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REVIEW

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NMDA receptor antagonist effects, cortical glutamatergic function, and schizophrenia: toward a paradigm shift in medication development

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Abstract There is an urgent need to improve the pharmacotherapy of schizophrenia despite the introduction of important new medications. New treatment insights may come from appreciating the therapeutic implications of model psychoses. In particular, basic and clinical studies have employed the N-methyl-D-aspartate (NMDA) glutamate receptor antagonist, ketamine, as a probe of NMDA receptor contributions to cognition and behavior. These studies illustrate a translational neuroscience approach for probing mechanistic hypotheses related to the neurobiology and treatment of schizophrenia and other disorders. Two particular pathophysiologic themes associated with schizophrenia, the disturbance of cortical connectivity and the disinhibition of glutamatergic activity may be modeled by the administration of NMDA receptor antagonists. The purpose of this review is to consider the possibility that agents that attenuate these two components of NMDA receptor antagonist response may play complementary roles in the treatment of schizophrenia.

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Introduction

Psychiatry is at a crossroads in the search for new pharmacotherapies for schizophrenia. Over the past 15 years a large number of new antipsychotic medications have greatly improved the tolerability and, to a lesser extent, increased the efficacy of pharmacotherapy for this disorder (Arvanitis and Miller 1997; Carpenter 1995, 1996; Daniel et al. 1999; Essock et al. 1996; Kane et al. 1988, 2002; Marder and Meibach 1994; Rosenheck et al. 1997; Tollefson and Sanger 1997). When prescribed optimally, these new treatments follow the same fundamental paradigm: substantial but incomplete attenuation of dopamine D_2 receptor function combined with blockade or inverse agonism of serotonin 5-HT_2 receptor function (Burris et al. 2002; Egan et al. 1998; Kapur et al. 1999; Meltzer et al. 1989; Stockmeier et al. 1993). This mechanistic redundancy may contribute to the failure of available treatments to effectively treat many patients and the finding that schizophrenia remains among the most disabling disorders in society (Gross et al. 1999).

To fundamentally advance the pharmacotherapy of schizophrenia, a path of high financial risk for the pharmaceutical industry will need to be explored: the pursuit of new treatment mechanisms. Most of the highly novel treatment mechanisms explored as stand-alone treatments for schizophrenia over the past 15 years failed in development, including selective D_4 receptor antagonism (Kramer et al. 1997), D_4-5-HT_{2A} receptor antagonism (Truffinet et al. 1999), selective 5-HT_2 receptor antagonism (Axelsson et al. 1991; Wiesel et al. 1994), cannabinnoid-1 receptor antagonism (Diana et al. 1998; Shen and Thayer 1999), and D_1 receptor antagonism (Loebel et al. 1999). The limitations of the agents tested as stand-alone pharmacotherapies do not rule out a

potential role for these agents in augmenting the efficacy of other neuroleptic medications. In fact, most of these mechanisms are common components of the receptor affinity of currently "atypical" neuroleptic medications (Meltzer et al. 1989; Zimbroff et al. 1997).

In response to the societal need and despite the risks, the pharmaceutical industry has demonstrated a sustained interest in exploring novel treatment mechanisms for schizophrenia. A spectrum of novel agents are in development including neuropeptide receptor agonists and antagonists (Alonso et al. 1999; Emonds-Alt et al. 1995; Gully et al. 1995; Kramer et al. 1998; Sarhan et al. 1997), agonists or partial agonists for nicotinic receptors bearing the α-7 subunit (Simosky et al. 2002), glycine transporter antagonists (Lopez-Corcuera et al. 2001), AMPAkines (Goff et al. 1999a), and metabotropic glutamate receptor 5 (mGluR5) agonists or positive allosteric modulators (Awad et al. 2000). Each of these agents is based on a novel and important aspect of corticolimbic circuitry. Further, technological advances at the molecular and biochemical levels are likely to produce many novel compounds (Krstulovic 1999; Spencer 1998; Van Hijfte et al. 1999). Both the academic community and the pharmaceutical industry, however, face major challenges in bridging the gap between promising compounds and effective treatments. A premise of this review is that a translational neuroscience perspective, including experimental human laboratory-based research, may be a critical component linking molecular neuroscience and psychiatric practice.

This review will discuss two pathophysiologic themes arising from recent schizophrenia research: (1) impaired cortical connectivity and (2) glutamatergic disinhibition. It will then describe the phenotypic similarities between schizophrenia and the subanesthetic effects of ketamine in healthy humans. A body of research will then be reviewed that suggests that the face validity of the ketamine "model" for schizophrenia may arise as a consequence of the capacity of NMDA receptor antagonism to produce transiently neural network dysfunction pertaining to the two pathophysiologic themes associated with schizophrenia. Building on more than a decade of psychopharmacology research involving ketamine, this review will then consider potential therapeutic implications of the actions of NMDA receptor antagonists for the treatment of schizophrenia.

Two pathophysiologic themes in schizophrenia research: abnormal cortical connectivity and glutamatergic disinhibition

There is growing consensus that schizophrenia is associated with abnormal or reduced cortical connectivity. In postmortem studies, these deficits are reflected by reduced cortical volume (Bogerts 1999), smaller glutamatergic somatic or neuropil size (Arnold et al. 1995; Rajkowska et al. 1998; Selemon and Goldman-Rakic 1999), decreased number of dendritic spines (Glantz and Lewis 2000, 2001; Rosoklija et al. 2000; see Fig. 1), disarray of neuronal orientation (Kovelman and Scheibel 1984), and reduced synaptic proteins (Eastwood et al. 1995; Glantz and Lewis 1997). Paradoxically, particular axonal projections may be relatively increased in schizophrenia (Benes et al. 1987) and schizophrenia is associated with regional increases and decreases in glutamate receptor gene expression and ligand binding (reviewed in Deakin and Simpson 1997; Krystal et al. 2000; Meador-Woodruff and Healy 2000). These postmortem studies are paralleled by in vivo structural neuroimaging findings indicating reduced cortical volumes (Lim et al. 1996; Weinberger et al. 1992; Wible et al. 1995), magnetic resonance spectroscopy studies consistent with reduced neuropil volume or viability (Bertolino and Weinberger 1999; Steel et al. 2001), and diffusion tensor imaging studies suggesting that cortical connectivity is disturbed (Buchsbaum et al. 1998; Kubicki et al. 2002; Lim et al. 1999). These synaptic deficits appear to interfere with the coherent activity of cortical networks (Hoffman et al. 1991; Koenig et al. 2001; Lawrie et al. 2002; Meyer-Lindenberg et al. 2001; Michelogiannis et al. 1991; Tauscher et al. 1998; Winterer et al. 2001), but may in some cases and using some research paradigms produce excessive coherence of regional brain activity (Mann et al. 1997; Wada et al. 1998). Consistent with these disturbances in cortical network functions, schizophrenic

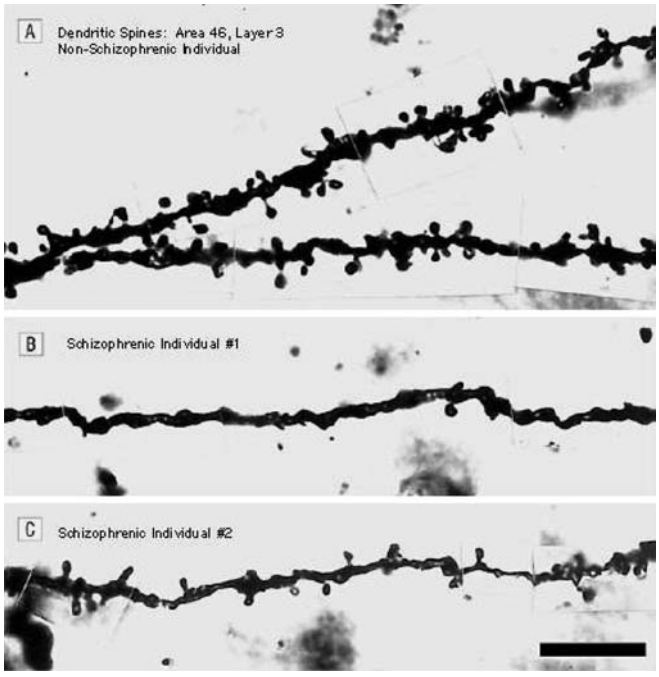

Fig. 1A–C Depiction of dendritic spines from area 46, layer 3, from postmortem human tissue from: **A** nonschizophrenic individual, **B** and **C** individual diagnosed with schizophrenia. In each figure, dendritic spines are the lollipop-like blebs that protrude from the dendrites. As is evident in these pictures, the number of dendritic spines in the tissue from the schizophrenic individuals are much lower than in the tissue from the nonschizophrenic individual. From Glantz and Lewis (2000)

patients may fail to show optimal task-related activity as reflected in particular frequencies of the electroencephalogram (Haig et al. 2000; Kwon et al. 1999; Lee et al. 2001), reduction in event-related potentials (Mathalon et al. 2000; McCarley et al. 2002), or decreased (or pathologically increased) cortical activation during task performance in functional neuroimaging studies (Barch et al. 2001; Fletcher et al. 1998; Weinberger et al. 1986). Presumably these disturbances in cortical network function underlie cognitive impairments that are evident during neuropsychological testing that, in turn, appear to underlie both symptoms and disability in schizophrenic patients (Bell and Bryson 2001; Bryson et al. 1998; Gold et al. 2002; Goldberg et al. 2001; Lysaker et al. 1996).

To the extent to which it occurs, it is not clear whether a deficit in NMDA receptor function in patients diagnosed with schizophrenia arises as a secondary consequence of neuropil reductions (Hoffman and McGlashan 1997) or as a primary impairment in NMDA receptor function (Olney and Farber 1995; Coyle 1996; Tamminga 1998). From this perspective, it is interesting that brain levels of two metabolites that antagonize NMDA receptor function, N-acetyl-aspartyl-glutamate (NAAG) (Tsai et al. 1995) and kynurenate (Schwarcz et al. 2001) were elevated in postmortem tissue from schizophrenic patients. These findings renew interest in the possibility that endogenous psychotigens contribute to schizophrenia symptoms, reminiscent of older, now abandoned, autointoxication hypotheses (Barbeau 1967; Carpenter et al. 1975). Recent studies also suggest that polymorphisms in glutamate-related genes that would be predicted to alter glutamatergic function are associated with schizophrenia. These polymorphisms include neureglin 1 (Stefansson et al. 2002), which may influence the insertion of NMDA receptor subunits into the membrane, and D-amino acid oxidase and G72 (Chumakov et al. 2002), proteins that interact to metabolize D-serine.

A second theme—increased glutamate release arising from disinhibition or hyperactivity—has received less attention, perhaps because it may contrast with the prevailing view that schizophrenia is associated with hypofrontality (Andreasen et al. 1997; Siegel et al. 1993). Also, as will be briefly reviewed below, research findings related to this research theme have been variable across studies. Some reports suggest that schizophrenia may be associated with normal frontal cortical metabolism (Biver et al. 1992; Gur et al. 1995) or metabolic activation (Catafau et al. 1994; Cleghorn et al. 1989). Studies of metabolic activation are supported by proton magnetic resonance imaging studies suggesting increased glutamate or glutamine levels in the frontal cortex in schizophrenic patients (Bartha et al. 1997; Cecil et al. 1999; Williamson et al. 1999). Even when patients as a group had normal or reduced metabolism, metabolic rates increased with increasing severity of positive symptoms (Gur et al. 1987), particularly auditory hallucinations (Dierks et al. 1999; Shergill et al. 2000).

To the extent that glutamatergic hyperactivity occurs, it may arise from deficits in GABAergic function. Postmortem studies suggest many possible scenarios for GABA deficiency: the number of GABA-releasing neurons might be reduced (Beasley and Reynolds 1997; Benes et al. 1991; Daviss and Lewis 1995). If the number of these neurons is not reduced (Lewis 2000; Woo et al. 1997), then GABA neurons may be located in the wrong cortical layers (Akbarian et al. 1993a, 1993b, 1996; Kalus et al. 1997) or unable to release GABA normally due to reduced levels of the GABA synthetic enzyme glutamic acid decarboxylase (GAD) (Akbarian et al. 1995; Impagnatiello et al. 1998; Volk et al. 2000) or absent terminal axon cartridges (Pierri et al. 1999; Simpson et al. 1989). In response to an observed or presumed deficit in GABAergic innervation, studies reported an up-regulation in gene expression for $GABA_A$ subunits (Ohnuma et al. 1999) or ligand binding to $GABA_A$ receptors (Benes et al. 1992, 1996; Dean et al. 1999; Hanada et al. 1984, 1987) and a down-regulation of $GABA_B$ receptors (Mizukami et al. 2000). A recent elegant study showed that GABA receptor up-regulation was synapse specific: when the terminal lacked the axon cartridge, the postsynaptic GABA receptors were up-regulated (Volk et al. 2002). In vivo studies of GABA receptors that used benzodiazepine ligands have not produced evidence of diagnosis-related alterations in $GABA_A$ receptors (Abi-Dargham et al. 1999), but they have produced some interesting secondary findings (Verhoeff et al. 1999), such as an association with the severity of psychosis (Busatto et al. 1997). There is also evidence that neuroleptic treatment may have a salutary effect on disturbances in GABA systems in schizophrenic patients (Pierri et al. 1999; Todtenkopf and Benes 1998).

The population of GABA cells that are most aberrant in schizophrenia, chandelier cells, may be particularly associated with glutamatergic disinhibition (Lewis 2000). These cells synapse on the proximal axon segments of glutamatergic neurons and provide both feedforward and feedback inhibition on cortical glutamatergic output. One predicted consequence of this glutamatergic disinhibition is excessive glutamate release and glutamate receptor–mediated neurotoxicity (Lewis et al. 1999). This view is consistent with a growing body of evidence from structural neuroimaging studies that the neuropathology of schizophrenia may be progressive (Mathalon et al. 2001; Thompson et al. 2001). A recent study also suggested that deficits in GABA receptor function increased the vulnerability to a pharmacologically induced psychosis (D'Souza et al. 2003). In addition, there is some evidence that the GABA abnormalities that are found in schizophrenic patients appear to be associated with mood disorders and schizoaffective disorder (Benes and Berretta 2001; Cotter et al. 2002). Thus, the treatment implications of disinhibitory neuropathology may be relevant to psychosis across these diagnoses, but may not generalize to all schizophrenic patients.

Other data may suggest that glutamatergic hyperactivity in schizophrenia may emerge via other mechanisms. For example, abnormalities of myelin formation schizophrenia (Foong et al. 2000) and dysregulation of myelin-

related genes (Hakak et al. 2001) may contribute to impaired glutamatergic regulation (Werner et al. 2001). Disturbance in glutamate transporters in thalamic neurons may also reflect abnormalities in the handling of glutamate in the cortex (Smith et al. 2001).

In summary, two themes of the emerging pathophysiology of schizophrenia—reduced connectivity and glutamatergic disinhibition—have emerged from postmortem analyses and in vivo neuroimaging studies. The subsequent review will highlight the manner in which studies of psychotigenic drugs help to articulate the functional significance and therapeutic implications of these two forms of pathology.

Psychotigenic drugs impair connectivity and activate cortical networks: therapeutic implications

NMDA receptor antagonists have been employed in human research studies that have attempted to characterize the contributions of NMDA receptors to human cognition and behavior with the long-term aim of identifying new treatments for schizophrenia and other psychiatric and substance abuse disorders (Farber et al. 1998; Heresco-Levy and Javitt 1998; Krystal et al. 1999e, 2003b; Newcomer and Krystal 2001). As highlighted in recent reviews (Krystal et al. 1999a; Vollenweider and Geyer 2001), the insights generated through the administration of ketamine to healthy humans and patient groups could not be generated through other means.

NMDA receptor antagonists and schizophrenia

NMDA receptor antagonist effects in healthy humans resemble the signs and symptoms of schizophrenia (Abi-Saab et al. 1998). The prototype uncompetitive NMDA receptor antagonist, phencyclidine (PCP), produced psychotic symptoms, thought disorder, blunted affect, and cognitive impairments that, for the initial investigative team, captured the gestalt of schizophrenia (Luby et al. 1959). Similarly, some individuals presenting to psychiatrists following PCP ingestion, generally in the context of multiple episodes of use of multiple substances, could not be distinguished from schizophrenic patients (Fauman et al. 1976).

Ketamine, rather than PCP, emerged as the prototypal NMDA receptor antagonist for experimental psychopharmacologic research. PCP was withdrawn from the clinical formulary in the 1960s as a result of its abuse liability. However, the PCP derivative, ketamine, remains an important anesthetic and analgesic medication with an excellent safety record (Green et al. 1998; Haas and Harper 1992; Mercadante 1996; Reich and Silvay 1989). Ketamine presented advantages over PCP for experimental psychopharmacologic research because it had a similar profile of effects in humans to that of PCP (Domino et al. 1965) but with lower NMDA receptor affinity (Anis et al. 1983) and shorter plasma half-life (Idvall et al. 1979; Wieber et al. 1975). As a result, during intravenous infusion, unpleasant ketamine effects may be terminated by halting the infusion without the need for supporting medications (J. Krystal, personal communication) and one can rapidly titrate plasma levels for experimental purposes (Bowdle et al. 1998). Further, with regard to settings where appropriate safety procedures are in place, there is extensive documentation of the safety of ketamine infusion in patients diagnosed with schizophrenia (Carpenter 1999). In the United States, ketamine is available only as a racemic mixture. However, in Europe, the S-isomer of ketamine is available, and it has greater selectivity for NMDA glutamate receptors than the R-isomer (Vollenweider et al. 1997). Overall, this record of ketamine safety supports continued psychopharmacologic research with this agent when the question under investigation is sufficiently important and the study design is informative (D'Souza et al. 1999).

The hypothesis that ketamine effects model aspects of schizophrenia is supported by the following observations: (1) it transiently produces symptoms in healthy subjects that are similar to the positive, negative, and disorganized symptoms of schizophrenia (Krystal et al. 1994, 1998a; Malhotra et al. 1997; Newcomer et al. 1999; Oye et al. 1992; Vollenweider et al. 1997; see Fig. 2); (2) ketamine-induced thought disorder in healthy subjects resembles thought disorder in schizophrenic patients when compared directly (Adler et al. 1998); (3) it briefly increases the signs and symptoms of the disorder in schizophrenic patients (Lahti et al. 1995b; Malhotra et al. 1997); (4) it produces executive cognitive impairments in healthy subjects that are associated with schizophrenia, including effects on attention, working memory, declarative memory, abstract reasoning, mental flexibility, insight, planning, and judgement (Krystal et al. 1994, 1998a, 1999d; Malhotra et al. 1997; Newcomer et al. 1999; see Fig. 2); and (5) it disturbs physiologic indexes of information processing in healthy subjects that resemble deficits in schizophrenia, including event-related potentials (Umbricht and Vollenweider 1999), smooth pursuit eye tracking (Avila et al. 2002; Radant et al. 1998), and cognitive activation of the prefrontal cortex as assessed with fMRI (Abel et al. 2003; Belger et al. 2003b).

The breadth of ketamine effects produced in healthy subjects suggests similarities to that in patients with nonparanoid schizophrenia or patients early in the course of their illness. The prominence of cognitive impairment and conceptual disorganization associated with ketamine effects are more consistent with the disorganized or undifferentiated subtypes of schizophrenia rather than paranoid schizophrenia. The paranoid/nonparanoid distinction has phenomenologic, prognostic, and biological significance (Fenton and McGlashan 1991a, 1991b; McGlashan and Fenton 1993). The distinction between NMDA receptor antagonist effects in healthy human subjects and paranoid schizophrenia is paralleled by the apparent relative independence of the ketamine psychosis of D_2 receptor function. In schizophrenic patients, particularly those with recent psychotic exacerbations, psy-

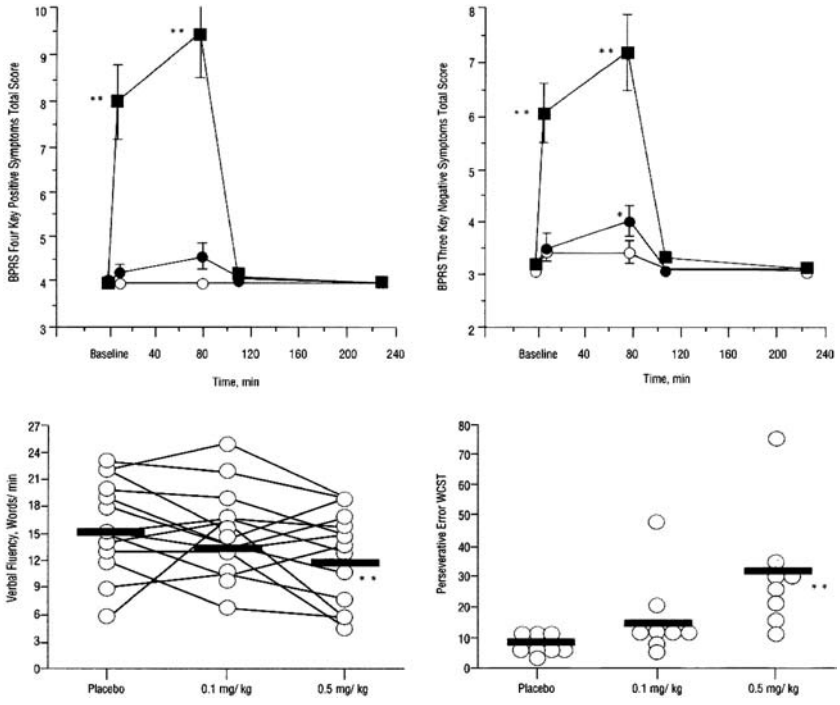

Fig. 2 Description of ketamine effects in healthy human subjects. *Top left figure* illustrates the dose-related elicitation of transient psychotic symptoms in healthy subjects (n=18) during ketamine infusion, as reflected in the Brief Psychiatric Rating Scale (BPRS) four key positive symptom score (BPRS items: hallucinatory behavior, suspiciousness, unusual thought content, conceptual disorganization). Data are presented as mean ± SEM for saline *(open circles)*, ketamine 0.1 mg/kg *(filled circles)*, and ketamine 0.5 mg/kg *(filled squares)*. The ketamine dose-by-time interaction effect was highly significant (p<.0001). *Top right figure* illustrates the transient dose-related production of symptoms resembling the negative symptoms of schizophrenia in the same group of healthy subjects, as reflected in the BPRS three key negative symptom score (BPRS items: blunted affect, emotional withdrawal, and motor retardation). Data are presented as mean ± SEM for saline *(open circles)*, ketamine 0.1 mg/kg *(filled circles)*, and ketamine 0.5 mg/kg *(filled squares)*. The ketamine dose-by-time interaction effect was highly significant (p<.0001). *Bottom left figure* illustrates the dose-related reduction in verbal fluency during ketamine infusion in healthy human subjects (n=15). *Open circles* represent individual subjects. Comparisons of ketamine test days with placebo test day, by a within-subjects post hoc contrast, **p<.01. The *bottom right figure* presents ketamine effects on the Wisconsin Card Sorting Test (WCST) perseverative error in healthy subjects (n=19) on their 1st test day. *Open circles* represent individual subjects. Comparisons of ketamine test days with placebo test day, by Student-Newman-Keuls test, **p<.01. Modified from Krystal et al. 1994

chotic symptoms are associated with dopaminergic hyperactivity (Abi-Dargham et al. 2000; Breier et al. 1997b; Laruelle et al. 1996, 1999). In contrast, the ketamine psychosis is not ameliorated by haloperidol pretreatment or worsened substantially by amphetamine coadministration (Krystal et al. 1999c, 1999d), even though amphetamine increases the activation of dopamine systems associated with ketamine administration (Kegeles et al. 1999). Alternatively, prominent perceptual distortions are more typically associated with young patients, particularly during the onset of schizophrenia, rather than chronic phases or elderly patients (Bowers and Freedman 1966; Davidson et al. 1995; Gouzoulis-Mayfrank et al. 1998).

While there are many parallels between the cognitive and behavioral effects of ketamine and schizophrenia, there are differences as well—as would be expected between a pharmacologic model and a neurodevelopmental disorder (Abi-Saab et al. 1998). Ketamine produces sedative and euphoric effects that resemble ethanol intoxication (Krystal et al. 1998a, 1998b). Also, in a pilot study, anecdotal reports suggested that the dissociation-like component of the perceptual effects of ketamine were recognized as not typical of their illness by most schizophrenic patients (J. Krystal, personal communication). The attempt to finely map the cognitive effects of ketamine upon the array of cognitive dysfunction in schizophrenia also has met methodologic challenges. First, the pattern of cognitive deficits associated with schizophrenia is consistent across studies when functions are considered generally, but the magnitude of impairment on a particular test may vary across patients, as would be expected from a heterogenous disorder that may be treated with a large number of psychotropic agents and that may be associated with progressive cognitive decline (Buchanan et al. 1994; Green et al. 1997; Harvey et al. 1998; Heaton et al. 1979; Saykin et al. 1994). Similarly, there is a general consensus related to the cognitve dysfunctions produced by ketamine across studies, but there are some differences across studies on whether a particular test will be a sensitive measure of ketamine effects. One reason for this inconsistency may be that

there is a steep dose-response relationship for the subanesthetic effects of ketamine upon cognitive function (Krystal et al. 1994; Newcomer et al. 1999). Across studies, different ketamine doses may be used and in studies that do not successfully hold ketamine levels steady during testing, tests may be performed when the subject is exposed to varying plasma levels of ketamine. Comparisons of the sensitivity of different cognitive domains to impairment by ketamine is also complicated by the use of different measures that vary in difficulty, to evaluate particular cognitive functions across studies. As a result, the fine mapping of the cognitive impairments produced by ketamine in healthy subjects upon the cognitive deficits of schizophrenia will be challenging and may not turn out to be a productive enterprise.

However, gross differences in ketamine response in schizophrenic patients and healthy subjects compared in the same study may provide insight into altered glutamatergic function associated with the pathophysiology of schizophrenia. Many dimensions of the ketamine response in schizophrenic patients and healthy subjects are similar in magnitude and form. Although equating symptoms in an ill person and a healthy person is risky, the magnitude of the worsening of delusions in schizophrenic patients appears to be comparable to the extent to which ketamine produces delusions in healthy individuals. In contrast, two preliminary observations have been made: there may be blunting of the negative symptom response (Lahti et al. 2001) and increased sensitivity to the hallucinogenic effects (particularly auditory hallucination) (J. Krystal, personal observation) of ketamine in schizophrenic patients relative to healthy control subjects. The finding of increased sensitivity to worsening of auditory hallucinations in patients, if it can be replicated, may suggest that ketamine exacerbates a glutamatergic deficit in patients in a pathway that contributes to auditory hallucinations. For example, frontotemporal connectivity deficit in schizophrenic patients has been hypothesized to contribute to auditory hallucinations (Ford et al. 2001a, 2002). Alternatively, reduced sensitivity to the evocation of negative symptoms in patients could reflect a complementary hyperinnervation in some pathways (Benes et al. 1987; Longson et al. 1996), consistent with some postmortem findings (Deakin and Simpson 1997).

Therapeutic implications of the impairment of functional connectivity by NMDA receptor antagonists

NMDA receptor antagonist effects may guide the development of at least two groups of agents related to the two mechanistic themes outlined above: abnormal cortical connectivity and glutamatergic disinhibition. One group, including glycine$_B$ receptor agonists, glycine transporter (GlyT-1) antagonists, AMPAkines, and mGluR5 agonists consists of agents that are intended to counteract a deficit in glutamatergic synaptic function. The other group of agents, reviewed in the next section, consists of drugs that might attenuate the impact of glutamatergic hyperactivity, including glutamate release inhibitors (GRIs) and non-NMDA glutamate receptor antagonists.

Glycinergic pharmacotherapies were the first treatment approach introduced based on the NMDA receptor antagonist model psychosis, and they were intended to correct a deficit in NMDA receptor function. Glycine is a coagonist of the NMDA receptor, meaning that this receptor cannot function optimally unless both glycine and glutamate are bound (Javitt and Zukin 1989; Johnson and Ascher 1987). Recent data suggest that glycine$_B$ binding sites of NMDA receptors are exposed to at least two types of agonist exposure: tonic and phasic. The tonic control synaptic glycine levels is controlled by high activity glycine transporters, such as GlyT-1, that rapidly take up glycine that passively diffuses into glutamatergic synapses and maintains these levels below those required to saturate glycine$_B$ sites (Supplisson and Bergman 1997). Consistent with this view, GlyT-1 antagonists are effective in enhancing NMDA receptor function in animals (Bergeron et al. 1998). One consequence of maintaining glycine levels below the receptor saturation level is that it enables another endogenous glycine$_B$ receptor agonist, D-serine, to enhance NMDA receptor function in an activity-dependent manner (Ivanovic et al. 1998; Schell et al. 1997). D-Serine may be released into synapses by glia in response to α-amino-3-hydroxy-5-methylisoxazolepropionic acid (AMPA) glutamate receptor stimulation associated with synaptic glutamate release (Schell et al. 1995). From this perspective, drugs that enhance AMPA receptor function, including the AMPAkines, also may enhance D-serine release and thereby increase NMDA receptor function.

Drugs that enhance glycine$_B$ binding site function reduce the behavioral effects of NMDA receptor antagonists in healthy humans and negative symptoms and cognitive impairments in schizophrenic patients. Glycine or glycine transporter antagonists attenuate some NMDA receptor antagonist effects acutely in both animals (Javitt et al. 1997; Toth and Lajtha 1986) and humans (D'Souza et al. 1997), perhaps related to interactions between the glycine and glutamate binding sites of the NMDA receptor (Grimwood et al. 1993; Priestley and Kemp 1994). With chronic administration, the glycine$_B$ receptor agonists, glycine and D-serine, and the partial agonist D-cycloserine are moderately successful in augmenting the efficacy of all neuroleptics, except perhaps clozapine, in treating negative symptoms and executive cognitive impairments (D'Souza et al. 1995; Goff et al. 1995, 1996, 1999b; Heresco-Levy et al. 1996, 1998, 1999; Javitt et al. 1994). D-Serine, which crosses the blood-brain barrier better than glycine and is not a substrate for GlyT-1, may offer the most promising approach that has been tested in patients to date (Tsai et al. 1998).

Despite the attractiveness of viewing glycine$_B$ receptor agonists as "anti-ketamines," the therapeutic reality appears more complicated. For example, glycine$_B$ receptor agonists have not shown clear promise as stand-alone treatments, their therapeutic effects emerge with chronic rather than acute administration, and chronic administra-

tion may reduce glycine$_B$ receptor function (Krystal and D'Souza 1998). Further, chronic antipsychotic administration, including the use of clozapine, appears to enhance NMDA receptor function and to down-regulate ligand binding to glycine$_B$ receptors (Banerjee et al. 1995; McCoy and Richfield 1996). These adaptations might suggest that neuroleptic treatment might reduce the impact of pro-glycine treatments.

An alternative view of glycine$_B$ receptor treatments is that they are neuroplasticity promotors. It is possible that the progressive volume loss of brain volume observed in some schizophrenic patients reflects a failure to manifest the neurotrophic impact of life experience–related brain network activity as opposed to increased neurotoxicity. In animals, for example, environmental enrichment may increase neurogenesis, protect against apoptosis, enhance synaptic plasticity, and improve learning and memory (Kempermann and Gage 1999; Kempermann et al. 1998; Tang et al. 2001; Young et al. 1999). It appears that NMDA receptor function is very important for the positive impact of environmental enrichment on neuroplasticity (Tang et al. 2001) and, in turn, experience-dependent activation increases the insertion of NMDA receptors into synaptic dendritic membranes (Quinlan et al. 1999). Thus, schizophrenic patients may suffer from two compounded obstacles with respect to the neurotrophic or neuroprotective impact of life experience. First, they have deficits in connectivity or in NMDA receptor function, in particular, that impede this important form of neuroplasticity. Second, the symptoms and cognitive deficits associated with schizophrenia may contribute to an impoverishment of life experience, particularly its most important aspect for neurotrophic functions: the novelty of environmental stimuli (Kempermann and Gage 1999).

From this perspective, one might expect therapeutic programs that enrich environmental experience for schizophrenic patients to synergize with pharmacologic treatments that enhance NMDA receptor–related neuroplasticity and clinical outcomes in patients diagnosed with schizophrenia. Cognitive remediation programs, for example, appear to enhance task-related cortical activation, performance on neuropsychological tests, and overall clinical outcome in schizophrenic patients (Bell et al. 2001; Wexler et al. 2000). However, in the face of deficient cortical connectivity or impairments in NMDA receptor function, one might expect that environmental enrichments, by themselves, might not compensate fully for a reduced capacity for neuroplasticity associated with schizophrenia. By facilitating NMDA receptor-related neuroplasticity, drugs that facilitate NMDA receptor function without promoting neurotoxicity might increase the capacity of cortical networks to undergo experience-dependent modification. From this perspective, the gradually accumulating efficacy associated with glycine treatment and the persistence of the therapeutic effects of glycine following medication discontinuation (Heresco-Levy et al. 1996, 1998) could represent the gradual accrual of nontransient forms of neuroplasticity.

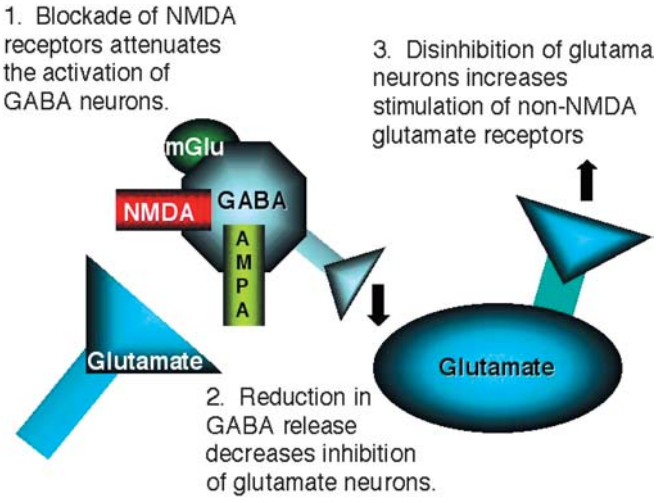

Fig. 3 Steps that may contribute to the increased activity of glutamatergic neurons in response to administration of NMDA glutamate receptor antagonists

Other agents may provide alternatives to glycine$_B$ receptor facilitation as a strategy for enhancing NMDA receptor function or facilitating glutamatergic neurotransmission. One might expect, for example, that drugs that facilitated other excitatory glutamate receptors might help to increase the level of neural network activity and to enhance the voltage-dependent recruitment of NMDA receptors (Yuste et al. 1999). One class of agents studied to enhance glutamatergic function are the AMPAkines that promote the activity of the AMPA glutamate receptor (Nagarajan et al. 2001; Suppiramaniam et al. 2001). The AMPAkine CX-516 reduced negative symptoms and cognitive deficits in neuroleptic-treated schizophrenic patients (Goff et al. 2001). Another approach would be to augment antipsychotic treatment with an agonist of another excitatory glutamate receptor, the group I mGluRs (Schoepp 2001). In particular, mGluR5 receptors are coupled to NMDA receptors (Tu et al. 1999). mGluR5 agonists enhance NMDA receptor function (Awad et al. 2000; Ugolini et al. 1999) and promote insertion of NMDA receptors into synaptic membranes (Lan et al. 2001). Other approaches might also include directly targeting NMDA receptor–related intracellular signaling cascades (Nicoll and Malenka 1999) and the function of dopamine$_1$ receptors (Dunah and Standaert 2001; Snyder et al. 1998).

Therapeutic implications of the disinhibition of glutamatergic networks by NMDA receptor antagonists

The capacity of subanesthetic doses of NMDA receptor antagonists to disinhibit glutamate release has generated a non-overlapping list of possible pharmacotherapies for schizophrenia (Krystal et al. 1999b; see Fig. 3). NMDA receptor antagonists appear to block the stimulation of GABA neurons with greater potency than they inhibit the

activation of glutamatergic neurons (Grunze et al. 1996; Maccaferri and Dingledine 2002), resulting in a drop in cortical extracellular GABA levels (Yonezawa et al. 1998) and an elevation of cortical and limbic extracellular glutamate levels (Moghaddam et al. 1997; Moghaddam and Adams 1998). With doses of NMDA receptor antagonists that are noticeably higher than those used in the human research, similar disinhibitory mechanisms appear to contribute to neurotoxicity (Farber et al. 2002; Olney and Farber 1995; Sharp et al. 2001). The disinhibition of glutamate release is also presumed to account for increases in human frontal cortex metabolism following the administration of ketamine (Bertolino 1999; Breier et al. 1997a; Lahti et al. 1995a; Vollenweider et al. 1997; Belger et al. 2003a).

Cortical glutamatergic activation by NMDA receptor antagonists stimulates monoaminergic terminals within the cortex and limbic system and monoaminergic cell bodies in the midbrain and brainstem via activation of non-NMDA receptors (Jentsch et al. 1997; Martin et al. 1998; Pallotta et al. 1998; Takahata and Moghaddam 1998). Supporting this view is the fact that the AMPA/kainate antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), blocks the capacity of NMDA receptor antagonists to raise cortical extracellular dopamine levels and to stimulate locomotor activity in rats (Moghaddam et al. 1997). It is not clear whether AMPA receptor antagonists are well-tolerated or antipsychotic in schizophrenic patients. Reduced number or function of AMPA receptors, particularly in the hippocampus, may be associated with schizophrenia (Meador-Woodruff and Healy 2000; Tamminga 1998) and AMPA receptor antagonists might worsen these deficits. To date, the only agent with AMPA receptor antagonist properties studied in schizophrenic patients, topiramate, did not augment the efficacy of neuroleptic treatment (Dursun and Deakin 2001).

A group of medications, lumped together as glutamate release inhibitors (GRIs) may attenuate the hyperglutamatergic effects of NMDA receptor antagonists and might play a role in treating schizophrenia. The most commonly prescribed examples of this class of medications are anticonvulsants. Anticonvulsant agents are widely prescribed to enhance neuroleptic efficacy (Baldessarini et al. 1995; Citrome et al. 1998; Wilson et al. 1985). However, there are limited supporting data for this application of anticonvulsants in schizophrenic patients (Carpenter et al. 1991; Casey et al. 2003; Dose et al. 1987, 1998; Greil et al. 1997; Klein et al. 1984; Nachshoni et al. 1994; Okuma et al. 1989).

Lamotrigine was the first anticonvulsant medication implicated in the treatment of schizophrenia by virture of its ability to attenuate ketamine effects in humans (Anand et al. 2000). Lamotrigine reduces glutamate release via blockade of voltage-dependent ion channels, particularly sodium channels and P- and N-type calcium channels and an outward potassium channel (Afanas'ev et al. 1999; Grunze et al. 1998; Stefani et al. 1996, 1997; Waldmeier et al. 1996; Wang et al. 1996). Thus, it was hypothesized that lamotrigine would attenuate those ketamine effects in humans that were mediated by the disinhibition of glutamate release. Consistent with this hypothesis, lamotrigine pretreatment reduced ketamine-induced psychosis, negative symptoms, and dissociation-like perceptual alterations, and it increased the euphoric or stimulatory effects of ketamine in healthy humans (Anand et al. 2000). In this study, lamotrigine also reduced the ketamine-induced enhancement of a time-dependent (30 min) decline in memory, but not the reduction in immediate recall produced by ketamine. In animals, lamotrigine also showed efficacy in two models that have predictive therapeutic value in schizophrenia: NMDA receptor antagonist–induced neurotoxicity (Farber et al. 1999) and NMDA receptor antagonist disruption of prepulse inhibition of the startle response (Brody et al. 2003).

Preliminary clinical evidence suggests that lamotrigine may augment antipsychotic efficacy in some patients diagnosed with schizophrenia (Durson et al. 1999; Dursun and Deakin 2001; Saba et al. 2002; Tiihonen et al. 2003), and definitive research is needed to establish the benefits and risks associated with this approach. Other calcium channel antagonists might also be explored in schizophrenia. For example, the L-type calcium channel antagonist, nimodipine, attenuated ketamine effects in humans (Krupitsky et al. 2001), and there is a very inconsistent literature of uneven quality that suggests that L-type calcium channel antagonists might reduce some symptoms in some schizophrenic patients when added to neuroleptic treatment (Bartko et al. 1991; Duncan et al. 1990; Grebb et al. 1986; Price 1987; Reiter et al. 1989; Stedman et al. 1991; Suddath et al. 1991; Yamada et al. 1996).

Other GRI classes might also be explored for the pharmacotherapy of schizophrenia. One potential approach are the mGluR2 receptor agonists. mGlurR2 receptors are located on glutamatergic terminals in many parts of the brain, where they provide feedback inhibition of glutamate release (Conn and Pin 1997; Lujan et al. 1997). At doses that inhibit the stimulation of cortical glutamatergic activation by PCP or serotonergic hallucinogens, the mGluR2 agonist LY354740 does not inhibit basal glutamate release in rats (Aghajanian and Marek 1999; Moghaddam and Adams 1998). Since glutamate provides the excitatory basis for most normal brain function, the preservation of basal glutamatergic tone may be important clinically. A recent study also suggests that LY354740 also reduces working memory impairments and perhaps psychotic symptoms transiently produced by ketamine in healthy human subjects (Krystal et al. 2003a). However, the impact of adding this medication to ongoing neuroleptic treatment has not yet been explored in schizophrenic patients. A related approach may be to enhance the accumulation of N-acetyl-aspartyl-glutamate (NAAG) via inhibition of the catabolic enzyme, glutamate carboxypeptidase II (GCPII) also known as N-acetyl-alpha-linked acidic dipeptidase (NAALADase) (Coyle 1997). NAAG stimulates the mGluR3 receptors and may also reduce glutamate release (Coyle 1997;

Jackson et al. 1996). Recent data suggest that GCPII inhibition attenuates some PCP effects in rats.

Challenges to the development of glutamatergic pharmacotherapies for schizophrenia

A number of challenges may predicted in the effort to develop glutamatergic agents for the treatment of schizophrenia: (1) nonlinear (inverted-U curve) relationships between basal activity and functional activation of glutamatergic function suggest that doses of glutamatergic agents might need careful adjustment; (2) the same individual may manifest reduction in cortical glutamatergic connectivity and hyperglutamatergic states in distinct regions or pathways; (3) glutamatergic agents may not work equally well in combination with all antipsychotic medication and particular pairings of medications may be needed; (4) the therapeutic implications of the cortical disinhibition may apply more broadly to patients with mood disorders than to patients with schizophrenia; and (5) glutamatergic pharmacotherapies may not treat all symptoms of schizophrenia and therefore may need to be developed as adjuncts to neuroleptic treatment.

Nonlinear relationships between basal activation and functional activation of networks may suggest that the utility of glutamatergic agents may be dose-limited. Neural network models involving opponent processes predict that the consequence of deficient glutamatergic activation may resemble the impact of excessive glutamatergic activation (Grossberg 1984, 1999). Opponent processes occur within neural networks when the activation of one excitatory pathway inhibits its neighboring excitatory pathway resulting in an inverted-U relationship between degree of basal activation and stimulus-dependent output. Related computational models describe how the recruitment of network inhibition and the distinctive kinetics of NMDA glutamate receptor function enable the hippocampus and cerebral cortex to store information in the form of sustained network activity (Grunze et al. 1996; Lisman et al. 1998; Wang 1999). Further, the experience-dependent manipulation of opponent processes appears to underlie the optimization or tuning of network functions related to the coherent encoding of environmental features within neural networks underlying working memory (Rao et al. 1999, 2000). In the ketamine model, there is evidence that stimulation of basal cortical network activity is associated with deficient task-related recruitment of cortical network activity (Belger et al. 2003a). However, the partial efficacy of lamotrigine (Anand et al. 2000) and LY354740 (Krystal et al. 2003a) in attenuating the cognitive and behavioral effects of ketamine in humans suggests that these hyperglutamatergic effects of NMDA receptor antagonists only partially account for the behavioral effects of this drug. Presumably, the ketamine effects that persist after pretreatment with GRIs reflect the direct consequences of NMDA receptor antagonism on neural network function. Therein may lie a conflict: reductions in glutamate release beyond some optimal level may further compromise NMDA receptor function and impair neural network function. Similarly, attempts to enhance NMDA receptor function by augmenting glutamatergic activity beyond an optimal level may further exacerbate the hyperglutamatergic effects of NMDA receptor antagonists and thereby worsen the disturbances in task-related recruitment of network function predicted by the parallel opponent process model of network function.

The population of patients diagnosed with schizophrenia may present a more heterogeneous array of disturbances in cortical connectivity and glutamatergic disinhibition than is produced by the ketamine model psychosis. This would suggest that it may be harder to predict, for an individual patient, the optimal dose of a facilitatory or inhibitory glutamatergic treatment. However, some preliminary experience with lamotrigine augmentation of neuroleptic treatment in schizophrenic patients may suggest that overcorrection of glutamatergic hyperactivity worsens symptoms of schizophrenia. A small preliminary double-blind randomized placebo-controlled study (E. Perry, D.C. D'Souza, W. Abi-Saab, J. Krystal, unpublished data) found that six of 12 (50%) patients treated with a higher target dose of lamotrigine (200 mg) had their medication discontinued due to lack of efficacy or worsening of symptoms of schizophrenia. In contrast, four of 21 (20%) patients randomized to placebo and one of five (20%) patients randomized to 50 mg of lamotrigine required medication to be discontinued during the study. Alternatively, overcorrection of deficient glutamatergic activation using AMPAkines might worsen symptoms related to glutamatergic disinhibition, perhaps related to the worsening of some patients who received an AMPAkine (Marenco et al. 2002).

As reviewed earlier, the same individual with schizophrenia may manifest deficient glutamatergic innervation in one region and excessive innervation in another (Deakin and Simpson 1997). These postmortem findings may be consistent with evidence that schizophrenic patients may exhibit deficient task-related activation of the prefrontal cortex, but hyperactivity of the hippocampus when performing working-memory tasks (Meyer-Lindenberg et al. 2001; Weinberger et al. 1992). These findings might suggest that addressing one component of network dysfunction would correct the other: for example, enhancing functional activation of prefrontal cortex would normalize hippocampal activation. However, with medications, there might be a risk that enhancing activation of the prefrontal cortex using a glutamatergic agonist might also promote the hyperactivity of the hippocampus or vice versa. In that case, dose-finding might balance the predicted desirable and undesirable effects on network function.

An alternative approach to pharmacotherapy would be to use transcranial magnetic stimulation to depress the actions of glutamate in specific pathways where increased glutamatergic response is presumed to occur. As noted earlier, patients who experience auditory hallucinations may fail to normally depress activity in auditory or

auditory association cortex when producing articulated speech or even nonarticulated or "inner" speech (Ford et al. 2001a, 2001b, 2002). The implication of this research is that auditory hallucinations may reflect the pathological activation of cortical auditory perception areas by one's thoughts and that these perceptions are perceived as arising from external stimuli. This view is consistent with the auditory perceptions associated with direct electrical stimulation of brain regions associated with the auditory function (Gloor 1990; Halgren et al. 1978; Penfield and Perot 1963) and the regional cortical activation patterns during auditory hallucinations (Dierks et al. 1999; Silbersweig et al. 1995; Shergill et al. 2000). Repeated transcranial magnetic stimulation (rTMS) of the brain has been shown to depress cortical activation with low frequency stimulation (1 Hz) and to potentiate the activity of particular pathways with higher frequency stimulation (10 Hz) (Speer et al. 2000). The capacity of low frequency rTMS to depress or depotentiate the functional activation of paricular brain regions has been likened to long-term depression (LTD) (Hoffman and Cavus 2002). In a series of studies, low frequency rTMS delivered over auditory and auditory association areas in the left temporoparietal cortex reduced or eliminated auditory hallucinations that had been resistant to pharmacotherapy in patients diagnosed with schizophrenia (Hoffman et al. 2000, 2003). The safety and tolerability of this approach suggests that there may value in utilizing rTMS or related approaches to selectively reduce activation of excessively active pathways while preserving the function of areas where there may be compromised activation due to disturbances in cortical connectivity. It is interesting to speculate that because rTMS may engage cellular mechanisms related to LTD or long-term potentiation (LTP), pharmacologic approaches might be developed to enhance the efficacy of rTMS based on preclinical research on the neurobiology and pharmacology of LTD and LTP.

A third challenge is that the glutamatergic agents may not work equally well in combination with all antipsychotic medications. In this regard, clozapine appears to stand apart from all other antipsychotic medications. For example, drugs that facilitate the glycine$_B$ site of NMDA receptors appear to be ineffective in reducing symptoms and may even exacerbate symptoms in patients treated with clozapine (Evins et al. 2000; Potkin et al. 1999; Tsai et al. 1999). In contrast, lamotrigine appears to be particularly effective when prescribed in combination with clozapine, but it may work less well in combination with other neuroleptics (Dursun and Deakin 2001). A better understanding of the actions of clozapine that account for its uniqueness with respect to combination pharmacotherapy may help to further medications development for schizophrenia.

In addition, the lack of diagnostic specificity of GABA deficits may point to applications of GRIs to disorders other than schizophrenia. As noted earlier, reductions in GABA neuronal populations have been described in schizoaffective disorder and mood disorders, as well as schizophrenia. Further, deficient glial function in these disorders may contribute to hyperglutamatergic states in mood disorders as well (Krystal et al. 2002; Ongur et al. 1998; Rajkowska et al. 1999). Mood disorders may be more amenable to GRI treatments than schizophrenia because the preservation of cortical innervation in mood disorders might enable these people to tolerate reductions of glutamatergic hyperactivity without showing worsening. From this perspective, several GRIs that reduce perceptual or psychotigenic effects of ketamine in humans, benzodiazepines, lamotrigine, and L-type calcium channel blockers (Anand et al. 2000; Krupitsky et al. 2001; Krystal et al. 1998a) may have greater safety or efficacy in treating mood disorders than they do in treating schizophrenia (reviewed in Krystal et al. 2002; Post 1999).

The most daunting challenge facing the development of glutamatergic pharmacotherapies for schizophrenic patients may be economic and regulatory. Glycine and AMPAkines are prototypes for the therapeutic opportunities that will arise from the addition of glutamatergic agents to neuroleptic treatment. They do not appear to be effective antipsychotic agents even though they enhance the efficacy of neuroleptic treatment. In particular, they appear to address negative symptoms and cognitive dysfunctions that may be the single strongest predictors of disability (Bell and Bryson 2001; Brekke et al. 2001). The prospect of the development of drugs that reduce the disabling consequences of schizophrenia is extremely important to patients, their families, and society. However, there is substantial finanacial risk involved for the pharmaceutical industry. First, these medications may not be antipsychotic, therefore their prescription may be limited to schizophrenic patients, as opposed to the common prescription of neuroleptics for indications other than schizophrenia. Consistent with this view, there is already concern in some components of the pharmaceutical industry that glutamatergic adjunctive agents may not be sufficiently profitable to warrant substantial investment. Second, these medications may need to be prescribed in combination with neuroleptic agents, in which case the availability of these medications may be limited by the efforts of health care systems to contain costs. Third, regulatory agencies, such as the US Food and Drug Administration do not currently recognize the capacity to reduce cognitive impairments as an indication for approval. However, there is a growing interest on the part of academia (Green and Braff 2001), the pharmaceutical industry, and the US National Institute of Mental Health (Hyman and Fenton 2003) to highlight the importance of cognition-enhancing agents for reducing the personal, familial, and societal burdens associated with schizophrenia. From this perspective, it appears that psychiatry and the pharmaceutical industry are heading toward a paradigm shift with respect to medications development for this disorder.

Toward new paradigms for the pharmacotherapy of schizophrenia

In summary, the field of schizophrenia research appears to be approaching a transition in medications development. It appears to be time to move beyond the atypical neuroleptics in the treatment of patients who have residual symptoms and cognitive deficits despite optimal treatment with available agents. One direction for medications development would be to focus on treatment mechanisms that seem to link the neuropathology and pathophysiology of schizophrenia to the action of psychotigenic drugs, such as the NMDA receptor antagonists. This review has highlighted two of these pathophysiologic themes: deficient or aberrant functional connectivity and the disinhibition of glutamatergic networks. Both of these features of schizophrenia are produced by NMDA receptor antagonist administration, perhaps accounting for the similarities between the symptoms and cognitive deficits associated with schizophrenia and the effects of ketamine infusion in healthy human subjects. Drugs that directly or indirectly facilitate NMDA receptor function and GRIs may play a role in the treatment of some symptoms and cognitive impairments in some patients. Achieving the maximum benefit from drugs that facilitate glutamate-related neuroplasticity may depend upon combining these agents with psychosocial rehabilitation approaches that enhance the functional engagement of particular cortical networks. However, the development of glutamatergic agents may present new challenges, including the need to maintain glutamatergic function with a functional range while attenuating hyperactivity, addressing glutamatergic deficiencies, or opposing changes in distinct brain regions or pathways. One strategy for addressing neural pathway–specific changes is to develop pathway-specific treatments, such as rTMS. The full range of benefits and limitations of glutamatergic treatments remains to be demonstrated, but the promise of these agents constitutes one of several hopeful new avenues for addressing the distress and disability that still often plagues those individuals suffering from schizophrenia.

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