or more. More recent studies investigated the relationship between poor tone matching ability and social/occupational outcomes. In Western languages, such as English, tonal modulation is heavily used to convey non-tonal information, such as emotion (eg, happy, sad) or attitude (eg, sincere, sarcastic). Schizophrenia patients are known to perform poorly in social settings and, in particular, show impaired ability to detect emotion from vocal intonation. Until recently, however, it was assumed that these deficits reflected dysfunction in emotional (ie, limbic) brain regions. However, as shown in Figure 2, much of the deficit in auditory emotion recognition in schizophrenia is driven simply by the inability to detect tonal variations. Similarly, patients are markedly impaired in detecting sarcasm, again because of the inability to process the change in intonation used to convey information. Patients who speak tonal languages, such as Mandarin Chinese, have deficits in discriminating words that differ only in tonality (eg, “ya” which may mean either tooth or duck, depending on intonation). As with impairments in social cognition, such deficits also correlate strongly with impaired vocational function. Even in Western languages, the ability to break down phonological processing (ie, the ability to blend sounds) leads to a sharp decline in reading ability during the years immediately surrounding onset of illness. Some individuals who do not have schizophrenia also have very poor tone discrimination ability (ie, congenital amusia). These individuals also have impaired social function. Recent findings indicate that roughly 50% of patients with schizophrenia meet criteria for amusia. Music therapy was once considered an important component of psychosocial rehabilitation in schizophrenia. It has now fallen out of favor because it does not fit with standard concepts of brain dysfunction in schizophrenia. It is hoped that with an outgrowth of glutamate models, there will be a renewed focus on simple sensory functions and their contributions to the persistent psychosocial deficits in schizophrenia.

Glutamate-related deficits are, of course, not confined to the auditory system, and deficits in other brain regions contribute to the distributed pattern of cognitive dysfunction that is observed in schizophrenia (Figure 3). These deficits may represent key bottlenecks in preventing individuals with schizophrenia from returning to premorbid levels of functioning.

**Anti-NMDA receptor encephalitis**

As vividly described by Susannah Cahalan in *Brain on Fire: My Month of Madness*, recent research has identified anti-NMDA receptor antibodies in patients who could receive a diagnosis of schizophrenia but who nevertheless recover when treated with specific immunological therapies. It is likely that such antibodies affect only a small percentage of patients with schizophrenia (probably no more than 1% to 2%). Nevertheless, as with PCP psychosis, the fact that compromising NMDA receptors can re-create a pattern that closely resembles schizophrenia suggests that NMDA-based models may be critical to the development of new antipsychotic treatments.

**Pharmacological implications**

To date, glutamate-based research on schizophrenia has provided new insights into the causes of schizophrenia and a new understanding of the pathways, from basic brain dysfunction to clinical symptoms. Unfortunately, attempts to develop glutamate-based medications have so far been unsuccessful. NMDA receptors contain binding sites for glycine, d-serine, and glutathione. Small-scale studies with all of these compounds have produced significant beneficial effects. However, results have not been replicated in large multicenter clinical trials. Moreover, 2 attempts to develop glutamate theories into widespread treatments have been unsuccessful. Pomaglumetad, a presynaptic glutamate modulator being developed by Eli Lilly, failed in late-stage clinical trials in 2012, despite the positive results seen in animal models. Similarly, bitopertin, a glycine reuptake inhibitor being developed by Roche, recently failed in phase 3 trials for treatment of persistent negative symptoms. Currently, the reasons for the lack of efficacy of these advance stage projects remain unknown. One possibility is that glutamatergic dysfunction during the prodromal and early first-episode period leads to irreversible atrophy of key brain structures. Although glutamate-based treatments are effective in preventing PCP-induced degeneration at least in rodents, reversing such deficits once
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they become established may be far more difficult. Early intervention, especially during the prodromal period, may be needed to prevent, rather than reverse, potentially irreversible changes in brain function.

Finally, an intriguing approach to the modulation of brain NMDA receptors is the use of extremely low level (≤ 2 mA) electric fields applied to specific brain regions using electrodes applied to the overlying scalp (Figure 4). Transcranial direct current stimulation is noninvasive, and unlike other approaches, such as deep brain stimulation, does not require implanted electrodes. In one recent application of this approach, currents applied over the auditory cortex led to rapid and long-lasting inhibition of treatment-refractory depression.26 If confirmed, these findings suggest that regionally targeted neuromodulatory treatments may provide an important alternative to pharmacotherapy for recalcitrant symptoms of schizophrenia. These treatments may be especially effective if combined with newer techniques for mapping sources of impaired interactions within and between target cortical regions.27,28

Summary

More than 100 years after the first description of schizophrenia, we still do not have a clear explanation of what causes the disease, and other than the chance discovery of antipsychotic agents more than 60 years ago, we do not have established classes of treatment. To date, the ability of NMDA receptor antagonists (eg, PCP, ketamine) to reproduce important aspects of the illness, including negative symptoms and cognitive deficits, remains one of the strongest clues to underlying etiology. Translating these effects into FDA-approved clinical interventions, however, has proved to be a challenge.

In the absence of a “one size fits all” pharmacological approach, clinicians must make do with what tools are available, including remediation of what can be remediated and compensation strategies for what cannot. Early intervention strategies may be critical, but resources for conducting such studies at present are limited. At the very least, glutamatergic models have led to greater understanding of the causes of social and occupational disability in schizophrenia, and thus have provided new targets for remediation and compensation strategies.

Disclosures:

Dr. Javitt is Professor and Director, division of experimental therapeutics, department of psychiatry and neuroscience, at Columbia University College of Physicians and Surgeons, in New York; and Director, Schizophrenia Research at the Nathan S. kline Institute for Psychiatric Research in
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