Title: Glutamatergic regulation of cognition and functional brain connectivity: insights from pharmacological, genetic and translational schizophrenia research

Authors: Dr Maria R Dauvermann[1,2], Dr Graham Lee[2], Dr Neil Dawson[3]

Affiliations:

1. School of Psychology, National University of Ireland, Galway, Galway, Ireland
2. McGovern Institute for Brain Research, Massachusetts Institute of Technology, 77 Massachusetts Ave, Cambridge, MA, 02139, USA
3. Division of Biomedical and Life Sciences, Faculty of Health and Medicine, Lancaster University, Lancaster, LA1 4YQ, UK

Abstract

The pharmacological modulation of glutamatergic neurotransmission to improve cognitive function has been a focus of intensive research, particularly in relation to the cognitive deficits seen in schizophrenia. Despite this effort there has been little success in the clinical use of glutamatergic compounds as procognitive drugs. Here we review a selection of the drugs used to modulate glutamatergic signalling and how they impact on cognitive function in rodents and humans. We highlight how glutamatergic dysfunction, and NMDA receptor hypofunction in particular, is a key mechanism contributing to the cognitive deficits observed in schizophrenia, and outline some of the glutamatergic targets that have been tested as putative procognitive targets for the disorder. Using translational research in this area as a leading exemplar, namely models of NMDA receptor hypofunction, we discuss how the study of functional brain network connectivity can provide new insight into how the glutamatergic system impacts on cognitive function. Future studies characterising functional brain network connectivity will increase our understanding of how glutamatergic compounds regulate cognition and could contribute to the future success of glutamatergic drug validation.

Abbreviations. **^{14}C-2-DG**, ^{14}C-2-deoxyglucose; **5-CSRTT**, 5-choice serial reaction time task; **ADX-47273**, (4-fluorophenyl)-[(3S)-3-[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]piperidin-1-yl]methanone; **BOLD**, blood oxygen level-dependent response; **CDPPB**, 3-cyano-N-[2,5-di(phenyl)pyrazol-3-yl]benzamide; **CIQ**, (3-Chlorophenyl)[3,4-dihydro-6,7-dimethoxy-1-[(4-methoxyphenoxy)methyl]-2(1H)-isoquinolinyl]methanone; **traxoprodil**, 1-[(1S,2S)-1-hydroxy-1-(4-hydroxyphenyl)propan-2-yl]-4-phenylpiperidin-4-ol; **CPT**, continuous performance task,; **CPPHA**, N-[4-chloro-2-[(1,3-dioxoisoindol-2-yl)methyl]phenyl]-2-hydroxybenzamide; **CTEP**, 2-chloro-4-[2-[2,5-dimethyl-1-[4-(trifluoromethoxy)phenyl]imidazol-4-yl]ethynyl]pyridine; **CX516**, 6-[(piperidin-1-yl)carbonyl]quinoxaline; **dizocilpine**, (5R,10S)-(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine; **DQP-1105**, 4-[3-(4-bromophenyl)-5-(6-methyl-2-oxo-4-phenyl-3H-quinolin-3-yl)-3,4-dihydropyrazol-2-yl]-4-oxobutanoic acid; **DLPFC**, dorsolateral prefrontal cortex; **DMN**, default mode network; **DMT**, dimethyltryptamine; **DR**, dorsal raphe; **ERP**, event related potential; **EEG**, electroencephalogram; **EST**, patients with established schizophrenia; **FC**, functional connectivity; **FES**, first episode schizophrenia; **FEP**, first episode psychosis; **fMRI**, functional magnetic resonance imaging; **GLYX-13**, rapastinel (Thr-Pro-Pro-Thr-NH_2); **HC**, healthy control; **HVLT**, Hopkins verbal learning task; **IFG**, inferior frontal gyrus; **iGluRs**, ionotropic glutamate receptors; **KA**, kainite; **LC**, locus coeruleus; **LY 2140023**, (−)-(1R,4S,5S,6S)-4-amino-2-sulfonylbicyclo[3.1.0]hexane-4,6-dicarboxylic acid; **eglumetad**, (1S,2S,5R,6S)-2-Aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid; **LY 395756**, (1S,2S,4R,5R,6S)-rel-2-Amino-4-methylbicyclo[3.1.0]hexane-2,6-dicarboxylic acid; **MEG**, magnetoencephalography; **MFG**, middle frontal gyrus; **mGlu**, metabotropic glutamate receptors; **MMN**, mismatch negativity; **MRS**, magnetic resonance spectroscopy; **MTEP**, 3-[2-(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine; **NA**, noradrenaline; **NAM**, negative allosteric modulator; **PAL**, paired associate learning task; **PAM**, positive allosteric modulator; **PANSS**, positive and negative symptoms scale; **PCP**, phencyclidine; **PFC,** prefrontal cortex; **Ro 25-6981**, (αR,βS)-α-(4-Hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol maleate; **basimglurant**, 2-chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine; **ROI**, region of interest; **RT**, response time; **Org 25935**, 2-([(1R,2S)-6-Methoxy-1-phenyl-1,2,3,4-tetrahydronaphthalen-2-yl]methyl-methylamino)acetic acid; **SAR218645**, (S)-2-(1,1-dimethyl-indan-5-yloxymethyl)-2,3-dihydro-oxazolo[3,2-a]pyrimidin-7-one; **SZ,** schizophrenia; **TUNL,** trial-unique, delayed nonmatching to location task. Drug and molecular nomenclature conforms to the British Journal of Pharmacology's Concise Guide to Pharmacology (Alexander et al., 2015).

The Glutamate System

Glutamatergic synapses in the central nervous system (CNS), responsible for fast excitatory neurotransmission, play a critical role in a broad range of cognitive functions. The structure of glutamate synapses and the molecular mechanisms underlying glutamatergic neurotransmission have previously been reviewed by others in detail (Sanz-Clemente *et al.*, 2013; Sudhof *et al.*, 2013; Volk *et al.*, 2015). In mature glutamatergic synapses a vast array of proteins are involved in the packaging of glutamate into synaptic vesicles, the localisation of these vesicles to presynaptic active zones and the docking and release of the contents of these vesicles into the synaptic cleft (Sudhof *et al.*, 2013). Post-synaptically, glutamate acts at both ionotropic glutamate receptors (iGluRs), including the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate (KA) and *N*-methyl-D-aspartate (NMDA) receptors, and metabotropic G-protein coupled glutamate (mGlu) receptors, to cause depolarisation in the post-synaptic neuron. mGlus are also present on the synaptic bouton that play an important role in the regulation of glutamate release as autoreceptors (see Niswinder & Conn, 2010 for review). The synaptic concentration of glutamate is also regulated by glutamate uptake, into both neurons and glial cells, mediated by a range of glutamate transporters (for review see Vandenberg and Ryan, 2013) and the cystine/glutamate antiporter (System Xc, Bridges *et al.*, 2012). Much research has been dedicated to elucidating the roles of these molecular components in the regulation of cognitive and brain function, in part due to the proposed central involvement of glutamate system dysfunction in a broad range of brain disorders with prominent cognitive deficits including schizophrenia (SZ) (Coyle *et al.*, 2006), bipolar disorder (McCloud *et al.*, 2015), major depressive disorder (deWilde *et al.*, 2015), autism spectrum disorders (Volk *et al.*, 2015) and Alzheimer's Disease (Lin *et al.*, 2014).

The role of the *N*-methyl-D-aspartate (NMDA) receptor in cognition

NMDA receptors are tetrameric structures assembled from two obligatory GluN1 subunits (formerly NR1) and two GluN2 (2A-D, formerly NR2A to NR2D) subunits. NMDA receptors may also contain GluN3 subunits, which are particularly abundant during early life and appear to have a role in limiting synapse maturation. The persistence of GluN3A-containing NMDA receptors into adulthood may contribute to the synaptic dysfunction in psychiatric disorders (Perez-Otano *et al.*, 2016), while the potential role of GluN3B is yet to be elucidated.

Diversity in NMDA receptor subunit composition results in functional and pharmacological diversity, as exemplified by the differing pharmacology of GluN2A versus GluN2B containing NMDA receptors (Smith *et al.*, 2011). The contribution of the different NMDA receptor subtypes to cognition is relatively poorly defined. However, recent studies in genetically modified mice have proved useful in further elucidating the complex relationship that exists between NMDA receptors with specific subunit compositions, their cellular and brain region

localisation and distinct cognitive functions (**Table 1**). In addition to these studies a multitude of pharmacological studies conducted in rodents, non-human primates and human participants have characterised the role of the NMDA receptor in cognition. Here we briefly review the general insights gained from these pharmacological studies.

Evidence from pharmacological studies in rodents

The impact of acute NMDA receptor antagonist administration

Acute administration of NMDA receptor antagonists, such as ketamine, phencyclidine (PCP) and dizocilpine, have been shown to negatively impact on domains of executive function in rodents, impairing cognitive flexibility (de Bruin *et al.*, 2013; Gastambide *et al.*, 2013) and disrupting attentional processing (Barnes *et al.*, 2016; Thomson *et al.*, 2011). Acute NMDA receptor antagonist administration also negatively impacts on other cognitive domains impairing spatial reference learning and memory (for review see Morris, 2013; Duan *et al.*, 2013; Ihalainen *et al.*, 2016), short term object recognition memory (Cloke & Winters, 2015; Rajagopal *et al.*, 2015), associative memory (as assessed in the paired associates learning task, Kumar *et al.*, 2015; Lins *et al.*, 2015) and episodic learning and memory (Bast *et al.*, 2005) in rodents. Acute NMDA receptor antagonist administration can also induce motivation deficits and motor impairments, which could potentially confound some of these cognitive measures (Noda *et al.*, 2000). However, the impact of these drugs on cognitive performance can be assessed at doses and time points after administration where these confounding effects are absent. A key consideration in these acute NMDA receptor antagonist studies, as with all pharmacological studies involving drugs targeting the glutamate system, is the importance of the temporal effects of each compound. These effects may contribute to some of the different behavioural and neural effects observed between different studies. Another concern is the non-selective pharmacology of the compounds used. For example, PCP also acts at nicotinic acetylcholine receptors (Fryer and Lukas, 1999) and dopamine (D_2) receptors (Seeman *et al.*, 2009) while ketamine binds to a wide range of non-glutamatergic targets (for review see Mion and Villevielle, 2013). Thus genetic studies and studies using more pharmacologically selective compounds have been instrumental in further supporting a key role for the NMDA receptor in cognition.

The impact of prolonged NMDA receptor hypofunction

A multitude of studies have characterised the effects of prolonged NMDA receptor hypofunction (induced by repeated, intermittent NMDA receptor antagonist treatment) on various cognitive functions in rodents. Cognitive testing in these studies is usually undertaken when animals are not experiencing the acute effects of these antagonists (i.e. when “drug free”). Thus the cognitive deficits present are thought to result from the plasticity changes that occur in the brain as a result of prolonged NMDA receptor

hypofunction. These plasticity effects include modifications in the function of non-glutamatergic neurotransmitter systems (Jentsch, *et al.*, 1998; Lindefors, *et al.*, 1998), including the function of parvalbumin positive (PV+) GABAergic interneurons (Bygrave, *et al.*, 2016), changes in synaptic plasticity (Nomura, *et al.*, 2016), alterations in regional neuronal activity, including prefrontal cortex (PFC) hypofunction (Dawson *et al.*, 2012), and altered brain network connectivity (see later discussion). In these studies, prolonged NMDA receptor antagonism has been shown to induce deficits in cognitive flexibility (Dawson *et al.*, 2012; McLean *et al.*, 2012), attentional processing (Thomson *et al.*, 2011; Barnes *et al.*, 2016), spatial reference learning and memory (Didricksen *et al.*, 2007), working memory (Seiller & Giuffrida, 2009) and short-term object recognition memory (Pyndt Jorgensen *et al.*, 2015; Horiguchi *et al.*, 2013; Rajagopal *et al.*, 2016). While the translational relevance of some of these behavioural tests to aspects of human cognition is in question (Kas, *et al.*, 2014; Pratt *et al.*, 2012; Pryce & Seifritz, 2011), the overall findings implicate a central role for the NMDA receptor in a broad range of cognitive processes.

In addition to these studies, conducted in adult animals, the impact of pharmacologically induced NMDA receptor hypofunction at specific developmental time points (either *in utero,* during early postnatal development or during adolescence) on cognitive function in the fully developed animal has also been assessed (Broberg *et al.*, 2008; Li *et al.*, 2011; Zhao *et al.*, 2014). These studies highlight the neurodevelopmental role of NMDA receptor activity, at defined epochs of brain development, in "setting up" the brain for effective cognitive function. This area of research certainly warrants further systematic investigation.

Insights from studies using NMDA receptor subtype selective drugs

Pharmacological studies have also attempted to elucidated the role of specific NMDA receptor subtypes in cognition. For example, the distinct pharmacology of GluN2A versus GluN2B containing NMDA receptors has allowed the recent characterization of the role of these receptor subtypes in different cognitive functions. The GluN2A-selective antagonist NVP-AMM077 has recently been shown to *decrease* accuracy in a task assessing sustained attention (5-choice serial reaction time task, 5-CSRTT (Smith *et al.*, 2011)), but has little effect on location discrimination, paired associate learning (PAL) and working memory (as assessed using the trial-unique, delayed nonmatching to location (TUNL) task (Kumar *et al.*, 2015)). By contrast, GluN2B-selective antagonists, such as Ro 25-6981 and Traxoprodil, appear to *improve* accuracy and processing speed in the 5-CSRTT (Higgins, *et al.*, 2005; Smith, *et al.*, 2011). However, antagonism of GluN2B using ifenprodil has been shown to impair performance in response time in the 5-CSRTT (Higgins, *et al.*, 2005). This conflicting finding, compared to the effects of other GluN2B antagonists, may be due to non-selective actions of ifenprodil or its relative weak affinity for GluN2B containing NMDA receptors. Further NMDA receptor subtype specific effects are supported by the observation that traxoprodil administration impairs location discrimination but not working memory in the

TUNL task (Kumar *et al.*, 2015). In addition, Ro 25-6981 ameliorates the impact of ketamine treatment on cognitive flexibility (assessed using the attentional set-shifting task (ASST), Kos *et al.*, 2010), supporting a primary role for GluN2B containing NMDA receptors in the impact of ketamine on cognitive flexibility.

There are a lack of studies reporting the cognitive impact of GluN2C and GluN2D -selective compounds. While GluN2C/D-selective compounds, such as the inhibitor DQP-1105 (Acker, *et al.*, 2011), are available their effects on cognition have not yet been tested. However, evidence for the role of GluN2C/D containing NMDA receptors in cognitive function is supported by studies conducted in genetically modified mice (**Table 1**). In addition, GluN2C/D containing NMDA receptor play an important role in the effects of the NMDA receptor antagonists ketamine and memantine (Kotermanski & Johnson, 2009), which may include their effects on cognitive functions. In addition, the absence of either GluN2C or GluN2D have been shown to have differential effects on the cortical oscillations induced by NMDA receptor blockade (Gupta, *et al.*, 2016; Sapkota, *et al.*, 2016). Other evidence supporting a role for GluN2C/D containing NMDA receptors in cognitive function comes from studies using positive allosteric modulators (PAMs), such as CIQ and D-cycloserine, discussed later in this review.

Insights from studies in genetically modified mice

A range of studies have used genetically modified mice to further determine the role of the different NMDA receptor subtypes in a range of cognitive functions (Table 1). These studies are often able to extend the understanding gained from relevant pharmacological studies, in part due to the greater assurance of NMDA receptor subtype specificity, but also by targeting either specific brain subsystems (GluN1; Rompala *et al.*, 2013; Taylor *et al.*, 2014) or cell populations (GluN1 in PV+ interneurons; Bygrave *et al.*, 2013). A limitation of these genetic studies is the neurodevelopmental role of NMDA receptors in the development of effective cognitive function, as highlighted by the persistent effects of non-selective NMDA receptor antagonists when selectively administered as specific developmental timepoints (Broberg *et al.*, 2008; Li *et al.*, 2011; Zhao *et al.*, 2014). Thus, the observed effects may be very different from those elicited by acute pharmacological regulation of these receptor subtypes. Nevertheless, studies using both genetic and pharmacological approaches offer complementary strategies to further elucidating the role of specific NMDA receptors subtypes in cognition, with modern genetic approaches offering new levels of granular neural system, temporal and cell-type resolution.

The NMDA receptor hypofunction hypothesis of schizophrenia

The 'glutamate hypothesis of SZ' posits that glutamatergic system dysfunction is a key pathophysiological mechanism contributing to the clinical symptoms seen in patients with

SZ (Luby *et al.* 1959; Carlsson *et al.* 2000; Farber *et al.* 2002; Javitt, 2007; Javitt *et al.* 2012). The 'NMDA receptor hypofunction hypothesis of SZ', a more specific theory of the glutamate dysfunction hypothesis, has its origins in the observation that the acute administration of the NMDA receptor antagonists, such as ketamine and PCP, induce psychotic-like symptoms (delusions and hallucinations) in healthy controls (HC) that are similar to those seen in patients with SZ (Krystal *et al.* 1994; Abi-Saab *et al.* 1998). In addition, individuals who chronically abuse PCP (presumably inducing repeated intermittent NMDA receptor hypoactivity) show deficits in executive function similar to those seen in patients (Cosgrove *et al.* 1991). These observations have led to the development of two distinct but overlapping models of the glutamate hypothesis of SZ: (i) the 'prolonged NMDA receptor hypofunction model' and (ii) the 'acute NMDA receptor hypofunction model'.

The 'prolonged NMDA receptor hypofunction model' postulates that prolonged hypoactivation of the NMDA receptor induces multiple pathological mechanisms involved in the disorder (Coyle, 2006; Coyle *et al.* 2010; Moghaddam and Krystal, 2012; Javitt *et al.* 2012) and that NMDA receptor hypofunction may be the final pathophysiological pathway for the positive, negative and cognitive symptoms experienced by patients with SZ (Carlsson *et al.* 1999; Goff and Coyle, 2001; Coyle, 2006; Javitt, 2010; Balu and Coyle, 2015). The 'acute NMDA receptor hypofunction model' originates from clinical trials when ketamine was administered to HCs. Early findings found that changes in glutamatergic signalling could explain the psychotomimetic effects of ketamine and PCP in terms of the positive symptoms present in individuals with first episode SZ (FES) or first episode psychosis (FEP) (Krystal *et al.* 1994; Krystal *et al.* 1999; Khlestova *et al.* 2016). While the findings from the acute ketamine administration model have particularly increased our understanding of the positive and negative symptoms seen in patients with SZ, evidence for translationally relevant alterations in cognitive functions is more limited. We outline some of these exemplary cognitive studies below and outline their translational alignment to observations made in patients with SZ.

Evidence from pharmacological studies in human participants

In HC acute ketamine administration has been shown to significantly impact on a range of cognitive functions, with the effects being similar to those seen in patients with SZ. Low dose ketamine administration (100 ng/mL of plasma) impacts on contingency learning in HC when assessed using a probabilistic learning task (Vinckier *et al.*, 2016), with ketamine administration inducing misleading cue-outcome associations. These findings contrast with those reported in an early study where the same dose of ketamine (100 ng/mL of plasma) failed to alter task performance (Corlett *et al.*, 2006). However, both studies did show similar effects of ketamine on blood oxygen level-dependent (BOLD) responses (increased) in regions of the PFC of participants undertaking the task. Deficits in contingency learning as well as increased BOLD responses in the PFC have also been reported in patients with SZ (Diaconescu *et al.*, 2011). However, decreased BOLD responses in the PFC of patients with

SZ during contingency learning have also been reported (Dowd *et al.*, 2016). In addition, increased BOLD responses in a range of other brain regions have also been reported in SZ patients undertaking this task (Diaconescu *et al.*, 2011; Park *et al.* 2015; White *et al.* 2015) that are different from those seen in ketamine fMRI studies in HC. It is important to note that different temporal effects of drug administration may contribute to some of the divergent findings in behavioural performance and neural function reported in these clinical studies.

Ketamine administration has also been shown to significantly impact on working and declarative memory in HC. Ketamine administration significantly reduced accuracy in the continuous performance task (CPT) and impairs both immediate and delayed recall in the Hopkins verbal learning task (HVLT, Krystal *et al.*, 2005). The effect of ketamine on working memory function was confirmed by another study (Honey *et al.*, 2008). The effects of ketamine on working and declarative memory tasks are similar to those seen in patients with SZ (Blokland *et al.* 2016; Green *et al.* 2016). However, the impact of ketamine on BOLD responses during working memory and declarative memory tasks in HC are more difficult to corroborate with the fMRI findings seen between SZ patients and HC, where both increased and reduced BOLD responses are observed in patients with SZ when compared to HC (Brown and Thompson, 2010; Dauvermann *et al.* 2014). While Anticevic *et al.* 2012 and Driesen *et al.* 2013 reported reduced BOLD responses in the dorsolateral PFC (DLPFC) and precuneus in HC treated with ketamine and SZ patients during working memory performance, the findings by Honey *et al.* 2008 (increased BOLD responses in the basal ganglia and thalamus of HC treated with ketamine during the task) are more difficult to align with observations made in patients with SZ.

Ketamine administration has also been shown to impact on attentional processing, when assessed using both visual and auditory tasks. In HC ketamine was found to significantly reduced the response time to target stimuli in a visual oddball task assessing attentional processing (Watson *et al.*, 2009), an effect that is similar to the reduced visual processing speed seen in patients with SZ (Urban *et al.*, 2008). Similarly, in HC ketamine (0.24 mg/kg) also impacts on attentional processing when assess using an auditory processing task, increasing the number of false alarms during the task (Umbricht *et al.*, 2000). In addition, in this study ketamine administration was also found to reduce the peak amplitude of the Mismatch Negativity (MMN) signal, an aspect of the event-related potential (ERP) detected using electroencephalogram (EEG) that is indicative of the arrival of an odd stimulus in a sequence of stimuli. Similar cognitive effects were independently observed when using both a low and high dose of ketamine, with only the higher dose inducing significant deficits in MMN (Heekeren *et al.*, 2008). The deficits in auditory attentional processing and MMN seen under ketamine administration are similar to those reported in patients with SZ (Milovan *et al.*, 2004). Summary outlines of these studies are provided in Table 2.

The impact of NMDA receptor co-agonists and partial agonists on cognition

Much research has been dedicated to elucidating the procognitive potential of activating NMDA receptors, with positive modulation rather than agonism (which risks inducing excitotoxicity) being a key area of research. The glycine site on NMDA receptor provides an attractive drug target because of its positive modulatory effects on NMDA receptor signalling. The amino acid derivatives D-serine and D-cycloserine act as partial agonists at this site (Mothet *et al.*, 2000; Watson *et al.*, 1990). The therapeutic potential of NMDA receptor positive modulators in schizophrenia patients has been reviewed previously (Kantrowitz & Javitt, 2010; Balu & Coyle, 2015; Goff, 2012). Here we highlight and discuss recent findings of rodent and human studies featuring these drugs with a particular focus on cognition and, where applicable, summarise neuroimaging findings from rodent and human studies.

Pharmacological studies in rodents

In rodent studies both D-serine and D-cycloserine have been shown to have procognitive effects. For example, D-cycloserine improves short term object recognition, potentiates contextual and cued fear extinction learning in rats (Sugiyama, *et al.*, 2015; Walker, *et al.*, 2002) and improves spatial learning in aged rats (Baxter *et al.*, 1991). In addition, intrahippocampal D-cycloserine administration has been shown to reverse dizocilpine induced impairments in working memory performance in the radial arm maze (Kawabe, *et al.*, 1998), suggesting that D-cycloserine administration can reduce the impact of acute NMDA receptor hypofunction on working memory. Similar effects have been shown for D-serine, which improves working memory performance in the T-maze alternation test and enhances novel object recognition, while also reversing the long-term memory deficits induced by dizocilpine (Bado, *et al.*, 2011). In addition, the recently developed tetrapeptide GLYX-13, a partial agonist of the NMDA receptor glycine site, has also been shown to improve learning and memory in young and aged rats (Burgdorf *et al.*, 2011) as well as restoring object recognition in mouse models of acute and prolonged NMDA receptor hypofunction (Rajagopal *et al.*, 2016).

D-cycloserine demonstrates greatest efficacy at NMDA receptor containing GluN2C subunits (Ogden, *et al.*, 2014) suggesting a central role for this NMDA receptor subtype in its procognitive effects. Potentiation of GluN2C/D–containing NMDA receptors using CIQ has been shown to facilitate fear learning and extinction in mice (Ogden, *et al.*, 2014), and reverses the deficit in working memory (spontaneous alternation test) in mice following acute dizocilpine administration (Suryavanshi *et al.*, 2014). A role for GluN2C subunit containing NMDA receptors in working memory is further supported by observations in GluN2C knockout mice (Hillman *et al.*, 2011, Table 1). Interestingly, these mice do not show deficits in spatial reference memory which contrasts with the ability of D-cycloserine to

improve spatial reference memory in aged rats (Baxter *et al.*, 1994). This suggests that the activity of D-cycloserine at other NMDA receptor subtypes may be more important for its effects on spatial reference memory, or that developmental adaptations prevent the impact on GluN2C knockout on spatial reference memory in GluN2C knockout mice.

Evidence from pharmacological studies in humans

In contrast to rodent studies supporting the procognitive potential of NMDA receptor partial agonism the evidence from studies in humans, including studies in patients with SZ, is less persuasive. In HC, glycine administration does not improve general cognitive performance on the CogState test battery (Neumeister *et al.*, 2006) or in a visual attention task (O'Neill *et al.*, 2011). Furthermore, D-cycloserine administration does not improve motor sequence learning in HC (Gunthner *et al.* 2016). By contrast, initial studies undertaken in a small sample of 12 HC males support a significant effect of the glycine transporter inhibitor Org 25935 on verbal learning and delayed recall, but not on any of the other cognitive tests employed (D'Souza *et al.*, 2012). More recently, Org 25935 administration was also shown not to improve performance in a visuo-spatial task, a working memory task or a verbal memory task in HC (Christmas *et al.*, 2016). This suggests that the procognitive potential of these compounds in HC may be limited. Given that NMDA receptor function may be optimal in HC, it may be considered unsurprising that these compounds fail to significantly improve cognitive performance in these studies. Despite these findings one might still predict that these compounds would have procognitive potential in patients with brain disorders thought to involve NMDA receptor hypofunction, such as patients with SZ. However, studies investigating the procognitive potential of drugs that positively modulate NMDA receptor activity in patients with SZ are negative overall. For example, D-cycloserine adjunctive treatment does not improve composite scores of general cognitive function, or most individual cognitive domain scores when assessed using standardised neuropsychological batteries, in patients with established SZ (EST) (Buchanan *et al.* 2007; Goff *et al.* 2005; Goff *et al.* 2008; Weiser *et al.* 2012; Cain *et al.* 2014). D-cycloserine treatment also fails to improve performance in the CPT and working memory tasks in patients with EST (Duncan *et al.*, 2004). However, there are also positive findings where D-cycloserine improved cognitive performance following a cognitive remediation programme in patients with EST (Cain *et al.*, 2014) and D-cycloserine has been shown to facilitate fear extinction therapies in people with anxiety disorders (Norberg *et al.* 2008). These findings suggest that D-cycloserine may yet hold therapeutic value by potentiating the efficacy of cognitive behavioural therapies, at least in some cognitive domains. Despite this suggestion, overall findings from recent meta-analysis do not support the procognitive efficacy of compounds potentiating NMDA receptor activity in SZ. While, Tsai and Lin, (2010) found a positive impact of NMDA receptor enhancing agents (D-cycloserine, glycine and sarcosine) on cognitive symptoms in patients with SZ (assessed using the PANSS cognitive subscale), two more recent meta-analyses found no effect (Choi *et al.* 2013; Iwata *et al.* 2015). Choi *et al.*, (2013) found that D-

cycloserine, D-serine and the AMPA receptor PAM CX516, as adjunctive treatments, did not significantly improve function in five cognitive domains (Choi *et al.* 2013). Furthermore, Iwata *et al.* found no significant effect for NMDA receptor glycine site drugs in eight cognitive domains (Iwata *et al.* 2015). Thus any procognitive effects of NMDA receptor glycine site modulators in patients with SZ are yet to be robustly established. One reason for the disparity between preclinical and clinical studies may be the testing of these compounds as adjunctive treatments in patients, while preclinically their procognitive efficacy has not been tested in the context of prolonged antipsychotic administration (Summary information from these studies is outlined in Table 3). Furthermore, clinical efficacy has only been tested in patients with EST and whether these drugs would be beneficial during earlier stages of the disease, such as in FES patients, has not yet been adequately tested. The temporal relevance of NMDA receptor hypofunction, and thus the procognitive potential of enhancing NMDA receptor signalling, over the time course of disease progression needs to be much more clearly defined. Finally, the relatively short treatment duration used in some clinical trials, typically between 4 to 24 weeks (Choi *et al.* 2013) with one study at a more lengthy 36 weeks (Iwata *et al.* 2015; Table 3), may also have contribute to the overall negative findings.

The role of AMPA-Rs in cognition

AMPA receptors are heterotetramers formed from distinct subunits (GluA1-4) or as Ca^{2+}-permeable homotetramers composed of GluA1 subunits (for review see Henley and Wilkinson, 2016). AMPA-R expression and trafficking is a highly dynamic process, regulated by neuronal activity, and they play a central role in neuronal plasticity. PAMs of AMPA-Rs typically potentiate the channel-open state of the receptor upon glutamate activation, enhance long-term potentiation (LTP) and have varying effects on long-term depression (LTD), depending on the class of compound (Arai & Kessler, 2007). Promising results from early studies reported that PAMs improve cognitive function in human participants and in rodents. For example administration of the AMPA receptor PAM CX516 improved associative and recognition memory performance in HC (Ingvar *et al.*, 1997). AMPA receptor PAMs have also been reported to improve cognitive performance in aging healthy participants, in measures such as delayed recall performance (Lynch *et al.*, 1997) and working memory (Wezenberg, *et al.*, 2007). These findings are corroborated in rodent studies, where administration of a benzamide AMPA receptor PAM improved performance in discriminative and spatial memory tasks in rats (Staubli, *et al.*, 1994). Rodent research has also shown the drug reverses cognitive deficits in subchronic PCP rodent models, relevant to SZ, in behaviours such as attentional set-shifting (Broberg, *et al.*, 2009) and novel object recognition (Damgaard, *et al.*, 2010). However, CX516 was shown to be ineffective in improving deficits in cognitive flexibility and working memory seen in patients with SZ, when given as an adjuvant with antipsychotic drugs (Goff, *et al.*, 2008). Therefore, the therapeutic

potential of AMPA receptor PAMs in SZ requires further investigation.

The role of metabotropic glutamate receptor subtypes 2 and 3 (mGlu$_2$ and mGlu$_3$) in cognition

Numerous studies have demonstrated efficacy of mGlu$_{2/3}$ agonists and PAMs in reversing cognitive dysfunction in animal models. For example, mGlu$_{2/3}$ agonists improve acute PCP-induced working memory deficits (Eglumetad; Moghaddam & Adams, 1998), deficits in working memory and latent inhibition in *GluN1* knockout mice (SAR218645; Griebel, *et al.*, 2016), and novel object recognition performance in a post-weaning social isolation rat model (LY379268; Jones, *et al.*, 2011). In addition, the mGlu$_2$ selective PAM was shown to improve cognitive flexibility in control rats (Nikiforuk *et al.*, 2010). However, some studies have failed to reproduce these findings, and also show that mGlu$_{2/3}$ agonists may actually worsen some aspects of cognition, including working memory, when given alone (Eglumetad in rodents and marmosets; Schlumberger, *et al.*, 2009; Spinelli, *et al.*, 2005) or have no significant effect in control animals (LY395756; Li *et al.*, 2015). Therefore, these compounds may only be effective in improving cognition in states of glutamatergic dysfunction.

In human studies mGlu$_{2/3}$ receptor agonists have provided some promising results in improving cognitive performance. For example, LY2140023 demonstrated encouraging results in treating positive and negative symptoms in patients with SZ (Patil, *et al.*, 2007) but ultimately the drug failed to pass Phase III clinical trials (Adams, *et al.*, 2014). Unfortunately, the procognitive effects of this drug in patients were not assessed and the putative procognitive effects of mGlu$_{2/3}$ PAMs in SZ is yet to be firmly established.

The role of metabotropic glutamate receptor subtype 5 (mGlu$_5$) in cognition

In disorders thought to involve NMDA receptor hypofunction, such as SZ, drugs active at mGlu$_5$ receptors have been proposed as potential therapeutics, due to close functional coupling between the two receptors and the ability of mGlu$_5$ activation to potentiate NMDA receptor activity (Awad *et al.*, 2000; Pisani *et al.*, 2001). A key focus of research has been on PAMs of the mGlu$_5$ receptor, drugs that act by binding to an allosteric site on the receptor to potentiate its activation by glutamate (CPPHA; Chen *et al.*, 2008; CDPPB; Uslaner *et al.*, 2009). In unimpaired (control) rodents mGlu$_5$ PAMs have been shown to improve object recognition memory (ADX47273; Liu, *et al.*, 2008; CDPPB; Uslaner *et al.*, 2009), spatial learning (CDPPB and ADX47273; Ayala *et al.*, 2009), contextual fear acquisition (DFPE; Gregory *et al.*, 2013) and extinction learning (CDPPB; Cleva *et al.*, 2011). In rodents mGlu$_5$ PAMs have also been shown to limit the impact of NMDA receptor antagonists on cognition. For example CDPPB reverses the dizocilpine induced deficits in NOR (Uslaner *et al.*, 2009) and cognitive flexibility, assessed using the ASST (Darrah, *et al.*, 2008; LaCrosse, *et al.*, 2015). The mGlu$_5$ PAM ADX47273 has also been shown to decrease premature responding in the 5-CSRTT test of impulsivity in trait-impulsive rats, and attenuates the increased impulsiveness

in rats following dizocilpine administration (Isherwood, *et al.*, 2015). These procognitive effects are thought to be mediated by the ability of $mGlu_5$ PAMS to enhance synaptic plasticity, through both the enhancement of LTP and LTD (Ayala *et al.*, 2009; Xu, *et al.*, 2013). However, while some of these effects may be dependent on the interaction of $mGlu_5$ with the NMDA receptor, others may be independent from this interaction (Rook *et al.*, 2015).

There is also evidence of cognitive improvement with negative allosteric modulation (NAM) of $mGlu_5$ receptors. For example, CTEP reverses an inhibitory avoidance deficit in mice with 16p11.2 microdeletion (Tian, *et al.*, 2015). However, injection of the $mGlu_5$ antagonist MPEP into the lateral ventricles of control rats prior to training impairs working memory performance in the radial arm maze (Manahan-Vaughan & Braunewell, 2005) and systemic pretreatment exacerbates dizocilpine-induced deficits in spatial working memory (Homayoun, *et al.*, 2004). The $mGlu_5$ NAMs, basimglurant and MTEP, also impair performance in the 5-CSRTT in control animals (Isherwood, *et al.*, 2015). Overall these data suggest that an optimal level of $mGlu_5$ activity is required for effective cognition and the preclinical research suggests that $mGlu_5$ receptors may be a promising therapeutic target to improve cognitive deficits, at least in some disorders. However, research in human subjects has yet to demonstrate the impact of $mGlu_5$-selective drugs on cognition (Berry-Kravis, *et al.*, 2016).

Glutamatergic regulation of functional brain network connectivity: insights from pharmacological studies targeting the NMDA receptor

The study of how drugs targeting the glutamate system alter functional brain network connectivity to influence cognition is in its extreme infancy. However, recent data from studies characterising the impact of NMDA receptor antagonists on brain network connectivity have given new insight into the glutamatergic regulation of brain connectivity. In addition, these studies have highlighted the potential translational value of the analysis of brain network connectivity, with the reported effects appearing to be conserved between species (rodents, primates and humans) and across imaging modalities, in measures of brain network connectivity. Here, we provide a brief overview of the studies that have characterised the impact of NMDA receptor antagonists on functional brain network connectivity. The results highlight the potential future utility of this approach in studying other manipulations of the glutamate system, whether they be pharmacological or genetic, that are known to impact on cognition.

Insights from rodent studies characterising the impact of NMDA receptor antagonists on functional brain network connectivity

Acute treatment with a subanaesthetic dose of ketamine induces abnormal increases in

functional brain network connectivity as analysed using ^{14}C-2-deoxyglucose functional brain imaging (Dawson *et al.*, 2014). Ketamine treatment increases the number of functional connections and alters the topographic properties of functional brain networks to increase clustering between local brain regions. This suggests that subanaesthetic ketamine treatment impacts on cognition by promoting abnormally enhanced functional connectivity in local subsystems. From a neural subsystems perspective, this includes abnormally increased local functional connectivity between subfields of the prefrontal cortex (Dawson *et al.*, 2013), which parallels the PFC regional hyperconnectivity induced by subaneasthetic ketamine treatment in primates (Gopinath *et al.*, 2016) as well as during resting-state in humans (Anticevic, *et al.*, 2015). By contrast, subanaesthetic ketamine treatment in rats impairs long range connectivity, including for example decreased PFC functional connectivity to thalamic inputs (Dawson *et al.*, 2013; 2014). This suggests that ketamine treatment both compromises the ability of the PFC to receive information from other neural subsystems and that enhanced local clustering within the PFC compromises the appropriate segregation of the information received at the local level. These two mechanisms may contribute to the impact of ketamine of PFC-dependent cognitive processes in rodents (Nikiforuk & Popik, 2014; Nikiforuk *et al.*, 2016). In addition, functional connectivity between neuromodulatory subsystems such as the dorsal raphe nucleus (DR), the origin of serotonergic (5-HT) innervation, and the locus coeruleus (LC), the origin of noradrenergic (NA) innervation to the PFC are abnormally enhanced by acute NMDA receptor blockade (Dawson *et al.*, 2013; 2014). Both 5-HT and NA are known to modulate PFC-dependent cognitive processes (Berridge & Spencer, 2016; Clarke *et al.*, 2007). Thus, the modification of the connectivity between neuromodulatory subsystems and the PFC may be a key mechanism contributing to the impact of acute NMDA receptor blockade on cognition, in addition to the local effects of ketamine in the PFC and other cognitive neural subsystems (e.g. hippocampus). The disruption of thalamo-cortical connectivity is a major impact of acute NMDA receptor antagonist treatment, with the thalamic reticular nucleus being a particularly important target (for review see Pratt *et al.*, 2015). Interestingly, disrupted thalamocortical connectivity is found both in rodents treated with ketamine, when brain networks are analysed using ^{14}C-2-DG, and in human participants treated with ketamine when analysed using resting-state magnetoencephalography (MEG, Rivolta *et al.*, 2015), supporting not only the conservation of alterations in functional connectivity (FC) across species but also across different imaging modalities. This conservation may be key to facilitating translation in the context of identifying procognitive glutamate system targeting drugs.

In contrast to the effects of acute NMDA receptor blockade, prolonged NMDA receptor hypofunction, as induced by subchronic PCP treatment induces compromised functional brain network connectivity in rodents (Dawson *et al.*, 2012; 2014). At the global network scale this results from a decreased number of functional connections in the brain network, decreased clustering and an increase in the number of functional connections that must be

traversed to reach one brain region to another (a measure known as average pathlength, Dawson *et al.*, 2014). These global alterations strongly parallel those reported in functional resting-state brain networks of EST (Li *et al.*, 2008; Micheloyannis *et al.*, 2006), supporting the translational potential of these network measures. Subchronic PCP treatment also results in decreased thalamic, hippocampal and PFC connectivity, and induces a decrease in the functional integration between the hippocampus and PFC (Dawson *et al.*, 2012), which could contribute to the cognitive deficits seen as a result of prolonged NMDA receptor hypofunction. Decreased hippocampal-PFC resting-state functional connectivity is also seen in patients with SZ (Kraguljac *et al.*, 2016) and genetic rodent models relevant to the disorder (Dawson *et al.*, 2015; Sigurdsson *et al.*, 2010). Again a central role for altered neuromodulatory system connectivity is indicated as a result of prolonged NMDA receptor hypofunction, with decreased PFC - LC connectivity supported (Dawson *et al.*, 2012).

Insights from human studies characterising brain network connectivity alterations induced by NMDA receptor antagonists

Graph theory approaches to characterising altered brain network connectivity have been widely applied in relation to brain network connectivity in SZ patients (Hadley *et al.*, 2016; Li *et al.*, 2008; Micheloyannis *et al.*, 2006; van den Heuvel, 2010) and in a range of other cognitive brain disorders. However, very few studies have applied graph theory network analysis in the context of pharmacologically induced NDMA-R hypofunction in HCs. For example, using task-free pharmacological MRI Joules *et al.*, report increased degree centrality, indicative of the number of functional connections a given region has in the context of the brain network, for the basal ganglia and decreased centrality for cortical regions, including regions in the frontal cortex, following ketamine administration (Joules *et al.*, 2015). No other graph theory measures were reported as a part of this study and the authors themselves highlight the additional insight that the application of these additional measures could give. The data driven approach taken in this study highlights the value of using graph theory approaches to define alterations in network connectivity. The reduced PFC connectivity induced by ketamine administration in this study contrasts with the increased PFC connectivity reported using FC analysis in HCs by others (Anticevic *et al.*, 2015) and the preclinical data that support the general enhancement of PFC connectivity following ketamine administration (Dawson *et al.*, 2014). The reasons for this disparity remain unclear, but may include the use of only one form of connectivity analysis in the Joules *et al.*, study (degree centrality) or that the regions of interest that were included in the analysis influenced the findings (as ketamine treatment has been shown to increase and decrease PFC connectivity to different brain regions (Dawson *et al.*, 2013). For example, another recent study used a seed regional approach to characterising the impact of ketamine on PFC-hippocampal connectivity in HCs, supporting a ketamine-induced increase in the functional connectivity between these neural subsystems (Grimm *et al.*, 2015). Interestingly, this investigation also confirmed similar effects in rodents using the same

approach, further highlighting the translational value of measuring functional brain network connectivity.

As the application of graph theory methods in the context of NMDA receptor antagonist induced alterations in brain network FC are relatively limited, here we also consider the effects on task-based FC from fMRI studies. To date the vast majority of these studies have been applied in the context of the influence of NMDA receptor antagonists during working memory tasks, which has potential translational confounds when attempting to compare the observed effects to those seen in resting state brain imaging data. However, overall the effects reported seem similar to those found when brain imaging is undertaken at rest, and in animal models. For example, Driesen *et al.* found that acute ketamine administration significantly reduced FC between the DLPFC and middle frontal gyrus (MFG), and impaired performance, during working memory function in HC (Driesen *et al.* 2013b). In a more recent study, dextromethophan led to increased FC within a brain network comprising 270 seed regions involving the DLPFC (Braun *et al.*, 2016). The findings parallel the increased DLPFC FC seen during working memory function in patients with SZ (Siebenhuehner *et al.*, 2013). Anticevic *et al.*, 2012 also found that ketamine administration increased task-based FC in the fronto-parietal network and reduced task-deactivated FC of the default mode network (DMN) network during a working memory task (Anticevic *et al.*, 2012), which also appear to be similar to effects seen in patients with SZ. To date only these three studies have reported the effects of NMDA receptor antagonists on alterations in task-based FC in HC. More research into the impact of NMDA receptor antagonists, and other glutamatergic compounds, on working memory and brain network connectivity is needed in order to gain a better understanding of the effects of glutamatergic modulators on cognitive function, and their role in SZ. Multi-modal studies during cognitive function, with the simultaneous measurement of glutamatergic concentrations (using Magnetic Resonance Spectroscopy (MRS)) in combination with BOLD fMRI may lead to greater insight into glutamatergic responses during cognitive functions in patients with SZ (for example see Taylor *et al.* 2015).

Conclusion

The glutamatergic system plays a primary role in the regulation of multiple domains of cognition. Targeting glutamatergic neurotransmission offers hope for the treatment of cognitive deficits seen in patients with SZ and other brain disorders with pronounced cognitive deficits. Characterising the impact of modified glutamate system function on brain network connectivity offers new systems-level insight into the mechanisms underlying the glutamatergic regulation of cognition. The study of how functional brain networks are modulated by glutamateric neurotransmission is in its extreme infancy. Here we have outlined recent studies that have characterized the impact of NMDA receptor antagonists on brain network connectivity as a leading exemplar of the new insight that can be gained from the study of how the glutamate system modulates brain network connectivity and

cognition. Taking this approach may have great translational value, as initial observations appear to be conserved across different species and imaging modalities. Future studies dedicated to studying the effects of other procognitive compounds and modifications of glutamate system function, whether they be pharmacological or genetic, should be undertaken in order to further understand the mechanisms through which these manipulations elicit their effects on cognition.

Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan *et al.*, 2015a; 2015b; 2016), and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 (Alexander *et al.*, 2015).

Tables

Table 1. Cognitive deficits reported in genetic mouse models targeting the NMDA receptor

NMDA-R gene	Mouse model	Cognitive deficit	Reference
GluN1	GluN1 hypomorphic mice	Impaired spontaneous alternation	Gregory *et al.*, 2013
	GluN1 hypomorphic mice	Reduced spontaneous alternation Impaired short-term object recognition memory Impaired spatial reference memory Impaired learning in a visual discrimination task	Barkus *et al.*, 2012
	Ablation of GluN1 in cortical excitatory neurons of mPFC and SSCTX	Impaired short-term object recognition Normal spatial working memory	Rompala *et al.*, 2013
	Ablation of GluN1 in HP (DG and CA1)	Impaired in spatial reversal learning (water maze) Not impaired in spatial discrimination (water maze)	Taylor *et al.*, 2014
	GluN1 knockout in Parvalbumin expressing interneurons	No deficit in cognitive flexibility, working memory or attentional processing	Bygrave *et al.*, 2016
GluN2A	*GluN2A* KO mice	Impaired spatial working memory No impairment in long term spatial reference memory	Bannerman *et al.*, 2008
	GluN2A KO mice	Impaired extra-dimensional set shifting Not impaired in discrimination or reversal learning	Marquardt *et al.*, 2014
	GluN2A KO in HP and CTX	Impaired reversal learning	Thompson *et al.*, 2015
GluN2B	*GluN2B* KO in principal neurons of the postnatal forebrain	Impairment in spatial working memory, spatial reference memory, impaired recognition memory, performance deficits in simple Morris water maze and visual discrimination tasks	von Engelhardt *et al.*, 2008
	GluN2B KO in HP (CA1 and DG)	Impaired spatial working memory and reversal learning No impairment in spatial reference memory	von Engelhardt *et al.*, 2008
GluN2C	*GluN2C* KO mice	Deficit in fear conditioning and spatial working memory No impairment in spatial reference memory	Hillman *et al.*, 2011

GluN2D	*GluN2D* KO mice	Impaired social memory No impairment in novel object recognition	Yamamoto *et al.*, 2017
GluN3A	*GluN3A* KO mice	Improved spatial learning and enhanced object recognition memory	Mohamad *et al.*, 2013
GluN3B	*GluN3B* KO mice	No difference in spatial reference memory and fear conditioning	Niemann *et al.*, 2007

Abbreviations. *CA1, cornu ammonis 1 subfield; CTX, cortex; DG, dentate gyrus; HP, hippocampus*

Table 2. Impact of NMDA-R antagonist administration on cognitive functions in human controls

Study (year)	**Experimental group/ patient group**		**Control group/ control matching criteria**		**Study design/ Drug administration**	**Task design for cognitive function**	**Main findings - Effects of drug on cognition and/or neural response measures during cognition**
	***N* (M:F)**	**Mean age in years (SD)**	***N* (M:F)**	**Mean age in years (SD)**			
Contingency Learning							
Vinckier *et al.* 2016	N/A		HC 21 (11:10) 28.7 (±3.2)		• Double-blind, placebo-controlled, randomised, within-subjects study design • Two separate drug challenge sessions (placebo/active drug): • Ketamine: low-dose bolus and iv. injection • Placebo: Saline	fMRI: Probabilistic learning task – parametric modulation. 1. GLM: Separation of categorical regressors for cue and outcome onsets 2. GLM: Outcome onsets modulated by two computational variables (ROI analysis)	<u>Effect of ketamine on cognitive performance:</u> • Ketamine ***decreases*** optimisation of outcomes given misleading unexpected outcomes <u>Effect of ketamine on BOLD response:</u> • Altered BOLD response in fronto-parietal regions based on contingency learning, mostly in regions of the cerebellum, MFG, DLPFC and inferior parietal cortex in ketamine when compared to placebo (ROI analysis)
Corlett *et al.* 2006	N/A		HC 15 (8:7) 29 (±7)		• Double-blind, placebo-controlled, randomised, within-subjects study design • Two separate drug challenge sessions (placebo/active drug): • Ketamine: low-dose bolus and iv.	fMRI: Associative learning task. • Associative relationships • Prediction error	<u>Effect of ketamine on cognitive performance:</u> • ***No difference*** in behavioural performance between ketamine and placebo <u>Effect of ketamine on BOLD response:</u> • ***Increased*** BOLD response in the right PFC in response to expected stimuli in ketamine when compared to placebo (prediction error)

			Injection while in scanner ● Ketamine: high-dose bolus and i.v. injection outside of ● Placebo: Saline		
Working memory and declarative memory					
Krystal *et al.* 2005	N/A	HC – Amphetamine group (14 study completers) HC – Ketamine group (13 study completers) 27 (16:11) 16 Male 33(±8.9) 11 Female 28(±5.2)	● Double-blind, randomised, placebo-controlled, study design ● Amphetamine group: 1) Infusion of 0.25mg/kg followed by saline, 2) Ketamine infusion of 0.23mg/kg, 3) Amphetamine placebo (saline), 4) Ketamine, 5) Placebo amphetamine, 6) Placebo ketamine. ● Ketamine group: Same idea as above but swapped between amphetamine and ketamine	1. CPT 2. HVLT (6 versions) 3. PANSS: Cognitive symptom score.	<u>Effect of ketamine on cognitive performance:</u> 1. Significant effect in accuracy on CPT for ketamine but not for amphetamine. 2. For HVLT immediate recall, there was a significant interactive effect of ketamine with amphetamine when compared to placebo. 2. For HVLT delayed recall, there was a significant interaction between ketamine and amphetamine.
Honey *et al.* *et al.* 2008	N/A	HC 15 (8:7) 29 (±7)	● Double-blind, placebo-controlled, randomised, within-subjects study design ● Two separate drug	fMRI: 1. Working memory (N-Back task). Button presses for targets and distractors. 2. CPT (Button press for	<u>Effect of ketamine on cognitive performance:</u> 1. Significant effect of ketamine for RT compared to placebo. 2. Significant effect of ketamine for RT compared to placebo.

			challenge sessions (placebo/active drug): ● Ketamine: low-dose bolus and iv. Injection while in scanner ● Ketamine: high-dose bolus and i.v. injection outside of ● Placebo: Saline	targets but not for distractors) 3. Sentence completion task (Button press for task completion) 4. Verbal self-monitoring task (Sub-vocalisation during sentence completion and incompletion)	Effect of ketamine on BOLD response; 1. ***Increased*** BOLD response of basal ganglia and thalamus after ketamine across all working memory load conditions with a strong effect for 2-Back (ROI analysis) 2. No effect of ketamine observed. 3. No effect of ketamine observed. 4. No effect of ketamine observed.
Anticevic *et al.* 2012	N/A	HC - Ketamine group 19 (10:9) 27.5 (±6.3)	● Double-blind, placebo-controlled, randomised, within-subjects study design ● Three separate drug challenge sessions (placebo/active drug): ● Ketamine: i.v. via initial bolus 0.23mg/kg over 1 min, followed by subsequent infusion (0.58mg/kg over 1 hour) ● Placebo: 1 saline injection	fMRI (FC): Delayed spatial working memory task	Effect of ketamine on cognitive performance: ● ***Decreased*** *a*ccuracy for working memory versus control trials under ketamine Effect of ketamine on BOLD response; ● Ketamine attenuated task-based activations of the DLPFC and precuneus for the working memory task and task-based deactivations for the DMN. Effect of ketamine on FC; ● Seed-based FC for the seed regions as part of the fronto-parietal and the DMN: Significant modulation of the task-based FC (delay part of the working memory task) and DMN under ketamine
Driesen *et al.* 2013b	N/A	HC – Ketamine group 22 (14:8) Missing	● Double-blind, placebo-controlled, randomised, within-subjects study design ● Three separate drug challenge sessions	fMRI (FC): Spatial '2-Back' and '4-Back' conditions. 1.Seed-based cross-correlation 2.Global-based connectivity	Effect of ketamine on cognitive performance: ● ***Decreased*** accuracy for working memory versus control trials under ketamine Effect of ketamine on BOLD response; ● Ketamine attenuated task-based activations of the DLPFC and precuneus for the working

			(placebo/active drug): ● Ketamine: i.v. via initial bolus 0.23mg/kg over 1 min, followed by subsequent infusion (0.58mg/kg over 1 hour) ● Placebo: 1 saline injection		memory task and task-based deactivations for the DMN. <u>Effect of ketamine on FC;</u> 1. ***Decreased*** FC between right DLPFC and MFG, IFG under ketamine when compared to placebo 2. ***Decreased*** FC within the left DLPFC
Braun *et al.* 2016	N/A	HC – Dextromethorphan group 37 (30:7) 25.3(±4.2)	● Double-blind, placebo-controlled, randomised, cross-over study design ● Two separate drug challenge sessions (placebo/active drug): ● Dextromethorphan: 120mg in capsule form ● Placebo: capsule	fMRI (FC): N-Back working memory task (0-Back and 2-Back conditions), Button presses for the target stimuli	<u>Effect of dextromethorphan on cognitive performance:</u> ● ***No differences*** for accuracy or RT in the working memory task between dextromethorphan versus placebo <u>Effect of dextromethorphan on FC;</u> ● FC for 270 regions in terms of network flexibility: ***Increased*** network flexibility under dextromethorphan when compared to placebo
Visual Attentional Processing					
Watson *et al.* 2009	N/A	HC 23 (15:8) 24.55 (±2.59)	● Double-blind, placebo-controlled study design ● Three separate drug challenge sessions: ● Saline (placebo) ● Ketamine (0.23mg/kg and infusion rate: 0.58mg/kg/hr)	EEG/ERP: 3-stimulus visual oddball task	<u>Effect of ketamine on thiopental on cognitive performance:</u> ● ***Decreased*** target RT after thiopental and ketamine when compared to placebo; stronger effect in thiopental <u>Effect of ketamine and thiopental on ERPs:</u> ● ***Decreased*** target P3b amplitude at electrode Pz after ketamine versus placebo ● ***Decreased*** target P3b amplitude at electrode Pz after

			● Thiopental (1.5mg/kg and infusion rate: 40mcg/kg/hr)		thiopental versus placebo ● ***No difference*** in target P3b amplitude between ketamine and thiopental ● Significant correlations between changes in P3b amplitude and target RT after thiopental but not ketamine at electrode Pz
Auditory Attentional Processing					
Umbricht *et al.* 2000	N/A	HC 20 (14:6) 24.6(±2.9)	● Double-blind, placebo-controlled study design ● Two separate drug challenge sessions (placebo/active drug): ● Ketamine: (0.24mg/kg and infusion rate: 0.0mg/kg/hr) ● Placebo: Physiological sodium chloride solution and 5% glucose	EEG/ERP Visual AX-CPT during the auditory test paradigm (MMN)	Effects of ketamine on cognitive performance: ● ***Decreased*** correct detection of hits after ketamine administration compared to baseline ● ***Increased*** false alarms after ketamine administration compared to baseline and placebo conditions Effects of ketamine on auditory ERPs: ● ***Decreased*** peak amplitudes of MMN after ketamine in pitch-deviance condition and duration-deviance condition compared to baseline condition and placebo condition, respectively. ● ***Increased*** N1 peak amplitude after ketamine administration compared to placebo
Heekeren *et al.* 2008	N/A	HC 15 (9:6) 38 (Missing)	● Randomized, double-blind, cross-over study design ● Low and high dose of the $5HT_{2A}$ agonist DMT ● Low and high dose of *S*-ketamine	EEG/ERP Visual AX-CPT during the auditory test paradigm (MMN)	Effects of ketamine on cognitive performance: ● Low-doses and high-doses of DMT and *S*-ketamine ***impair*** behavioural performance during the AX-CPT Effects of ketamine on auditory ERPs: ● ***Decrease*** in generation of MMN after *S*-ketamine > DMT ● Trend ***decrease*** in the frequency-deviant-induced MMN at electrode Fz after low-dose *S*-ketamine ● ***Decreased*** duration-deviant MMN at electrodes Fz, F3, F4 after low-dose and high-dose *S*-ketamine

Abbreviations. BOLD response, Blood oxygen level-dependent response; CPT, Continuous Performance Test; DLPFC, dorsolateral prefrontal cortex; DMN, default-mode network; DMT, dimethyltryptamine; FC, functional connectivity; HC, healthy controls; HVLT, Hopkins Verbal Learning Test; IFG, inferior frontal gyrus; MFG, middle frontal

gyrus; MMN, Mismatch Negativity; N/A, not applicable; *N*-methyl-D-aspartic acid (NMDA); PANSS, Positive and Negative Symptoms Scale; PFC, prefrontal cortex; ROI, region of interest; RT, response time; SD, standard deviation.

Table 3. Impact of NMDA-R coagonists and partial agonists on cognition

Study (year)	**Experimental group/ patient group Phase of schizophrenia**		**Control group/ control matching criteria**		**Study design/ Drug administration**	**Task design for cognitive function**	**Main findings - Effects of drug on cognition and/or neural response measures during cognition**
	***N* (M:F)**	**Mean age in years (SD)**	***N* (M:F)**	**Mean age in years (SD)**			
General Cognition							
Goff *et al.* 2005	EST- D-Cycloserine group (adjunctive treatment) 27 (24:3) 45.9(±7.4) EST – Placebo group 28 (20:8) 47.0(±8.6)		N/A		• Randomised double-blind, placebo-controlled, parallel group study design • 6 month trial • D-Cycloserine: 50 mg capsule at bedtime in adjunct with conventional antipsychotic medication • Placebo: Capsule at bedtime in adjunct with conventional antipsychotic medication	Cognitive battery: 1. CVLT 2. IQ estimation (Vocabulary, Information, Digit Span and Block Design) 3. ANART 4. Stroop Test 5. Categories 6. Finger Tapping 7. WCST	<u>Effect of D-Cycloserine on cognitive performance:</u> • ***No difference*** between treatment groups on any cognitive task at weeks 8, 12 and 24 compared to baseline.
Neumeister *et al.* 2006	N/A		HC 12 (8:4) 28.5(±10.5)		• Double-blind, randomised, balanced cross-over study design • Two separate drug challenge sessions (placebo/active drug):	Neuropsychological testing outside of PET scanner: 1. CogState computerised battery (i.e.	<u>Effect of glycine on cognitive performance:</u> • No significant effect of glycine on any of the neuropsychological tests compared to placebo <u>Effect of glycine on PET measures:</u> • ***Decreased*** whole-brain cerebral metabolic rate of glucose (CMRGlu) in glycine treated HCs when

			● Glycine: 200mg/kg body weight for 45 mins i.v. ● Placebo: Saline	attention, visual, verbal and working memory, executive function, speed of processing)	compared to placebo ● ***Decreased*** rCMRGlu in cerebellum and DLPFC without whole-brain correction (ROI analysis)
Buchanan *et al.* 2007	EST - D-Cycloserine group 53 (Missing) 44.4(±10.4) EST – Glycine group (adjunctive treatment) 52 (Missing) 42.6(±10.8) EST –Placebo group 52 (Missing) 43.4(±11.4)	N/A	● 16 week double-blind, double-dummy, parallel group, randomised study design ● Three treatment groups (pill-based): 1. Active glycine + placebo D-cycloserine 2. Placebo glycine + active D-cycloserine 3. Placebo glycine + placebo D-cycloserine	Battery: 2. Processing speed 3. Verbal fluency 4. Motor speed 5. Vigilance 6. Auditory memory 7. Visual spatial memory 8. Auditory working memory 9. Visuo-spatial working memory 10. Executive function	<u>Effect of glycine on cognitive performance:</u> ● ***No difference*** between glycine and placebo on the composite cognition summary score ● No significant glycine/placebo or D-cycloserine/placebo differences
Liem-Moolenaar *et al.* 2010	N/A	HC 45 (45:0) 18-55 Four treatment groups of each 15 subjects	● Double-blind, placebo-controlled, four-period cross-over ascending dose study design ● Scopolamine 0.5mg or placebo i.v. for 15 mins and 0, 3, 10, 30 mg of R213129	Adaptive tracking, finger tapping, Stroop test, VVLT	<u>Effect of scopolamine on cognitive performance:</u> ● ***Decrease*** in all parameters of VVLT with scopolamine when compared to placebo ● ***Decrease*** in all parameters of the Stroop test with scopolamine when compared to placebo

			or placebo oral administration		
Weiser et a. 2012	EST - D-serine group (adjunctive treatment) 97 (74:23) 39.39 (±12.0) EST – Placebo group 98 (70:28) 39.75(±12.3)	N/A	• 16 week double-blind, randomised, placebo-controlled study design • Over course of study between 1.6g/day and 2g/day of D-serine	Hebrew version of the MATRCIS with 10 subtests	<u>Effect of D-serine on cognitive performance:</u> • **No effect** of treatment group or group-by-time interaction for the composite score and the individual scores
Cain *et al.* 2014	EST - D-Cycloserine group (adjunctive treatment) 18 (16:2) 48.8(±11.5) EST – Placebo group 18 (15:3) 46.2(±13.3)	N/A	• 8 week single-blind, randomised, placebo-controlled study design • D-cycloserine 50 mg/week or placebo (capsule)	• Cognitive Remediation between 3 – 5 timed weekly – Brain Fitness Program • Auditory discrimination training • MATRICS neuropsychological test battery	<u>Effect of D-Cycloserine on cognitive performance:</u> • ***No difference*** in auditory discrimination training in D-Cycloserine when compared to placebo at baseline • ***Increase*** **i**n auditory discrimination training in D-Cycloserine when compared to placebo at each visit after baseline • ***No difference*** in the composite sore or individual scores of the MATRICS in D-Cycloserine when compared to placebo • ***Increase*** in composite score and individual scores of some MATRICS tests in placebo when compared to D-Cycloserine
Christmas *et al.* 2014	N/A	HC – Org 25935 group 16?(16:0) 23.8(±Missing) HC – Placebo grouo 16?(16:0)	• Double-blind, randomised, placebo-controlled, parallel group, single-dose study design • Org 25935: Oral dose of 12mg • Matching placebo	• Visuo-spatial cognitive task (Manikin task) • Digit span • Verbal memory task	<u>Effect of Org 25925 on cognitive performance:</u> • ***No difference*** between the groups in the Manikin task or any of the other tasks

		25.3(±Missing)			
Working memory					
Duncan *et al.* 2004	EST - D-Cycloserine group (adjunctive treatment) 10 (10:0) 48.7 (±5.1) EST- Placebo group 12(12:0) 54.5(±6.8)	N/A	• 4-week double-blind, randomised, parallel-group study design • D-cycloserine: 50 mg (capsule) or placebo (capsule)	1. AX-CPT 2. Sternberg Short Term Memory Scanning Paradigm • At baseline, after 2 weeks and 4 weeks • In subgroup of 7 EST in the D-cycloserine group and 8 in the placebo group	Effect of D-cycloserine on cognitive performance: 1. ***No differences*** in accuracy or RT on the CPT between D-cycloserine and placebo at all three time points 2. ***No differences*** in accuracy or RT on the Sternberg test between D-cycloserine and placebo at all three time points

Abbreviations. ANART, Adult North American Reading Test; CVLT, California Verbal Learning Test; EST, patients with established schizophrenia; HVLT, Hopkins Verbal Learning Test; N/A, not applicable; *N*-methyl-D-aspartic acid; NMDA; PANSS, Positive and Negative Symptoms Scale; RT, response time; SD, standard deviation; WCST, Wisconsin Card Sorting Test.

References

ABI-SAAB WM, D'SOUZA DC, MOGHADDAM B, KRYSTAL JH. 1998. The NMDA antagonist model for schizophrenia: promise and pitfalls. Pharmacopsychiatry, 31 Suppl 2, 104-9.

ACKER TM, YUAN H, HANSEN KB, VANCE KM, OGDEN KK, JENSEN HS, *et al*. 2011. Mechanism for noncompetitive inhibition by novel GluN2C/D N-methyl-D-aspartate receptor subunit-selective modulators. Mol Pharmacol, 80, 782-95.

ADAMS DH, ZHANG L, MILLEN BA, KINON BJ, GOMEZ JC. 2014. Pomaglumetad Methionil (LY2140023 Monohydrate) and Aripiprazole in Patients with Schizophrenia: A Phase 3, Multicenter, Double-Blind Comparison. Schizophr Res Treatment, 2014, 758212.

ALEXANDER SPH, BENSON HE, FACCENDA E, PAWSON AJ, SHARMAN JL, SPEDDING M, PETERS JA and HARMAR AJ, CGTP Collaborators. (2015) The Concise Guide to PHARMACOLOGY 2015/16: G Protein-Coupled Receptors. Br J Pharmacol. 170: 1459-1581.

AMITAI N, MARKOU A. 2010. Disruption of performance in the five-choice serial reaction time task induced by administration of N-methyl-D-aspartate receptor antagonists: relevance to cognitive dysfunction in schizophrenia. Biol Psychiatry, 68, 5-16.

ANTICEVIC A, CORLETT PR, COLE MW, SAVIC A, GANCSOS M, TANG Y, *et al*. 2015. N-methyl-D-aspartate receptor antagonist effects on prefrontal cortical connectivity better model early than chronic schizophrenia. Biol Psychiatry, 77, 569-80.

ANTICEVIC A, GANCSOS M, MURRAY JD, REPOVS G, DRIESEN NR, ENNIS DJ, *et al*. 2012. NMDA receptor function in large-scale anticorrelated neural systems with implications for cognition and schizophrenia. Proc Natl Acad Sci U S A, 109, 16720-5.

ARAI AC, KESSLER M. 2007. Pharmacology of ampakine modulators: from AMPA receptors to synapses and behavior. Curr Drug Targets, 8, 583-602.

AWAD H, HUBERT GW, SMITH Y, LEVEY AI, CONN PJ. 2000. Activation of metabotropic glutamate receptor 5 has direct excitatory effects and potentiates NMDA receptor currents in neurons of the subthalamic nucleus. J Neurosci, 20, 7871-9.

AYALA JE, CHEN Y, BANKO JL, SHEFFLER DJ, WILLIAMS R, TELK A N, *et al*. 2009. mGluR5 positive allosteric modulators facilitate both hippocampal LTP and LTD and enhance spatial learning. Neuropsychopharmacology, 34, 2057-71.

BADO P, MADEIRA C, VARGAS-LOPES C, MOULIN T C, WASILEWSKA-SAMPAIO AP, MARETTI L, *et al*. 2011. Effects of low-dose D-serine on recognition and working memory in mice. Psychopharmacology (Berl), 218, 461-70.

BALU DT, COYLE JT. 2015. The NMDA receptor 'glycine modulatory site' in schizophrenia: D-serine,

glycine, and beyond. Curr Opin Pharmacol, 20, 109-15.

BARNES SA, YOUNG JW, BATE ST, NEILL JC. 2016. Dopamine D1 receptor activation improves PCP-induced performance disruption in the 5C-CPT by reducing inappropriate responding. Behav Brain Res, 300, 45-55.

BAST T, DA SILVA BM, MORRIS RG. 2005. Distinct contributions of hippocampal NMDA and AMPA receptors to encoding and retrieval of one-trial place memory. J Neurosci, 25, 5845-56.

BAXTER MG, LANTHORN TH, FRICK KM, GOLSKI S, WAN RQ, OLTON DS. 1994. D-cycloserine, a novel cognitive enhancer, improves spatial memory in aged rats. Neurobiol Aging, 15, 207-13.

BERRIDGE CW, SPENCER R C. 2016. Differential cognitive actions of norepinephrine a2 and a1 receptor signaling in the prefrontal cortex. Brain Res, 1641, 189-96.

BERRY-KRAVIS E, DES PORTES, V., HAGERMAN, R., JACQUEMONT, S., CHARLES, P., VISOOTSAK, J. *et al*. 2016. Mavoglurant in fragile X syndrome: Results of two randomized, double-blind, placebo-controlled trials. Sci Transl Med, 8, 321ra5.

BLOKLAND GA, MESHOLAM-GATELY RI, TOULOPOULOU T, DEL RE EC, LAM M, DELISI LE, *et al*. 2016. Heritability of Neuropsychological Measures in Schizophrenia and Nonpsychiatric Populations: A Systematic Review and Meta-analysis. Schizophr Bull.

BRAUN U, SCHAFER A, BASSETT DS, RAUSCH F, SCHWEIGER JI, BILEK E, *et al*. 2016. Dynamic brain network reconfiguration as a potential schizophrenia genetic risk mechanism modulated by NMDA receptor function. Proc Natl Acad Sci U S A, 113, 12568-12573.

BRIDGES RJ, NATALE NR, PATEL SA. (2012) System X(C)(-) Cystine/Glutamate Antiporter: An Update on Molecular Pharmacology and Roles within the Cns. British Journal of Pharmacology 165: 20-34.

BROBERG BV, DIAS R, GLENTHOJ BY, OLSEN CK. 2008. Evaluation of a neurodevelopmental model of schizophrenia--early postnatal PCP treatment in attentional set-shifting. Behav Brain Res, 190, 160-3.

BROBERG BV, GLENTHOJ BY, DIAS R, LARSEN DB, OLSEN CK. 2009. Reversal of cognitive deficits by an ampakine (CX516) and sertindole in two animal models of schizophrenia--sub-chronic and early postnatal PCP treatment in attentional set-shifting. Psychopharmacology (Berl), 206, 631-40.

BROWN GG, THOMPSON WK. 2010. Functional brain imaging in schizophrenia: selected results and methods. Curr Top Behav Neurosci, 4, 181-214.

BUCHANAN RW, JAVITT DC, MARDER SR, SCHOOLER NR, GOLD JM, MCMAHON RP, *et al*. 2007. The Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST): the efficacy of glutamatergic agents for negative symptoms and cognitive impairments. Am J Psychiatry, 164, 1593-602.

BURGDORF J, KROES RA, ZHANG XL, GROSS AL, SCHMIDT M, WEISS C, *et al*. 2015. Rapastinel (GLYX-

13) has therapeutic potential for the treatment of post-traumatic stress disorder: Characterization of a NMDA receptor-mediated metaplasticity process in the medial prefrontal cortex of rats. Behav Brain Res, 294, 177-85.

BYGRAVE AM, MASIULIS S, NICHOLSON E, BERKEMANN M, BARKUS C, SPRENGEL R, *et al*. 2016. Knockout of NMDA receptor from parvalbumin interneurons sensitizes to schizophrenia-related deficits induced by MK-801. Transl Psychiatry, 6, e778.

CAIN CK, MCCUE M, BELLO I, CREEDON T, TANG DI, LASKA E, *et al*. 2014. d-Cycloserine augmentation of cognitive remediation in schizophrenia. Schizophr Res, 153, 177-83.

CARLSSON A, HANSSON LO, WATERS N, CARLSSON ML. 1999. A glutamatergic deficiency model of schizophrenia. Br J Psychiatry Suppl, 2-6.

CARLSSON A, WATERS N, WATERS S, CARLSSON ML. 2000. Network interactions in schizophrenia - therapeutic implications. Brain Res Brain Res Rev, 31, 342-9.

CHEN Y, GOUDET C, PIN JP, CONN PJ. 2008. N-{4-Chloro-2-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]phenyl}-2-hydroxybe nzamide (CPPHA) acts through a novel site as a positive allosteric modulator of group 1 metabotropic glutamate receptors. Mol Pharmacol, 73, 909-18.

CHOI KH, WYKES, T. & KURTZ, M. M. 2013. Adjunctive pharmacotherapy for cognitive deficits in schizophrenia: meta-analytical investigation of efficacy. Br J Psychiatry, 203, 172-8.

CHRISTMAS D, DIAPER A, WILSON S, RICH A, PHILLIPS S, UDO DE HAES J, *et al*. 2014. A randomised trial of the effect of the glycine reuptake inhibitor Org 25935 on cognitive performance in healthy male volunteers. Hum Psychopharmacol, 29, 163-71.

CLARKE HF, WALKER SC, DALLEY JW, ROBBINS TW, ROBERTS AC. 2007. Cognitive inflexibility after prefrontal serotonin depletion is behaviorally and neurochemically specific. Cereb Cortex, 17, 18-27.

CLEVA RM, OLIVE MF. 2011. Positive allosteric modulators of type 5 metabotropic glutamate receptors (mGluR5) and their therapeutic potential for the treatment of CNS disorders. Molecules, 16, 2097-106.

CLOKE JM, WINTERS BD. 2015. alpha(4)beta(2) Nicotinic receptor stimulation of the GABAergic system within the orbitofrontal cortex ameliorates the severe crossmodal object recognition impairment in ketamine-treated rats: implications for cognitive dysfunction in schizophrenia. Neuropharmacology, 90, 42-52.

CORLETT PR, HONEY GD, AITKEN MR, DICKINSON A, SHANKS DR, ABSALOM AR, *et al*. 2006. Frontal responses during learning predict vulnerability to the psychotogenic effects of ketamine: linking cognition, brain activity, and psychosis. Arch Gen Psychiatry, 63, 611-21.

COSGROVE J, NEWELL TG. 1991. Recovery of neuropsychological functions during reduction in use of

phencyclidine. J Clin Psychol, 47, 159-69.

COYLE JT. 2006. Glutamate and schizophrenia: beyond the dopamine hypothesis. Cell Mol Neurobiol, 26, 365-84.

COYLE JT, BALU D, BENNEYWORTH M, BASU A, ROSEMAN A. 2010. Beyond the dopamine receptor: novel therapeutic targets for treating schizophrenia. Dialogues Clin Neurosci, 12, 359-82.

D'SOUZA DC, SINGH N, ELANDER J, CARBUTO M, PITTMAN B, UDO DE HAES J, *et al*. 2012. Glycine transporter inhibitor attenuates the psychotomimetic effects of ketamine in healthy males: preliminary evidence. Neuropsychopharmacology, 37, 1036-46.

DAMGAARD T, LARSEN DB, HANSEN SL, GRAYSON B, NEILL JC, PLATH N. 2010. Positive modulation of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors reverses sub-chronic PCP-induced deficits in the novel object recognition task in rats. Behav Brain Res, 207, 144-50.

DARRAH JM, STEFANI MR, MOGHADDAM B. 2008. Interaction of N-methyl-D-aspartate and group 5 metabotropic glutamate receptors on behavioral flexibility using a novel operant set-shift paradigm. Behav Pharmacol, 19, 225-34.

DAUVERMANN MR, WHALLEY HC, SCHMIDT A, LEE GL, ROMANIUK L, ROBERTS N, *et al*. 2014. Computational neuropsychiatry - schizophrenia as a cognitive brain network disorder. Front Psychiatry, 5, 30.

DAWSON N, KURIHARA M, THOMSON DM, WINCHESTER CL, MCVIE A, HEDDE JR, *et al*. 2015. Altered functional brain network connectivity and glutamate system function in transgenic mice expressing truncated Disrupted-in-Schizophrenia 1. Transl Psychiatry, 5, e569.

DAWSON N, MCDONALD M, HIGHAM DJ, MORRIS BJ, PRATT JA. 2014. Subanesthetic ketamine treatment promotes abnormal interactions between neural subsystems and alters the properties of functional brain networks. Neuropsychopharmacology, 39, 1786-98.

DAWSON N, MORRIS BJ, PRATT JA. 2013. Subanaesthetic ketamine treatment alters prefrontal cortex connectivity with thalamus and ascending subcortical systems. Schizophr Bull, 39, 366-77.

DAWSON N, THOMPSON RJ, MCVIE A, THOMSON DM, MORRIS BJ, PRATT JA. 2012. Modafinil reverses phencyclidine-induced deficits in cognitive flexibility, cerebral metabolism, and functional brain connectivity. Schizophr Bull, 38, 457-74.

DE BRUIN NM, VAN DRIMMELEN M, KOPS M, VAN ELK J, WETERING MM, SCHWIENBACHER I. 2013. Effects of risperidone, clozapine and the 5-HT6 antagonist GSK-742457 on PCP-induced deficits in reversal learning in the two-lever operant task in male Sprague Dawley rats. Behav Brain Res, 244, 15-28.

DEWILDE KE, LEVITCH CF, MURROUGH JW, MATHEW SJ, IOSIFESCU DV. 2015. The promise of

ketamine for treatment-resistant depression: current evidence and future directions. Ann N Y Acad Sci, 1345, 47-58.

DIACONESCU AO, JENSEN J, WANG H, WILLEIT M, MENON M, KAPUR S, *et al*. 2011. Aberrant Effective Connectivity in Schizophrenia Patients during Appetitive Conditioning. Front Hum Neurosci, 4, 239.

DIDRIKSEN M, SKARSFELDT T, ARNT J. 2007. Reversal of PCP-induced learning and memory deficits in the Morris' water maze by sertindole and other antipsychotics. Psychopharmacology (Berl), 193, 225-33.

DOWD EC, FRANK MJ, COLLINS A, GOLD JM, BARCH DM. 2016. Probabilistic Reinforcement Learning in Patients With Schizophrenia: Relationships to Anhedonia and Avolition. Biol Psychiatry Cogn Neurosci Neuroimaging, 1, 460-473.

DRIESEN NR, MCCARTHY G, BHAGWAGAR Z, BLOCH M, CALHOUN V, D'SOUZA DC, *et al*. 2013. Relationship of resting brain hyperconnectivity and schizophrenia-like symptoms produced by the NMDA receptor antagonist ketamine in humans. Mol Psychiatry, 18, 1199-204.

DRIESEN NR, MCCARTHY G, BHAGWAGAR Z, BLOCH M, CALHOUN V, D'SOUZA DC, *et al*. 2013b. The impact of NMDA receptor blockade on human working memory-related prefrontal function and connectivity. Neuropsychopharmacology 38:2613-2622.

DUAN TT, TAN JW, YUAN Q, CAO J, ZHOU QX, XU L. 2013. Acute ketamine induces hippocampal synaptic depression and spatial memory impairment through dopamine D1/D5 receptors. Psychopharmacology (Berl), 228, 451-61.

DUNCAN EJ, SZILAGYI S, SCHWARTZ MP, BUGARSKI-KIROLA D, KUNZOVA A, NEGI S, *et al*. 2004. Effects of D-cycloserine on negative symptoms in schizophrenia. Schizophr Res, 71, 239-48.

FARBER NB, KIM SH, DIKRANIAN K, JIANG XP, HEINKEL C. 2002. Receptor mechanisms and circuitry underlying NMDA antagonist neurotoxicity. Mol Psychiatry, 7, 32-43.

FROHLICH J, VAN HORN JD. 2014. Reviewing the ketamine model for schizophrenia. J Psychopharmacol, 28, 287-302.

FRYER JD, LUKAS RJ. 1999. Noncompetitive Functional Inhibition at Diverse, Human Nicotinic Acetylcholine Receptor Subtypes by Bupropion, Phencyclidine, and Ibogaine. J Pharmacol Exp Ther 288: 88-92.

GASTAMBIDE F, MITCHELL SN, ROBBINS TW, TRICKLEBANK MD, GILMOUR G. 2013. Temporally distinct cognitive effects following acute administration of ketamine and phencyclidine in the rat. Eur Neuropsychopharmacol, 23, 1414-22.

GLAHN DC, RAGLAND JD, ABRAMOFF A, BARRETT J, LAIRD AR, BEARDEN CE, *et al*. 2005. Beyond

hypofrontality: a quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia. Hum Brain Mapp, 25, 60-9.

GOFF DC, COYLE JT. 2001. The emerging role of glutamate in the pathophysiology and treatment of schizophrenia. Am J Psychiatry, 158, 1367-77.

GOFF DC, HERZ L, POSEVER T, SHIH V, TSAI G, HENDERSON DC, *et al*. 2005. A six-month, placebo-controlled trial of D-cycloserine co-administered with conventional antipsychotics in schizophrenia patients. Psychopharmacology (Berl), 179, 144-50.

GOFF DC, LAMBERTI JS, LEON AC, GREEN MF, MILLER AL, PATEL J, *et al*. 2008. A placebo-controlled add-on trial of the Ampakine, CX516, for cognitive deficits in schizophrenia. Neuropsychopharmacology, 33, 465-72.

GOFF DC. (2012) D-Cycloserine: An Evolving Role in Learning and Neuroplasticity in Schizophrenia. Schizophrenia Research, 38, 936 –941.

GOPINATH K, MALTBIE E, URUSHINO N, KEMPF D, HOWELL L. 2016. Ketamine-induced changes in connectivity of functional brain networks in awake female nonhuman primates: a translational functional imaging model. Psychopharmacology (Berl), 233, 3673-3684.

GREEN MF. 2016. Impact of cognitive and social cognitive impairment on functional outcomes in patients with schizophrenia. J Clin Psychiatry, 77 Suppl 2, 8-11.

GREGORY KJ, HERMAN EJ, RAMSEY AJ, HAMMOND AS, BYUN NE, STAUFFER SR, *et al*. 2013. Aryl Piperazine Metabotropic Glutamate Receptor 5 Positive Allosteric Modulators Possess Efficacy in Preclinical Models of Nmda Hypofunction and Cognitive Enhancement. Journal of Pharmacology and Experimental Therapeutics 347: 438.

GRIEBEL G, PICHAT P, BOULAY D, NAIMOLI V, POTESTIO L, FEATHERSTONE R, *et al*. 2016. The mGluR2 positive allosteric modulator, SAR218645, improves memory and attention deficits in translational models of cognitive symptoms associated with schizophrenia. Sci Rep, 6, 35320.

GRIMM O, GASS N, WEBER-FAHR W, SARTORIUS A, SCHENKER E, SPEDDING M, RISTERUCCI C, *et al*. 2015. Acute ketamine challenge increases resting state prefrontal-hippocampal connectivity in both humans and rats. Psychopharmacology (Berl), 232, 4231-41.

GUNDUZ-BRUCE H. 2009. The acute effects of NMDA antagonism: from the rodent to the human brain. Brain Res Rev, 60, 279-86.

GUNTHNER J, SCHOLL J, FAVARON E, HARMER CJ, JOHANSEN-BERG H, REINECKE A. 2016. The NMDA receptor partial agonist d-cycloserine does not enhance motor learning. J Psychopharmacol, 30, 994-9.

GUPTA SC, RAVIKRISHNAN A, LIU J, MAO Z, PAVULURI R, HILLMAN BG, *et al*. 2016. The NMDA receptor GluN2C subunit controls cortical excitatory-inhibitory balance, neuronal oscillations and cognitive function. Sci Rep, 6, 38321.

HADLEY JA, KRAGULJAC NV, WHITE DM, VER HOEF L, TABORA J, LAHTI AC. 2016. Change in brain network topology as a function of treatment response in schizophrenia: a longitudinal resting-state fMRI study using graph theory. NPJ Schizophr. 2:16014.

HEEKEREN K, DAUMANN J, NEUKIRCH A, STOCK C, KAWOHL W, NORRA C, *et al*. 2008. Mismatch negativity generation in the human 5HT2A agonist and NMDA antagonist model of psychosis. Psychopharmacology (Berl), 199, 77-88.

HENLEY JM, WILKINSON KA. 2016. Synaptic AMPA receptor composition in development, plasticity and disease. Nat Rev Neurosci, 17, 337-50.

HERESCO-LEVY U, ERMILOV M, SHIMONI J, SHAPIRA B, SILIPO G, JAVITT DC. 2002. Placebo-controlled trial of D-cycloserine added to conventional neuroleptics, olanzapine, or risperidone in schizophrenia. Am J Psychiatry, 159, 480-2.

HIGGINS GA, BALLARD TM, ENDERLIN M, HAMAN M, KEMP JA. 2005. Evidence for improved performance in cognitive tasks following selective NR2B NMDA receptor antagonist pre-treatment in the rat. Psychopharmacology (Berl), 179, 85-98.

HILLMAN BG, GUPTA SC, STAIRS DJ, BUONANNO A, DRAVID SM. 2011. Behavioral analysis of NR2C knockout mouse reveals deficit in acquisition of conditioned fear and working memory. Neurobiol Learn Mem, 95, 404-14.

HOMAYOUN H, STEFANI MR, ADAMS BW, TAMAGAN GD, MOGHADDAM B. 2004. Functional Interaction Between NMDA and mGlu5 Receptors: Effects on Working Memory, Instrumental Learning, Motor Behaviors, and Dopamine Release. Neuropsychopharmacology, 29, 1259-69.

HONEY GD, CORLETT PR, ABSALOM AR, LEE M, POMAROL-CLOTET E, MURRAY GK, *et al*. 2008. Individual differences in psychotic effects of ketamine are predicted by brain function measured under placebo. J Neurosci, 28, 6295-303.

HORIGUCHI M, HANNAWAY KE, ADELEKUN AE, HUANG M, JAYATHILAKE K, MELTZER HY. 2013. D(1) receptor agonists reverse the subchronic phencyclidine (PCP)-induced novel object recognition (NOR) deficit in female rats. Behav Brain Res, 238, 36-43.

IHALAINEN J, SAVOLAINEN K, TANILA H, FORSBERG MM. 2016. Comparison of phencyclidine-induced spatial learning and memory deficits and reversal by sertindole and risperidone between Lister Hooded and Wistar rats. Behav Brain Res, 305, 140-7.

INGVAR M, AMBROS-INGERSON J, DAVIS M, GRANGER R, KESSLER M, ROGERS GA, *et al*. 1997. Enhancement by an ampakine of memory encoding in humans. Exp Neurol, 146, 553-9.

ISHERWOOD SN, PEKCEC A, NICHOLSON JR, ROBBINS TW, DALLEY JW. 2015. Dissociable effects of mGluR5 allosteric modulation on distinct forms of impulsivity in rats: interaction with NMDA receptor antagonism. Psychopharmacology (Berl), 232, 3327-44.

IWATA Y, NAKAJIMA S, SUZUKI T, KEEFE RS, PLITMAN E, CHUNG JK, *et al*. 2015. Effects of glutamate positive modulators on cognitive deficits in schizophrenia: a systematic review and meta-analysis of double-blind randomized controlled trials. Mol Psychiatry, 20, 1151-60.

JAVITT DC. 2007. Glutamate and schizophrenia: phencyclidine, N-methyl-D-aspartate receptors, and dopamine-glutamate interactions. Int Rev Neurobiol, 78, 69-108.

JAVITT DC. 2010. Glutamatergic theories of schizophrenia. Isr J Psychiatry Relat Sci, 47, 4-16.

JAVITT DC, ZUKIN SR, HERESCO-LEVY U, UMBRICHT D. 2012. Has an angel shown the way? Etiological and therapeutic implications of the PCP/NMDA model of schizophrenia. Schizophr Bull, 38, 958-66.

JENTSCH JD, TRAN A, TAYLOR JR, ROTH RH. 1998. Prefrontal cortical involvement in phencyclidine-induced activation of the mesolimbic dopamine system: behavioral and neurochemical evidence. Psychopharmacology (Berl), 138, 89-95.

JONES CA, BROWN AM, AUER DP, FONE KC. 2011. The mGluR2/3 agonist LY379268 reverses post-weaning social isolation-induced recognition memory deficits in the rat. Psychopharmacology (Berl), 214, 269-83.

JOULES R, DOYLE OM, SCHWARZ AJ, O'DALY OG, BRAMMER M, WILLIAMS SC, *et al*. 2015. Ketamine induces a robust whole-brain connectivity pattern that can be differentially modulated by drugs of different mechanism and clinical profile. Psychopharmacology (Berl), 232, 4205-18.

KANTROWITZ JT, JAVITT DC 2010. N-methyl-D-aspartate (NMDA) receptor dysfunction or dysregulation: the final common pathway on the road to schizophrenia? Brain Res Bull 83(3-4), 108-121.

KAS MJ, GLENNON JC, BUITELAAR J, EY E, BIEMANS B, CRAWLEY J, *et al*. 2014. Assessing behavioural and cognitive domains of autism spectrum disorders in rodents: current status and future perspectives. Psychopharmacology (Berl), 231, 1125-46.

KAWABE K, YOSHIHARA T, ICHITANI Y, IWASAKI T. 1998. Intrahippocampal D-cycloserine improves MK-801-induced memory deficits: radial-arm maze performance in rats. Brain Res, 814, 226-30.

KHLESTOVA E, JOHNSON JW, KRYSTAL JH, LISMAN J. 2016. The Role of GluN2C-Containing NMDA Receptors in Ketamine's Psychotogenic Action and in Schizophrenia Models. J Neurosci, 36, 11151-11157.

KOS T, NIKIFORUK A, RAFA D, POPIK P. 2011. The effects of NMDA receptor antagonists on

attentional set-shifting task performance in mice. Psychopharmacology (Berl), 214, 911-21.

KOTERMANSKI SE, JOHNSON JW. 2009. Mg2+ imparts NMDA receptor subtype selectivity to the Alzheimer's drug memantine. J Neurosci, 29, 2774-9.

KRAGULJAC NV, FROLICH MA, TRAN S, WHITE DM, NICHOLS N, BARTON-MCARDLE A, *et al*. 2016. Ketamine modulates hippocampal neurochemistry and functional connectivity: a combined magnetic resonance spectroscopy and resting-state fMRI study in healthy volunteers. Mol Psychiatry.

KRYSTAL JH, ABI-SAAB W, PERRY E, D'SOUZA DC, LIU N, GUEORGUIEVA R, *et al*. 2005. Preliminary evidence of attenuation of the disruptive effects of the NMDA glutamate receptor antagonist, ketamine, on working memory by pretreatment with the group II metabotropic glutamate receptor agonist, LY354740, in healthy human subjects. Psychopharmacology (Berl), 179, 303-9.

KRYSTAL JH, D'SOUZA DC, KARPER LP, BENNETT A, ABI-DARGHAM A, ABI-SAAB D, *et al*. 1999. Interactive effects of subanesthetic ketamine and haloperidol in healthy humans. Psychopharmacology (Berl), 145, 193-204.

KRYSTAL JH, KARPER LP, SEIBYL JP, FREEMAN GK, DELANEY R, BREMNER JD, *et al.* 1994. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry, 51, 199-214.

KUMAR G, OLLEY J, STECKLER T, TALPOS J. 2015. Dissociable effects of NR2A and NR2B NMDA receptor antagonism on cognitive flexibility but not pattern separation. Psychopharmacology (Berl), 232, 3991-4003.

LACROSSE AL, BURROWS BT, ANGULO RM, CONRAD PR, HIMES SM, MATHEWS N, *et al*. 2015. mGluR5 positive allosteric modulation and its effects on MK-801 induced set-shifting impairments in a rat operant delayed matching/non-matching-to-sample task. Psychopharmacology (Berl), 232, 251-8.

LI JT, SU YA, GUO CM, FENG Y, YANG Y, HUANG RH, *et al*. 2011. Persisting cognitive deficits induced by low-dose, subchronic treatment with MK-801 in adolescent rats. Eur J Pharmacol, 652, 65-72.

LI M L, YANG SS, XING B, FERGUSON BR, GULCHINA Y, LI YC, *et al*. 2015. LY395756, an mGluR2 agonist and mGluR3 antagonist, enhances NMDA receptor expression and function in the normal adult rat prefrontal cortex, but fails to improve working memory and reverse MK801-induced working memory impairment. Exp Neurol, 273, 190-201.

LIN CH, HUANG YJ, LIN CJ, LANE HY, TSAI GE. 2014. NMDA neurotransmission dysfunction in mild cognitive impairment and Alzheimer's disease. Curr Pharm Des, 20, 5169-79.

LINDEFORS N, BARATI S, O'CONNOR WT. 1997. Differential effects of single and repeated ketamine

administration on dopamine, serotonin and GABA transmission in rat medial prefrontal cortex. Brain Res, 759, 205-12.

LINS BR, PHILLIPS AG, HOWLAND JG. 2015. Effects of D- and L-govadine on the disruption of touchscreen object-location paired associates learning in rats by acute MK-801 treatment. Psychopharmacology (Berl), 232, 4371-82.

LISMAN JE, FELLOUS JM, WANG XJ. 1998. A role for NMDA receptor channels in working memory. Nat Neurosci, 1, 273-5.

LIU F, GRAUER S, KELLEY C, NAVARRA R, GRAF R, ZHANG G, *et al*. 2008. ADX47273 [S-(4-fluoro-phenyl)-{3-[3-(4-fluoro-phenyl)-[1,2,4]-oxadiazol-5-yl]-piperidin-1- yl}-methanone]: a novel metabotropic glutamate receptor 5-selective positive allosteric modulator with preclinical antipsychotic-like and procognitive activities. J Pharmacol Exp Ther, 327, 827-39.

LUBY ED, COHEN BD, ROSENBAUM G, GOTTLIEB JS, KELLEY R. 1959. Study of a new schizophrenomimetic drug; sernyl. AMA Arch Neurol Psychiatry, 81, 363-9.

LYNCH G, GRANGER R, AMBROS-INGERSON J, DAVIS CM, KESSLER M, SCHEHR R. 1997. Evidence that a positive modulator of AMPA-type glutamate receptors improves delayed recall in aged humans. Exp Neurol, 145, 89-92.

MANAHAN-VAUGHAN D, BRAUNEWELL KH. 2005. The metabotropic glutamate receptor, mGluR5, is a key determinant of good and bad spatial learning performance and hippocampal synaptic plasticity. Cereb Cortex, 15, 1703-13.

MANOACH DS. 2003. Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings. Schizophr Res, 60, 285-98.

MAREK GJ, BEHL B, BESPALOV AY, GROSS G, LEE Y, SCHOEMAKER H. 2010. Glutamatergic (N-methyl-D-aspartate receptor) hypofrontality in schizophrenia: too little juice or a miswired brain? Mol Pharmacol, 77, 317-26.

MARIN O. 2012. Interneuron dysfunction in psychiatric disorders. Nat Rev Neurosci, 13, 107-20.

MATHUR P, GRAYBEAL C, FEYDER M, DAVIS MI, HOLMES A. 2009. Fear memory impairing effects of systemic treatment with the NMDA NR2B subunit antagonist, Ro 25-6981, in mice: attenuation with ageing. Pharmacol Biochem Behav, 91, 453-60.

MCCLOUD TL, CADDY C, JOCHIM J, RENDELL JM, DIAMOND PR, SHUTTLEWORTH C, *et al*. 2015. Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults. Cochrane Database Syst Rev, CD011611.

MCLEAN SL, IDRIS NF, GRAYSON B, GENDLE DF, MACKIE C, LESAGE AS, *et al*. 2012. PNU-120596, a positive allosteric modulator of alpha7 nicotinic acetylcholine receptors, reverses a sub-chronic

phencyclidine-induced cognitive deficit in the attentional set-shifting task in female rats. J Psychopharmacol, 26, 1265-70.

MICHELOYANNIS S, PACHOU E, STAM CJ, BREAKSPEAR M, BITSIOS P, VOURKAS M, *et al*. 2006. Small-world networks and disturbed functional connectivity in schizophrenia. Schizophr Res, 87, 60-6.

MILLAN MJ. 2005. N-Methyl-D-aspartate receptors as a target for improved antipsychotic agents: novel insights and clinical perspectives. Psychopharmacology (Berl), 179, 30-53.

MILOVAN DL, BARIBEAU J, ROTH RM, STIP E. 2004. ERP study of pre-attentive auditory processing in treatment-refractory schizophrenia. Brain Cogn, 55, 355-7.

MION G, VILLEVIELLE T. 2013. Ketamine Pharmacology: An Update (Pharmacodynamics and Molecular Aspects, Recent Findings). CNS Neurosci Ther 19, 370-380.

MOGHADDAM B, ADAMS BW. 1998. Reversal of phencyclidine effects by a group II metabotropic glutamate receptor agonist in rats. Science, 281, 1349-52.

MOGHADDAM B, KRYSTAL JH. 2012. Capturing the angel in "angel dust": twenty years of translational neuroscience studies of NMDA receptor antagonists in animals and humans. Schizophr Bull, 38, 942-9.

MORRIS RG. 2013. NMDA receptors and memory encoding. Neuropharmacology, 74, 32-40.

MOTHET JP, LE BAIL M, BILLARD JM. 2015. Time and space profiling of NMDA receptor co-agonist functions. J Neurochem, 135, 210-25.

MOTHET JP, PARENT AT, WOLOSKER H, BRADY RO JR, LINDEN DJ, FERRIS CD, *et al*. 2000. D-serine is an endogenous ligand for the glycine site of the N-methyl-D-aspartate receptor. Proc Natl Acad Sci U S A, 97, 4926-31.

NEUMEISTER A, CARSON R, HENRY S, PLANETA-WILSON B, BINNEMAN B, MAGUIRE RP, *et al*. 2006. Cerebral metabolic effects of intravenous glycine in healthy human subjects. J Clin Psychopharmacol, 26, 595-9.

NIKIFORUK A, KOS T, HOLUJ M, POTASIEWICZ A, POPIK P. 2016. Positive allosteric modulators of alpha 7 nicotinic acetylcholine receptors reverse ketamine-induced schizophrenia-like deficits in rats. Neuropharmacology, 101, 389-400.

NIKIFORUK A, POPIK P. 2014. The effects of acute and repeated administration of ketamine on attentional performance in the five-choice serial reaction time task in rats. Eur Neuropsychopharmacol, 24, 1381-93.

NIKIFORUK A, POPIK P, DRESCHER KU, VAN GAALEN M, RELO AL, MEZLER M, *et al*. 2010. Effects of a positive allosteric modulator of group II metabotropic glutamate receptors, LY487379, on cognitive

flexibility and impulsive-like responding in rats. J Pharmacol Exp Ther, 335, 665-73.

NISWENDER CM, CONN PJ. 2010. Metabotropic glutamate receptors: physiology, pharmacology, and disease. Annu Rev Pharmacol Toxicol, 50, 295-322.

NODA Y, KAMEI H, MAMIYA T, FURUKAWA H, NABESHIMA T. 2000. Repeated phencyclidine treatment induces negative symptom-like behavior in forced swimming test in mice: imbalance of prefrontal serotonergic and dopaminergic functions. Neuropsychopharmacology, 23, 375-87.

NOMURA T, OYAMADA Y, FERNANDES HB, REMMERS CL, XU J, MELTZER HY, CONTRACTOR A. 2016. Subchronic phencyclidine treatment in adult mice increases GABAergic transmission and LTP threshold in the hippocampus. Neuropharmacology, 100, 90-7.

NORBERG MM, KRYSTAL JH, TOLIN DF. 2008. A meta-analysis of D-cycloserine and the facilitation of fear extinction and exposure therapy. Biol Psychiatry, 63, 1118-26.

O'NEILL BV, CROFT RJ, MANN C, DANG O, LEUNG S, GALLOWAY MP, *et al*. 2011. High-dose glycine impairs the prepulse inhibition measure of sensorimotor gating in humans. J Psychopharmacol, 25, 1632-8.

OGDEN KK, KHATRI A, TRAYNELIS SF, HELDT SA. 2014. Potentiation of GluN2C/D NMDA receptor subtypes in the amygdala facilitates the retention of fear and extinction learning in mice. Neuropsychopharmacology, 39, 625-37.

PARK IH, CHUN JW, PARK HJ, KOO MS, PARK S, KIM SH. *et al*. 2015. Altered cingulo-striatal function underlies reward drive deficits in schizophrenia. Schizophr Res, 161, 229-36.

PATIL ST, ZHANG L, MARTENYI F, LOWE SL, JACKSON KA, ANDREEV BV, *et al.* 2007. Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized Phase 2 clinical trial. Nat Med, 13, 1102-7.

PEREZ-OTANO I, LARSEN RS, WESSELING JF. 2016. Emerging roles of GluN3-containing NMDA receptors in the CNS. Nat Rev Neurosci, 17, 623-35.

PETTERSSON-YEO W, BENETTI S, FRISCIATA S, CATANI M, WILLIAMS SC, ALLEN P, *et al*. 2015. Does neuroanatomy account for superior temporal dysfunction in early psychosis? A multimodal MRI investigation. J Psychiatry Neurosci, 40, 100-7.

PISANI A, GUBELLINI P, BONSI P, CONQUET F, PICCONI B, CENTONZE D, *et al*. 2001. Metabotropic glutamate receptor 5 mediates the potentiation of N-methyl-D-aspartate responses in medium spiny striatal neurons. Neuroscience, 106, 579-87.

PRATT J, WINCHESTER C, DAWSON N, MORRIS B. 2012. Advancing schizophrenia drug discovery: optimizing rodent models to bridge the translational gap. Nat Rev Drug Discov, 11, 560-79.

PRATT JA, MORRIS BJ. 2015. The thalamic reticular nucleus: a functional hub for thalamocortical network dysfunction in schizophrenia and a target for drug discovery. J Psychopharmacol, 29, 127-37.

PRYCE CR, SEIFRITZ E. 2011. A translational research framework for enhanced validity of mouse models of psychopathological states in depression. Psychoneuroendocrinology, 36, 308-29.

PYNDT JORGENSEN B, KRYCH L, PEDERSEN TB, PLATH N, REDROBE JP, HANSEN AK, *et al*. 2015. Investigating the long-term effect of subchronic phencyclidine-treatment on novel object recognition and the association between the gut microbiota and behavior in the animal model of schizophrenia. Physiol Behav, 141, 32-9.

RAJAGOPAL L, BURGDORF JS, MOSKAL JR, MELTZER HY. 2016. GLYX-13 (rapastinel) ameliorates subchronic phencyclidine- and ketamine-induced declarative memory deficits in mice. Behav Brain Res, 299, 105-10.

RIVOLTA D, HEIDEGGER T, SCHELLER B, SAUER A, SCHAUM M, BIRKNER K, *et al*. 2015. Ketamine Dysregulates the Amplitude and Connectivity of High-Frequency Oscillations in Cortical-Subcortical Networks in Humans: Evidence From Resting-State Magnetoencephalography-Recordings. Schizophr Bull, 41, 1105-14.

ROMPALA GR, ZSIROS V, ZHANG S, KOLATA SM, NAKAZAWA K. 2013. Contribution of NMDA receptor hypofunction in prefrontal and cortical excitatory neurons to schizophrenia-like phenotypes. PLoS One, 8, e61278.

ROOK JM, XIANG Z, LV X, GHOSHAL A, DICKERSON JW, BRIDGES TM, JOHNSON KA, *et al*. 2015. Biased mGlu5-Positive Allosteric Modulators Provide In Vivo Efficacy without Potentiating mGlu5 Modulation of NMDAR Currents. Neuron, 86, 1029-40.

SANZ-CLEMENTE A, NICOLL RA, ROCHE KW. 2013. Diversity in NMDA receptor composition: many regulators, many consequences. Neuroscientist, 19, 62-75.

SAPKOTA K, MAO Z, SYNOWICKI P, LIEBER D, LIU M, IKEZU T, *et al*. 2016. GluN2D N-Methyl-d-Aspartate Receptor Subunit Contribution to the Stimulation of Brain Activity and Gamma Oscillations by Ketamine: Implications for Schizophrenia. J Pharmacol Exp Ther, 356, 702-11.

SCHLUMBERGER C, SCHAFER D, BARBERI C, MORE L, NAGEL J, PIETRASZEK M, *et al*. 2009. Effects of a metabotropic glutamate receptor group II agonist LY354740 in animal models of positive schizophrenia symptoms and cognition. Behav Pharmacol, 20, 56-66.

SEAMANS JK, NOGUEIRA L, LAVIN A. 2003. Synaptic basis of persistent activity in prefrontal cortex in vivo and in organotypic cultures. Cereb Cortex, 13, 1242-50.

SEEMAN P, GUAN HC, and HIRBEC H. 2009. Dopamine D2high Receptors Stimulated by Phencyclidines, Lysergic Acid Diethylamide, Salvinorin a, and Modafinil. Synapse. 63, 698-704.

SEILLIER A, GIUFFRIDA A. 2009. Evaluation of NMDA receptor models of schizophrenia: divergences in the behavioral effects of sub-chronic PCP and MK-801. Behav Brain Res, 204, 410-5.

SIEBENHUHNER F, WEISS SA, COPPOLA R, WEINBERGER DR, BASSETT DS. 2013. Intra- and inter-frequency brain network structure in health and schizophrenia. PLoS One, 8, e72351.

SIGURDSSON T, STARK KL, KARAYIORGOU M, GOGOS JA, GORDON JA. 2010. Impaired hippocampal-prefrontal synchrony in a genetic mouse model of schizophrenia. Nature, 464, 763-7.

SMITH JW, GASTAMBIDE F, GILMOUR G, DIX S, FOSS J, LLOYD K, *et al*. 2011. A comparison of the effects of ketamine and phencyclidine with other antagonists of the NMDA receptor in rodent assays of attention and working memory. Psychopharmacology (Berl), 217, 255-69.

SOUTHAN C, SHARMAN JL, BENSON HE, FACCENDA E, PAWSON AJ, ALEXANDER SP, *et al.* (2015a). The IUPHAR/BPS Guide to PHARMACOLOGY in 2015/2016: Ligand gated ion channels. Br J Pharmacology, 172: 5870-5903.

SOUTHAN C, SHARMAN JL, BENSON HE, FACCENDA E, PAWSON AJ, ALEXANDER SP, *et al.* (2015b). The IUPHAR/BPS Guide to PHARMACOLOGY in 2015/2016: G protein-coupled receptors. Br J Pharmacology, 172: 5744-5869.

SOUTHAN C, SHARMAN JL, BENSON HE, FACCENDA E, PAWSON AJ, ALEXANDER SP, *et al.* (2016). The IUPHAR/BPS Guide to PHARMACOLOGY in 2016: towards curated quantitative interactions between 1300 protein targets and 6000 ligands. Nucl Acids Res 44: D1054-1068.

SPINELLI S, BALLARD T, GATTI-MCARTHUR S, RICHARDS GJ, KAPPS M, WOLTERING T, *et al*. 2005. Effects of the mGluR2/3 agonist LY354740 on computerized tasks of attention and working memory in marmoset monkeys. Psychopharmacology (Berl), 179, 292-302.

STAUBLI U, ROGERS G, LYNCH G. 1994. Facilitation of glutamate receptors enhances memory. Proc Natl Acad Sci U S A, 91, 777-81.

SUDHOF TC. 2013. Neurotransmitter release: the last millisecond in the life of a synaptic vesicle. Neuron, 80, 675-90.

SUGIYAMA A, SAITOH A, INAGAKI M, OKA J, YAMADA M. 2015. Systemic administration of riluzole enhances recognition memory and facilitates extinction of fear memory in rats. Neuropharmacology, 97, 322-8.

SURYAVANSHI PS, UGALE RR, YILMAZER-HANKE D, STAIRS DJ, DRAVID SM. 2014. GluN2C/GluN2D subunit-selective NMDA receptor potentiator CIQ reverses MK-801-induced impairment in prepulse inhibition and working memory in Y-maze test in mice. Br J Pharmacol, 171, 799-809.

TAYLOR AM, BUS T, SPRENGEL R, SEEBURG PH, RAWLINS JN, BANNERMAN DM. 2014. Hippocampal

NMDA receptors are important for behavioural inhibition but not for encoding associative spatial memories. Philos Trans R Soc Lond B Biol Sci, 369, 20130149.

TAYLOR R, NEUFELD RW, SCHAEFER B, DENSMORE M, RAJAKUMAR N, OSUCH EA, *et al*. 2015. Functional magnetic resonance spectroscopy of glutamate in schizophrenia and major depressive disorder: anterior cingulate activity during a color-word Stroop task. NPJ Schizophr, 1, 15028.

THOMSON DM, MCVIE A, MORRIS BJ, PRATT JA. 2011. Dissociation of acute and chronic intermittent phencyclidine-induced performance deficits in the 5-choice serial reaction time task: influence of clozapine. Psychopharmacology (Berl), 213, 681-95.

TIAN D, STOPPEL LJ, HEYNEN AJ, LINDEMANN L, JAESCHKE G, MILLS AA, *et al*. 2015. Contribution of mGluR5 to pathophysiology in a mouse model of human chromosome 16p11.2 microdeletion. Nat Neurosci, 18, 182-4.

TSAI GE, LIN PY. 2010. Strategies to enhance N-methyl-D-aspartate receptor-mediated neurotransmission in schizophrenia, a critical review and meta-analysis. Curr Pharm Des, 16, 522-37.

UMBRICHT D, SCHMID L, KOLLER R, VOLLENWEIDER FX, HELL D, JAVITT DC. 2000. Ketamine-induced deficits in auditory and visual context-dependent processing in healthy volunteers: implications for models of cognitive deficits in schizophrenia. Arch Gen Psychiatry, 57, 1139-47.

URBAN A, KREMLACEK J, MASOPUST J, LIBIGER J. 2008. Visual mismatch negativity among patients with schizophrenia. Schizophr Res, 102, 320-8.

USLANER JM, PARMENTIER-BATTEUR S, FLICK RB, SURLES NO, LAM JS, MCNAUGHTON CH, *et al*. 2009. Dose-dependent effect of CDPPB, the mGluR5 positive allosteric modulator, on recognition memory is associated with GluR1 and CREB phosphorylation in the prefrontal cortex and hippocampus. Neuropharmacology, 57, 531-8.

VANDENBERG RJ, RYAN RM. 2013. Mechanisms of Glutamate Transport. Physiological Reviews 93, 1621-1657.

VAN DEN HEUVEL MP, MANDL RC, STAM CJ, KAHN RS, HULSHOFF POL HE. 2010. Aberrant frontal and temporal complex network structure in schizophrenia: a graph theoretical analysis. J Neurosci, 30, 15915-15926.

VINCKIER F, GAILLARD R, PALMINTERI S, RIGOUX L, SALVADOR A, FORNITO A, *et al*. 2016. Confidence and psychosis: a neuro-computational account of contingency learning disruption by NMDA blockade. Mol Psychiatry, 21, 946-55.

VOLK L, CHIU SL, SHARMA K, HUGANIR RL. 2015. Glutamate synapses in human cognitive disorders. Annu Rev Neurosci, 38, 127-49.

WALKER DL, RESSLER KJ, LU KT, DAVIS M. 2002. Facilitation of conditioned fear extinction by

systemic administration or intra-amygdala infusions of D-cycloserine as assessed with fear-potentiated startle in rats. J Neurosci, 22, 2343-51.

WATSON GB, BOLANOWSKI MA, BAGANOFF MP, DEPPELER CL, LANTHORN, TH. 1990. D-cycloserine acts as a partial agonist at the glycine modulatory site of the NMDA receptor expressed in Xenopus oocytes. Brain Res, 510, 158-60.

WATSON TD, PETRAKIS IL, EDGECOMBE J, PERRINO A, KRYSTAL JH, MATHALON DH. 2009. Modulation of the cortical processing of novel and target stimuli by drugs affecting glutamate and GABA neurotransmission. Int J Neuropsychopharmacol, 12, 357-70.

WEISER M, HERESCO-LEVY U, DAVIDSON M, JAVITT DC, WERBELOFF N, GERSHON AA, *et al*. 2012. A multicenter, add-on randomized controlled trial of low-dose d-serine for negative and cognitive symptoms of schizophrenia. J Clin Psychiatry, 73, e728-34.

WEZENBERG E, VERKES RJ, RUIGT GS, HULSTIJN W, SABBE BG. 2007. Acute effects of the ampakine farampator on memory and information processing in healthy elderly volunteers. Neuropsychopharmacology, 32, 1272-83.

WHITE DM, KRAGULJAC NV, REID MA, LAHTI A. C. 2015. Contribution of substantia nigra glutamate to prediction error signals in schizophrenia: a combined magnetic resonance spectroscopy/functional imaging study. NPJ Schizophr, 1, 14001.

WILTGEN BJ, ROYLE GA, GRAY EE, ABDIPRANOTO A, THANGTHAENG N, JACOBS N, *et al*. 2010. A role for calcium-permeable AMPA receptors in synaptic plasticity and learning. PLoS One, 5.

XU J, ZHU Y, KRANIOTIS S, HE Q, MARSHALL JJ, NOMURA T, *et al*. 2013. Potentiating mGluR5 function with a positive allosteric modulator enhances adaptive learning. Learn Mem, 20, 438-45.

ZHAO T, LI Y, WEI W, SAVAGE S, ZHOU L, MA D. 2014. Ketamine administered to pregnant rats in the second trimester causes long-lasting behavioral disorders in offspring. Neurobiol Dis, 68, 145-55.

ZINK M, CORRELL CU. 2015. Glutamatergic agents for schizophrenia: current evidence and perspectives. Expert Rev Clin Pharmacol, 8, 335-52.

Conflicts of Interest: The authors declare no conflicts of interest.