REVIEWING THE KETAMINE MODEL FOR SCHIZOPHRENIA

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Abstract

The observation that antagonists of the N-methyl-D-aspartate glutamate receptor (NMDAR), such as phencyclidine (PCP) and ketamine, transiently induce symptoms of acute schizophrenia had led to a paradigm shift from dopaminergic to glutamatergic dysfunction in pharmacological models of schizophrenia. The glutamate hypothesis can explain negative and cognitive symptoms of schizophrenia better than the dopamine hypothesis, and has the potential to explain dopamine dysfunction itself. The pharmacological and psychomimetic effects of ketamine, which is safer for human subjects than phencyclidine, are herein reviewed. Ketamine binds to a variety of receptors, but principally acts at the NMDAR, and convergent genetic and molecular evidence point to NMDAR hypofunction in schizophrenia. Furthermore, NMDAR hypofunction can explain connectional and oscillatory abnormalities in schizophrenia in terms of both weakened excitation of inhibitory -aminobutyric acidergic (GABAergic) interneurons that synchronize cortical networks and disinhibition of principal cells. Individuals with prenatal aberrations of NMDAR might experience the onset of schizophrenia towards the completion of synaptic pruning in adolescence, when network connectivity drops below a critical value. We conclude that ketamine challenge is useful for studying the positive, negative, and cognitive symptoms, dopaminergic and GABAergic dysfunction, age of onset, functional dysconnectivity, and abnormal cortical oscillations observed in acute schizophrenia.

Keywords

Ketamine; Glutamate; N-methyl-D-aspartate receptor; Schizophrenia

INTRODUCTION

Schizophrenia is a mental disorder characterized by both positive and negative symptoms, as well as social and occupational dysfunction. The positive symptoms of schizophrenia, such as delusions, hallucinations, disorganized speech, and catatonic behavior, are additions to or disturbances of normal, healthy function. The negative symptoms, such as avolition, alogia, and affective flattening, are deficits in normal, healthy function (American Psychiatric Association, 2000). Schizophrenia has a lifetime prevalence of 0.30–0.66% (McGrath et al., 2008), and patients live 12–15 years shorter than the average lifespan, a gap that is still rising (Saha et al., 2007).

The two neurotransmitter systems most frequently implicated in the pathogenesis of schizophrenia are those of dopamine and glutamate. The relationship between these neurotransmitter systems is complicated, as are efforts to disentangle the responsibility of each in generating the principal categories of schizophrenic symptoms. The observation that dopamine D_2 receptor antagonists such as chlorpromazine alleviate psychosis lead to the dopamine hypothesis of schizophrenia, developed during the 1960s and 70s (Table 1) (Howes and Kapur, 2009). The dopamine hypothesis postulates that hyperdopaminergia is responsible for positive symptoms of schizophrenia (Lau et al., 2013). Later refinements to this theory have added a new caveat: striatal regions suffer from hyperdopaminergia, while prefrontal cortical regions suffer from hypodopaminergia (Lau et al., 2013; Howes and Kapur, 2009). The need for a mechanism explaining this differential subcortical and cortical dopamine dysfunction has been cited as a shortcoming of the dopamine hypothesis (Javitt, 2007); nevertheless, exponents of the dopamine hypothesis have formulated plausible theories to account for this discrepancy (Kapur, 2003; Grace, 1991). A notable example is the tonic/phasic model of dopamine release, in which the prefrontal cortex (PFC) regulates the tonic release of ambient dopamine, which serves to modulate the more familiar phasic, subcortical dopamine system responsive to behaviorally relevant stimuli. Schizophrenic hypofrontality is hypothesized to lessen tonic dopamine release, and phasic dopamine release is in turn increased as a homeostatic compensation mechanism (Grace, 1991).

A more commonly cited weakness of the dopamine hypothesis is the poor efficacy of D_2 receptor antagonists in alleviating the negative and cognitive symptoms of schizophrenia (Javitt et al., 2012; Javitt, 2007). However, other evidence still allows for the relevance of dopamine to these symptoms by showing dopamine D_1 and D_2 receptors to be involved in working memory and psychosis, respectively (Goldman-Rakic et al., 2004: 1). Exponents of this theory draw on such lines of research as radiotracer positron emission tomography (PET) studies correlating changes in D_1 receptor binding potential with cognitive symptoms (Kashima, 1991; Karlsson et al., 2002; Abi-Dargham et al., 2002) and reduced working memory performance in animal models following injection of D_1 receptor antagonists into PFC (Sawaguchi and Goldman-Rakic, 1991).

The glutamate hypothesis of schizophrenia is a newer hypothesis, formulated roughly two decades ago, which implicates glutamergic dysfunction as a mechanism underlying both positive and negative symptoms, as well as cognitive dysfunction, in schizophrenia (Olney and Farber, 1995). The glutamate hypothesis is based on the observation that *N*-methyl-D-

aspartate-type glutamate receptor (NMDAR) antagonists, such as phencyclidine (PCP) and ketamine, transiently induce symptoms and cognitive deficits characteristic of schizophrenia in humans (Thornberg and Saklad, 1996; Stone et al., 2008; Newcomer et al., 1999; Olney et al., 1999; Morris et al., 2005). For instance, single photon emission computed tomography (SPECT) imaging of healthy subjects shows a strong ($r = 0.96$) correlation between negative symptoms and ketamine-induced changes in the binding of an [^{123}I]CNS-1261 radiotracer to NMDAR (Stone et al., 2008). Furthermore, interactions between dopamine D_1 receptors and NMDAR might place dopaminergic dysfunction as a later step in a longer pathway rooted in NMDAR hypofunction (Roberts et al., 2010). The exact level of this interaction is uncertain; however, given the dysfunctional role of cortico-limbocortico-thalamic circuitry in schizophrenia (Tsai and Coyle, 2002) and the importance of dopamine and glutamate to these circuits, a systems level interaction is plausible. Before reviewing evidence supporting NMDAR antagonist models of schizophrenia, with an emphasis on ketamine as the safest human model, principles of glutamatergic neurotransmission, physiology of the NMDAR, and ketamine's pharmacological mechanism of action will be reviewed.

Molecular Physiology and Pharmacology of NMDAR

Glutamate, an amino acid, is the principal excitatory neurotransmitter of the central nervous system (Fain, 1999). In addition to NMDAR, two other classes of ligand-gated ionotropic glutamate receptors have been described: α-amino-3-hyrdoxy-5-methyl-4-isoxazoleproprionic acid receptors (AMPAR) and kainate receptors. The NMDAR is an ionotropic receptor named after *N*-methyl-D-aspartate, a selective agonist of the receptor (Figure 1). The amino acid glycine is a co-agonist required for activation of NMDAR. At most synapses, glutamate is the agonist released from the presynaptic terminal, while ambient, micromolar concentrations of glycine are thought to activate the glycine binding site (Fain, 1999). Other agonists of the glycine binding site include D-serine and D-cycloserine. Activation of the glycine binding site is necessary but not sufficient for channel opening; it is an allosteric modulatory site regulating the time constant and desensitization rate of the channel (Javitt, 2007). Glycine type 1 (GLYT1) transporters and small neutral amino acid transporters (SNATs) are thought to modulate synaptic glycine and D-serine levels (Supplisson and Bergman, 1997; Mackenzie and Erickson, 2004; Nakanishi et al., 2001).

NMDAR antagonists that block the glutamate or glycine binding sites are competitive antagonists, such as 2-amino-7-phosphonoheptanoic acid (AP7) (Fain, 1999). This review, however, concerns itself with the uncompetitive antagonists, as it is these pharmacological agents that reproduce symptoms of schizophrenia. Uncompetitive NMDAR antagonists bind to a PCP binding site within the pore of the ion channel. Such uncompetitive antagonists include, in order of descending affinity, dizocilpine (MK-801), PCP, and ketamine (Fain, 1999; Daniell, 1990).

NMDAR are also sensitive to heavy metal cations, such as Zn^{2+} and Cd^{2+}, and as well as polyamines, protons, and redox agents. Critical to its role in the Hebbian mechanism of long-term potentiation (LTP), the NMDAR is clogged by an Mg^{2+} ion at resting membrane potentials. Sufficient depolarization of the postsynaptic cell removes the Mg^{2+} block, and

Ca^{2+} influx through the NMDAR induces LTP. Thus, the NMDAR is necessary for the induction of LTP, a comprehensive delineation of which is beyond the scope of this review (Fain, 1999).

The biophysical properties of NMDAR are dependent on their subunit composition. NMDAR are heteromeric, composed of an NR1 subunit and modulatory subunits of the NR2 (NR2A-D) family (Fain, 1999). The NR3 (NR3A-B) family of modulatory subunits confers interesting properties on NMDAR: low Ca^{2+} permeability and insensitivity to channel blockers such as Mg^{2+}, MK-801, and competitive antagonists. Furthermore, D-serine, normally an agonist of NMDAR, inhibits channels containing a subunit of the NR3 family (Chatterton et al., 2002).

Uses and Properties of Ketamine

Ketamine (2-chlorphenyl-2-methylamino-cyclohexanone), the uncompetitive NMDAR antagonist on which this review focuses, is a PCP derivative, first synthesized by Calvin Stevens of the Parke-Davis pharmaceutical company in 1962 (Rowland, 2005) and formally described in 1965 (Domino et al., 1965), eight years after the initial synthesis of PCP (Thornberg and Saklad, 1996). Because of PCP's neurotoxicity and emergence reactions, such as hallucinations, confusion, and delirium, ketamine was intended as a safer alternative to PCP (Rowland, 2005). For similar ethical reasons, ketamine is preferred over PCP in pharmacological challenge of human subjects in neuroimaging or neuropsychological studies. Appropriately, we have chosen to focus our review on ketamine to inform researchers working with human subjects. Ketamine is recognized as a dissociative anesthetic (Corssen and Domino, 1966), with additional analgesic, amnesic, and possible fast acting antidepressant properties still under investigation (Aroni et al., 2009; Niesters et al., 2012; Rowland, 2005; Berman et al., 2000). Today, ketamine is used internationally as a general anesthetic in human and veterinary medicine (Rowland, 2005), but typically not used as a primary anesthetic. It is recognized by the World Health Organization as an essential medicine for any basic health care system (Anon, 2011). It is also a Schedule III controlled substance in the United States, due to its psychedelic properties and potential for abuse (Rowland, 2005). The legality of ketamine varies within the European Union, where it is controlled at the country level. It is a class C controlled substance in the United Kingdom, a controlled substance in Italy under Tables I – II, A of the DPR 309/90, and controlled as a *stupéfiant*, or narcotic, in France (Anon, 2008).

While the emergence reactions of ketamine are less severe than those of PCP, adverse reactions have been reported, including hallucinations, blurred vision, delirium, floating sensations, and vivid dreams. Hallucinations are reported at a frequency ranging from 5–30%. Notably, hallucinations are most common in patients over 16 years of age and rarest in children (Reich and Silvay, 1989). Indeed, the most frequent use of ketamine in the United States is for children (Rowland, 2005). These data support the ketamine model of schizophrenia, as the rarity of hallucinations in children younger than 16 years of age is consistent with the age of onset for schizophrenia, which is late-adolescence to early adulthood (Coyle et al., 2012).

Ketamine's two enantiomers, (R)-ketamine and (S)-ketamine, have different pharmacological properties, as well as differential effects on psychiatric symptoms and cerebral metabolism in healthy volunteers (Oye et al., 1992; Vollenweider et al., 1997). (S)-ketamine has a higher affinity for the NMDAR PCP binding site than (R)-ketamine by a factor of 4–5 (Oye et al., 1992). Whereas (R)-ketamine does not significantly alter scores on psychiatric assessments, (S)-ketamine produces symptoms of depersonalization, derealisation, visual disturbances, thought disorders, and apathy (Vollenweider et al., 1997). PET imaging using [^{18}F] fluorodeoxyglucose (FDG) shows (S)-ketamine to increase cerebral metabolic rates of glucose in many brain regions and (R)-ketamine to do generally the opposite. However, neither enantiomer significantly increases or decreases whole brain metabolism (Vollenweider et al., 1997).

Ketamine Pharmacology

Though ketamine is principally an NMDAR ligand, it also has varying affinities for many other receptors (Figure 3; Table 1). Perhaps the most notable of its many confusing and promiscuous affinities is its partial agonism, shared by PCP, for the high-affinity state of the D_2 dopamine receptor, a confound that threatens the foundations of the glutamate hypothesis. According to the work of Kapur and Seeman (2002), ketamine's affinity for D_2 receptors ($K_i = 0.5 \pm 0.2$ μM) is equal to its affinity for NMDAR. However, lack of replication elsewhere has rendered this finding contentious. Also of potential interest is ketamine's weaker affinity for serotonin 5-HT$_{2A}$ receptors ($K_i = 15 \pm 5$ μM) (Kapur and Seeman, 2002), which are implicated in visual hallucinations induced by serotoninergic agents (Kometer et al., 2013). Taken together, these facts distinguish a ketamine model of schizophrenia from the glutamate hypothesis. In fact, a ketamine model has potential to unify the competing glutamate and dopamine hypotheses into a single, multi-transmitter hypothesis that may also include other transmitter systems, herein reviewed.

Moving beyond the three aforementioned receptors, ketamine is a ligand for many other receptors and shows weak affinity for the sigma receptor ($K_i = 66.0 \pm 10.0$ μM) (Oye et al., 1992; Smith et al., 1987). This fact holds possible relevance for the pathophysiology of schizophrenia (Debonnel, 1993; Hashimoto, 2010; Ishikawa and Hashimoto, 2010). The sigma receptor is a nonopioid receptor found in the endoplasmic reticulum (Hayashi and Su, 2004). The sigma-1 receptor (one of two subtypes), described as a "receptor chaperone," is involved in mitochondrial Ca^{2+} signaling, neuroprotection, neuroplasticity, and neurite outgrowth, thus leading to the hypothesis that it is also necessary for optimal cognition and cerebral metabolism (Hayashi and Su, 2007; Ishikawa and Hashimoto, 2010). It has been demonstrated that sigma receptor ligands can protect dopaminergic cells from the excitotoxic effects of NMDA (but not ionomycin) *in vitro*, suggesting that sigma receptors regulate NMDAR (Shimazu et al., 2000). One postmortem study of schizophrenic brains revealed a reduction of sigma receptors in temporal cortex (Weissman et al., 1991), but a later study, which failed to replicate these findings, instead found an increase in sigma receptors in superior parietal cortex (Shibuya et al., 1992). Supporting the idea that schizophrenia patients suffer from a deficit in sigma receptors, mice that are repeatedly administered PCP show fronto-cortical (Ishima et al., 2009) and hippocampal (Kunitachi et al., 2009) reductions of the sigma-1 receptor.

SKF10047 is a sigma-1 receptor agonist that, like ketamine, induces schizophrenia-like symptoms (Masatomo et al., 2010). Furthermore, the antipsychotic drug haloperidol is known to bind to sigma receptors (Tam and Cook, 1984). These facts invite the question of whether sigma-1 receptor dysfunction, rather than or in addition to NMDAR dysfunction, can explain the effects of ketamine and the symptoms of schizophrenia. This question might be partially resolved with the consideration of two facts. Firstly, SKF10047 is also an NMDAR antagonist with affinity for the PCP binding site (Whittemore et al., 1997). Second, induction of schizophrenic symptoms and sigma-1 receptor activation are accomplished by different ketamine enantiomers (Aroni et al., 2009; Vollenweider et al., 1997; Oye et al., 1992). (S)-ketamine has negligible affinity for the sigma receptor, compared to the mild affinity of (R)-ketamine for sigma receptors (Oye et al., 1992). Clearly, sigma receptors and the PCP binding site of NMDAR share common ligands, and more research is required to ascertain what role, if any, sigma receptors play in the pathophysiology of schizophrenia.

Studies conducted in guinea-pig ileum preparation also show ketamine to be an agonist of the kappa opioid receptor (Hustveit et al., 1995), its affinity for which ($K_i = 85.2 \pm 26.0\ \mu M$) is comparable to that for sigma receptors (Smith et al., 1987). As with the sigma receptor, there is reason to implicate the kappa receptor in the pathophysiology of schizophrenia. Kappa receptor agonists have not only analgesic but also psychomimetic properties (Pfeiffer et al., 1986). Salvinorin A, in particular, is a kappa receptor agonist and the most potent naturally occurring hallucinogen. In contrast to most hallucinogens, salvinorin A does not activate or bind to the 5-HT$_{2A}$ serotonin receptor (Sheffler and Roth, 2003). Although findings have been mixed, many studies report a positive correlation between levels of dynorphins, endogenous kappa receptor ligands, in the cerebrospinal fluid of schizophrenia patients and psychotic symptoms (Tejeda et al., 2012). An abnormal laminar distribution of kappa receptors in the hippocampus has also been reported for schizophrenia patients (Royston et al., 1991). Finally, kappa receptor agonists administered to rats have varied effects on prepulse inhibition, which is reduced in schizophrenia, depending on which agonist is used (Tejeda et al., 2012). Further research is needed to demonstrate both causal relationships between kappa receptor dysfunction and schizophrenia and to measure the psychomimetic similarities between ketamine and kappa receptor agonists such as salvinorin A.

Besides NMDAR, sigma receptors, and kappa opioid receptors, the relevance to schizophrenia of ketamine's interactions with other receptors is largely unknown. In the frog peripheral nervous system, ketamine blocks Na$^+$ currents, but its washout also triggers spontaneous action potentials, implying that it modifies some Na$^+$ channels it an excitable way (Benoit et al., 1986). At doses above what is used for general anesthesia, ketamine blocks human central nervous system Na$^+$ channels (Frenkel and Urban, 1992). Ketamine has an inhibitory effect on Ca^{2+} currents in smooth (Yamakage et al., 1995) and cardiac (Baum and Tecson, 1991) muscle and also blocks both open and closed nicotinic acetylcholine receptors *in vitro* (Scheller et al., 1996). Furthermore, it shows affinity for the muscarinic acetylcholine receptor in guinea-pig ileum preparation (Hustveit et al., 1995; Hirota, 1996; Hirota et al., 2002). Besides the kappa opioid receptor, already discussed,

ketamine is known also to have affinity for the delta and mu opioid receptors (Gupta et al., 2011; Hirota et al., 1999), synergistically enhancing the effects of opioids at the mu receptor (Gupta et al., 2011). Recently, the antidepressant effects of ketamine have been blocked in mice using NBQX, an AMPAR antagonist, suggesting that ketamine interacts with the AMPAR, though this interaction may or may not be direct. For instance, these data could be explained by the possibility that ketamine merely changes the relative throughputs of AMPAR and NMDAR. (Maeng et al., 2008).

Evidence for NMDAR Dysfunction

Although determining what proportion of ketamine's analgesic and psychomimetic effects can be attributed to which receptors is arguably still a challenge for the ketamine model of schizophrenia, much evidence points to NMDAR dysfunction in schizophrenia. Having explored ketamine's varied effects at other receptors, it is important to note that ketamine's effects at NMDAR are complex and somewhat counterintuitive. While an NMDAR antagonist, evidence from magnetic resonance spectroscopy (MRS) and microdialysis has demonstrated that ketamine and other uncompetitive NMDAR antagonists have a net positive effect on excitatory transmission by inducing excessive release of glutamate (Rowland et al., 2005; Stone et al., 2012; Kim et al., 2011) and acetylcholine (Hasegawa et al., 1993; Giovannini et al., 1994). In ketamine challenge of humans subjects, pretreatment with the anticonvulsant lamotrigine, a Na^+ channel blocker that reduces glutamate release, attenuates both many subjective effects and blood oxygen-level-dependent (BOLD) signal responses induced by ketamine (Deakin et al., 2008). Olney and colleagues (1999) have proposed that chronic over-release of excitatory neurotransmitters can explain both cognitive and behavioral symptoms of schizophrenia, as well as morphological changes and neurodegeneration in patients' brains. Indeed, ketamine-induced release of glutamate in anterior cingulated cortex (ACC) is correlated with positive psychotic symptom scores in healthy human subjects ($r = 0.72$) (Stone et al., 2012). Furthermore, NMDAR antagonists play known roles in neurodegenration and excitotoxicity, including apoptosis of mature corticolimbic pyramidal cells (Zhou et al., 2007; Farber and Olney, 2003; Horváth et al., 1997; Wozniak et al., 1998), thus offering NMDAR hypofunction as a possible basis for brain atrophy observed in schizophrenia (Rais et al., 2012; Andreone, et al., 2007; Rais et al., 2008; Goldman et al., 2007; Ferrari et al., 2006).

Much molecular evidence points to NDMAR dysfunction in schizophrenia. Schizophrenic brains have reduced levels of a protein linked to NMDAR function and working memory (Karlsgodt et al., 2011), dystrobrevin-binding-protein-1 (dysbindin) (Talbot et al., 2004), and dysbindin mRNA (Weickert et al., 2004), in hippocampal formation and dorsolateral prefrontal cortex (DLPFC), respectively. Polymorphisms of DTNBP1 (Voisey et al., 2010), the gene encoding dysbindin, and GRIN2B (Li and He, 2007a), the gene encoding the NR2B subunit of NMDAR, have been associated with schizophrenia. The growth factor Neuregulin-1 (NRG1), its receptor, erbB4, and the scaffold protein known as postsynaptic density protein of 95 kDa (PSD-95) further suggest a link between NMDAR and schizophrenia. NRG1 inhibits prefrontal cortical NMDAR in humans, and schizophrenics have increased interactions between erbB4 and PSD-95 (Hahn et al., 2006).

Further molecular evidence for NMDAR dysfunction in schizophrenia comes from genes regulating the NMDAR co-agonist D-serine. D-amino acid oxidase (DAAO) is an enzyme that degrades D-serine by oxidation. Several single nucleotide polymorphisms (SNPs) in DAAO have been linked to schizophrenia (Chumakov et al., 2002). Additionally, G72 (also known as D-amino acid oxidase activator: DAOA) and G30, overlapping genes that interact with DAAO, have SNPs associated with schizophrenia (Li and He, 2007b: 30; Shinkai et al., 2007). Consistent with these associations, an early clinical trial of D-serine supplementation of antipsychotic regimens for schizophrenia treatment reported the following mean reductions of symptoms six weeks after baseline: Positive and Negative Syndrome Scale (PANSS) positive, 17.4%, $p = 0.004$; Scale for the Assessment of Negative Symptoms (SANS), 20.6%, $p = 0.0004$; PANSS cognitive, 11.6%, $p = 0.004$; Clinical Global Impression Scale (CGI), 45.8%, $p = 0.004$ (Tsai et al., 1998). Supporting these findings, meta-analyses (Singh and Singh, 2011; Tsai and Lin, 2010) have found that supplementing antipsychotic medication with D-serine alleviates the negative ($p = 0.02$; pooled effect size (ES) = 0.48), cognitive ($p = 0.007$; ES = 0.42), and total ($p = 0.02$; ES = 0.4) symptoms of schizophrenia (Tsai and Lin, 2010).

If the above genetic evidence is to be seen as inconclusive, more direct lines of evidence from *in situ* hybridization histochemistry (ISHH) and SPECT have directly established the presence of NMDAR hypofunction in schizophrenia patients (Law and Deakin, 2001; Pilowsky et al., 2006). A SPECT imaging study using [^{123}I]CNS-1261 as an intrachannel NMDAR radiotracer found reduced binding in the left hippocampus of medication-free schizophrenia patients, the first *in vivo* evidence of NMDAR hypofunction in schizophrenia (Pilowsky et al., 2006). An earlier ISHH study of postmortem brain tissue from psychiatric patients found significant reductions in all psychiatric groups (schizophrenic, depressive, and bipolar) for GRIN1 mRNA encoding the NR1 subunit of NMDAR in the dentate gyrus. Unique to the schizophrenia cohort was the left-lateralization of this finding (Law and Deakin, 2001). While the similar findings in affective disorder cohorts initially seem to undermine the importance of NMADR hypofunction to schizophrenia, a recent, large genome-wide meta-analysis has found associations between SNPs at the same four loci and five different psychiatric disorders, including the three disorders examined in the aforementioned postmortem study (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). This suggests a larger trend in which seemingly disparate psychiatric disorders share similar molecular dysfunctions.

Taken together, the above evidence not only supports NMDAR as the principal site of ketamine's psychomimetic effects, but also favors the ketamine model of schizophrenia over competing models. Both adrenochrome (an autoxidative metabolite of epinephrine) (Smythies, 2002) and Δ-9-tetrahydrocannabinol (Δ-9-THC) (D'Souza et al., 2004), the main active ingredient in cannabis, can also induce schizophrenia-like symptoms, but neither of these models have accumulated as much evidence as the ketamine model. It remains possible, however, that these and other hypotheses of schizophrenia are compatible with and/or auxiliary to the ketamine model and the glutamate hypothesis. For instance, dreaming has been proposed as a novel model of schizophrenia due to similarities in psychological state, cortical connectivity, sensory gating, hypofrontality, and neuromodulation

(Gottesmann, 2006), but it and the glutamate hypothesis are not necessarily mutually exclusive, as there is decreased release of glutamate in the nucleus accumbens during REM sleep (Lena et al., 2006).

Neurotransmitter Effects and Impact on Cognition

Of course, the main competitor to the glutamate hypothesis is the dopamine hypothesis, already introduced earlier in this review. As previously noted, ketamine models of schizophrenia are distinct from the glutamate hypothesis due to ketamine's affinity for many non-glutamate receptors and its effect of increasing glutamate release. Nonetheless, it will be useful to herein compare the dopamine and glutamate hypotheses and delineate possible advantages of glutamatergic theories. Some formulations of the glutamate hypothesis postulate that the glutamatergic system exerts influence over the dopaminergic system, while other formulations postulate that D_2 receptors regulate glutamate release at NMDAR synapses (Figure 3) (Kehrer et al., 2008; Olney et al., 1999). Pharmacological evidence suggests that NMDAR dysfunction underlies dopaminergic dysfunction in schizophrenia. PET has shown the severity of ketamine induced positive symptoms to be correlated with dopamine release in lateral prefrontal and anterior cingulate cortex (Aalto et al., 2005). Rats treated both chronically and subchronically with PCP at blood levels comparable to PCP psychosis in humans (mean concentrations of 69.3 ng/ml and 85.4 ng/ml for chronic and subchronic, respectively) show potentiation of amphetamine-induced prefrontal cortical and striatal dopamine release (Javitt et al., 2004). This enhanced sensitivity to the dopaminergic effects of amphetamine challenge is also characteristic of schizophrenia patients, as revealed by PET and SPECT imaging (Laruelle et al., 1996; Breier et al., 1997). These PCP-induced effects in rats are treatable with both glycine and NFPS, a glycine transport antagonist (Javitt et al., 2004). Similarly, MK-801 administered to rats increases dopaminergic (as well as serotonergic) activity in frontal cortex, nucleus accumbens, and striatum (Löscher et al., 1991).

Furthermore, NMDAR dysfunction easily accounts for many cognitive symptoms of schizophrenia, in part because NMDAR are ubiquitous in the cortex, whereas implicated dopamine receptors are more localized. Because NMDAR are necessary for LTP, their dysfunction offers a more straightforward explanation for learning and memory deficits in schizophrenia patients than dopaminergic models. The established role of NMDAR in mismatch negativity (MMN) generation can also predict and explain schizophrenia patients' reduced MMN auditory event-related potentials (ERP) in auditory oddball paradigms, where an odd auditory stimulus is included in a series of repetitive tones (Javitt et al., 2012). In fact, MMN amplitude predicts the susceptibility of healthy volunteers to the effects of ketamine (but not the hallucinogen psilocybin) (Umbricht et al., 2002). Ketamine has been shown to reduce MMN generation in a visual oddball paradigm, and concurrent functional magnetic resonance imaging (fMRI) data show this reduction to be associated with reduced activation in sensory cortex (Musso et al., 2011), further suggesting that attentional deficits in schizophrenia are actually sensory in nature. This is hardly a trivial finding: by shifting the focus of pathology posteriorly from frontal circuits to sensory cortex, one exits the neurochemical "jurisdiction" of dopamine (Nieoullon, 2002), placing greater responsibility on glutamatergic transmission.

Returning anteriorly to frontal circuits, chronic PCP exposure induces hypofrontality in rats (Cochran et al., 2003). Pharmacological fMRI studies have also demonstrated that ketamine reduces ventromedial frontal activation, elucidating the neurochemical mechanism of this deactivation in the process (Deakin et al., 2008). Hypofrontality is a symptom of schizophrenia whose underlying cause is often assumed to be dopamine dysfunction (Liemburg et al., 2012; Coppa-Hopman et al., 2009; Nagai et al., 2010; Nieoullon, 2002); however, administration of lamotrigine prior to ketamine challenge in humans has shown that increased glutamate release, induced by katamine, explains observed frontal deactivation (Deakin et al., 2008). That changes in glutamate release so strongly affect data from functional imaging is perhaps unsurprising considering that cerebral metabolism and the BOLD signal are believed to strongly reflect glutamate cycling through astrocytes at excitatory synapses (Raichle and Mintun, 2006).

Finally, prefrontal hypodopaminergia models predict that during task-switching paradigms, schizophrenia patients should have increased switch cost (poorer performance immediately following switching) (Javitt et al., 2012). Yet instead, schizophrenia patients have switch costs equal to controls. Their performance is similar to that of monkeys administered ketamine: worse performance for incongruent stimuli than congruent stimuli (Wylie et al., 2010). Thus, some cognitive tasks that are independent of NMDAR might be unaffected in schizophrenia (Javitt et al., 2012).

Disruptions to Connectivity

The glutamate hypothesis is also an attractive model because it offers an explanation for schizophrenia's age of onset in early adulthood (Kehrer et al., 2008). Explanations for this age of onset dating as far back as 30 years ago point to synaptic pruning, the programmed elimination of a large fraction of synaptic connections, that takes place in late adolescence, suggesting that schizophrenia may, in fact, be an over-pruning syndrome (Feinberg, 1982; Granger, 1996). On the basis of recent knowledge about NMDAR dysfunction in schizophrenia, this synaptic pruning need not necessarily be excessive or aberrant to trigger pathology. Rather, NMDAR dysfunction is perhaps a weakness that manifests itself during prenatal development, and the completion of synaptic pruning late in adolescence is the proverbial straw that, so to speak, breaks the camel's back (Granger, 1996; Kehrer et al., 2008; Olney and Farber, 1997). This idea is supported by the fact that ketamine induced hallucinations are most common in persons older than 16 years of age (Reich and Silvay, 1989).

Recently, the roles of brain rhythms and neural synchrony in neurodevelopment and schizophrenia have also been examined. The dynamics of neural systems such as cortical networks are nonlinear (Breakspear, 2006). While a comprehensive summary of nonlinear systems theory is beyond the scope of this review, per se, some fundamental terms will be defined herein. Nonlinear systems are often multistable, meaning that several stable, steady states are possible (e.g., regular oscillations, quiescence, chaotic behavior, etc.). Control parameters are those which induce transitions between stable, steady states in dynamical systems when tuned past critical values. Such transitions are referred to as phase transitions or bifurcations (Stam, 2005). Viewing cortical networks in a nonlinear dynamics context, it

has been suggested that the maturation of such networks during adolescent development occurs by a phase transition, and that a failure of networks to synchronize and integrate information signifies that a pathological phase transition has occurred (Uhlhaas and Singer, 2011). Could it be that glutamatergic connectivity is a control parameter for such a bifurcation? In support of this hypothesis, pruning connections in neural network models increases the dimensional complexity of simulated electroencephalogram (EEG) and simulates hallucinations in speech perception networks (Friston, 1996; Hoffman and McGlashan, 1997).

The idea of disturbed network connectivity in schizophrenia meshes well with characterizations of schizophrenia as a disconnection syndrome (Sporns, 2011), a very old hypothesis dating back to Wernicke (1906), who attributed psychosis to disruptions of association fibers, and Bleuler (1908), who chose the word schizophrenia to describe the splitting of the mind in the disorder. Almost 80 years later, Weinberger (1987) hypothesized that schizophrenic symptoms occur due to a lesion or developmental defect disconnecting a mesocortical-corticofugal feedback loop regulating dopamine activity. The same year, a PET study of schizophrenia patients reported fewer functional interactions between brain regions than controls, including reduced correlations between activation of anterior and posterior regions and between thalamic and cortical regions (Volkow et al., 1988). Global reductions in functional connectivity (i.e., temporal cross correlations) between brain regions have since been found using other modalities, such as fMRI and EEG (Calhoun et al., 2009). Graph theoretical measures of both functional and anatomical brain networks in schizophrenia patients have revealed inefficient connectivity in these networks. Anatomical networks in patients are more sparsely connected when analyzed both in terms of axonal connectivity and cortical thickness (an indirect measure of the former) (Zalesky et al., 2011; Bassett et al., 2008; Wang et al., 2011). Resting-state functional networks in patients show reduced connection density ("clustering"), fewer "hub" regions with very high interconnectivity, and reduced efficiency ("small-worldness") of connections (Lynall et al., 2010).

Such weakened global connectivity in schizophrenia is consistent with the ubiquity of presumably dysfunctional NMDAR in cortex and the coincidence of synaptic pruning with the disease's onset. However, the story is not so simple: the default mode network (DMN), a set of brain regions deactivated by cognitive tasks and forming a functional module in resting state functional networks observed with fMRI (Sporns, 2012), has increased connectivity in schizophrenia patients. What's more, the extent of strengthened connectivity within the DMN is correlated with the severity of psychiatric symptoms (Whitfield-Gabrieli et al., 2009). Similarly, data from simultaneous EEG and transcranial magnetic stimulation (TMS) have shown that TMS-evoked waves of excitation propagate longer and farther in schizophrenia patients than controls (Frantseva et al., 2012).

While these findings initially seem to contradict both the disconnection hypothesis and current models of the role NMDAR play in schizophrenic pathology, this contradiction is largely resolved upon further examination of the function of NMDAR in cortical microcircuits. NMDAR drive the excitation of inhibitory γ-aminobutyric acidergic (GABAergic) interneurons, particularly parvalbumin-positive fast-spiking interneurons,

which in turn both inhibit pyramidal cells and synchronize their oscillations (Homayoun and Moghaddam, 2007; Korotkova et al., 2010; Behrens et al., 2007). Indeed, both mice and cultured interneurons challenged with ketamine exhibit a loss of GABA markers such as the Ca^{2+} binding protein parvalbumin and the enzyme glutamic acid decarboxylase of 67 kDa (GAD67), which produces GABA from glutamate by decarboxylation (Behrens et al., 2007; Kinney et al., 2006). Similar finding have been reported in rat PFC *in vivo* after PCP challenge (Cochran et al., 2003; Amitai et al., 2012). Other such *in vivo* microdialysis studies of rats have also shown that both PCP and MK-801 increase extracellular GABA levels in medial PFC. Conversely, the GABA$_A$ receptor agonist muscimol alleviates PCP and MK-801 induced increases in extracellular dopamine in the medial PFC (Yonezawa et al., 1998). Another GABA$_A$ receptor agonist, TPA023, blocks ketamine induced working memory deficits in rhesus monkeys (Table 1) (Castner et al., 2010). Postmortem studies of PFC tissue from schizophrenic patients reinforce the above findings by revealing reduced numbers of GABAergic interneurons expressing GAD67 (Volk et al., 2000; Hashimoto et al., 2003), parvalbumin (Hashimoto et al., 2003), and GABA transporter-1 (GAT-1) mRNA (Volk et al., 2001). PFC chandelier cells, GABAergic neurons that regulate pyramidal cell output, have lower axon cartridge (terminal array) density in schizophrenia patients (Pierri et al., 1999).

In light of these facts, NMDAR hypofunction appears to disinhibit some cortical networks by inhibiting (Homayoun and Moghaddam, 2007) and inducing long term adaptations (Cochran et al., 2003; Amitai et al., 2012) in GABAergic interneurons (Figure 3). Appropriately, the more neutral term "dysconnectivity" is now applied to both pathological increases and decreases in network connectivity in schizophrenia (Pettersson-Yeo et al., 2011). As expected, ketamine challenge in both animals and humans alters functional connectivity in ways that mirror dysconnectivity in schizophrenia. Extracellular recordings in low Mg^{2+} mouse neocortical slices challenged with ketamine show decoupling beginning at a spatial scale of 4 mm, a significant finding in 42% of slices (Voss et al., 2012). Autoradiographic imaging, also conducted in mice, using a subanaesthetic dose of ketamine combined with a ^{14}C-2-deoxyglucose tracer, reveals both increases and decreases in the functional connectivity of a neural circuit composed of the dorsal reticular thalamic nucleus, anteroventral/mediodorsal thalamic nuclei, and PFC (Dawson et al., 2013). Using the same radiotracer, similar findings, including dysconnectivity between PFC and hippocampus, have been found in rats treated subchronically with PCP (Dawson et al., 2012). These are especially noteworthy findings given that several lines of evidence converge to implicate the thalamic reticular nucleus in the pathology of schizophrenia (Ferrarelli and Tononi, 2011). In human resting-state fMRI, ketamine challenge increases global-based connectivity (GBC), i.e., functional correlations of each voxel with every other voxel. In particular, the increased GBC of six clusters are associated with positive symptoms, whereas constant or decreased GBC in the dorsal and medial striatum and thalamus is associated with negative symptoms (Driesen et al., 2013). Ketamine also weakens the anticorrelated relationship between a task-positive network and the DMN during a working memory task (Anticevic et al., 2012), mirroring the reduced DMN suppression during working memory tasks observed in schizophrenia patients and their first-degree relatives (Whitfield-Gabrieli et al., 2009). Other ketamine induced resting state network changes include reduced connectivity between

both the DMN and the affective network with the dorsal medial PFC (Scheidegger et al., 2012), reduced connectivity between the auditory and somatosensory network and pain processing areas, and increased connectivity between both cerebellum and visual cortex with the medial visual network (Niesters et al., 2012).

Cortical Oscillations

Although fMRI is limited by slow temporal resolution, the faster temporal resolution of EEG has revealed abnormal oscillatory activity in schizophrenia, particularly in the gamma band (30–80 Hz) (Uhlhaas, 2013; Uhlhaas and Singer, 2011; Kehrer et al., 2008; Roopun et al., 2008). The gamma rhythm is principally generated by fast-spiking GABAergic interneurons (Table 1) (Hájos et al., 2004; Gloveli et al., 2005), whose output induces $GABA_A$ receptor mediated inhibitory postsynaptic potentials (IPSPs) in principal cells (Roopun et al., 2008). Interneurons are excited in unison, either by afferent fibers or reciprocal connections from principal cells (Metherate and Cruikshank, 1999; Traub et al., 1996; Roopun et al., 2008); the interneurons, in turn, have reciprocal inhibitory connections with one another, limiting their firing to a synchronous pattern (Roopun et al., 2008). Gamma rhythms are associated with short-term memory (Tallon-Baudry et al., 1998), working memory (Haenschel et al., 2009), selective attention (Tiitinen et al., 1993), primary sensory representation (Singer and Gray, 1995), cognitive control (Cho et al., 2006), social cognition (Williams et al., 2009), and integrative processing (Herrmann and Demiralp, 2005). Many reductions in the gamma rhythm have been reported in schizophrenia patients. As with the abnormalities of functional networks observed with fMRI, the nature of gamma band abnormalities is complicated; while gamma oscillations in schizophrenia are often reduced, increases have also been observed (Bucci et al., 2007). Like resting-state GBC, decreases are often associated with negative symptoms and increases are often associated with positive symptoms (Figure 3) (Kehrer et al., 2008; Bucci et al., 2007; Baldeweg et al., 1998; Spencer et al., 2008: 2). Visual-evoked gamma band oscillations have lower frequency in schizophrenia patients (Spencer et al., 2004), as well as reduced phase locking (Spencer et al., 2008), decreased interhemispheric phase coherence (in contradistinction to the increased anterior-posterior phase coherence seen in healthy controls), and increased latency to coherence changes (Spencer et al., 2003). All of these abnormalities suggest a mechanism by which visual information is not integrated both within visual cortex and across cortical networks. Schizophrenia patients have difficulty with visual perception tasks such as contour integration (Keane et al., 2012), suggesting faulty binding of visual information within visual cortex or even later in the dorsal visual stream, which may depend on gamma coherence. Furthermore, schizophrenia patients' deficits in top-down visual processing (Dima et al., 2011: 300) could be explained by poor gamma coherence (and thus functional integration) between posterior, visual and anterior, cognitive networks.

Schizophrenia patients' auditory steady-state responses (ASSR) are reduced in both phase locking and evoked power, and phase locking of the 40-Hz harmonic of the 20-Hz ASSR is positively correlated with positive symptoms (Spencer et al., 2008). Based on these data, it is reasonable to suspect aberrant, gamma-mediated neural computations in faulty auditory processing in schizophrenia, including auditory hallucinations. Similarly, cognitive control induced modulation of prefrontal gamma band activity, correlated with cognitive control

demand and task performance in healthy controls, is not observed in schizophrenia patients (Cho et al., 2006). N-back tests of working memory induce excessive frontal gamma band activity in schizophrenia patients, whose performance is worse than that of healthy controls (Barr et al., 2010; Barr et al., 2011). One might draw a crude analogy between the schizophrenic PFC and an overworked engine: frontal networks in schizophrenia appear inflexible and inefficient, thus serving as weaker substrates for working memory. Facial emotion processing in schizophrenia patients reduces gamma synchrony relative to pre-stimulus baseline, yet patients have higher absolute gamma synchrony relative to controls (Williams et al., 2009). Here again, schizophrenia patients' cortical circuits generate gamma synchrony, perhaps even excessively, but cannot appropriately modulate it. In a sense, the "inappropriateness" of gamma modulation is reminiscent of the inappropriate affect central to schizophrenia's negative symptoms: both seem to reflect misplaced salience of stimuli, a disconnection with the external world, and an inefficient use of resources. If cognitive symptoms are driven by inappropriate gamma modulation, could it be that the negative and cognitive symptoms of schizophrenia are unified on a more abstract level? Abnormally low dopaminergic input to the PFC might deprive both emotional and task-related stimuli of their appropriate salience, unifying these symptoms on a causal level, as well. While this isomorphism between symptoms offers welcome simplicity, the assumption that gamma rhythmogenesis per se is unimpaired in schizophrenia is challenged by evidence from TMS studies that seek to elucidate effective cortical relationships. Schizophrenia patients have reduced gamma oscillations elicited by TMS over right premotor cortex in the resting state (Ferrarelli et al., 2008) and by 20-Hz repetitive TMS (rTMS) over DLPFC during an N-back working memory task (Barr et al., 2011). Moreover, rTMS of DLPFC suppresses frontal gamma oscillations in schizophrenia patients in as little as one session (Barr et al., 2011; Farzan et al., 2012). This ultimately suggests that inappropriate gamma modulation is a problem rooted not in prefrontal hypodopaminergia, but rather in faulty gamma rhythmogenesis, which is in turn rooted in abnormal glutamatergic and GABAergic transmission at NMDAR and GABA$_A$ receptors, respectively. Cortical networks in schizophrenia appear rigid and inflexible, as judged from their gamma band activity. By contrast, complex physiological systems often operate on the "edge of chaos," meaning their control parameters are posed near critical values, allowing the system to quickly and flexibly transitions between many possible states (Fraiman et al., 2009; Tagliazucchi et al., 2012; Haimovici, et al., 2013; Sporns, 2011). In fact, the very complexity that lends the system necessary flexibility is due to a healthy degree of nonlinear chaos. Note that chaos in this context is defined as extreme sensitivity to initial conditions, a state in which effects are disproportional to their causes (Rickles 2007; Coffey, 1998; Breakspear, 2006). This is distinct from popular notions of chaos as randomness or genuine disorder. Loss of complexity (i.e., a transition to lower dimensional dynamics) in physiology is often pathological (Otero-Siliceo and Arriada-Mendicoa, 2003; Rickles, 2007; Manor and Lipsitz, 2013). For instance, a heartbeat that is too regular is linked to cardiac pathologies such as congestive heart failure (Poon and Merrill, 1997; Norris et al., 2008; Ho et al., 2011). By the same token, an epileptic seizure manifests itself as an interictal-ictal phase transition in which EEG dynamics shift from complex to highly regular (Stam, 2005; Rickles et al., 2007). Along these same lines, schizophrenic pathology might be due in part to reduced complexity and flexibility of gamma oscillations. Future studies should analyze

schizophrenia patients' EEG oscillations in the context of nonlinear dynamics and complexity science.

The gamma band is not the only frequency band with abnormal oscillatory activity in schizophrenia. Various abnormalities have been detected in the high beta (20–29 Hz), alpha, theta, and delta bands in schizophrenia patients (Uhlhaas and Singer, 2011; Roopun et al., 2008: 2; Uhlhaas, 2013; Uhlhaas and Singer, 2012). As we have chosen to focus this section on gamma oscillations, a detailed delineation of findings in lower frequency bands is not appropriate here. However, it is important to note that, as with the gamma band, schizophrenia patients' oscillations in lower frequencies bands include both abnormal increases and decreases in power during both induced and resting oscillations (Uhlhaas and Singer, 2011). All of these brain rhythms undergo maturation in healthy humans during ages at which the onset of schizophrenia often occurs, implying that schizophrenia is a neurodevelopmental disorder involving inappropriate neural synchrony (Uhlhaas and Singer, 2011). Drawing on correlations between conscious awareness and increased coherence between distributed brain regions, Tononi and Edelman (2000) have suggested that schizophrenia is a disease of faulty reentrant interactions, defined as reciprocal signals between functionally segregated brain areas that allow for functional integration (Edelman and Tononi, 2000).

Like the above hypotheses, any theory drawn from these findings must attempt to make sense of varied and sometimes even contradictory data. Naturally, one might hope for insight from a ketamine model. At it turns out, the effects of ketamine on cortical rhythms are just as varied and context dependent as cortical rhythms observed in schizophrenia. Subanesthetic doses of ketamine and MK-801 both increase gamma power in rat neocortex (Pinault, 2008) and hippocampus (Ma and Leung, 2007) *in vivo*, yet contradictory, null results are reported for ketamine's effect on hippocampal gamma power *in vitro* (Cunningham et al., 2006; Dickinson et al., 2003), suggesting gamma rhythms there are generated from a distant origin. By contrast, ketamine attenuates gamma rhythmogenesis in rat medial entorhinal cortex *in vitro* (Cunningham et al., 2006; Roopun et al., 2008). If hippocampal gamma rhythms are, in fact, generated locally, than an alternate explanation for the varied effects of ketamine on gamma rhythmogenesis is that NMDAR mediated excitation modulates gamma power differentially across cortical layers and regions. Might these differential effects also explain context dependent increases and reductions of gamma activity in schizophrenia? Curiously, ketamine administered to patients for general anesthesia prior to surgery increases the amplitude of the 40-Hz ASSR (Plourde et al., 1997), whereas in schizophrenia patients, the amplitude of 40-Hz ASSR is instead reduced (Hamm et al., 2011; Uhlhaas and Singer, 2011). Should this finding call into question the validity of the ketamine model or merely the appropriateness of using anesthetic doses of ketamine to model schizophrenic symptoms? A more recent study administering subanaesthetic doses of ketamine to healthy subjects shows that ketamine increases gamma oscillations and reduces delta oscillations in response to auditory clicks (Hong et al., 2010). Similarly, cortical slices bathed in kainate and challenged with ketamine show increases in gamma power in primary auditory cortex (Roopun et al., 2008). In rat visual cortex, both ketamine and PCP induce phase coupling of gamma oscillations across cortical layers and

decelerate high-frequency gamma oscillations, providing a possible physiological basis for psychotic visual hallucinations (Anver et al., 2011). NMDAR antagonists that are nonspecific or specific to the NR2A subunit increase gamma power in rat cortex, whereas antagonists specific to other NMDAR subunits have weak effects (Kocsis, 2012). This finding implies that the NR2A subunit may have special significance to the etiology of NMDAR hypofunction and schizophrenia.

Because changes in gamma power are largely context dependent in schizophrenia, it is difficult to assess the fidelity with which ketamine replicates these changes in healthy subjects. Although the auditory response of gamma oscillations under ketamine challenge is opposite that usually observed in schizophrenia patients (Plourde et al., 1997; Hong et al., 2010), the general theta-to-gamma shift observed in schizophrenia is replicated using ketamine (Ehrlichman et al., 2009). Ketamine also increases the power of 20–29 Hz oscillations in the beta band in association cortex and PFC, a finding likely compatible with increased frontal and parietal resting beta oscillations in schizophrenia patients with auditory hallucinations (Roopun et al., 2008; Mulert et al., 2011; Lee et al., 2006).

Alterations of Brain Signaling Dynamics

Having considered many lines of research, it is appropriate to take a step back and view the problem from a larger perspective. Abnormalities of cortical oscillations in schizophrenia and other psychiatric illnesses are generally attributable to alterations of a parameter that transcends the ketamine model, the balance of excitation and inhibition (E/I-balance) (Uhlhaas, 2013; Uhlhaas and Singer, 2012; Kehrer et al., 2008; Anticevic et al., 2012). This parameter reflects interactions between two transmitter systems involved in NMDAR hypofunction: the glutamatergic and GABAergic systems. Neural synchrony subtly depends on E/I balance (Uhlhaas and Singer, 2012), and maturations of E/I balance during adolescence offers insight into schizophrenia's age of onset and support for the neurodevelopmental hypothesis of schizophrenia (Uhlhaas and Singer, 2011; Uhlhaas, 2013). Moreover, E/I-balance is an important parameter for understanding emergent properties of cortical networks in light of Turing instability, the principle by which self-organized spatial patterns can emerge from a system with homogenously distributed sources of activation and inhibition (Turing, 1952). By reducing the conductance of excitatory cells onto inhibitory cells (as would happen after ketamine challenge) in a biophysical model of working memory, a simulated BOLD signal results that matches that of empirical data (Anticevic et al., 2012). It has been postulated that schizophrenia itself is a dynamical diseases resulting from the tuning of a control parameter past a critical value (an der Heiden, 2006; Breakspear, 2006; Friston, 1996), and indeed, schizophrenia patients show nonlinearity in their EEG time series (Carlino et al., 2012; Lee et al., 2001). Future dynamical models of schizophrenia might attempt explain the onset of symptoms using E/I-balance as a control parameter.

Conclusions, Limitations, and Future Directions

The ketamine model of acute schizophrenia is useful for explaining the positive and negative symptoms, cognitive deficits, dopaminergic dysfunction, GABAergic dysfunction, age of

onset, functional dysconnectivity, and abnormal cortical oscillations observed in schizophrenia in terms of NMDAR hypofunction and interactions with D_2, opioid, and other receptors (Figure 3). Although the ketamine model has strong explanatory and epistemic value, it is not without its weaknesses. Perhaps due in part to ketamine's promiscuity, some discrepancy exists between ketamine intoxication and schizophrenic symptoms. Because visual disturbances—induced by ketamine—are rare in established (chronic) schizophrenia and hallucinatory voices—common in established schizophrenia—are rarely induced by ketamine, the hallucinatory pattern of ketamine better matches that of acute schizophrenia, in which hallucinatory symptoms are still developing, than chronic schizophrenia (Javitt, 2007). As mentioned earlier, ASSR under ketamine challenge do not match those of schizophrenia patients, and *in vitro* ketamine challenge induces spatially differential modulations of gamma power that are difficult to interpret. Moreover, methodological problems exist with interpretations of phase synchronization in sensor space; future studies should aim to analyze phase synchronization in source space using source reconstruction (Uhlhaas, 2013). Beyond these smaller issues, there is still a need to integrate the ketamine model with other compatible pharmacological models of schizophrenia. For instance, -9-THC induces positive and negative symptoms of schizophrenia (D'Souza et al., 2004), transiently disturbs glutamate and GABA release in adolescence, and cannabis use increases the risk of developing schizophrenia (Table 1) (Bossong and Niesink, 2010). How can these findings be unified with the ketamine model? Future studies should look at different pharmacological manipulations within the same group of subjects. Relatively few studies have challenged the same subjects with both ketamine and, for instance, amphetamine to simultaneously test the glutamate and dopamine hypotheses (Javitt, 2007). More comparisons between ketamine and salvinorin A, another dissociative with similar properties, are also greatly needed. Finally, although some authors have already framed schizophrenia in the context of nonlinear dynamics by suggesting that phase transitions might be important for understanding its pathogenesis (an der Heiden, 2006; Uhlhaas and Singer, 2011; Breakspear, 2006; Friston, 1996), few studies have actually examined schizophrenia in a nonlinear systems context. Future investigations should look for nonlinearity and evidence of bifurcations after ketamine infusion in the EEG of healthy volunteers.

Acknowledgments

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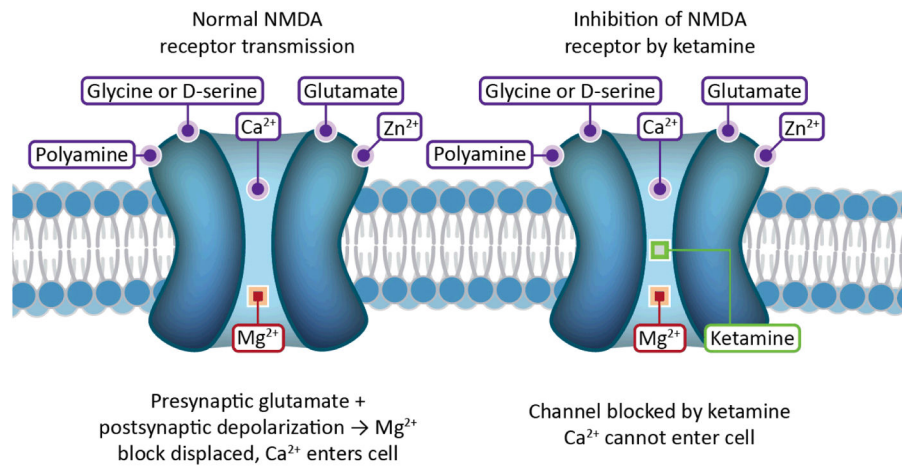
Figure 1. Pharmacology of NMDAR

The NMDAR is an ionotropic glutamate receptor and nonselective cation channel with many ligands. Ketamine is one of several uncompetitive antagonists that block the channel at a PCP binding site within the pore. Glycine/D-serine and glutamate are coagonists that bind to the extracellular domain of the receptor. Both are necessary for channel opening; however, the NMDAR is rarely considered a glycine receptor because it is glutamate that is released from the presynaptic terminal, with micromolar background levels of glycine sufficing for channel activation. Polyamines, which modulate the effects of other ligands, and heavy metal cations, which can block or potentiate the channel, also have distinct binding sites. Mg^{2+} is a voltage dependent channel blocker that mediates the Hebbian mechanism of LTP.
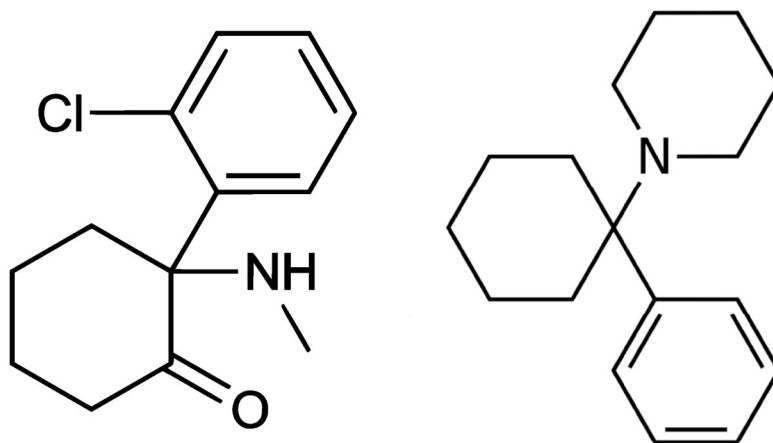
Figure 2. Chemical Structures of (S)-ketamine and Phencyclidine
(S)-ketamine, left, is the more potent of ketamine's two enantiomers. It is known as 2-chlorphenyl-2-methylamino-cyclohexanone by International Union of Pure and Applied Chemists (IUPAC) nomenclature. Phencyclidine (PCP, right) and ketamine share a binding site within the pore of the NMDAR and induce similar effects. Both chemicals are dissociative anesthetics and share structural similarities such as aromaticity.
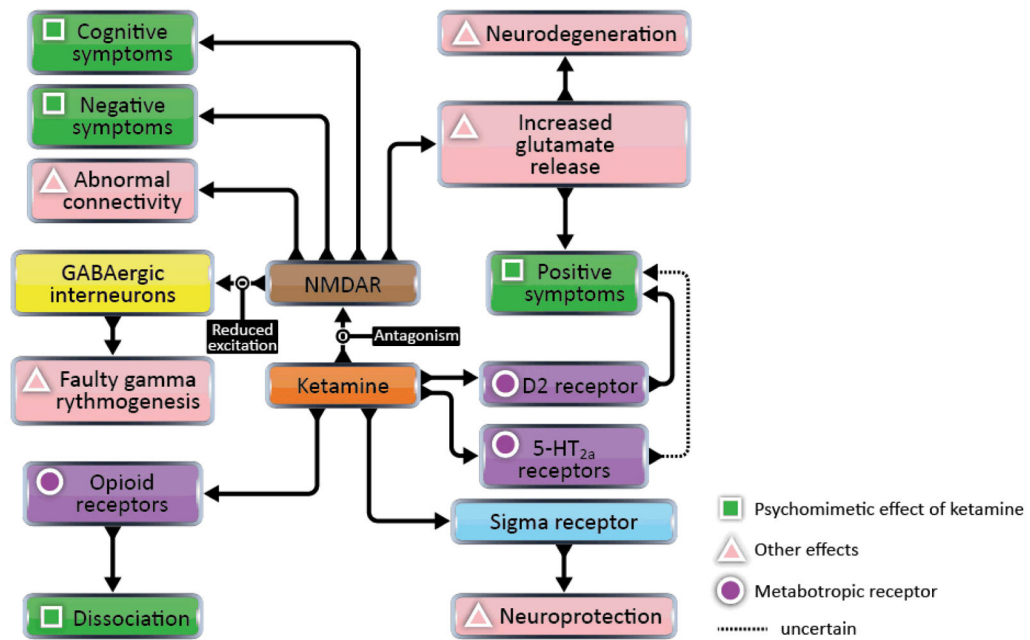
Figure 3. Diverse effects of ketamine at many receptors

Ketamine is a ligand of many diverse receptors. Ascertaining which receptors mediate which of ketamine's effects is a challenge for a ketamine model of schizophrenia. Above, we have mapped out speculative, causal relationships between receptors and the effects of ketamine, underscoring the multi-transmitter nature of the ketamine model of schizophrenia. Note that multiple pathways may converge to cause positive symptoms. Effects of D1 dopamine receptors and NMDAR may also converge to cause cognitive symptoms; however, only receptors that interact directly with ketamine are pictured here.

TABLE 1

Receptors involved in schizophrenia

Receptor	Type	Notable ligands	Mediated effects	Ketamine affinity	Relevance to schizophrenia?
N-methyl-D-aspartate glutamate receptor (NMDAR)	Ionotropic	• Glutamate (agonist) • Glycine (agonist) • D-serine (agonist) • D-cycloserine (agonist) • NMDA (agonist) • Ketamine (antagonist) • PCP (antagonist) • MK-801 (antagonist)	• Neural synchrony • Gamma rhythmogenesis • Psychosis (hypofunction) • Negative symptoms (hypofunction) • Dopamine regulation • Long term potentiation (LTP)	$K_i = 0.5 \pm 0.15\ \mu M$	Established
Dopamine D$_2$ receptor	Metabotropic	• Dopamine (agonist) • Chlorpromazine (antagonist) • Haloperidol (antagonist)	• Psychosis (hyperfunction)	$K_i = 0.5 \pm 0.2\ \mu M$ *(disputed)*	Established
γ-aminobutyric acid $_A$ receptor (GABA$_A$R)	Ionotropic	• GABA (agonist) • Muscimol (agonist) • TPA023 (agonist)	• Gamma rhythmogenesis • Working memory	• No affinity	Fairly well established
Sigma-1 receptor	Receptor chaperone	• Ketamine (agonist) • PCP (agonist) • SKF10047 (agonist) • Haloperidol (antagonist)	• Neuroprotection • Neurite outgrowth • Cognition? • NMDAR regulation	$K_i = 66.0 \pm 10.0\ \mu M$	Postulated
Kappa receptor	Opioid	• Ketamine (agonist) • Salvinorin A (agonist)	• Dissociation • Hallucinations	$K_i = 85.2 \pm 26.0\ \mu M$	Postulated
Cannabinoid receptor type 1 (CB1)	Metabotropic	• -9-tetrahydrocannabinol (agonist) • Endocannabinoids (agonists)	• Glutamate regulation • Brain maturation	• No affinity	Postulated
Muscarinic acetylcholine receptors	Metabotropic	• Aceylcholine (agonist) • Muscarine (agonist)	• Autonomic function • Memory	$K_i = 45\ \mu M$ (M1 receptor) $K_i = 294\ \mu M$ (M2 receptor)	Unknown

Receptor	Type	Notable ligands	Mediated effects	Ketamine affinity	Relevance to schizophrenia?
		• Atropine (antagonist)	• No known role in schizophrenia	K_i = 246 μM (M3 receptor)	