

Has an Angel Shown the Way? Etiological and Therapeutic Implications of the PCP/NMDA Model of Schizophrenia

Daniel C. Javitt^{*1}, Stephen R. Zuckin², Uriel Heresco-Levy³, and Daniel Umbricht⁴

¹Departments of Psychiatry and Neuroscience, Nathan Kline Institute for Psychiatric Research/Columbia University College of Physicians and Surgeons, Orangeburg, NY 10962; ²Departments of Psychiatry and Radiology, Johns Hopkins School of Medicine, Baltimore, MD 21205, and Senior Director, Forest Research Institute, Jersey City, NJ 07311; ³Department of Psychiatry, Herzog Memorial Hospital/Hadassah Medical School, Jerusalem, Israel; ⁴Translational Medicine Leader in Neurosciences, F. Hoffman-La Roche, Ltd, Switzerland

*To whom correspondence should be addressed; 140 Old Orangeburg Rd, Orangeburg, NY 10962; tel: 845-398-6534 (personal)/6546 (admin), fax: 845-398-6545, e-mail: javitt@nki.rfmh.org

Over the last 20 years, glutamatergic models of schizophrenia have become increasingly accepted as etiopathological models of schizophrenia, based on the observation that phencyclidine (PCP) induces a schizophrenia-like psychosis by blocking neurotransmission at *N*-methyl-D-aspartate (NMDA)-type glutamate receptors. This article reviews developments in two key predictions of the model: first, that neurocognitive deficits in schizophrenia should follow the pattern of deficit predicted based on underlying NMDAR dysfunction and, second, that agents that stimulate NMDAR function should be therapeutically beneficial. As opposed to dopamine receptors, NMDAR are widely distributed throughout the brain, including subcortical as well as cortical brain regions, and sensory as well as association cortex. Studies over the past 20 years have documented severe sensory dysfunction in schizophrenia using behavioral, neurophysiological, and functional brain imaging approaches, including impaired generation of key sensory-related potentials such as mismatch negativity and visual P1 potentials. Similar deficits are observed in humans following administration of NMDAR antagonists such as ketamine in either humans or animal models. Sensory dysfunction, in turn, predicts impairments in higher order cognitive functions such as auditory or visual emotion recognition. Treatment studies have been performed with compounds acting directly at the NMDAR glycine site, such as glycine, D-serine, or D-cycloserine, and, more recently, with high-affinity glycine transport inhibitors such as RG1678 (Roche). More limited studies have been performed with compounds targeting the redox site. Overall, these compounds have been found to induce significant beneficial effects on persistent symptoms, suggesting novel approaches for treatment and prevention of schizophrenia.

Key words: schizophrenia/NMDA receptors/ neurophysiology/cognition/ negative symptoms/glycine/ glycine transport inhibitors

Introduction

Glutamatergic models of schizophrenia were first proposed approximately 20 years ago^{1–4} based on the early observation that phencyclidine (PCP), ketamine, and related drugs induced schizophrenia-like psychotic effects (Domino, this volume), followed later by the observation that these compounds induce their unique behavioral effects by blocking neurotransmission at *N*-methyl-D-aspartate-type glutamate receptors (NMDAR)² (Coyle, this issue) and that NMDAR antagonists such as ketamine could reproduce specific aspects of the disorder (Moghaddam, this issue). Since that time, neurochemical models based on actions of PCP and ketamine have become increasingly well established, with increased focus on glutamatergic dysfunction as a basis for both symptoms and cognitive dysfunction in schizophrenia.

At the time when the PCP/NMDA model was first proposed, it led to two strong forward predictions. First, it predicted that patterns of brain dysfunction in schizophrenia should follow the distribution and function of NMDAR within brain. Second, it predicted that treatments aimed at potentiating brain NMDAR function should be therapeutically beneficial. This article reviews studies performed over the past 20 years in support of these early etiological and treatment predictions. Treatment approaches predicted based on PCP/NMDA models are only now reaching pivotal clinical trials, with hope for developing treatments that may modify course of illness and ongoing symptoms.

Pathophysiological and Conceptual Implications of the PCP/NMDA Model of Schizophrenia

Dopamine theories of schizophrenia were first proposed in the early 1960s based on the fortuitous discovery of the antipsychotic effects of chlorpromazine and other D2 antagonists. More recently, the dopamine theory has been reconceptualized to view dopaminergic dysfunction simply as a final common pathway to psychosis, without necessarily implying intrinsic dysfunction of dopaminergic circuits themselves.⁵ In this model, both extrinsic factors, such as NMDAR dysfunction, and intrinsic dopaminergic factors, such as genetic polymorphisms, contribute to the presumed dopaminergic hyperactivity of schizophrenia. An ongoing acknowledged limitation of dopaminergic models is that negative symptoms and patterns of cognitive deficit associated with schizophrenia are poorly modeled by either dopamine agonists or antagonists in humans. D1 receptors, which interact functionally with NMDAR, may represent an effective therapeutic target in schizophrenia.^{6,7} Nevertheless, cortical dysfunction is not limited to brain regions with predominant dopaminergic function, but are instead generalized throughout brain, suggesting need for alternative conceptualizations.

As opposed to dopamine receptors, which are highly localized to frontostriatal brain systems, NMDAR show a widespread distribution in brain with high density in subcortical and cortical brain regions and, in cortex, in sensory and associative brain regions (figure 1). Thus, NMDAR models of schizophrenia predict widespread cortical dysfunction, with deficits that are regionally diffuse, but restricted to NMDAR-mediated processes. In particular, NMDA receptors are known to play a critical role in dopaminergic regulation, coincidence detection, cortical plasticity, “context dependent” processing, and nonlinear gain mechanisms (reviewed by Kantrowitz and Javitt)⁸. Over the past 20 years, significant advancements have been made in determining the basis for NMDAR dysfunction in schizophrenia, along with understanding the role played by NMDAR within sensory and associative brain regions, leading to convergent support for NMDAR-based models.

Evidence for NMDAR Dysfunction in Schizophrenia. Although mechanisms underlying NMDAR dysfunction in schizophrenia remain to be determined, both presynaptic, postsynaptic, and more general metabolic factors can be considered. Presynaptically, disturbances of glutamatergic release are reported (see Coyle, this volume), as well as associations with presynaptic genes such as dysbindin^{9,10} may lead to impaired presynaptic function. Polymorphisms of the GRIN2B subunit have also been associated with schizophrenia,^{11,12} as have abnormalities in genes regulating D-serine synthesis including serine racemase, D-amino acid oxidase (DAAO),¹³ and DAAO activator/G72¹⁴ and those regulating glutathione synthesis/oxidative stress.¹⁵ NMDAR function also depend crucially on integrity of synaptic/dendritic function, and so can be influenced by growth factors

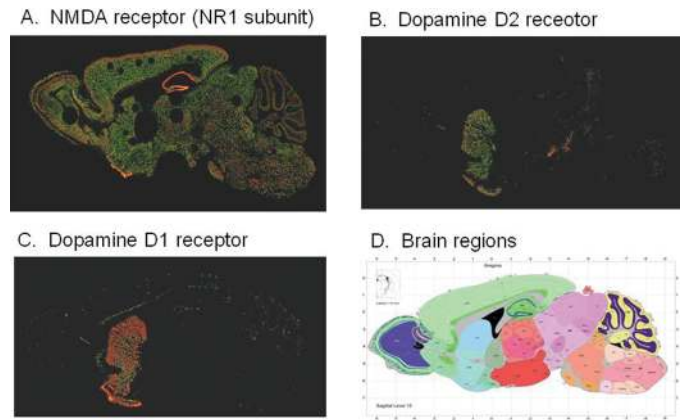


Fig. 1. Relative distribution of *N*-methyl-D-aspartate (NMDAR) (A) and dopamine D2 (B) and D1 (C) receptors in brain. As opposed to dopamine receptors, NMDAR receptors are diffusely distributed throughout brain in both cortical and subcortical regions (D), consistent with recent findings of generalized brain dysfunction in schizophrenia. From Allen Brain Atlas (www.brain-map.org).

such as neuregulin, acting through ErbB4 receptors.¹⁶ Within each individual subject with schizophrenia, multiple factors may contribute, with NMDAR dysfunction representing a final common pathway to schizophrenia.⁸

NMDAR Contributions to Dopaminergic Dysfunction in Schizophrenia. D2-blockers remain the primary treatments for schizophrenia. Nevertheless, mechanisms underlying dopaminergic dysfunction remain poorly understood. In vivo dopaminergic dysfunction has been demonstrated in schizophrenia by measurement amphetamine-induced dopamine release using D2 SPECT and/or PET radioreceptor imaging,¹⁷ and, more recently using measures of presynaptic striatal dopaminergic metabolism.¹⁸ Both effects are concentrated in associative, rather than limbic or sensorimotor, striatum. Deficits are presently conceptualized as being most related to expression of psychotic symptoms across disorders, rather than to the schizophrenia disease process. Thus, dopaminergic dysregulation is best viewed as final common pathway leading to psychosis in general, rather than specifically schizophrenia.

Despite the well-established nature of dopaminergic dysfunction in schizophrenia, underlying mechanisms remain unknown. Alterations in dopamine similar to those of schizophrenia are induced by ketamine administration in normal volunteers.¹⁷ In addition, severity of psychotic symptoms observed after ketamine challenge correlates to levels of extracellular prefrontal dopamine release,¹⁹ suggesting that NMDAR dysfunction on its own may be sufficient to account for dopaminergic dysfunction. In rodents, as in humans, PCP treatment leads to enhanced amphetamine-induced dopamine release in frontal cortex and dorsal—but not ventral—striatum, consistent with findings in schizophrenia.^{20–22} Effects in rodents, moreover, are reversed by simultaneous

treatment with NMDAR/glycine-site agonists,^{21,23} supporting the role of NMDAR in dopaminergic regulation.

Hippocampal Dysfunction. At the time when the PCP/NMDA model was first proposed, the role of NMDAR in hippocampal long-term potentiation was already well established, as were analogous deficits in learning and long-term memory formation in schizophrenia.² These deficits continue to represent an area of pathology in schizophrenia that conforms poorly to dopaminergic models, but is accounted for well by underlying NMDAR dysfunction (see Tamminga, this volume). Regional changes in cerebral blood flow in the CA1 hippocampal subfield may also be among the earliest reflections of progression to psychosis.²⁴

Sensory Cortical Dysfunction in Schizophrenia. In addition to localization to striatum and hippocampus, NMDAR are diffusely distributed throughout cortex, with strong expression in sensory and higher cortical brain regions. Thus, whereas sensory function has classically been considered to be an “intact simple function” based on classical models in schizophrenia,²⁵ the significant expression of NMDAR within sensory regions predicts that significant deficits should be present even in early sensory processes and that sensory processes requiring NMDAR involvement should be particularly affected.

One of the first sensory processes shown to depend on intact NMDAR function is generation of the mismatch negativity (MMN) auditory event-related potential (ERP). MMN is generated in an auditory oddball paradigm, in which a sequence of repetitive tones is interrupted by physically or contextually deviant oddball stimuli. In this paradigm, therefore, the same physical tone elicits differential cortical response dependent on underlying context. MMN generation was first shown to depend specifically on NMDAR function based on studies in monkey auditory cortex.²⁶ This finding was subsequently confirmed in both humans and rodents (reviewed by Javitt et al.).²⁷ In contrast to ketamine, other psychotomimetic agents such as psilocybin²⁸ or LSD²⁹ do not disrupt MMN, although they do impair generation of other, frontoparietally generated potentials (eg, P3). Conversely, memantine, a compound that is often classified as an NMDAR antagonist but paradoxically does not produce psychosis in humans,³⁰ also paradoxically enhances MMN in humans³¹ despite blocking MMN generation in rodents,³² suggesting that MMN is sensitive to the net neurophysiological events associated with psychosis and cognitive impairments in humans, rather than to the a priori classification of a drug based on animal models.

Finally, in normal volunteers reduced MMN amplitude predicts susceptibility to ketamine-induced psychosis³³ while in patients with prodromal symptoms, reduced MMN amplitude predicts risk for psychosis,³⁴ suggesting that MMN indexes a subpopulation predisposed

to development of schizophrenia. Other auditory ERP, including auditory N1 and the auditory steady-state response may also reflect underlying NMDAR dysfunction in both humans³⁵ and in animal models.³⁶

Similar deficits have also been observed within the early visual system. In particular, the magnocellular visual system functions primarily in a nonlinear gain mode, with large responses to low contrast (<12%) stimuli but saturating responses at high contrasts (>32%). In schizophrenia, gain of the magnocellular response function is blunted similar to observed in animal NMDAR models.³⁷ Over recent years, deficits in magnocellular function have been confirmed in schizophrenia using psychophysical, neurophysiological, and functional imaging-based approaches.^{38–41}

Finally, deficits in both auditory and visual processing in schizophrenia have been linked to impairments in higher order cognitive. Thus, deficits in auditory tone matching ability in schizophrenia lead to impairments in detection of tonal modulations in voice (“prosody”) which, in turn, lead to impairments in auditory emotion recognition and social cognition (figure 2A)⁴² (Disturbances in visual processing lead to impairments in coding of visual information, which in turn affect such processes as face emotion recognition,^{43,44} perceptual closure⁴⁰ (figure 2B) or continuous performance task performance⁴¹ (figure 2C). Most recently, ketamine-induced reductions in a visual oddball task was associated primarily with activation reductions in sensory, as opposed to frontal, brain regions,⁴⁵ suggesting that many deficits that have been attributed to

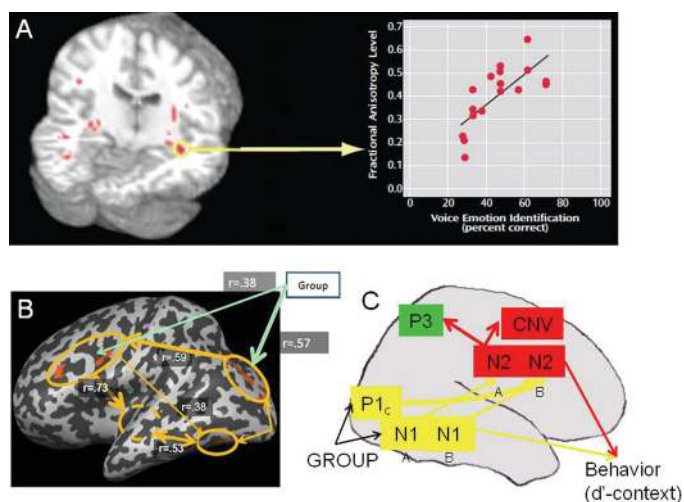


Fig. 2. Sensory contributions to cognitive dysfunction in schizophrenia. In the auditory system, structural and functional disturbances at the level of primary auditory cortex correlate with impairments in higher auditory auditory function such as auditory emotion recognition⁷³ (A). In the visual system, deficits in early visual activation lead to impairments in frontal activation during tasks such as perceptual closure⁴⁰ (B) or AX-type continuous performance task (C)⁴¹ performance.

impairments of attention in schizophrenia may instead reflect impaired processing of physical stimulus features at the level of primary sensory cortex.

Higher Cognitive Deficits in Schizophrenia. In addition to predicting that some, but not all, sensory level impairments will be impaired in schizophrenia, PCP/NMDA models predict that some, but not all, higher level cognitive functions will be impaired as well, dependent on underlying NMDAR involvement. NMDAR are present at high density within frontoparietal and temporal brain regions, suggesting that dysfunction of these receptors may underlie higher cognitive deficits associated in schizophrenia. For example, ketamine administration reproduces deficits in semantic priming, verbal fluency, auditory self-monitoring, and executive processing (reviewed by Kantrowitz et al.),⁸ consistent with hypothesis that many of the higher cortical deficits in schizophrenia in fact reflect specifically impairments of NMDAR within these brain regions.

Notably, however, multiple paradigms have been identified that depend heavily on prefrontal function, which do not show impairments in schizophrenia. In particular, in task switching paradigms, subjects typically show a “switch cost” in which they are slower and less accurate responding immediately after a switch than they are immediately prior, related to functioning of underlying frontoparietal brain circuits. Despite the involvement of association brain regions in this task, patients do not show increased switch costs during task switching than controls, but do show increased slowing when the competing tasks would lead to conflicting vs identical responses. This pattern is similar to the pattern observed following ketamine administration in monkeys,⁴⁶ and suggests that even within higher brain regions only processes dependent on underlying NMDAR function are impaired, whereas NMDAR-independent functions are intact.

Brain Adaptations to Chronic NMDAR Function. Although many features of schizophrenia are reproduced by acute NMDAR antagonism, other features appear only following chronic administration. For example, schizophrenia-like auditory hallucinations are not observed during acute ketamine administration. In monkeys, such phenomena are observed during sub-chronic, but not acute ketamine administration,⁴⁷ suggesting that they may reflect secondary consequences of persistent NMDAR dysfunction. Psychotic symptoms, including hallucinations, are also observed in autoimmune disorders associated with anti-NMDA antibodies.⁴⁸ Although downstream consequences of NMDAR dysfunction have yet to be fully investigated, one critical mechanism appears to be oxidative stress, leading to downregulation of cortical parvalbumin (PV) neurotransmission.⁴⁹ This may lead particularly to impairments in generation of stimulus- and task-driven gamma in regions such as auditory and prefrontal cortex (see

Lewis, this volume), reflecting local dysfunction within distributed brain regions.

Treatment Implications

A second major prediction of the PCP/NMDA model was that treatments that stimulate NMDAR receptor function should be therapeutically beneficial. The most direct test of this hypothesis comes from compounds that target specific binding sites on the NMDAR complex either directly or indirectly. Most studies have focused on the glycine/D-serine modulatory site, which was first characterized in 1987,^{50,51} although a more recent study has targeted the redox/GSH site.⁵² Most compounds studied to date have been compounds-of-convenience, which were able to be studied either because they are natural compounds or fortuitously cross-react with NMDAR as a secondary effect. These compounds have been used almost exclusively as add-on treatments, although one monotherapy study in acute patients has been reported.⁵³ Recently, however, high-affinity compounds have been developed for several proposed mechanisms, and entered into definitive clinical trials.

NMDAR Glycine Site Agonists. Initial controlled clinical studies with glycine were performed in the early 1990s. These studies showed significant proof of concept results, although doses required for treatment (approximately 60 g/day) proved impractical for long-term use.⁵⁴ Subsequent studies were done with D-serine, which showed similar levels of benefit but at significantly lower doses (2–8 g/day). A concern at higher doses is a potential for nephrotoxicity, although no significant adverse events have yet been observed at doses of ≤ 4 g/day. Recent meta-analyses support use of full NMDAR agonists in combination with non-clozapine antipsychotics with moderate effect size across studies, not all of which were individually significant.^{55–57}

D-cycloserine, a partial NMDA/glycine-site agonist, has also been used for treatment of persistent symptoms (see Goff, this volume). Although less effective for symptomatic relief than full agonists during daily dosing,^{55–57} they may be useful for cognitive remediation during persistent treatment. Drug companies have attempted repeatedly to develop novel, high potency direct agonists for the glycine binding site, but the small molecular size of this target has prevented further drug optimization.

Interestingly, potential beneficial effects of NMDAR agonists are not confined to behavioral symptoms of schizophrenia, but may extend to motor symptoms also. In most trials of NMDAR agonists, patients have had relatively low levels of motor symptoms because of inclusion/exclusion criteria and use of anticholinergics. However, in some trials, significant baseline Parkinsonian symptoms and tardive dyskinesia was observed. In such studies, highly significant, large effect size improvement

in antipsychotic-induced motor symptoms was observed (figure 3). Although glycine-site agonists have been tested most for schizophrenia, the ability to manipulate NMDA receptors may be relevant to conditions others than schizophrenia, such as Parkinson's disease,⁵⁸ where motor symptoms are primary.

Glycine Transport Inhibitors. Extracellular glycine levels in brain are typically above the level needed to fully saturate the glycine binding site of the NMDA receptor. NMDAR are protected from these circulating levels by glycine (GlyT1) transporters that are co-localized with NMDAR and serve to maintain low-subsaturating glycine levels within the local region of the NMDAR synapse (figure 4). Initial studies were performed with the low-affinity glycine derivative glycyldodecylamide (GDA). This compound was known to reverse PCP-induced hyperactivity at doses far lower than glycine itself, although mechanisms at the time were unknown. Studies initiated in the mid-1990s demonstrated that GDA induced its effects by blocking glycine transport,⁵⁹ thereby leading to increased glycine levels in the immediate vicinity of the NMDAR. A subsequent study demonstrated parallel structure activity relationships across a range of glycineamides,⁶⁰ as well as the ability of these compounds to modulate striatal dopamine release in vitro,⁶¹ confirming the relevance of these compounds for schizophrenia.

Initial follow-up studies were performed with the high-affinity compound NFPS, which, like GDA, was shown to enhance NMDA receptor-mediated neurotransmission and modulate dopamine in vitro and reverse PCP-induced hyperactivity and striatal dopamine release in vivo (reviewed by Javitt)⁵⁴. Studies conducted throughout the past decade subsequently confirmed the effectiveness of high-affinity glycine transport inhibitors

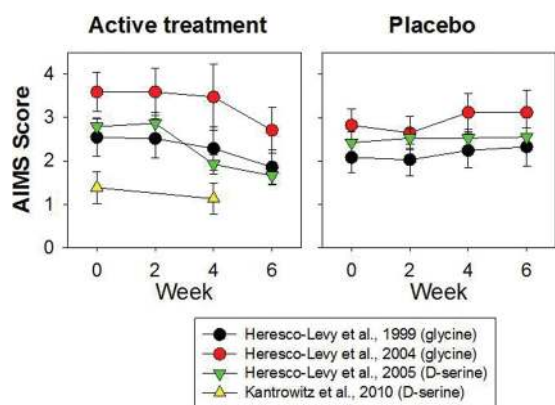


Fig. 3. Effect of NMDAR glycine-site agonists on motor symptoms (tardive dyskinesia) as reflected in Abnormal Involuntary Movement Scale (AIMS) score. Data are from studies of glycine^{74,75} or D-serine.^{76,77} Across all studies, D-serine treatment led to a highly significant ($t = 4.86$, $df = 192$, $P < .00001$, $d = .83$) improvement in AIMS symptom, suggesting benefit of NMDAR agonist on motor and neuropsychological symptoms in schizophrenia.

in a large variety of rodent⁵⁴ and primate⁶² models relevant to schizophrenia. Most recently, the first of these compounds, bitopertin (RG1678, Roche)⁶³ has been entered into preclinical and clinical testing. As predicted, it was shown to induce significant beneficial effects on treatment refractory negative symptoms in individuals treated in accordance with protocol. Secondary outcome measures, including percentage responders, also favored bitopertin. GlyT1 occupancy associated with beneficial treatment response was in the range of 30%–50%, with loss of efficacy at higher occupancies suggesting a critical therapeutic window and a need for careful dose selection in phase 2 studies (Umbricht et al., unpublished data).⁶⁴ If confirmed in ongoing phase 3 studies, this will be the first compound developed specifically for treatment of schizophrenia based on PCP/NMDA models.

D-serine Modulators. The ability of glycine transport inhibitors to induce beneficial effects in animal models of schizophrenia as well as schizophrenia itself suggests that similar approaches to enhancement of NMDAR-mediated neurotransmission should also be possible through manipulation of brain D-serine levels. D-serine (SR) is synthesized in brain via serine racemase and degraded by D-amino acid oxidase (DAAO). Genes for both SR and DAAO have been linked to schizophrenia. In addition, reduced D-serine levels have been demonstrated in both serum and cerebrospinal fluid,²⁷ suggesting that D-serine disturbances may be closer to the pathophysiology of schizophrenia. Inhibition of DAAO is also reported to augment D-serine effectiveness in vitro,⁶⁵ although this approach may be limited by the low levels of DAAO expressed in cortex as opposed to cerebellum. Several D-serine transporters, including a novel alanine-sensitive transporters,⁶⁶ have also been identified, and thus may be appropriate targets for further treatment development.

Other Treatment Approaches. To the extent that schizophrenia results from underlying NMDAR dysfunction, manipulations that affect NMDAR function, presynaptic glutamate release or postsynaptic signal transduction may be therapeutically beneficial. In addition to the glycine/D-serine modulatory site, NMDAR contain a redox sensitive site that can be modulated by polyamines or glutathione (GSH). *N*-acetylcysteine (NAC), a precursor to GSH, has been studied in schizophrenia and observed to induce significant pro-therapeutic effects⁵² and well as amelioration of neurophysiological deficits.⁶⁷ Elevations have been reported in levels of endogenous NMDAR antagonists such as homocysteine⁶⁸ or kynurenic acid,⁶⁹ suggesting that treatments designed to normalize such deficits may also be clinically beneficial.

Alpha7 nicotinic receptors are highly localized to presynaptic glutamate terminals and serve to enhance presynaptic glutamate release. Nicotinic activation potentiates NMDA receptor-mediated responses not only in

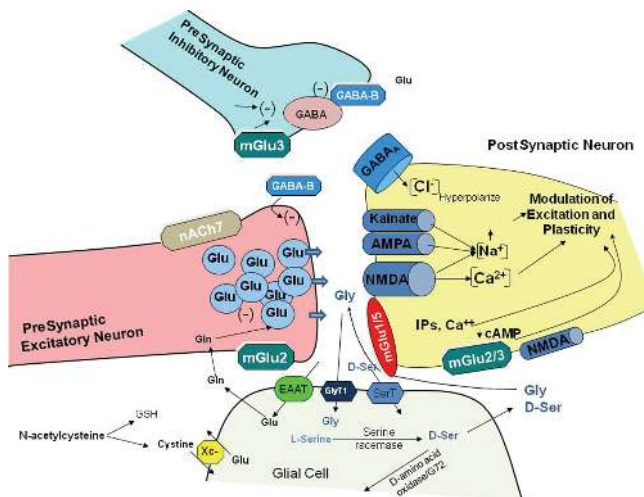


Fig. 4. Schematic diagram of glutamate synapses showing potential sites of interaction for modulation of NMDAR function. mGlu, metabotropic glutamate receptor; nACh7, alpha7 nicotinic receptor; EAAT, excitatory amino acid transporter; GlyT1, glycine type 1 transporter; SerT, high-affinity D-serine transporter; Xc⁻, cystine/glutamate antiporter; Glu, glutamate; Gly, glycine; D-Ser, D-serine; GSH, glutathione. Adapted from Javitt et al.²⁷

prefrontal brain regions but also in visual and auditory regions, and so may affect sensory, as well as higher cognitive deficits associated with schizophrenia. Conversely, chronic PCP treatment downregulates frontal nicotinic receptor density in monkey cortex,⁷⁰ suggesting bidirectional interactions between nicotinic and NMDAR systems. Similarly, GABA_B receptors may be located both presynaptically and postsynaptically, and may normalize presynaptic dopamine release,⁷¹ leading to beneficial clinical response.⁷²

mGluR5 receptors are localized on postsynaptic terminals and serve to potentiate NMDAR response, suggesting potential efficacy for mGluR5 agonists or positive allosteric modulators,²⁷ while mGluR2/3 are located presynaptically and may serve to normalize presynaptic glutamate release (Moghaddam et al., this volume). Although many of these approaches are being tested in isolation, a critical issue is how these processes may interact, and which mechanisms produce synergistic vs competitive effects on underlying NMDAR function. At present, animal models are not required for further validation of these approaches because most are presently in early stage clinical development. In contrast, animal models may be critical to evaluate interaction between mechanisms and to enable next stages of clinical intervention.

Synthesis: Schizophrenia as the Clinical Condition Resulting from NMDAR Dysfunction

It has now been over 100 years since schizophrenia was first described, 50 years since the first description of PCP-induced psychotic symptoms, and 20 years since the

realization of the potential role played by NMDAR dysfunction in the pathophysiology of schizophrenia. Despite this, the conceptualization of schizophrenia as a discrete illness continues to be elusive and available treatments for schizophrenia control symptoms, but do not appear to substantially modify the course of the underlying illness. Both genes and environmental influences have been identified that increase risk for schizophrenia, but typically with only small effect and large overlap between affected individuals and the general population. Fifty years after the PCP psychosis was first described, it remains the best acute intervention model for schizophrenia.

Rather than viewing schizophrenia as a disease with specific underlying pathophysiological process, findings to date suggest that the clinical syndrome of schizophrenia may reflect simply the behavioral pattern resulting from generalized disruption of NMDAR-mediated neurotransmission within brain. Similarly, ultimate treatment for schizophrenia may require correction of a range of underlying neurochemical disturbances that converge at the NMDAR, with direct stimulation of NMDAR representing only one component of a multipronged nutritional, psychopharmacological, and brain stimulation approach.

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Dr Javitt holds intellectual property rights for use of NMDA agonists, including glycine, D-serine, and glycine transport inhibitors in treatment of schizophrenia and related psychotic and movement disorders. Dr Javitt is a major shareholder in Glytech, Inc., and Amino Acids Solutions, Inc. Within the past year, Dr Javitt has served as a paid consultant to Sepracor, AstraZeneca, Cypress, Merck, Sunovion, Eli Lilly, Takeda, Guidepoint Global, and BMS. Dr Heresco holds intellectual property rights for use of D-serine in treatment of Parkinson's disease and other movement disorders. Dr Zukin is an employee of Forest Research Institute. Dr Umbricht is an employee of Hoffman-La Roche.

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