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## Tinking Glutamatergically: Changing Concepts of Schizophrenia Based Upon Changing Neurochemical Models

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### Abstract

Clinical concepts of mental illness have always been modulated by underlying theoretical considerations. For the past fifty years, schizophrenia has been considered primarily a disease of dopaminergic neurotransmission. Although this conceptualization has helped greatly in explaining the clinical effects of psychostimulants and guiding the clinical use of both typical and atypical antipsychotics, it has nevertheless shaded how we look at the disorder from both a pathophysiological and therapeutic perspective. For example, most explanatory research in schizophrenia has focused on dopamine-rich regions of the brain, with little investigation of regions of the brain that are relatively dopamine poor. Starting approximately twenty years ago, an alternative formulation of schizophrenia was proposed based upon actions of the “dissociative anesthetic” class of psychotomimetic agents, including phencyclidine (PCP), ketamine and various designer drugs. These compounds induce psychosis by blocking neurotransmission at N-methyl-D-aspartate (NMDA)-type glutamate receptors, suggesting an alternative model for pathogenesis in schizophrenia. As opposed to dopamine, the glutamatergic system is widely distributed throughout the brain and plays a prominent role in sensory processing as well as in subsequent stages of cortical analysis. Glutamatergic theories of schizophrenia, thus, predict that cortical dysfunction will be regionally diffuse but process specific. In addition, NMDA receptors incorporate binding sites for specific endogenous brain compounds, including the amino acids glycine and D-serine and the redox modulator glutathione, and interact closely with dopaminergic, cholinergic and  $\gamma$ -aminobutyric acid (GABA)-ergic systems. Glutamatergic theories, thus, open new potential approaches for treatment of schizophrenia, most of which are only now entering clinical evaluation.

### Keywords

Schizophrenia; Glutamate; NMDA Receptor; Visual; Auditory; Review

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### Conflict of Interest

Dr. Javitt holds intellectual property rights for use of glycine, D-serine and glycine transport inhibitors in treatment of schizophrenia and related disorders.

## Introduction

Schizophrenia is a severe mental disorder associated with both a specific profile of symptoms and a complex pattern of neurocognitive dysfunction. The first effective treatments for schizophrenia were discovered fortuitously in the mid-1950s (1), and were subsequently shown to mediate their effects at dopamine (DA) D2 receptors in the mid-1970s (2, 3). The DA hypothesis has been the dominant neurochemical model of schizophrenia (4) and has proven heuristically valuable since that time. For example, all current treatments for schizophrenia mediate their effects via blockade of the DA (D2) receptor.

Given the limited distribution of DA neurons in the brain, schizophrenia was traditionally seen as a disease affecting only a few key brain regions. More recent findings, however, implicate widespread cortical and subcortical dysfunction, suggesting more generalized etiology. Over the past twenty years, attention has turned increasingly to dysfunction of the brain glutamate system as a fundamental mechanism underlying brain dysfunction in schizophrenia. Glutamate is a widespread neurotransmitter in both cortex and subcortical systems and accounts for as many as 60% of brain synapses (see [5] for review). Based on observations that the N-methyl-D-aspartate (NMDA)-type glutamate receptors antagonists, such as phencyclidine (PCP) or ketamine, uniquely reproduce the symptomatic, neurocognitive and neurochemical aspects of the disorder, particular emphasis has been placed on NMDA dysfunction as a potential final common pathway leading from pathogenesis to symptoms, as reviewed in (6).

## Clinical Phenomenology of Schizophrenia

Clinicians have grown comfortable dividing symptoms of schizophrenia into positive and negative factors, and in considering treatment effects on each factor independently (7, 8). Further, Kraepelin's original conceptualization (9) of schizophrenia as a dementia has returned greatly to prominence. Positive symptoms, while they obviously remain distressing to a large number of patients and debilitating for some, can often be controlled to the point where they do not of themselves limit recovery.

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Although subfractionation of the phenomenology of schizophrenia is extremely valuable for assessment and new treatment development, what is frequently lost is the conceptualization of schizophrenia as a syndromal whole. Positive and negative symptoms, while independent factors, fluctuate in parallel (10) (e.g., improve or worsen in parallel) and must be viewed as separate manifestations of the same underlying pathogenic mechanisms, rather than as separate and distinct nosological entities. The treatment of positive symptoms, such as hallucinations and delusions, is clearly important, but may only account for 5% of the variance of quality of life (11). In contrast, most studies have found that the persistent disability of schizophrenia often comes from negative symptoms and cognitive difficulties (12–15). In a recent analysis, negative symptoms affected interpersonal skills independently

of other symptoms (16). Moreover, negative symptoms can have an additive effect with neuropsychological deficits on overall functioning and, according to a meta-analysis, patients with primary negative symptoms perform especially poorly on tests of global cognition (Cohen's  $d=0.52$ ) (17).

Accordingly, another key component of schizophrenia is neurocognitive dysfunction. When tested on basic IQ tests, such as the Wechsler Adult Intelligence Scale (WAIS), patients with established schizophrenia typically score about 1 standard deviation, or 15 IQ points, below the population mean. While positive symptoms fluctuate in severity throughout the course of the illness (see [18] for a review), cognitive deficits are typically present at first episode and remain relatively constant over the course of the illness (19) and see (20) for review. In studies that have utilized comprehensive neuropsychological batteries, similar levels of deficit have been observed across multiple neurocognitive domains, particularly in learning and declarative memory formation (19, 21–23) and not prefrontal “executive” dysfunction *per se*. Prevalence of cognitive dysfunction can also be estimated using baseline data from the large scale Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia study in which, despite cognitive dysfunction not being part of the inclusion criteria, the majority of patients had profound cognitive deficits (21). Moreover, the global composite was significantly correlated with Positive and Negative Symptoms Scale (PANSS) negative symptoms ( $r=0.27$ ,  $p<0.0001$ ), but unrelated to positive symptoms, suggesting both an interrelationship between these core deficits and a relative distinction from positive symptoms.

While positive symptoms increase dramatically just prior to the first hospitalization (24), prospective, follow-back and cross-sectional data suggest that cognitive functioning may decline during the three to four years immediately preceding the onset of schizophrenia symptoms. For example, in one prospective study, poor educational achievement at age fifteen was a significant predictor of schizophrenia (25). Two follow-back studies have investigated performance on standardized educational testing (Iowa test) during childhood and adolescence in individuals who subsequently developed schizophrenia. Compared with the general population, such individuals showed only modest deficits even when assessed during 4th and 8th grade, but showed a marked decline in performance between 8th and 11th grade (26, 27).

Similarly, individuals with prodromal schizophrenia who have not yet converted to psychosis show cognitive deficits that are intermediate between those of first-episode and control subjects, and such deficits may predict subsequent conversion to psychosis (28). In one study, lower than expected IQ at age seventeen—based upon childhood reading and spelling abilities—was a significant risk factor for schizophrenia but not bipolar disorders, such that individuals showing a 10 point or greater discrepancy between expected and actual IQ showed an approximately twofold elevated risk for developing schizophrenia (29).

It also appears that intellectual performance remains relatively constant between age seventeen and subsequent illness onset in individuals who go on to develop schizophrenia, suggesting that most of the cognitive decline occurs premorbidly, although further deterioration in some domains may be observed (30). While multiple other factors (31, 32),

including positive symptoms, also significantly contribute to quality of life and functional impairment, overall, these findings highlight neurocognitive dysfunction as a key manifestation of schizophrenia that precedes onset of symptoms, and must therefore be considered central to etiological hypotheses.

## Neurochemical Models of Schizophrenia

Neurochemical models of schizophrenia based upon DA have had substantial heuristic value in explaining key symptoms of schizophrenia; in particular, positive symptoms, and in guiding treatment considerations. Nevertheless, significant limitations with regard to the DA hypothesis remain. First, few intrinsic deficits have been observed within the DA system to account for the presumed hyperdopaminergia associated with schizophrenia (see [6] and [33] for reviews). Second, reconceptualizations of the DA hypothesis propose that subcortical hyperdopaminergia may coexist with cortical hypodopaminergia, although mechanisms underlying the differential cortical and subcortical abnormalities remain to be determined (see [34] for review). Finally, dopaminergic dysfunction, in general, accounts poorly for both symptom classes in schizophrenia and for the pattern of neurocognitive dysfunction associated with schizophrenia (see [35] for review). Thus, alternative conceptual models of schizophrenia have been proposed.

In initial studies with PCP and ketamine in the early 1960s, it was noted that both agents produced what would now be considered positive, negative and cognitive symptoms of schizophrenia (see [36, 37] for reviews), although no formal rating scales were used. However, recent studies in healthy volunteers using scales such as the PANSS or the Brief Psychosis Rating Scale (BPRS), or the Scale of Assessment of Negative Symptoms (SANS), have documented significant increases not only in positive symptoms, but also in negative and cognitive symptoms after ketamine administration (38–40). Levels of symptoms during acute ketamine challenge, moreover, tend to show a similar pattern across factors as they do in schizophrenia. When patients with schizophrenia are exposed to ketamine, they also show increases in positive symptoms, as well as negative symptoms (41, 42), suggesting that NMDA antagonists affect a brain system that is already vulnerable in schizophrenia. This model has been increasingly adopted and is now considered to be one of the useful models for both etiological conceptualization of schizophrenia and new treatment development (see [43–47] for reviews).

No objective measures have been developed that adequately differentiate primarily positive from primarily negative patients. Because PCP produces negative symptoms as prominently or more than positive symptoms, it has occasionally been argued that PCP psychosis should be seen primarily as a model for negative-symptom schizophrenia, whereas amphetamine or lysergic acid diethylamide (LSD, e.g., serotonergic) psychosis should be seen as a model for positive symptoms (48). However, in PCP- or ketamine-induced psychosis, the relative proportions of positive and negative symptoms are highly similar to those observed in both acute and chronic schizophrenia, whereas in amphetamine- or LSD-induced psychosis the ratio of positive to negative symptoms is far in excess of the pattern observed even in acute schizophrenia stages (35, 48). Thus, dopaminergic models may be most appropriate to those patients with primarily positive symptoms and rapid response to antipsychotic; NMDA

models may be more appropriate to individuals with more balanced positive and negative symptoms and poor antipsychotic response, as reviewed in (6).

Nevertheless, a potentially informative difference between ketamine-induced symptoms and those of schizophrenia is in the production of hallucinations. In established schizophrenia, auditory hallucinations consisting of voices of various types are common, whereas visual hallucinations are rare; but during ketamine-induced psychosis, visual perceptual distortions are common but organized auditory hallucinations are rare. Therefore, the pattern of hallucinations observed during ketamine challenge does not closely resemble the pattern observed in established schizophrenia.

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The pattern of ketamine-induced auditory and visual disturbances, however, does resemble the pattern observed early in the course in schizophrenia (49, 50), where both auditory and visual perceptual disturbances are common, and auditory hallucinations have not yet crystallized to the point of being identifiable as speech. Additional support for the similarities between early psychosis and glutamatergic models comes from imaging studies. A significant increase of glutamine was seen in the anterior cingulate cortex following ketamine administration to healthy human volunteers (Rowland et al., 2005), which is similar to the increases seen in studies of first-episode (51) and prodromal patients (52). Thus, acute ketamine challenge may be viewed best as a model of prodromal or acute incipient schizophrenia, rather than later, more chronic, phases.

## **Pathological and Genetic Evidence**

### **NMDA in Neurodegenerative and Neurodevelopmental Models of Schizophrenia**

In addition to producing symptoms and cognitive deficits in acute challenge experiments in humans, preclinically, NMDA antagonists lead to neurodegenerative and neurodevelopmental changes. These changes are seen in specific populations of cortical pyramidal neurons, particularly in frontal, posterior cingulate and retrosplenial brain regions, although delayed spread to larger brain networks (e.g., parietal, temporal, entorhinal cortex, hippocampus and amygdala) (43, 53). Neurotoxicity was observed following even a single large dose of PCP, although it could also be seen following longer duration, lower dose administration (54). NMDA receptors are also expressed as well in oligodendrocytes (which give rise to myelin), and play a critical role both in neurodevelopment and in ischemia-induced damage (55, 56).

### **NMDA in Excitotoxicity Models**

NMDA blockade may lead to rebound hyperglutamatergia, presumably due to reduced excitatory drive within local GABAergic feedback loops. Because glutamatergic transmission is designed to be highly phasic, the elevation of tonic glutamate levels is pathological, and leads to impairments in function over and above those induced by NMDA

blockade itself. Based upon this theory, the primary goal of glutamate-based treatments is neither to increase nor decrease NMDA function per se, but rather to restore balance between excitation and inhibition within cortical regions (57, 58). Non-neuronal NMDA receptors have also been studied in excitotoxicity models (59), but would also predict that a reduction in NMDA receptor stimulation would lead to reduced oligodendrocyte growth and proliferation during adulthood (60), consistent with the observations in schizophrenia.

### Linkage/Association Studies in Schizophrenia

A consistent finding from genetic studies in schizophrenia is that several of the identified genes interact closely with glutamatergic mechanisms in general and NMDA receptors in particular. As such, these studies provide additional support for glutamatergic theories of the disorder. One of the best established candidate genes for schizophrenia is neuregulin (NRG1), which might mediate its risk-enhancing effects based upon interaction with NMDA receptors (see [61] for a review). D-amino acid oxidase (DAAO), the enzyme responsible for D-serine (an NMDA receptor modulator) metabolism, has been linked to schizophrenia (62), as has the DAAO regulator, D-amino oxidase activator (DAOA) (62–66) (see Figure 1).

Other potential risk genes for schizophrenia such as dysbindin (DTNBP1) (see [67] for review), Disrupted-in-schizophrenia-1 (DISC-1), and RGS4 may also converge on glutamatergic systems (68–70), although further clarification of the role of these genes in normal brain function is required. Linkages to metabotropic glutamate receptor genes, including GRM3 (71, 72) and GRM7 (73) have also been reported.

### Cognitive Deficits Following NMDA Antagonist Treatment

Glutamatergic models provide a framework from which to view the pattern of neuropsychological dysfunction associated with schizophrenia. Although glutamatergic systems are widespread, within each brain region, NMDA receptors participate in only a subset of processes. For example, NMDA receptor activation is required for the initiation, but not maintenance, of long-term potentiation (74). The observation that patients with schizophrenia (as opposed to those with the amnesic syndrome) show deficits in memory formation (19), but not retention, is thus consistent with an NMDA pattern of dysfunction (35, 75–80).

As with symptoms, initial studies conducted with PCP in the early 1960s also showed cognitive deficits that are highly reminiscent of schizophrenia (see [37] for review). Studies conducted with ketamine over the last fifteen years have further confirmed and extended these findings. NMDA antagonists also reproduce core neuropsychological abnormalities of schizophrenia, including executive functioning (38, 81–83), attention/vigilance (35, 81, 82, 84–86), verbal fluency (38, 77, 87), visual and verbal working memory (35, 76, 78, 81, 82, 86–92). Moreover, in monkeys treated with ketamine, characteristic, schizophrenia-like deficits in a task-switching paradigm (93, 94) are reproduced. Ketamine infusion also reproduces both the severity and type of thought disorder seen in schizophrenia with both, for example, being associated with high levels of poverty of speech, circumstantiality and loss of goal, and relatively low levels of distractive or stilted speech or paraphasias (95). Given the importance of neurocognitive dysfunction to the conceptualization of



schizophrenia, these findings support the etiological involvement of NMDA dysfunction in the pathophysiology of schizophrenia.

As opposed to ketamine, administration of dopaminergic agonists such as amphetamine does not reproduce the pattern of deficit observed in schizophrenia. For example, in one study that directly compared effects of amphetamine and ketamine in normal volunteers, both ketamine and amphetamine induced positive symptoms and conceptual disorganization. However, only ketamine produced perceptual changes, concrete ideation or negative symptoms. Further, only ketamine induced schizophrenia-like disruptions in delayed recall. Finally, amphetamine did not induce working memory disturbances, and it significantly reversed ketamine-induced disruptions. These findings suggest that augmentation, rather than blockade of frontal dopaminergic systems, may be beneficial in schizophrenia (35).

In schizophrenia, amphetamine treatment does not further impair cognition and may, in fact, lead to cognitive improvement in schizophrenia (96). These findings, therefore, suggest greater involvement of NMDA, rather than DA, receptors in the pathophysiology of cognitive impairment in schizophrenia. Thus, reduction in NMDA functioning within the brain could serve as a single unifying feature to account for the otherwise complex pattern of deficits observed in the disorder.

## **NMDA Dysfunction and Sensory Processing Impairment**

Another key difference between dopaminergic and NMDA models of schizophrenia is the predicted involvement of sensory processing. As opposed to D2 receptors, which are strongly localized to striatum and frontotemporal systems (97), NMDA receptors are diffusely distributed throughout brain, with nearly equal representation in both lower and higher order brain regions. Thus, NMDA receptor models suggest that deficits in sensory processing should co-exist in schizophrenia with deficits in more complex forms of cognition such as memory, attention or working memory. Such deficits were not emphasized in dopaminergic models of schizophrenia. However, over the past decade, such deficits have become increasingly well documented and, in several cases, shown to conform to the pattern induced by NMDA antagonists, such as ketamine, in animal models and normal volunteers. Such deficits thus provide convergent evidence for NMDA receptor dysfunction in schizophrenia.

Behavioral and electrophysiological studies of sensory dysfunction in schizophrenia have been performed primarily in auditory and visual systems, although schizophrenia is known to affect other sensory processes such as weight discrimination (98) and other somatosensory processes (99). Because of its high temporal resolution and noninvasive nature, the electroencephalogram (EEG) and event-related potentials (ERP) are excellent measures of the neurophysiology and early sensory processing of the brain. ERPs are standardized reactions of the brain to a particular stimulus, and because they index underlying neuronal processes, they allow us to look at the basic functioning of the brain and the root cause of neuropsychological dysfunction (see [100] for a review). These deficits are often highly heritable, stable across time and well validated.

In the auditory system, one of the strongest indices of sensory dysfunction is impaired generation of an ERP component termed mismatch negativity (MMN). MMN is elicited by a paradigm in which a sequence of repetitive standard stimuli is infrequently interrupted by stimuli that differ in a physical stimulus dimension such as pitch, duration, intensity or location. MMN reflects response of the auditory cortex to infrequent changes in a repetitive pattern of auditory stimulation and MMN deficits are well-established in schizophrenia, with a mean effect size of  $\sim 1$  d across studies (101). Similar deficits in MMN can be induced in animals by infusion of PCP (102, 103) and in normal volunteers by infusion of ketamine (40). MMN deficits are associated with impaired ability to match tones following brief delay (104). Deficits in tone matching contribute significantly to impairments in higher order functions that rely on tone matching ability (105), such as the ability to determine emotion based upon vocal modulation (prosody), which are thought to be rate limiting in terms of functional outcome (106).

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Similarly, NMDA receptors are located at multiple levels of the early visual system, and studies have also investigated the consequences of NMDA dysfunction in the early visual system. The early visual system consists of two main components: a magnocellular and parvocellular pathway. The magnocellular pathway, which conducts low-resolution visual information rapidly to cortex, is involved in attentional capture and processing of overall stimulus organization (107). In contrast, the parvocellular pathway, which is primarily involved in processing fine-grained stimuli and object recognition, is relatively intact. NMDA receptors may be particularly important in the magnocellular pathway (108).

Early visual processing deficits include Visual P1 (109–111), a measure that reflects responses within the magnocellular pathway and has been shown to predict community outcome (112, 113). Further, deficits in early visual processing produce subsequent impairments on higher order processes such as object identification (114), motion processing (115), reading (116) and illusion sensitivity (117). Change in the physical properties of stimuli can lead to significant improvement in performance in such high-level tasks such as the Wisconsin Card Sorting Test (118). Thus, as evidenced by associations between these NMDA-dependent early auditory and visual processes and higher order functioning, deficits in NMDA activity within sensory regions may lead to impairment in more complex processes (see [119] for review).

## **Glutamate-DA and Glutamate-GABA Interactions**

NMDA dysfunction may also account for both the impaired dopaminergic regulation and the impaired GABAergic neurotransmission that has been documented in schizophrenia. Positron emission (PET) and single photon emission (SPECT) tomographic studies provide insights into patterns of neurochemical receptor dysfunction in schizophrenia. Patients with schizophrenia, as a group, show enhanced DA release to amphetamine challenge, consistent with endogenous dopaminergic hyperactivity/dysregulation (see [120] for review). The enhanced release, however, is observed specifically during acute decompensation, and not during a remission phase, and is associated specifically with increased severity of positive



symptoms. Based upon these findings, it has been suggested that dopaminergic instability may account only for the increased severity of symptoms associated with acute decompensation (33). In normal volunteers, pretreatment with ketamine leads to dopaminergic dysregulation similar to that observed in schizophrenia (121), even under conditions where no effect on basal DA release is observed. Similar augmentation of amphetamine-induced DA release is observed in rodents treated with NMDA antagonists (122–124). A primary site of NMDA appears to be local inhibitory interneurons within key brain regions (125). These serve as a “brake” on glutamate-stimulated DA release (126). Thus, failure of this brake may lead to dysregulated DA release of the type observed in schizophrenia.

Changes in GABAergic neurotransmission have also been increasingly well documented over recent years (127–131). GABAergic dysfunction may be directly linked to well-documented deficits in working memory function, and may, therefore, represent an appropriate target of pharmacological intervention (132). There is also evidence for NMDA receptors modulating their regulation of DA in part through presynaptic GABAB and on DA terminals (133).

## NMDA-Based Treatments

A critical issue is whether treatment approaches based upon glutamatergic and NMDA models can lead to new treatment approaches. Over the past decade, several new treatment strategies have been proposed. First, direct and indirect approaches have targeted the glycine modulatory site of the NMDA receptor complex (see Figure 1). Direct agonists have included treatment with the naturally occurring amino acids glycine and D-serine, which serve as endogenous modulators of NMDA receptors in vivo, as well the antituberculosis drug D-cycloserine, which fortuitously cross-reacts with the NMDA/glycine site (see [134] for a review). These agents have proven effective in several preclinical models, including reversal of PCP effects in both rodents (135, 137) and primates (137).

A potential indirect approach is to use glycine type I (GlyT1) transport inhibitors (GTIs). Rather than serving as direct glycine precursors, these compounds function similarly to selective serotonin reuptake inhibitors (SSRIs) and increase glycine levels in the brain by preventing glycine removal from the synaptic cleft, leading to endogenous increases in CSF glycine levels (138) (see Figure 1). An initial study with glycyldodeclamide, a relatively low-affinity agent, demonstrated significant reversal of PCP-induced hyperactivity in rodents (139, 140). Since then, the naturally occurring sarcosine has shown preliminary effectiveness, and high affinity GTIs have been synthesized by several pharmaceutical companies, and have shown to be effective in multiple animal models. Several of these compounds are currently in early-stage clinical trials, with results expected over the next several years.

Other treatment strategies have been proposed utilizing nonglycine modulatory sites of the NMDA receptor. One involves examination of the redoxsensitive site on the NMDA receptor. This site is modulated by the oxidized form of glutathione (GSH) (141, 142). Schizophrenia has also been shown to be associated with reduced levels of GSH (143–145),

leading to potential dysfunction of NMDA receptors (146). Early studies testing this mechanism have utilized N-acetylcysteine, a glutathione precursor, as a potential psychopharmacological agent.

Another treatment possibility, based upon the observation that NMDA blockade leads to rebound increases in glutamate release that may themselves be pathological (147), proposes that compounds that inhibit presynaptic glutamate release may also be therapeutic (148). Examples of such compounds include the antiepilepsy drug lamotrigine (88) and agonists of metabotropic glutamate type 2/3 (mGluR2/3) receptors (57, 149), which have been shown to be effective in reversing behavioral effects of NMDA antagonists in human and rodent models supporting the potential efficacy of these compounds as novel antipsychotic agents. Other metabotropic ligands, including mGluR5 (150, 151) and mGluR8 (152) agonists, have also been proposed as potential treatments for schizophrenia based upon their ability to modulate NMDA receptor-mediated neurotransmission (153). N-acetylaspartylglutamate (NAAG) may be an endogenous ligand for mGlu2/3 receptors in CNS. NAAG has been tested preclinically and shown to inhibit NMDA antagonist-induced behaviors in animals, consistent with an effect on NMDA receptor-mediated neurotransmission (154, 155).

## Results of Clinical Studies

The most studies to date have been performed with NMDA agonists, primarily because several of the agents used have been natural compounds, and so it has not been necessary to wait for structure activity optimization or preclinical toxicity testing (see Figure 2). As permeability of these agents may be limited, delivering optimal doses, therefore, may be impossible (135). Nevertheless, positive studies with these compounds have provided proof-of-concept for development of compounds with higher affinity and specificity.

Studies with naturally occurring compounds to date have primarily used glycine, administered at a dose of up to 800 mg/kg (approx. 60 g/d) (156–159); D-serine, administered at a dose of 30 mg/kg (approx. 2.1 g/d) (160, 161) or D-alanine, administered at a dose of 100 mg/kg (162); and, sarcosine, administered at a dose of 30 mg/kg (approx. 2.1 g/d) (163, 164). For glycine, this represents the highest practical dose because of the quantity of amino acid needed to significantly increase brain glycine levels. Most recently, high dose D-serine (>60 mg/kg) was shown to be more efficacious than lower doses in treating neurocognitive deficits (165). For other compounds, formal dose findings studies have not been performed, and maximum tolerated doses are presently unknown.

Overall, NMDA-based treatments appear to be efficacious in schizophrenia. A meta-analysis conducted in 2005 (166) concluded that in the first 132 patients studied with NMDA allosteric modulators, a highly significant ( $p=0.0004$ ), moderate effect size improvement in negative symptoms was observed across studies. A more recent meta-analysis (167), which included 312 patients, continues to suggest a moderate effect size, highly significant improvement in negative symptoms ( $p<0.001$ ). Variability in findings across studies was related primarily to degree of placebo effect within individual trial, with all studies showing a consistent, 15 to 20% improvement in negative symptoms within the experimental group.

One study has evaluated effects of open-label glycine in individuals showing prodromal symptoms of schizophrenia. In that study, large effect-size improvement was observed, including early remission in 3 of 10 subjects (168). These data, if confirmed by double-blind trials, would indicate that NMDA agonists might have potential utility in the schizophrenia prodrome.

## Summary

Glutamatergic models of schizophrenia were first proposed over two decades ago, based upon the effects of the agents PCP and ketamine, which were shown to induce their unique psychotomimetic effects by blocking neurotransmission at NMDA-type glutamate receptors. Since that time, glutamatergic models have been strongly supported by NMDA antagonist studies in animals, as well as ketamine challenge studies in humans. Over that time, potential molecular contributors to NMDA dysfunction have been increasingly documented. New treatment approaches based upon glutamatergic approaches are only now reaching the clinical trial stage, and will serve to further elucidate and refine these models over upcoming years. Glutamatergic approaches offer particular hope for treatment of negative symptoms and cognitive deficits in schizophrenia and, thus, for improvement of the clinical situation of millions of patients worldwide.

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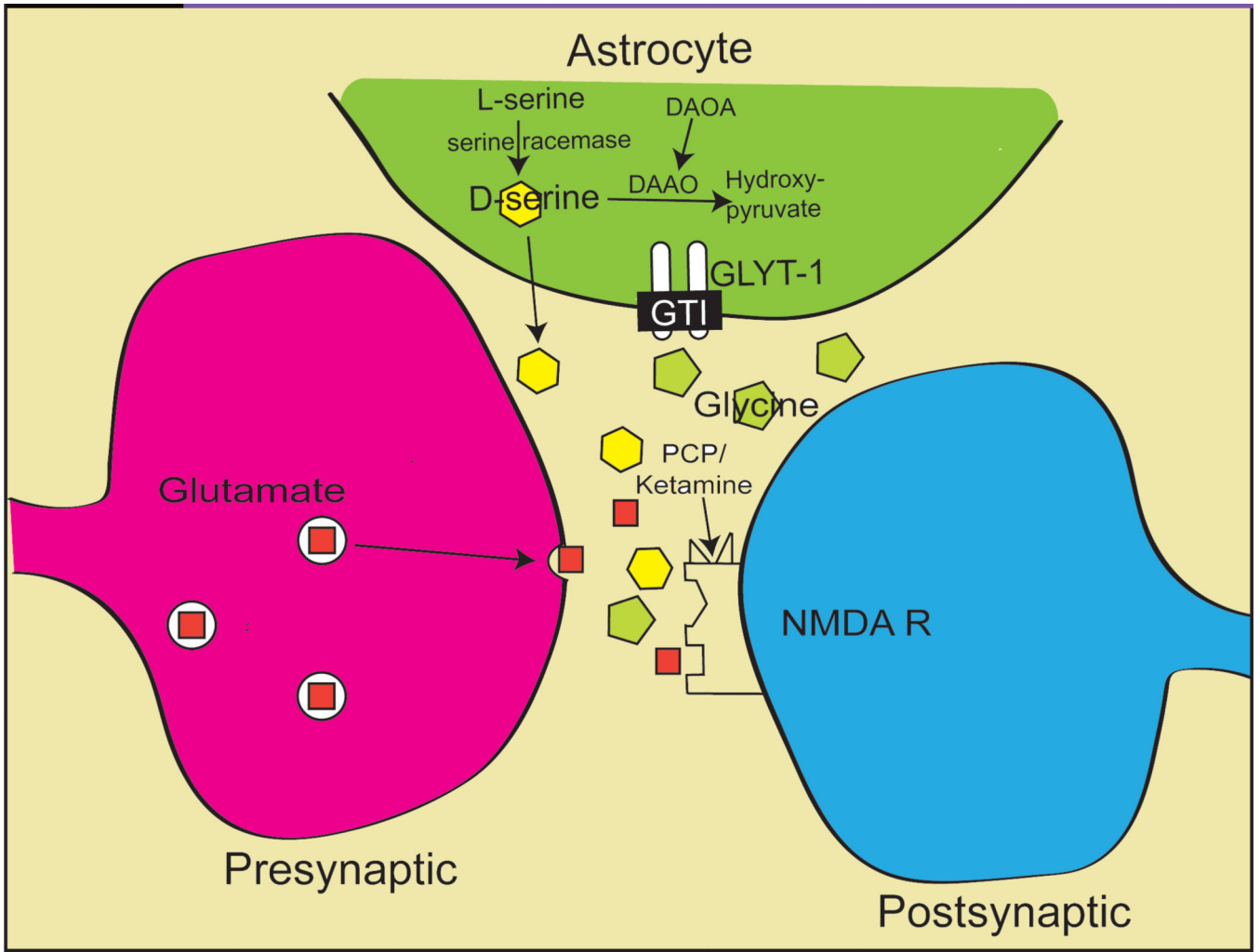
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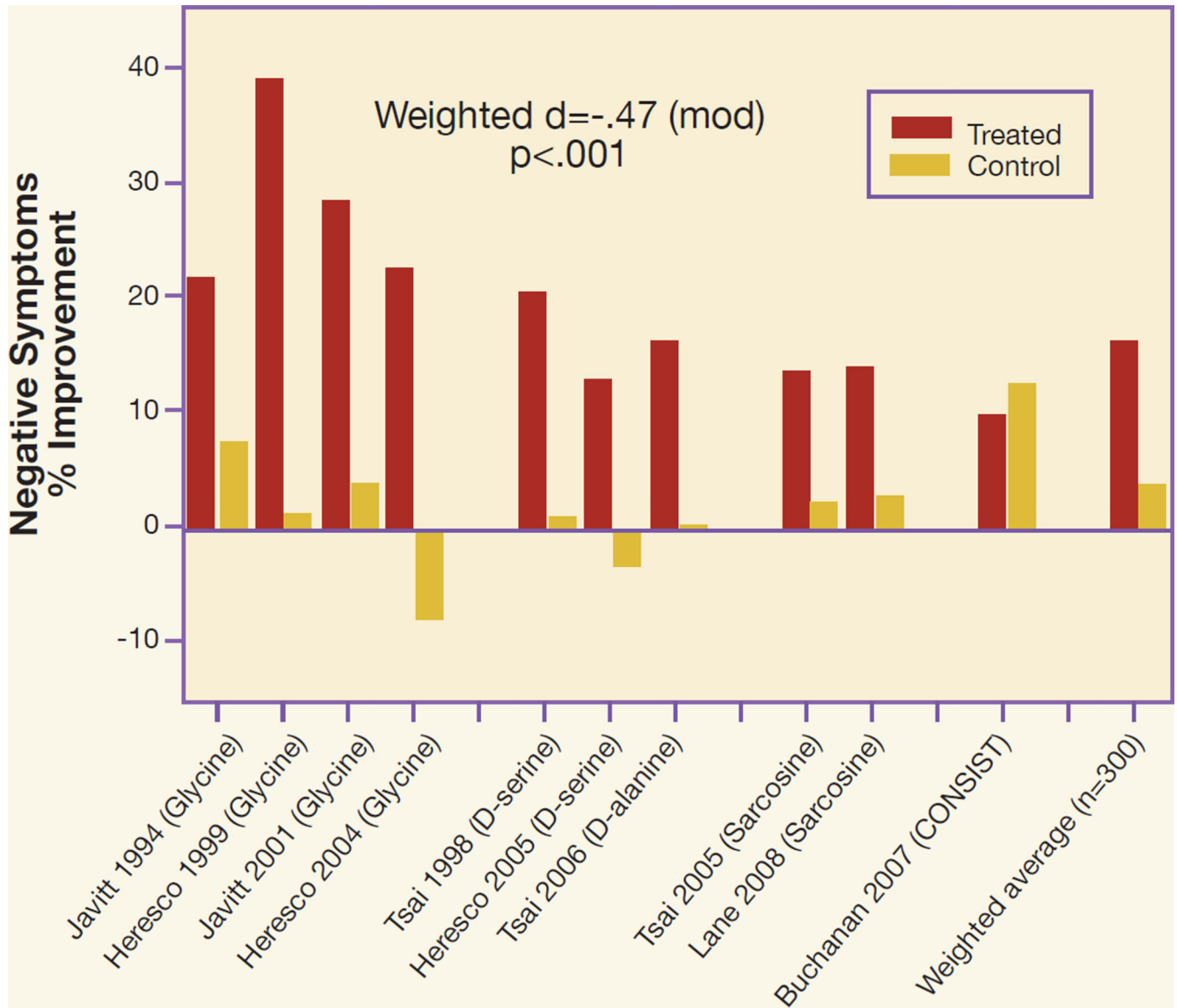
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**Figure 1.** Schematic Model of the NMDA Receptor Complex and Synaptic Glutamate , D-serine , and Glycine , Regulation and Metabolism. (The non-physiologic NMDA antagonist PCP and ketamine site is also shown.)



**Figure 2.** Summary of Clinical Trials Performed to Date with Full NMDA Agonists Combined with Antipsychotics other than Clozapine  
 Further details about individual studies are provided in reference #134. CONSIST refers to the Cognitive and Negative Symptoms in Schizophrenia Trial (169). Statistics were calculated as weighted average of % change scores for negative symptoms, across trials.