Current Neuropharmacology, 2017, *15*, 21-34

REVIEW ARTICLE

D-cycloserine in Schizophrenia: New Strategies for Improving Clinical Outcomes by Enhancing Plasticity

Donald C. Goff*

Nathan Kline Institute for Psychiatric Research, NYU School of Medicine, USA

Abstract: ***Background***: Dysregulation of N-methyl D-aspartate (NMDA) receptor signaling is strongly implicated in schizophrenia. Based on the ketamine model of NMDA receptor hypoactivity, therapeutic approaches designed to maintain a sustained increase in agonist activity at the glycine site of the NMDA receptor have produced promising, although inconsistent, efficacy for negative symptoms.

Methods: A review of the published literature on D-cycloserine (DCS) pharmacology in animal models and in clinical studies was performed. Findings relevant to DCS effects on memory and plasticity and their potential clinical application to schizophrenia were summarized.

Results: Studies in animals and clinical trials in patients with anxiety disorders have demonstrated that single or intermittent dosing with DCS enhances memory consolidation. Preliminary trials in patients with schizophrenia suggest that intermittent dosing with DCS may produce persistent improvement of negative symptoms and enhance learning when combined with cognitive behavioral therapy for delusions or with cognitive remediation. The pharmacology of DCS is complex, since it acts as a "super agonist" at NMDA receptors containing GluN2C subunits and, under certain conditions, it may act as an antagonist at NMDA receptors containing GluN2B subunits.

Conclusions: There are preliminary findings that support a role for D-cycloserine in schizophrenia as a strategy to enhance neuroplasticity and memory. However, additional studies with DCS are needed to confirm these findings. In addition, clinical trials with positive and negative allosteric modulators with greater specificity for NMDA receptor subtypes are needed to identify the optimal strategy for enhancing neuroplasticity in schizophrenia.

Donald C. Goff

ARTICLE HISTORY

Received: June 08, 2015
Revised: August 13, 2015
Accepted: January 30, 2016

DOI:
10.2174/1570159X14666160225154812

Keywords: Cognition, D-cycloserine, glutamate, memory, NMDA, pharmacology, plasticity, schizophrenia.

INTRODUCTION

The potential role of dysregulated glutamatergic signaling in psychiatric illness was first recognized in schizophrenia over 20 years ago. Since then, therapeutic efforts to modulate glutamatergic transmission based on the ketamine model of NMDA receptor hypofunction have produced promising but often inconsistent results [1]. A hypothesized early neurodevelopmental modification of NMDA signaling in response to inflammation or hypoxia may represent a compensatory neuroprotective response which comes at the cost of reduced neuroplasticity. Strategies focused on enhancing plasticity as a therapeutic approach for schizophrenia include pharmacologic agents targeting the NMDA receptor, as well as neurostimulatory approaches, such as transcranial direct current stimulation (tDCS). The treatment of refractory depression with ketamine infusion is one example of targeting NMDA receptors to produce a relatively sustained therapeutic effect. A similarly robust NMDA receptor-based intervention has not yet been achieved in schizophrenia, but preliminary evidence suggests that once-weekly dosing of the glycine site partial agonist, D-cycloserine (DCS), may produce persistent benefits for negative symptoms and memory deficits. This paper will review the pharmacology of D-cycloserine, with an emphasis upon behavioral effects in animal models and cognitive effects in humans. The impact of environmental factors and psychiatric illness upon NMDA receptor regulation and the implications for therapeutic interventions will also be discussed.

*Address correspondence to this author at the Nathan Kline Institute for Psychiatric Research, NYU School of Medicine, USA; Tel: 845 398 5502; E-mail: Donald.goff@nyumc.org

1875-6190/17 $58.00+.00

SCHIZOPHRENIA: EVIDENCE FOR NMDA RECEPTOR DYSREGULATION

Schizophrenia is a neurodevelopmental syndrome with both genetic and environmental risk factors that typically develops in young adulthood and is characterized by psychosis, apathy, reduced emotional expressivity and impairments of memory and executive functioning (Fig. **1**). Many of the symptoms of schizophrenia can be viewed as the consequence of cognitive deficits, such as the inability to recognize prediction errors based on delusional beliefs (*e.g.*, to "reality test") and to revise one's schema of reality accordingly, or the inability to recall past hedonic experiences and to initiate purposeful activity in anticipation of similarly rewarding experience (*e.g.*, "apathy"). In the 1950s it was observed that phencyclidine (PCP) produces the full range of schizophrenia symptoms in adults, including delusions, social withdrawal and memory deficits, whereas children younger than the age of onset for schizophrenia tended to be spared these adverse effects [2]. Thirty years later, blockade of NMDA receptor-gated ion channels was identified as the mechanism responsible for the psychotomimetic effects of PCP and ketamine, and NMDA receptor hypofunction was added to the prevailing model of dopamine dysregulation as a principle molecular basis for schizophrenia [7, 8]. Subsequently, genetic linkage studies have implicated several genes involved in NMDA/ calcium signaling, neurodevelopment and inflammatory response [3, 4]. In addition, DNA methylation studies have identified epigenetic patterns consistent with early hypoxia and inflammation [5]. Exposure to maternal immune activation in utero provides a compelling animal model for schizophrenia, including structural and functional alterations that are consistent with the developmental timing of symptom emergence in schizophrenia [6]. It is notable that both depression and schizophrenia have been associated with neuroinflammation; however, inflammation-related biomarkers in schizophrenia include elevation of the tryptophan metabolite, kynurenic acid, which is a potentially neuroprotective glycine site antagonist, whereas in depression tryptophan metabolism is

1. One month duration (unless successfully treated) of at least 2 of the following (must include a, b or c):
    a. Delusions
    b. Hallucinations
    c. Disorganized speech
    d. Grossly disorganized or catatonic behavior
    e. Negative symptoms
2. Social or occupational dysfunction
3. Persistent signs of the disturbance persist for at least 6 months (unless successfully treated)

Fig. (1). DSM-5 Diagnostic Criteria for Schizophrenia [136].

Table 1. Pharmacology of NMDA subunits.

Subunit	DCS Activity Compared to Glycine	Characteristics	Effect of Knock-out	Effect of Agonist	Effect of Antagonist
NR1/NR2A	90%	Synaptic, Mg++ block	Attenuates abnormal behavioral effects of methamphetamine [135]		Antidepressant [136], Neurotoxic, disrupts synchrony [73]; reduces GAD67 in PV interneurons [71]
NR1/NR2B	65%	Extra-synaptic, Mg++ block	Knockout is lethal; deletion in adulthood produces memory impairment [74]; replacement of NR2B with NR2A produces hyper-locomotion and social withdrawal [70]		Antidepresant [136]; Neuroprotective [72], does not affect synchrony [73]
NR1/NR2C/NR2D	200%	Synaptic, decreased sensitivity to Mg++ block, prominent on hippocampal interneurons	Impaired working memory and fear conditioning [94]	Attenuates some MK801 motor and cognitive effects [137]	

primarily shunted to quinolinic acid, which is a potentially neurotoxic NMDA receptor agonist [7].

GLUTAMATERGIC PHARMACOLOGY IN SCHIZOPHRENIA

The demonstration that a single infusion of ketamine produces social withdrawal, attenuated psychotic symptoms and memory impairment in healthy subjects [8] and produces a transient relapse of psychosis in schizophrenia patients stabilized on haloperidol [9] paved the way for ketamine infusion to serve as the dominant model for drug discovery in schizophrenia. Because the atypical antipsychotic, clozapine, blunted ketamine effects in patients [10], it was hoped that the ketamine challenge would identify novel agents for treatment refractory symptoms. Therapeutic trials

Table 2. Placebo controlled trials of D-cycloserine in schizophrenia.

Study	Participants	DCS Dose	Outcome	Comments
Goff 1995 [23]	9 SZ treated with FGA	15, 50, 250 mg daily for 2 weeks	Neg Sx and working memory improved with 50 mg dose only	Single blind, escalating dose, video ratings blind to treatment
Rosse 1996 [138]	13 SZ treated with molindone	10 mg or 30 mg daily	No effect	
Van Berckel 1996 [24]	26 SZ treated with FGA	100 mg daily for 8 weeks	Worsening of Pos Sx	
Goff 1996 [139]	10 SZ treated with clozapine	5,15,50, 250 mg daily for 2 weeks	Worsening of Neg Sx with 50 mg dose only	
Herresco-Levy 1998 [140]	9 SZ treated with FGA and SGA	50 mg daily for 4 weeks (cross-over)	No effect of DCS compared to placebo	Neg Sx improved with DCS compared to baseline
Van Berckel 1999 [141]	26 SZ treated with SGA	100 mg daily for 8 weeks	Worsening of Neg Sx	
Goff 1999a [25]	47 SZ with deficit syndrome treated with FGA	50 mg daily for 8 weeks	Neg Sx improved	No relationship between DCS blood level and response
Goff 1999b [130]	17 SZ treated with clozapine	50 mg daily for 6 weeks (cross-over)	Worsening of Neg Sx	
Heresco-Levy 2002 [31]	24 SZ treated with FGA & SGA	50 mg daily for 6 weeks (cross-over)	Neg Sx improved	No difference in effects with FGA vs SGA
Evins 2002 [142]	10 SZ treated with risperidone	5,15,50, 250 mg daily for 2 weeks	Neg Sx improved with 50 mg dose only	Single blind, escalating dose, video ratings blind to treatment
Duncan 2004 [30]	22 SZ treated with FGA	50 mg daily for 4 weeks	No effect on Neg Sx or cognition	
Goff 2005 [32]	55 SZ treated with FGA	50 mg daily for 6 months	No effect	53% attrition rate
Yurgelun-Todd 2005 [26]	12 SZ treated with FGA	50 mg daily for 8 weeks	Increased temporal lobe activation during verbal fluency task	Temporal lobe activation correlated with improvement of Neg Sx
Buchanan, 2007 [12]	157 SZ; 86% SGA	50 mg daily DCS or glycine 60 g daily for 16 weeks	No effect on Neg Sx or cognition	FGA associated with significantly greater Neg Sx response than SGA
Goff 2008 [122]	38 SZ; 87% treated with SGA	50 mg once-weekly for 8 weeks	Neg Sx improved	7-day delayed thematic recall improved after 1st dose
Gottlieb 2011 [124]	21 SZ; 87% treated with SGA	50 mg prior to CBT session	Delusions improved if DCS administered before the 1st of two sessions	
Cain 2014 [91]	36 SZ; 81% treated with SGA	50 mg once-weekly for 8 weeks plus cognitive remediation 3-5 times per week	Auditory discrimination improved; Neg Sx improved in participants with SANS> 20 at baseline	

DCS= D-cycloserine, SZ= individuals with schizophrenia, Neg Sx= Negative symptoms, Pos Sx= Positive Symptoms, FGA= First generation antipsychotic, SGA= Second generation antipsychotic, SANS= Scale for Assessment of Negative Symptoms, CBT= Cognitive behavioral therapy,

initially focused on agonists at the glycine co-agonist site of the NMDA receptor since direct agonists at the NMDA receptor might result in excessive calcium influx and excitotoxicity. Early add-on trials with the full agonists, glycine and D-serine, were quite encouraging, with largest effects observed for response of negative symptoms [11]. However, these results were not replicated in subsequent larger trials [12-14]. Similarly, the glycine type I reuptake transporter (GlyT1) inhibitor, bitopertin, improved negative symptoms in an initial trial [15] but failed in two subsequent trials [16]. A recent add-on trial of the D-amino acid oxidase inhibitor, sodium benzoate, which increases D-serine concentrations, produced improvement in positive, negative and cognitive symptoms, but these results have not yet been replicated [17]. In addition to agents that increase activity at the glycine recognition site [18], agents that inhibit glutamate release, such as the metabotropic type II agonists [19] and lamotrigine [20], also attenuate ketamine's psychotomimetic effects but were not consistently effective in clinical trials [21, 22].

The glycine site partial agonist, D-cycloserine (DCS) was shown to improve negative symptoms at a daily dose of 50 mg, but not at 250 mg, in an initial dose-finding trial in patients treated with first generation antipsychotics [23] and at a dose of 100 mg/d in a dose finding trial in medication-free patients [24]. In an 8-week, placebo-controlled trial D-cycloserine 50 mg/d added to first generation antipsychotics significantly improved negative symptoms without affecting positive symptoms or cognition [25]; response of negative symptoms correlated with increased activation of the left temporal lobe during a verbal fluency task [26]. However, psychotic symptoms worsened in D-cycloserine trials employing doses of 100 mg/d [27], 250 mg/d [28] and 500 mg/d or higher [29]. Subsequent trials of D-cycloserine 50 mg/d produced mixed results [30-32], including the multi-center CONSIST trial in which neither DCS or glycine improved negative symptoms or cognition when added to predominantly second generation antipsychotics [12]. Of note, response of negative symptoms in the few participants treated with first generation antipsychotics was significantly greater than in participants treated with second generation antipsychotics [12]. In contrast to glycine, efficacy for DCS did not achieve statistical significance in a meta-analysis of add-on trials [11].

It is unclear why NMDA channel blockade by ketamine produces the full range of schizophrenia symptoms in healthy adults, whereas treatments intended to enhance NMDA activity in patients at best appear only to improve negative symptoms and have been inconsistent in clinical trials [1]. With the exception of one open-label high-dose trial of D-serine [33], these agents have generally failed to improve cognitive functioning despite the well-established role of NMDA receptors in learning and memory. The pattern of initial successes followed by negative trials may merely reflect the growing unreliability of clinical trials in schizophrenia [34]. In addition, issues of disease heterogeneity, poor CNS bioavailablity, and the complication of adding these agents to second generation antipsychotics which also influence glutamatergic signaling [35] may all have contributed. In addition, the mixed results with DCS may reflect increased antagonist activity at higher concentrations [36], the rapid deterioration of DCS when exposed to humidity [37] and the recent finding that DCS may be ineffective when combined with antidepressants [38]. Regardless, these experiences indicate that approaches that produce sustained activation of the glycine co-agonist site or that inhibit glutamate release do not produce effects that are large enough to produce consistent efficacy in multi-site clinical trials in schizophrenia and raise questions about the predictive value of ketamine challenge for drug development in schizophrenia.

DCS EFFECTS ON MEMORY IN ANIMAL MODELS

The lack of cognitive effect found in clinical trials with glycine site agonists in schizophrenia is in marked contrast to a large animal literature in which DCS consistently enhances memory [39]. The disparity in results may reflect the fact that memory effects are rapidly lost with repeated dosing [40, 41], possibly reflecting the facilitating role of the glycine site for inward trafficking of NMDA receptors [42]. A single dose of DCS administered within 2 hours before or after training does not affect immediate recall, but enhances delayed recall measured after 24 hours. Memory recall after a 24 hour delay traditionally has not been tested in clinical trials. In animal models, memory enhancement with DCS has been best demonstrated for fear extinction [39] but has also been found to enhance extinction of operant reward responding for food [43], cocaine [44] and alcohol [45], as well as extinction of conditioned taste aversion [46]. DCS effects on memory consolidation are not restricted to extinction; DCS has been shown to enhance maze learning [47], object location memory [48] and episodic-like memory in mice [49]. Infusion of DCS directly into the prefrontal cortex (PFC) or hippocampus enhanced consolidation of fear extinction [50-52]. DCS effects appear to be limited to novel learning; for example, if an animal has previously experienced extinction training, a second round of extinction training following restoration of fear conditioning is not facilitated by DCS [53]. Extinction training accompanied by DCS differs from extinction training without DCS in generalizing to other cues [54]. In addition, whereas classical extinction learning appears to require the acquisition of a second "safety" memory that negates the original fear-conditioned memory and which may fade over time, there is some evidence that addition of DCS to extinction training "erases" the fear memory. This process of "erasure" is associated with internalization of post-synaptic AMPA receptors [55]. However, the fear memory is only "erased" by DCS if extinction training is of sufficient duration or intensity. If administered in conjunction with insufficient extinction training, DCS may strengthen the fear memory [56]. This distinction has been observed in clinical trials using DCS to facilitate cognitive behavioral therapy for anxiety disorders; DCS may worsen anxiety symptoms if desensitization does not occur during the session, whereas persistent reduction in anxiety compared to placebo was achieved when desensitization was successful during sessions augmented by DCS [57]. D-serine is the principle endogenous glycine-site ligand in hippocampus [58]. Elevation of D-serine levels by administration of a D-amino acid oxidase (DAO) inhibitor produced enhancement of 24

hour recall of hippocampal dependent tasks including contextual fear conditioning and novel object recognition [59] and enhancement of LTP in the hippocampal CA1 subfield similar to that produced by DCS [59]. Elevation of D-serine levels by knockdown of DAO or by administration of exogenous D-serine produced no effect on initial learning of platform location in the Morris Water Task, but a significant enhancement of reversal learning when the platform was moved [60]. This study did not find evidence for attenuation of cognitive effects with prolonged exposure to elevated concentrations of D-serine.

THE IMPACT OF NMDA SUBUNIT COMPOSITION ON DCS ACTIVITY

DCS activity at NMDA receptors is determined by the GluN2 subunit composition (Table **1**). For NMDA receptors containing GluN2B subunits, DCS activity was 65% compared to glycine when both are at saturating concentrations, and roughly 90% for NMDA receptors containing GluN2A or GluN2D subunits [61]. In contrast, DCS exhibits approximately 200% activity compared to glycine at NMDA receptors containing the GluN2C subunit [61]. Based on these data, DCS would be expected to act as an agonist at NMDA receptors containing GluN2C subunits, whereas the effect at other NMDA receptors is dependent upon the relative occupancy by endogenous full agonists (D-serine, glycine and D-alanine) and the endogenous antagonist, kynurenic acid. Under conditions of relatively high occupancy by endogenous glycine site agonists, DCS would be expected to act as an antagonist at NMDA receptors containing GluN2B subunits. Activity at NMDA receptors containing GluN2A subunits would be relatively similar to glycine. Because D-cycloserine's affinity for GluN2C containing receptors is greater than its affinity for GluN2A and GluN2B subunits, at low DCS concentrations, maximal activity may be primarily at GluN2C containing NMDA receptors.

THE DEVELOPMENTAL EXPRESSION AND CHARACTERISTICS OF NMDA SUBUNITS

The relative activity of DCS at different populations of NMDA receptors may have important pharmacologic consequences. NMDA receptor subunit composition determines the rate and magnitude of calcium conductance and resulting depolarization and is influenced by many factors, including developmental stage, cell type, and synaptic activity [62]. Several psychotropic medications, including antipsychotics, also alter NMDA subunit expression [35]. Tight control of calcium influx is crucial to facilitate use-dependent gene expression which underlies plasticity, while avoiding excitotoxicty as a result of excessive calcium influx. NMDA receptors are tetramers composed of two obligatory GluN1 subunits in combination with two subunits from eight categories of GluN2 or GluN3 subunits. The majority of synaptic NMDA receptors in forebrain may be triheteromeric combinations of GluN1, GluN2A and GluN2B [74]. Receptors containing GluN2A subunits are primarily synaptic whereas those containing GluN2B subunits are enriched in the extra-synaptic space. NMDA receptors containing GluN2A or GluN2B subunits require partial depolarization to remove the magnesium blockade of the channel before agonist occupancy at the glutamate and glycine sites can open the channel and produce an excitatory postsynaptic current (EPSC); these receptors are known as "coincidence detectors" since multiple depolarizing events are required. GluN2C - containing receptors have a higher affinity for glutamate and are less sensitive to magnesium blockade; they are primarily found in cerebellum, but also in thalamus and on PV-expressing interneurons in PFC and hippocampus [63-65]. In layer 4 of the sensory cortex, GluN2C subunits are found on spiny stellate cells which are the major targets of thalamocortical input [66]. Early in development, during a period of rapid synapse formation and myelination, GluN2B-containing NMDA receptors and AMPA receptors lacking the GluR2 subunit are prominent; these two classes of receptors allow maximum calcium conductance to guide synapse formation but also place cells at risk for neurotoxicity in the face of inflammation or hypoxia [67]. In the neonate, LTP induction triggers the switch from GluN2B to GluN2A [68] and the transition to GluN2A is associated with reduced susceptibility to LTP [69]. GluN2B subunits are essential in early development; knockout of GluN2B subunits is lethal [70]. GluN2A-containing NMDA receptors on interneurons are primarily responsible for the development and maintenance of GAD67 and parvalbumin (PV) expression [71] and promote neuroprotection [72], sensory gating and GAMA oscillations [73]. GluN2B-containing NMDA receptors are also required for LTP; deletion of hippocampal GluN2B subunits in adult rats modestly impairs memory [74], whereas increased expression of GluN2B subunits enhances memory [75]. GluN2B subunits are coupled to mTOR pathways *via* calcium/calmodulin-dependent protein kinase II (CaMKII) and their activation inhibits protein synthesis and AMPA receptor expression underlying neuroplasticity [70]. In addition to their involvement in plasticity, GluN2B-containing NMDA receptors are coupled to pro-apoptotic pathways [76], are required for long term depression (LTD), and may be essential for reversal learning, or cognitive flexibility [77]. Some evidence suggests that long term potentiation (LTP) requires channel opening by GluN2A subunits in combination with the intracellular tails of GluN2B subunits, whereas the GluN2A intracellular tail may inhibit LTP [78]. Increased expression of GluN2B subunits is associated with greater synaptic plasticity; insertion of GluN2A subunits may stabilize neuroplastic changes [78]. Given the complex interaction between GluN2A and GluN2B subunits, effects of pharmacologic intervention may be determined either by conformational changes in calcium channel permeability produced by binding to the extracellular receptor protein, or by secondary effects on subunit expression [79], which may affect LTP in part *via* scaffolding functions of the subunit tails [78]. As an example of the latter mechanism, DCS has been shown to increase GluN2B expression in hippocampus [52].

In addition, pharmacologic effects are dependent upon cell type and developmental stage. Deletion of NMDA receptors prior to adolescence results in a loss of PV expressing interneurons and disruption of gamma oscillations consistent with schizophrenia, whereas the effect

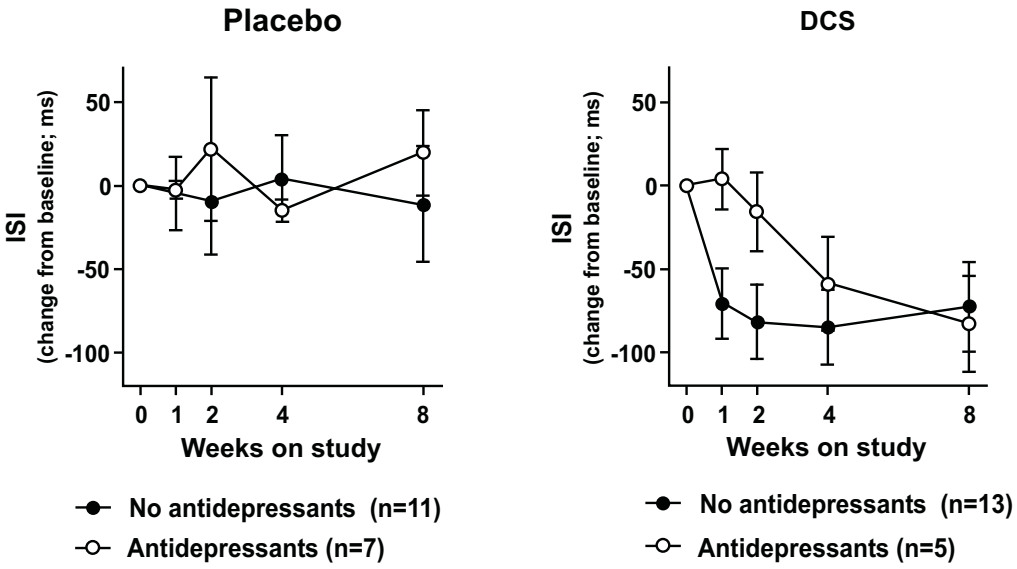

Fig. (2). Antidepressant effects on DCS augmentation of cognitive remediation (auditory discrimination) [92]. ISI= interstimulus interval (shorter interstimulus interval represents improved auditory discrimination performance).

is markedly reduced if deletion occurs after adolescence [80]. In adulthood, blockade of GluN2A-containing subunits disrupts cortical synchrony and may produce neurotoxicity, whereas blockade of GluN2B containing receptors is neuroprotective but may disrupt reversal learning and cause perseveration [73, 77]. Interneurons co-expressing GluN2A and PV are selectively decreased in schizophrenia cortex [81]. In prefrontal cortex, GluN1 and GluN2A subunit expression is decreased postmortem in both schizophrenia and depression, whereas GluN2C subunit expression is decreased in schizophrenia only and GluN2B subunit expression does not differ from healthy control brain [82].

DCS effects on memory are also influenced by the activity of brain derived neurotrophic factor (BDNF). Early stages of memory consolidation involve GABA A receptors in hippocampus which modulate BDNF release during a 3 hour period after initial learning [83]. BDNF in turn is required for acquisition and early consolidation of most forms of hippocampal-based learning including object recognition, episodic memory, spatial learning, and fear extinction, but not fear conditioning [46, 84] and is also involved in conditioned taste aversion, a hippocampal independent task [46]. Hippocampal release of BDNF up-regulates NMDA receptor activity by increasing expression of GluN1, GluN2A and GluN2B subunits [85], whereas BDNF was found to decrease expression of GluN2C subunits in cerebellum [86]. BDNF deletion in hippocampus impairs fear extinction learning but not acquisition of fear conditioning [84]. Similarly, BDNF genotype influences extinction learning in mice and hippocampal-dependent learning in humans [46]. DCS enhanced extinction in animals with reduced BDNF activity and reversed the impairment of social behavior produced by a GABA A inverse agonist [46, 87]. When administered 24 hours after closed head injury in mice, a single dose of DCS restored BDNF levels in the hippocampal CA1 subfield and improved performance on the object recognition task compared to vehicle-treated mice [88]. DCS also reversed the impairment of context-based extinction learning that is associated with reduced PFC expression of BDNF during adolescence [89, 90]. However, pretreatment with BDNF-releasing antidepressants attenuated DCS effects on extinction memory in rats [38] and was associated with loss of efficacy for DCS facilitation of cognitive behavioral therapy in obsessive compulsive disorder [38]. A re-analysis of results from our study of DCS augmentation of cognitive remediation in schizophrenia [91] also suggests that antidepressants may interfere with DCS enhancement of memory (Fig. **2**). BDNF transcriptional and translational expression is also influenced by inflammation and stress. Excessive levels of inflammatory cytokines reduce both BDNF expression and NMDA receptor expression in hippocampus and impair memory consolidation [92, 93]. DCS was found to reverse memory impairment produced by immune activation; this effect occurred in the absence of an effect on BDNF concentrations or expression of GluN2C subunit expression [93]. DCS has also been demonstrated to increase neurogenesis in dentate gyrus [52].

Because DCS exhibits unique high-potency agonist activity at NMDA receptors containing GluN2C subunits, the role of these receptors in cognition and behavior is of particular interest. GluN2C knockout mice display impairments of working memory and fear conditioning with preservation of novel object recognition and of working and reference memory tested in an 8-arm radial maze [94]. The impairment of fear conditioning in these animals complicates the study of fear extinction; however, it appeared that initial extinction learning was intact whereas 24 hour delayed extinction recall was compromised. In addition, Lisman and colleagues have proposed that decreased activity of GluN2C in the thalamic reticular nucleus may contribute to symptoms of schizophrenia [95, 96]. They demonstrated that GluN2C-containing NMDA receptors modulate the oscillatory activity of the thalamic reticular nucleus and that blockade of these receptors produces delta frequency bursting which is reversed by D2 antagonists, consistent with findings in

schizophrenia. A selective GluN2C/GluN2D potentiator, CIQ, enhanced acquisition of fear conditioning and extinction but did not affect spatial learning in the Morris Water Maze [97]. Of note, both D-serine and DCS also failed to improve performance on the Morris Water Maze in healthy rats, whereas DCS improved performance in aged and scopolamine-treated rats [98-100] and D-serine selectively improved reversal learning following movement of the platform [60].

DCS EFFECTS ON MEMORY IN HUMAN STUDIES

In 2004 Ressler and colleagues [101] demonstrated that DCS augmentation of two sessions of exposure therapy successfully reduced symptoms and behaviors related to acrophobia (fear of heights) compared to placebo; therapeutic effects persisted at three-month follow-up. Since that landmark study, several studies have found efficacy for DCS augmentation of fear-extinction exposure therapy for anxiety disorders. A meta-analysis of ten studies found that DCS efficacy compared to placebo was greatest with a fewer number of sessions but was independent of DCS dose within a range of 50 mg to 500 mg [102]. The diminishing efficacy compared to placebo in studies with a larger number of sessions may either reflect tachyphylaxis with repeated dosing or the fact that exposure therapy alone is quite effective given a sufficient number of sessions. Therapeutic effects have been less consistent for PTSD, generalized anxiety disorder and substance abuse, possibly because extinction is often not achieved during sessions that are augmented by DCS. Results of DCS augmentation of fear extinction have been less impressive in laboratory studies of healthy volunteers compared to trials in clinical populations [103]. In healthy humans, DCS facilitated procedural memory consolidation in one study and enhanced declarative memory consolidation in one of two studies [104-106]. DCS also facilitated recall of fear memory after a 72 hour delay in healthy humans which was associated with increased activity in posterior hippocampus and PFC [107]. DCS enhanced retention of word pairs only if given before sleep but had no effect on retention during wakefulness [108]. Contrary to expectation, DCS reduced power of sleep spindles, which have been linked to memory consolidation [108]. Nitsche and colleagues examined the effect of DCS 100 mg on plasticity when co-administered with transcranial direct current stimulation and found that DCS significantly increased the duration of enhanced cortical excitability as measured by transcranial magnetic stimulation-elicited motor evoked potentials but DCS did not affect cortical excitability when administered alone [109].

RELEVANCE OF DCS EFFECTS ON MEMORY CONSOLIDATION TO SCHIZOPHRENIA

Although quite variable, individuals with schizophrenia have a broad range of cognitive impairments, including deficits in processing speed, episodic memory, working memory, and executive function. These impairments map onto functional deficits in medial temporal lobes [110, 111] and the prefrontal cortex [112] and are typically present prior to the onset of psychosis [113, 114]. Of note, contextual fear conditioning is relatively intact in schizophrenia, as is immediate recall of fear extinction [115, 116]. However, consolidation of contextual fear extinction measured 24 hours after extinction training is impaired in individuals with schizophrenia compared to healthy controls [115, 116]. This impairment in 24 hour retention of fear extinction is associated with a failure to active vmPFC and with the presence of delusions independent of medication status [115]. Similarly, individuals with schizophrenia are able to learn a procedural learning task at a rate similar to healthy controls, but fail to consolidate this learning after 12 hours [117]. The failure to consolidate the procedural learning task was associated with a reduction in frequency and amplitude of slow-wave sleep spindles, which in turn was associated with severity of psychosis [118]. In contrast, the impairment in learning verbal and visual tasks appears to be primarily the result of deficits in encoding and early consolidation rather than later consolidation [119]. In addition to impairment of extinction learning, individuals with schizophrenia exhibit marked cognitive inflexibility on tests of set shifting and reversal learning [120, 121].

SINGLE AND INTERMITTENT DOSING OF DCS IN SCHIZOPHRENIA

A single dose of DCS 50 mg administered prior to the logical memory test of the Revised Wechsler Memory Scale had no effect on immediate recall of items or thematic units contained in a brief story compared to placebo in individuals with schizophrenia [122]. However, when recall was tested after 7 days, participants who received DCS recalled significantly more themes from the story than did subjects who received placebo (effect size 0.9). Recall of specific items of the story did not differ between groups. In contrast, DCS 50 mg did not affect immediate or 24 hour delayed recall on the logical memory test in healthy subjects [105]. Studies of sleep effects on memory in healthy individuals suggest that the "gist" of information rather than details are consolidated during sleep [123], which may account for the preferential effect of DCS on thematic recall in schizophrenia. In two placebo-controlled trials in subjects with schizophrenia, DCS 50 mg administered once-weekly added to second generation antipsychotics improved negative symptoms measured 7 days after the last dose of DCS [91, 122]. When added to an 8 week cognitive remediation training program that emphasized an auditory discrimination exercise, DCS significantly enhanced performance on the practiced auditory discrimination task but did not improve performance on tasks that were not practiced [91]. In fact, performance on other cognitive domains improved less in the DCS group than in the placebo group at a trend level of significance, suggesting that DCS enhancement of learning on a practiced task may come at the cost of less improvement in unpracticed cognitive tasks, consistent with use-dependent plasticity. DCS facilitation of learning on the auditory discrimination task appeared to be delayed in participants taking selective serotonin reuptake inhibitors (SSRIs), consistent with findings in DCS augmentation of CBT for OCD (Fig. **2**) [38]. Finally, when a single dose of DCS 50 mg was combined with a cognitive behavioral therapy (CBT) exercise emphasizing cognitive flexibility in a placebo-controlled, two-session, random-

order, crossover design, schizophrenia subjects who received DCS prior to the first CBT session demonstrated a large improvement in delusional severity compared to participants who received DCS prior to the second session (effect size 0.8) [124]. This finding requires replication in a parallel-group design, but is consistent with observations from animal studies that DCS preferentially enhances consolidation of novel memories but may not improve retention of training to which the animal was previously exposed [53]. A larger replication trial of DCS augmentation of CBT for delusions is currently underway.

CONCLUSION

In summary, although strongly implicated in schizophrenia, the specific role of NMDA receptors in the production of symptoms remains unclear, as does the mechanism by which DCS may alleviate negative symptoms and memory deficits. During early neurodevelopment, NMDA receptors are critical for regulation of use-dependent neuronal survival and synaptic connectivity [125] and for the development and maintenance of PV+ interneurons which modulate brain synchrony [126]. These effects are critical for multiple aspects of cognition. In adulthood, NMDA receptors are involved in the neuroplastic adaptation to environmental change, such as learning in response to novel stimuli and reversal learning or extinction. Deficits in neuroplastic functions required for adaptation to a changing environment may result in persistence of delusions as well as diminished motivational response to new sources of reward. NMDA receptors also play an important role in the modulation of dopamine release as evidenced by the reduction by ketamine of striatal dopamine release in response to psychostimulant in healthy subjects which closely mimics the response to psychostimulant observed in schizophrenia subjects [127].

The evidence from clinical trials of daily dosing with glycine site agonists in schizophrenia has been inconsistent and the evidence from single or intermittent dosing with DCS is sparse (Table **2**). However, with daily dosing of glycine site agonists it appears that response of negative symptoms gradually evolves over a period of approximately 6-8 weeks and tachyphylaxis has not been observed. In contrast, memory effects with DCS are produced by a single dose and rapidly are lost with repeated dosing, suggesting that different mechanisms underlie these two potential therapeutic actions. Daily dosing with the full agonists (glycine and D-serine) may be more effective than DCS for negative symptoms based on results from early trials [11], although an advantage for glycine over DCS was not evident in the head-to-head comparison provided by the CONSIST trial [12]. The poor brain penetrance of glycine and D-serine has raised the possibility that the full therapeutic potential of glycine site agonists has not been realized. However, the GlyT1 inhibitor, bitopertin, has good bioavailability and examination of CSF glycine concentrations in animals and human subjects in response to bitopertin, combined with PET ligand occupancy studies, revealed an inverted U-shaped dose response curve for response of negative symptoms [128]. Despite optimization of glycine concentrations, the effect of bitopertin on negative symptoms was not large [15] and was not replicated. One must be very cautious in interpreting indirect comparisons between agents that were studied under different conditions, however, the effect size of negative symptom response has been similar between positive trials of daily dosing with glycine, D-serine and DCS and with once-weekly dosing with DCS. Thus, in the absence of compelling data from head-to-head comparisons of these agents, the current clinical data are insufficient to determine whether the different pharmacologic actions of these agents at subpopulations of NMDA receptors confers therapeutic advantage, or whether the efficacy associated with intermittent dosing differs from daily dosing. The data are highly suggestive, however, that DCS differs from the other agents in provoking a worsening of psychotic symptoms at high doses. This effect appears to be limited to individuals with schizophrenia since it has not been observed in patients with anxiety disorders treated with high dose DCS [102]. DCS differs from D-serine and glycine primarily by possessing stronger agonist activity at GluN2C and weaker agonist activity at GluN2B subunit-containing receptors; the propensity for worsening of psychotic symptoms most likely is attributable to relative antagonism at GluN2B subunits. This explanation is supported by the finding that a GluN2B subunit-selective NMDA antagonist, CP101-606, was psychotomimetic in patients with depression at high doses [129]. DCS also is unique among glycine site agonists in worsening negative symptoms when added to clozapine [130]. This effect occurs at low doses of DCS, suggesting that clozapine may alter the pharmacodynamic activity of DCS, possibly by increasing endogenous glycine concentrations [131].

Limited evidence has suggested that antagonism at GluN2B might be neuroprotective but could interfere with reversal learning and hence diminish cognitive flexibility. D-serine in particular has been found to improve reversal learning in animal models, whether levels are increased by knock-out of D-amino acid oxidase or by direct administration of exogenous D-serine [132]. Interestingly, at high doses, DCS elevates D-serine levels in forebrain, but it is not clear if this effect is relevant in clinical trials in which much lower concentrations are achieved [59]. In healthy human subjects, ketamine impairs cognitive flexibility as reflected by increased perseverative errors on the Wisconsin Card Sorting Test (WCST) [8]; however, Tsai and colleagues did not find a reduction in perseverative errors on the WCST in schizophrenia subjects after six-weeks of daily dosing with D-serine [133]. In a study in which a single dose of DCS enhanced delayed thematic recall on the logical memory test, schizophrenia subjects who received placebo displayed a worsening of delayed recall compared to their performance at baseline—this worsening of performance may have resulted from proactive interference from the prior presentation of a different story at baseline [122]. The elimination of a proactive interference effect with DCS may represent, in part, an improvement in cognitive flexibility. Whether the 'super agonist" effect of DCS at GluN2C-containing NMDA receptors confers a unique benefit for memory enhancement remains to be determined. The observations of persistence of memory enhancing effects with single dosing, persistence of effects on negative symptoms with intermittent dosing, and loss of memory

effect with repeated dosing have only been made with DCS. Of interest, Glyx13, an NMDA partial agonist with 20% activity compared to glycine, enhanced memory following a single low dose and improved behaviors associated with depression following a higher dose in animal studies [134]. Glyx13 has recently been found to improve depression in patients [134], an effect that persists after a single dose and which has been linked to increased expression of GluN2B subunits in PFC [134]. Tolerance for Glyx 13 memory and antidepressant effects with repeated dosing has not been observed [134]. Answers to these questions await clinical trials with agents that are selective for NMDA receptor subtypes; partial allosteric positive and negative modulators with subunit selectivity are currently in development. The very promising results of trials of DCS enhancement of CBT for anxiety disorders and ketamine infusion for refractory depression clearly support the development of therapeutic strategies targeting neuroplasticity with agents acting at NMDA receptors. The optimal approach for enhancing neuroplasticity in schizophrenia remains to be clarified, but preliminary evidence with DCS is encouraging.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Goff, D.C. Drug development in schizophrenia: are glutamatergic targets still worth aiming at? *Curr. Opin. Psychiatry,* **2015**, *28*(3), 207-215. [http://dx.doi.org/10.1097/YCO.0000000000000152] [PMID: 25710242]

[2] Luby, E.D.; Cohen, B.D.; Rosenbaum, G.; Gottlieb, J.S.; Kelley, R. Study of a new schizophrenomimetic drug; sernyl. *AMA Arch. Neurol. Psychiatry,* **1959**, *81*(3), 363-369. [http://dx.doi.org/10.1001/archneurpsyc.1959.02340150095011] [PMID: 13626287]

[3] Fromer, M.; Pocklington, A.J.; Kavanagh, D.H.; Williams, H.J.; Dwyer, S.; Gormley, P.; Georgieva, L.; Rees, E.; Palta, P.; Ruderfer, D.M.; Carrera, N.; Humphreys, I.; Johnson, J.S.; Roussos, P.; Barker, D.D.; Banks, E.; Milanova, V.; Grant, S.G.; Hannon, E.; Rose, S.A.; Chambert, K.; Mahajan, M.; Scolnick, E.M.; Moran, J.L.; Kirov, G.; Palotie, A.; McCarroll, S.A.; Holmans, P.; Sklar, P.; Owen, M.J.; Purcell, S.M.; ODonovan, M.C. De novo mutations in schizophrenia implicate synaptic networks. *Nature,* **2014**, *506*(7487), 179-184. [http://dx.doi.org/10.1038/nature12929] [PMID: 24463507]

[4] Ripke, S.; ODushlaine, C.; Chambert, K.; Moran, J.L.; Kähler, A.K.; Akterin, S.; Bergen, S.E.; Collins, A.L.; Crowley, J.J.; Fromer, M.; Kim, Y.; Lee, S.H.; Magnusson, P.K.; Sanchez, N.; Stahl, E.A.; Williams, S.; Wray, N.R.; Xia, K.; Bettella, F.; Borglum, A.D.; Bulik-Sullivan, B.K.; Cormican, P.; Craddock, N.; de Leeuw, C.; Durmishi, N.; Gill, M.; Golimbet, V.; Hamshere, M.L.; Holmans, P.; Hougaard, D.M.; Kendler, K.S.; Lin, K.; Morris, D.W.; Mors, O.; Mortensen, P.B.; Neale, B.M.; ONeill, F.A.; Owen, M.J.; Milovancevic, M.P.; Posthuma, D.; Powell, J.; Richards, A.L.; Riley, B.P.; Ruderfer, D.; Rujescu, D.; Sigurdsson, E.; Silagadze, T.; Smit, A.B.; Stefansson, H.; Steinberg, S.; Suvisaari, J.; Tosato, S.; Verhage, M.; Walters, J.T.; Levinson, D.F.; Gejman, P.V.; Kendler, K.S.; Laurent, C.; Mowry, B.J.; ODonovan, M.C.; Owen, M.J.; Pulver, A.E.; Riley, B.P.; Schwab, S.G.; Wildenauer, D.B.; Dudbridge, F.; Holmans, P.; Shi, J.; Albus, M.; Alexander, M.; Campion, D.; Cohen, D.; Dikeos, D.; Duan, J.; Eichhammer, P.; Godard, S.; Hansen, M.; Lerer, F.B.; Liang, K.Y.; Maier, W.; Mallet, J.; Nertney, D.A.; Nestadt, G.; Norton, N.; ONeill, F.A.; Papadimitriou, G.N.; Ribble, R.; Sanders, A.R.; Silverman, J.M.; Walsh, D.; Williams, N.M.; Wormley, B.; Arranz, M.J.; Bakker, S.; Bender, S.; Bramon, E.; Collier, D.; Crespo-Facorro, B.; Hall, J.; Iyegbe, C.; Jablensky, A.; Kahn, R.S.; Kalaydjieva, L.; Lawrie, S.; Lewis, C.M.; Lin, K.; Linszen, D.H.; Mata, I.; McIntosh, A.; Murray, R.M.; Ophoff, R.A.; Powell, J.; Rujescu, D.; Van Os, J.; Walshe, M.; Weisbrod, M.; Wiersma, D.; Donnelly, P.; Barroso, I.; Blackwell, J.M.; Bramon, E.; Brown, M.A.; Casas, J.P.; Corvin, A.P.; Deloukas, P.; Duncanson, A.; Jankowski, J.; Markus, H.S.; Mathew, C.G.; Palmer, C.N.; Plomin, R.; Rautanen, A.; Sawcer, S.J.; Trembath, R.C.; Viswanathan, A.C.; Wood, N.W.; Spencer, C.C.; Band, G.; Bellenguez, C.; Freeman, C.; Hellenthal, G.; Giannoulatou, E.; Pirinen, M.; Pearson, R.D.; Strange, A.; Su, Z.; Vukcevic, D.; Donnelly, P.; Langford, C.; Hunt, S.E.; Edkins, S.; Gwilliam, R.; Blackburn, H.; Bumpstead, S.J.; Dronov, S.; Gillman, M.; Gray, E.; Hammond, N.; Jayakumar, A.; McCann, O.T.; Liddle, J.; Potter, S.C.; Ravindrarajah, R.; Ricketts, M.; Tashakkori-Ghanbaria, A.; Waller, M.J.; Weston, P.; Widaa, S.; Whittaker, P.; Barroso, I.; Deloukas, P.; Mathew, C.G.; Blackwell, J.M.; Brown, M.A.; Corvin, A.P.; McCarthy, M.I.; Spencer, C.C.; Bramon, E.; Corvin, A.P.; ODonovan, M.C.; Stefansson, K.; Scolnick, E.; Purcell, S.; McCarroll, S.A.; Sklar, P.; Hultman, C.M.; Sullivan, P.F. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. *Nat. Genet.,* **2013**, *45*(10), 1150-1159. [http://dx.doi.org/10.1038/ng.2742] [PMID: 23974872]

[5] Aberg, K.A.; McClay, J.L.; Nerella, S.; Clark, S.; Kumar, G.; Chen, W.; Khachane, A.N.; Xie, L.; Hudson, A.; Gao, G.; Harada, A.; Hultman, C.M.; Sullivan, P.F.; Magnusson, P.K.; van den Oord, E.J. Methylome-wide association study of schizophrenia: identifying blood biomarker signatures of environmental insults. *JAMA Psychiatry,* **2014**, *71*(3), 255-264. [http://dx.doi.org/10.1001/jamapsychiatry.2013.3730] [PMID: 24402055]

[6] Knuesel, I.; Chicha, L.; Britschgi, M.; Schobel, S.A.; Bodmer, M.; Hellings, J.A.; Toovey, S.; Prinssen, E.P. Maternal immune activation and abnormal brain development across CNS disorders. *Nat. Rev. Neurol.,* **2014**, *10*(11), 643-660. [http://dx.doi.org/10.1038/nrneurol.2014.187] [PMID: 25311587]

[7] Schwarcz, R. The kynurenine pathway of tryptophan degradation as a drug target. *Curr. Opin. Pharmacol.,* **2004**, *4*(1), 12-17. [http://dx.doi.org/10.1016/j.coph.2003.10.006] [PMID: 15018833]

[8] Krystal, J.H.; Karper, L.P.; Seibyl, J.P.; Freeman, G.K.; Delaney, R.; Bremner, J.D.; Heninger, G.R.; Bowers, M.B., Jr; Charney, D.S. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch. Gen. Psychiatry,* **1994**, *51*(3), 199-214. [http://dx.doi.org/10.1001/archpsyc.1994.03950030035004] [PMID: 8122957]

[9] Lahti, AC; Koffel, B; LaPorte, D; Tamminga, CA Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. *Neuropsychopharmacology,* **1995**, *13*, 9-19. [http://dx.doi.org/10.1016/0893-133X(94)00131-I]

[10] Malhotra, A.K.; Adler, C.M.; Kennison, S.D.; Elman, I.; Pickar, D.; Breier, A. Clozapine blunts N-methyl-D-aspartate antagonist-induced psychosis: a study with ketamine. *Biol. Psychiatry,* **1997**, *42*(8), 664-668. [http://dx.doi.org/10.1016/S0006-3223(96)00546-X] [PMID: 9325559]

[11] Tuominen, H.J.; Tiihonen, J.; Wahlbeck, K. Glutamatergic drugs for schizophrenia: a systematic review and meta-analysis. *Schizophr. Res.,* **2005**, *72*(2-3), 225-234. [http://dx.doi.org/10.1016/j.schres.2004.05.005] [PMID: 15560967]

[12] Buchanan, R.W.; Javitt, D.C.; Marder, S.R.; Schooler, N.R.; Gold, J.M.; McMahon, R.P.; Heresco-Levy, U.; Carpenter, W.T. The Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST): the efficacy of glutamatergic agents for negative symptoms and cognitive impairments. *Am. J. Psychiatry,* **2007**, *164*(10), 1593-1602. [http://dx.doi.org/10.1176/appi.ajp.2007.06081358] [PMID: 17898352]

[13] Weiser, M.; Heresco-Levy, U.; Davidson, M.; Javitt, D.C.; Werbeloff, N.; Gershon, A.A.; Abramovich, Y.; Amital, D.; Doron, A.; Konas, S.; Levkovitz, Y.; Liba, D.; Teitelbaum, A.; Mashiach, M.; Zimmerman, Y. A multicenter, add-on randomized controlled trial of low-dose d-serine for negative and cognitive symptoms of schizophrenia. *J. Clin. Psychiatry,* **2012**, *73*(6), e728-e734. [http://dx.doi.org/10.4088/JCP.11m07031] [PMID: 22795211]

[14] D'Souza, DC; Radhakrishnan, R; Perry, E; Bhakta, S; Singh, NM; Yadav, R; Abi-Saab, D; Pittman, B; Chaturvedi, SK; Sharma, MP; Bell, M; Andrade, C Feasibility, safety, and efficacy of the combination of d-serine and computerized cognitive retraining in schizophrenia: an international collaborative pilot study. *Neuropsychopharmacology,* **2013**, *38*, 492-503. [http://dx.doi.org/10.1038/npp.2012.208]

[15] Umbricht, D.; Alberati, D.; Martin-Facklam, M.; Borroni, E.; Youssef, E.A.; Ostland, M.; Wallace, T.L.; Knoflach, F.; Dorflinger, E.; Wettstein, J.G.; Bausch, A.; Garibaldi, G.; Santarelli, L. A randomized, double-blind, proof-of-concept study of the effect of bitopertin, a glycine reuptake 2 inhibitor, on negative symptoms of schizophrenia. *JAMA Psychiatry,* **2014**. [http://dx.doi.org/10.1001/jamapsychiatry.2014.163]

[16] Goff, D.C. Bitopertin: the good news and bad news. *JAMA Psychiatry,* **2014**, *71*(6), 621-622. [http://dx.doi.org/10.1001/jamapsychiatry.2014.257] [PMID: 24696065]

[17] Lane, H.Y.; Lin, C.H.; Green, M.F.; Hellemann, G.; Huang, C.C.; Chen, P.W.; Tun, R.; Chang, Y.C.; Tsai, G.E. Add-on treatment of benzoate for schizophrenia: a randomized, double-blind, placebo-controlled trial of D-amino acid oxidase inhibitor. *JAMA Psychiatry,* **2013**, *70*(12), 1267-1275. [http://dx.doi.org/10.1001/jamapsychiatry.2013.2159] [PMID: 24089054]

[18] Javitt, D.C.; Balla, A.; Sershen, H.; Lajtha, A. Reversal of the behavioral and neurochemical effects of phencylidine by glycine and glycine transport inhibitors. *Biol. Psychiatry,* **1999**, *45*, 668-679. [http://dx.doi.org/10.1016/S0006-3223(98)00237-6] [PMID: 10187996]

[19] Krystal, J.H.; Abi-Saab, W.; Perry, E.; DSouza, D.C.; Liu, N.; Gueorguieva, R.; McDougall, L.; Hunsberger, T.; Belger, A.; Levine, L.; Breier, A. 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.),* **2005**, *179*(1), 303-309. [http://dx.doi.org/10.1007/s00213-004-1982-8] [PMID: 15309376]

[20] Anand, A.; Charney, D.S.; Oren, D.A.; Berman, R.M.; Hu, X.S.; Cappiello, A.; Krystal, J.H. Attentuation of the neuropsychiatric effects of ketamine with lamotrigine. *Arch. Gen. Psychiatry,* **2000**, *57*, 270-276. [http://dx.doi.org/10.1001/archpsyc.57.3.270] [PMID: 10711913]

[21] Stauffer, V.L.; Millen, B.A.; Andersen, S.; Kinon, B.J.; Lagrandeur, L.; Lindenmayer, J.P.; Gomez, J.C. Pomaglumetad methionil: no significant difference as an adjunctive treatment for patients with prominent negative symptoms of schizophrenia compared to placebo. *Schizophr. Res.,* **2013**, *150*(2-3), 434-441. [http://dx.doi.org/10.1016/j.schres.2013.08.020] [PMID: 24035403]

[22] Goff, D.C.; Keefe, R.; Citrome, L.; Davy, K.; Krystal, J.H.; Large, C.; Thompson, T.R.; Volavka, J.; Webster, E.L. Lamotrigine as add-on therapy in schizophrenia: results of 2 placebo-controlled trials. *J. Clin. Psychopharmacol.,* **2007**, *27*(6), 582-589. [http://dx.doi.org/10.1097/jcp.0b013e31815abf34] [PMID: 18004124]

[23] Goff, D.C.; Tsai, G.; Manoach, D.S.; Coyle, J.T. Dose-finding trial of D-cycloserine added to neuroleptics for negative symptoms in schizophrenia. *Am. J. Psychiatry,* **1995**, *152*(8), 1213-1215. [http://dx.doi.org/10.1176/ajp.152.8.1213] [PMID: 7625475]

[24] van Berckel, B.N.; Hijman, R.; van der Linden, J.A.; Westenberg, H.G.; van Ree, J.M.; Kahn, R.S. Efficacy and tolerance of D-cycloserine in drug-free schizophrenic patients. *Biol. Psychiatry,* **1996**, *40*(12), 1298-1300. [http://dx.doi.org/10.1016/S0006-3223(96)00311-3] [PMID: 8959296]

[25] Goff, D.C.; Tsai, G.; Levitt, J.; Amico, E.; Manoach, D.; Schoenfeld, D.A.; Hayden, D.L.; McCarley, R.; Coyle, J.T. A placebo-controlled trial of D-cycloserine added to conventional neuroleptics in patients with schizophrenia. *Arch. Gen. Psychiatry,* **1999**, *56*(1), 21-27. [http://dx.doi.org/10.1001/archpsyc.56.1.21] [PMID: 9892252]

[26] Yurgelun-Todd, D.A.; Coyle, J.T.; Gruber, S.A.; Renshaw, P.F.; Silveri, M.M.; Amico, E.; Cohen, B.; Goff, D.C. Functional magnetic resonance imaging studies of schizophrenic patients during word production: effects of D-cycloserine. *Psychiatry Res.,* **2005**, *138*(1), 23-31. [http://dx.doi.org/10.1016/j.pscychresns.2004.11.006] [PMID: 15708298]

[27] van Berckel, BNM; Evenblij, CN; van Loon, BJAM; Maas, MF; van der Geld, MAM; Wynne, HJ; van Ree, JM; Kahn, RS D-cycloserine increases positive symptoms in chronic schizophrenic patients when administered in addition to antipsychotics: A double-blind, parallel, placebo-controlled study. *Neuropsychopharmacology,* **1999**, *21*, 203-210.

[28] Cascella, N.G.; Macciardi, F.; Cavallini, C.; Smeraldi, E. d-cycloserine adjuvant therapy to conventional neuroleptic treatment in schizophrenia: an open-label study. *J. Neural Transm.,* **1994**, *95*(2), 105-111. [Gen Sect]. [http://dx.doi.org/10.1007/BF01276429] [PMID: 7865165]

[29] Simeon, J.; Fink, M.; Itil, T.M.; Ponce, D. d-Cycloserine therapy of psychosis by symptom provocation. *Compr. Psychiatry,* **1970**, *11*(1), 80-88. [http://dx.doi.org/10.1016/0010-440X(70)90207-5] [PMID: 5411216]

[30] Duncan, E.J.; Szilagyi, S.; Schwartz, M.P.; Bugarski-Kirola, D.; Kunzova, A.; Negi, S.; Stephanides, M.; Efferen, T.R.; Angrist, B.; Peselow, E.; Corwin, J.; Gonzenbach, S.; Rotrosen, J.P. Effects of D-cycloserine on negative symptoms in schizophrenia. *Schizophr. Res.,* **2004**, *71*(2-3), 239-248. [http://dx.doi.org/10.1016/j.schres.2004.03.013] [PMID: 15474895]

[31] Heresco-Levy, U.; Ermilov, M.; Shimoni, J.; Shapira, B.; Silipo, G.; Javitt, D.C. Placebo-controlled trial of D-cycloserine added to conventional neuroleptics, olanzapine, or risperidone in schizophrenia. *Am. J. Psychiatry,* **2002**, *159*(3), 480-482. [http://dx.doi.org/10.1176/appi.ajp.159.3.480] [PMID: 11870017]

[32] Goff, D.C.; Herz, L.; Posever, T.; Shih, V.; Tsai, G.; Henderson, D.C.; Freudenreich, O.; Evins, A.E.; Yovel, I.; Zhang, H.; Schoenfeld, D. A six-month, placebo-controlled trial of D-cycloserine co-administered with conventional antipsychotics in schizophrenia patients. *Psychopharmacology (Berl.),* **2005**, *179*(1), 144-150. [http://dx.doi.org/10.1007/s00213-004-2032-2] [PMID: 15502972]

[33] Kantrowitz, J.T.; Malhotra, A.K.; Cornblatt, B.; Silipo, G.; Balla, A.; Suckow, R.F.; DSouza, C.; Saksa, J.; Woods, S.W.; Javitt, D.C. High dose D-serine in the treatment of schizophrenia. *Schizophr. Res.,* **2010**, *121*(1-3), 125-130. [http://dx.doi.org/10.1016/j.schres.2010.05.012] [PMID: 20541910]

[34] Rutherford, B.R.; Pott, E.; Tandler, J.M.; Wall, M.M.; Roose, S.P.; Lieberman, J.A. Placebo response in antipsychotic clinical trials: a meta-analysis. *JAMA Psychiatry,* **2014**, *71*(12), 1409-1421. [http://dx.doi.org/10.1001/jamapsychiatry.2014.1319] [PMID: 25321611]

[35] Zink, M.; Englisch, S.; Schmitt, A. Antipsychotic treatment modulates glutamate transport and NMDA receptor expression. *Eur. Arch. Psychiatry Clin. Neurosci.,* **2014**, *264*(Suppl. 1), S67-S82. [http://dx.doi.org/10.1007/s00406-014-0534-4] [PMID: 25214389]

[36] Emmett, M.R.; Mick, S.J.; Cler, J.A.; Rao, T.S.; Iyengar, S.; Wood, P.L. Actions of D-cycloserine at the N-methyl-D-aspartate-associated glycine receptor site *in vivo*. *Neuropharmacology,* **1991**, *30*(11), 1167-1171. [http://dx.doi.org/10.1016/0028-3908(91)90161-4] [PMID: 1663594]

[37] Rao, K.V.; Eidus, L.; Evans, C.; Kailasam, S.; Radhakrishna, S.; Somasundaram, P.R.; Stott, H.; Subbammal, S.; Tripathy, S.P. Deterioration of cycloserine in the tropics. *Bull. World Health Organ.,* **1968**, *39*(5), 781-789. [PMID: 5306125]

[38] Werner-Seidler, A.; Richardson, R. Effects of D-cycloserine on extinction: consequences of prior exposure to imipramine. *Biol. Psychiatry,* **2007**, *62*(10), 1195-1197. [http://dx.doi.org/10.1016/j.biopsych.2007.04.010] [PMID: 17555721]

[39] Davis, M.; Ressler, K.; Rothbaum, B.O.; Richardson, R. Effects of D-cycloserine on extinction: translation from preclinical to clinical work. *Biol. Psychiatry,* **2006**, *60*(4), 369-375. [http://dx.doi.org/10.1016/j.biopsych.2006.03.084] [PMID: 16919524]

[40] Parnas, A.S.; Weber, M.; Richardson, R. Effects of multiple exposures to D-cycloserine on extinction of conditioned fear in rats. *Neurobiol. Learn. Mem.,* **2005**, *83*(3), 224-231. [http://dx.doi.org/10.1016/j.nlm.2005.01.001] [PMID: 15820858]

[41] Quartermain, D.; Mower, J.; Rafferty, M.F.; Herting, R.L.; Lanthorn, T.H. Acute but not chronic activation of the NMDA-coupled glycine receptor with D-cycloserine facilitates learning and retention. *Eur. J. Pharmacol.,* **1994**, *257*(1-2), 7-12. [http://dx.doi.org/10.1016/0014-2999(94)90687-4] [PMID: 8082709]

[42] Nong, Y.; Huang, Y.Q.; Ju, W.; Kalia, L.V.; Ahmadian, G.; Wang, Y.T.; Salter, M.W. Glycine binding primes NMDA receptor internalization. *Nature,* **2003**, *422*(6929), 302-307. [http://dx.doi.org/10.1038/nature01497] [PMID: 12646920]

[43] Shaw, D.; Norwood, K.; Sharp, K.; Quigley, L.; McGovern, S.F.; Leslie, J.C. Facilitation of extinction of operant behaviour in mice by D-cycloserine. *Psychopharmacology (Berl.),* **2009**, *202*(1-3), 397-402. [http://dx.doi.org/10.1007/s00213-008-1312-7] [PMID: 18781295]

[44] Nic Dhonnchadha, BA; Szalay, JJ; Achat-Mendes, C; Platt, DM; Otto, MW; Spealman, RD; Kantak, KM D-cycloserine deters reacquisition of cocaine self-administration by augmenting extinction learning. *Neuropsychopharmacology,* **2010**, *35*, 357-367.

[45] Vengeliene, V.; Kiefer, F.; Spanagel, R. D-cycloserine facilitates extinction of conditioned alcohol-seeking behaviour in rats. *Alcohol Alcohol.,* **2008**, *43*(6), 626-629. [http://dx.doi.org/10.1093/alcalc/agn067] [PMID: 18945754]

[46] Yu, H.; Wang, Y.; Pattwell, S.; Jing, D.; Liu, T.; Zhang, Y.; Bath, K.G.; Lee, F.S.; Chen, Z.Y. Variant BDNF Val66Met polymorphism affects extinction of conditioned aversive memory. *J. Neurosci.,* **2009**, *29*(13), 4056-4064. [http://dx.doi.org/10.1523/JNEUROSCI.5539-08.2009] [PMID: 19339601]

[47] Rodgers, R.J.; Harvest, H.; Hassall, C.; Kaddour, L.A. D-cycloserine enhances memory consolidation in the plus-maze retest paradigm. *Behav. Neurosci.,* **2011**, *125*(1), 106-116. [http://dx.doi.org/10.1037/a0022343] [PMID: 21319892]

[48] Assini, F.L.; Duzzioni, M.; Takahashi, R.N. Object location memory in mice: pharmacological validation and further evidence of hippocampal CA1 participation. *Behav. Brain Res.,* **2009**, *204*(1), 206-211. [http://dx.doi.org/10.1016/j.bbr.2009.06.005] [PMID: 19523494]

[49] Zlomuzica, A.; De Souza Silva, M.A.; Huston, J.P.; Dere, E. NMDA receptor modulation by D-cycloserine promotes episodic-like memory in mice. *Psychopharmacology (Berl.),* **2007**, *193*(4), 503-509. [http://dx.doi.org/10.1007/s00213-007-0816-x] [PMID: 17497136]

[50] Peters, J.; De Vries, T.J. D-cycloserine administered directly to infralimbic medial prefrontal cortex enhances extinction memory in sucrose-seeking animals. *Neuroscience,* **2013**, *230*, 24-30. [http://dx.doi.org/10.1016/j.neuroscience.2012.11.004] [PMID: 23159319]

[51] Chang, C.H.; Maren, S. Medial prefrontal cortex activation facilitates re-extinction of fear in rats. *Learn. Mem.,* **2011**, *18*(4), 221-225. [http://dx.doi.org/10.1101/lm.2070111] [PMID: 21430044]

[52] Ren, J.; Li, X.; Zhang, X.; Li, M.; Wang, Y.; Ma, Y. The effects of intra-hippocampal microinfusion of D-cycloserine on fear extinction, and the expression of NMDA receptor subunit NR2B and neurogenesis in the hippocampus in rats. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2013**, *44*, 257-264. [http://dx.doi.org/10.1016/j.pnpbp.2013.02.017] [PMID: 23523746]

[53] Langton, JM; Richardson, R D-cycloserine facilitates extinction the first time but not the second time: an examination of the role of NMDA across the course of repeated extinction sessions. *Neuropsychopharmacology,* **2008**, *33*, 3096-3102.

[54] Ledgerwood, L.; Richardson, R.; Cranney, J. D-cycloserine facilitates extinction of learned fear: effects on reacquisition and generalized extinction. *Biol. Psychiatry,* **2005**, *57*(8), 841-847. [http://dx.doi.org/10.1016/j.biopsych.2005.01.023] [PMID: 15820704]

[55] Mao, SC; Lin, HC; Gean, PW Augmentation of fear extinction by D-cycloserine is blocked by proteasome inhibitors. *Neuropsychopharmacology,* **2008**, *33*, 3085-3095.

[56] Lee, J.L.; Milton, A.L.; Everitt, B.J. Reconsolidation and extinction of conditioned fear: inhibition and potentiation. *J. Neurosci.,* **2006**, *26*(39), 10051-10056. [http://dx.doi.org/10.1523/JNEUROSCI.2466-06.2006] [PMID: 17005868]

[57] Smits, J.A.; Rosenfield, D.; Otto, M.W.; Marques, L.; Davis, M.L.; Meuret, A.E.; Simon, N.M.; Pollack, M.H.; Hofmann, S.G. D-cycloserine enhancement of exposure therapy for social anxiety disorder depends on the success of exposure sessions. *J. Psychiatr. Res.,* **2013**, *47*(10), 1455-1461. [http://dx.doi.org/10.1016/j.jpsychires.2013.06.020] [PMID: 23870811]

[58] Yang, Y.; Ge, W.; Chen, Y.; Zhang, Z.; Shen, W.; Wu, C.; Poo, M.; Duan, S. Contribution of astrocytes to hippocampal long-term potentiation through release of D-serine. *Proc. Natl. Acad. Sci. USA,* **2003**, *100*(25), 15194-15199. [http://dx.doi.org/10.1073/pnas.2431073100] [PMID: 14638938]

[59] Hopkins, S.C.; Campbell, U.C.; Heffernan, M.L.; Spear, K.L.; Jeggo, R.D.; Spanswick, D.C.; Varney, M.A.; Large, T.H. Effects of D-amino acid oxidase inhibition on memory performance and long-term potentiation *in vivo*. *Pharmacol. Res. Perspect.,* **2013**, *1*(1), e00007. [http://dx.doi.org/10.1002/prp2.7] [PMID: 25505561]

[60] Labrie, V.; Duffy, S.; Wang, W.; Barger, S.W.; Baker, G.B.; Roder, J.C. Genetic inactivation of D-amino acid oxidase enhances extinction and reversal learning in mice. *Learn. Mem.,* **2008**, *16*(1), 28-37. [http://dx.doi.org/10.1101/lm.1112209] [PMID: 19117914]

[61] Dravid, S.M.; Burger, P.B.; Prakash, A.; Geballe, M.T.; Yadav, R.; Le, P.; Vellano, K.; Snyder, J.P.; Traynelis, S.F. Structural determinants of D-cycloserine efficacy at the NR1/NR2C NMDA receptors. *J. Neurosci.,* **2010**, *30*(7), 2741-2754. [http://dx.doi.org/10.1523/JNEUROSCI.5390-09.2010] [PMID: 20164358]

[62] Sanz-Clemente, A; Nicoll, RA; Roche, KW Diversity in NMDA receptor composition: many regulators, many consequences. *The Neuroscientist,* **2013**, *19*, 62-75. [http://dx.doi.org/10.1177/1073858411435129]

[63] Xi, D.; Keeler, B.; Zhang, W.; Houle, J.D.; Gao, W.J. NMDA receptor subunit expression in GABAergic interneurons in the prefrontal cortex: application of laser microdissection technique. *J. Neurosci. Methods,* **2009**, *176*(2), 172-181. [http://dx.doi.org/10.1016/j.jneumeth.2008.09.013] [PMID: 18845188]

[64] Karavanova, I.; Vasudevan, K.; Cheng, J.; Buonanno, A. Novel regional and developmental NMDA receptor expression patterns uncovered in NR2C subunit-beta-galactosidase knock-in mice. *Mol. Cell. Neurosci.,* **2007**, *34*(3), 468-480. [http://dx.doi.org/10.1016/j.mcn.2006.12.001] [PMID: 17276696]

[65] Monyer, H.; Burnashev, N.; Laurie, D.J.; Sakmann, B.; Seeburg, P.H. Developmental and regional expression in the rat brain and functional properties of four NMDA receptors. *Neuron,* **1994**, *12*(3), 529-540. [http://dx.doi.org/10.1016/0896-6273(94)90210-0] [PMID: 7512349]

[66] Binshtok, A.M.; Fleidervish, I.A.; Sprengel, R.; Gutnick, M.J. NMDA receptors in layer 4 spiny stellate cells of the mouse barrel cortex contain the NR2C subunit. *J. Neurosci.,* **2006**, *26*(2), 708-715. [http://dx.doi.org/10.1523/JNEUROSCI.4409-05.2006] [PMID: 16407568]

[67] Jantzie, L.L.; Talos, D.M.; Jackson, M.C.; Park, H.K.; Graham, D.A.; Lechpammer, M.; Folkerth, R.D.; Volpe, J.J.; Jensen, F.E. Developmental Expression of N-Methyl-D-Aspartate (NMDA) Receptor Subunits in Human White and Gray Matter: Potential Mechanism of Increased Vulnerability in the Immature Brain. *Cereb. Cortex,* **2013**. [PMID: 24046081]

[68] Matta, J.A.; Ashby, M.C.; Sanz-Clemente, A.; Roche, K.W.; Isaac, J.T. mGluR5 and NMDA receptors drive the experience- and activity-dependent NMDA receptor NR2B to NR2A subunit switch. *Neuron,* **2011**, *70*(2), 339-351. [http://dx.doi.org/10.1016/j.neuron.2011.02.045] [PMID: 21521618]

[69] Barth, A.L.; Malenka, R.C. NMDAR EPSC kinetics do not regulate the critical period for LTP at thalamocortical synapses. *Nat. Neurosci.,* **2001**, *4*(3), 235-236. [http://dx.doi.org/10.1038/85070] [PMID: 11224537]

[70] Wang, C.C.; Held, R.G.; Chang, S.C.; Yang, L.; Delpire, E.; Ghosh, A.; Hall, B.J. A critical role for GluN2B-containing NMDA receptors in cortical development and function. *Neuron,* **2011**, *72*(5), 789-805. [http://dx.doi.org/10.1016/j.neuron.2011.09.023] [PMID: 22153375]

[71] Kinney, J.W.; Davis, C.N.; Tabarean, I.; Conti, B.; Bartfai, T.; Behrens, M.M. A specific role for NR2A-containing NMDA receptors in the maintenance of parvalbumin and GAD67 immunoreactivity in cultured interneurons. *J. Neurosci.,* **2006**, *26*(5), 1604-1615. [http://dx.doi.org/10.1523/JNEUROSCI.4722-05.2006] [PMID: 16452684]

[72] Liu, Y.; Wong, T.P.; Aarts, M.; Rooyakkers, A.; Liu, L.; Lai, T.W.; Wu, D.C.; Lu, J.; Tymianski, M.; Craig, A.M.; Wang, Y.T. NMDA receptor subunits have differential roles in mediating excitotoxic neuronal death both *in vitro* and *in vivo*. *J. Neurosci.,* **2007**, *27*(11), 2846-2857. [http://dx.doi.org/10.1523/JNEUROSCI.0116-07.2007] [PMID: 17360906]

[73] Kocsis, B. Differential role of NR2A and NR2B subunits in N-methyl-D-aspartate receptor antagonist-induced aberrant cortical gamma oscillations. *Biol. Psychiatry,* **2012**, *71*(11), 987-995. [http://dx.doi.org/10.1016/j.biopsych.2011.10.002] [PMID: 22055014]

[74] Rauner, C.; Köhr, G. Triheteromeric NR1/NR2A/NR2B receptors constitute the major N-methyl-D-aspartate receptor population in adult hippocampal synapses. *J. Biol. Chem.,* **2011**, *286*(9), 7558-7566. [http://dx.doi.org/10.1074/jbc.M110.182600] [PMID: 21190942]

[75] Menniti, F.S.; Lindsley, C.W.; Conn, P.J.; Pandit, J.; Zagouras, P.; Volkmann, R.A. Allosteric modulators for the treatment of schizophrenia: targeting glutamatergic networks. *Curr. Top. Med. Chem.,* **2013**, *13*(1), 26-54. [http://dx.doi.org/10.2174/1568026611313010005] [PMID: 23409764]

[76] Anastasio, N.C.; Xia, Y.; OConnor, Z.R.; Johnson, K.M. Differential role of N-methyl-D-aspartate receptor subunits 2A and 2B in mediating phencyclidine-induced perinatal neuronal apoptosis and behavioral deficits. *Neuroscience,* **2009**, *163*(4), 1181-1191. [http://dx.doi.org/10.1016/j.neuroscience.2009.07.058] [PMID: 19654040]

[77] Duffy, S; Labrie, V; Roder, JC D-Serine Augments NMDA-NR2B Receptor-Dependent Hippocampal Long-Term Depression and Spatial Reversal Learning. *Neuropsychopharmacology,* **2007**.

[78] Foster, K.A.; McLaughlin, N.; Edbauer, D.; Phillips, M.; Bolton, A.; Constantine-Paton, M.; Sheng, M. Distinct roles of NR2A and NR2B cytoplasmic tails in long-term potentiation. *J. Neurosci.,* **2010**, *30*(7), 2676-2685. [http://dx.doi.org/10.1523/JNEUROSCI.4022-09.2010] [PMID: 20164351]

[79] Burgdorf, J; Zhang, XL; Nicholson, KL; Balster, RL; Leander, JD; Stanton, PK; Gross, AL; Kroes, RA; Moskal, JR GLYX-13, a NMDA receptor glycine-site functional partial agonist, induces antidepressant-like effects without ketamine-like side effects. *Neuropsychopharmacology,* **2013**, *38*, 729-742.

[80] Belforte, J.E.; Zsiros, V.; Sklar, E.R.; Jiang, Z.; Yu, G.; Li, Y.; Quinlan, E.M.; Nakazawa, K. Postnatal NMDA receptor ablation in corticolimbic interneurons confers schizophrenia-like phenotypes. *Nat. Neurosci.,* **2010**, *13*(1), 76-83. [http://dx.doi.org/10.1038/nn.2447] [PMID: 19915563]

[81] Woo, T.U.; Walsh, J.P.; Benes, F.M. Density of glutamic acid decarboxylase 67 messenger RNA-containing neurons that express the N-methyl-D-aspartate receptor subunit NR2A in the anterior cingulate cortex in schizophrenia and bipolar disorder. *Arch. Gen. Psychiatry,* **2004**, *61*(7), 649-657. [http://dx.doi.org/10.1001/archpsyc.61.7.649] [PMID: 15237077]

[82] Beneyto, M; Meador-Woodruff, JH Lamina-specific abnormalities of NMDA receptor-associated postsynaptic protein transcripts in the prefrontal cortex in schizophrenia and bipolar disorder. *Neuropsychopharmacology,* **2008**, *33*, 2175-2186. [http://dx.doi.org/10.1038/sj.npp.1301604]

[83] Kim, J.H.; Richardson, R. New findings on extinction of conditioned fear early in development: theoretical and clinical implications. *Biol. Psychiatry,* **2010**, *67*(4), 297-303. [http://dx.doi.org/10.1016/j.biopsych.2009.09.003] [PMID: 19846065]

[84] Heldt, S.A.; Stanek, L.; Chhatwal, J.P.; Ressler, K.J. Hippocampus-specific deletion of BDNF in adult mice impairs spatial memory and extinction of aversive memories. *Mol. Psychiatry,* **2007**, *12*(7), 656-670. [http://dx.doi.org/10.1038/sj.mp.4001957] [PMID: 17264839]

[85] Caldeira, M.V.; Melo, C.V.; Pereira, D.B.; Carvalho, R.F.; Carvalho, A.L.; Duarte, C.B. BDNF regulates the expression and traffic of NMDA receptors in cultured hippocampal neurons. *Mol. Cell. Neurosci.,* **2007**, *35*(2), 208-219. [http://dx.doi.org/10.1016/j.mcn.2007.02.019] [PMID: 17428676]

[86] Brandoli, C.; Sanna, A.; De Bernardi, M.A.; Follesa, P.; Brooker, G.; Mocchetti, I. Brain-derived neurotrophic factor and basic fibroblast growth factor downregulate NMDA receptor function in cerebellar granule cells. *J. Neurosci.,* **1998**, *18*(19), 7953-7961. [PMID: 9742162]

[87] Hanks, A.N.; Dlugolenski, K.; Hughes, Z.A.; Seymour, P.A.; Majchrzak, M.J. Pharmacological disruption of mouse social approach behavior: relevance to negative symptoms of schizophrenia. *Behav. Brain Res.,* **2013**, *252*, 405-414. [http://dx.doi.org/10.1016/j.bbr.2013.06.017] [PMID: 23806621]

[88] Yaka, R; Biegon, A; Grigoriadis, N; Simeonidou, C; Grigoriadis, S; Alexandrovich, AG; Matzner, H; Schumann, J; Trembovler, V; Tsenter, J; Shohami, E D-cycloserine improves functional recovery and reinstates long-term potentiation (LTP) in a mouse model of closed head injury. *FASEB,* **2007**, *21*, 2033-2041.

[89] McCallum, J; Kim, JH; Richardson, R Impaired extinction retention in adolescent rats: effects of D-cycloserine. *Neuropsychopharmacology,* **2010**, *35*, 2134-2142.

[90] Pattwell, S.S.; Duhoux, S.; Hartley, C.A.; Johnson, D.C.; Jing, D.; Elliott, M.D.; Ruberry, E.J.; Powers, A.; Mehta, N.; Yang, R.R.; Soliman, F.; Glatt, C.E.; Casey, B.J.; Ninan, I.; Lee, F.S. Altered fear learning across development in both mouse and human. *Proc. Natl. Acad. Sci. USA,* **2012**, *109*(40), 16318-16323. [http://dx.doi.org/10.1073/pnas.1206834109] [PMID: 22988092]

[91] Cain, C.K.; McCue, M.; Bello, I.; Creedon, T.; Tang, D.I.; Laska, E.; Goff, D.C. d-Cycloserine augmentation of cognitive remediation in schizophrenia. *Schizophr. Res.,* **2014**, *153*(1-3), 177-183. [http://dx.doi.org/10.1016/j.schres.2014.01.016] [PMID: 24485587]

[92] Guan, Z.; Fang, J. Peripheral immune activation by lipopolysaccharide decreases neurotrophins in the cortex and hippocampus in rats. *Brain Behav. Immun.,* **2006**, *20*(1), 64-71. [http://dx.doi.org/10.1016/j.bbi.2005.04.005] [PMID: 15922558]

[93] Kranjac, D.; Koster, K.M.; Kahn, M.S.; Eimerbrink, M.J.; Womble, B.M.; Cooper, B.G.; Chumley, M.J.; Boehm, G.W. Peripheral administration of D-cycloserine rescues memory consolidation following bacterial endotoxin exposure. *Behav. Brain Res.,* **2013**, *243*, 38-43. [http://dx.doi.org/10.1016/j.bbr.2012.12.053] [PMID: 23295393]

[94] Hillman, B.G.; Gupta, S.C.; Stairs, D.J.; Buonanno, A.; Dravid, S.M. Behavioral analysis of NR2C knockout mouse reveals deficit in acquisition of conditioned fear and working memory. *Neurobiol. Learn. Mem.,* **2011**, *95*(4), 404-414. [http://dx.doi.org/10.1016/j.nlm.2011.01.008] [PMID: 21295149]

[95] Lisman, J.E.; Pi, H.J.; Zhang, Y.; Otmakhova, N.A. A thalamo-hippocampal-ventral tegmental area loop may produce the positive feedback that underlies the psychotic break in schizophrenia. *Biol. Psychiatry,* **2010**, *68*(1), 17-24. [http://dx.doi.org/10.1016/j.biopsych.2010.04.007] [PMID: 20553749]

[96] Zhang, Y.; Llinas, R.R.; Lisman, J.E. Inhibition of NMDARs in the Nucleus Reticularis of the Thalamus Produces Delta Frequency Bursting. *Front. Neural Circuits,* **2009**, *3*, 20. [PMID: 20057928]

[97] Ogden, KK; Khatri, A; Traynelis, SF; Heldt, SA Potentiation of GluN2C/D NMDA receptor subtypes in the amygdala facilitates the retention of fear and extinction learning in mice. *Neuropsychopharmacology,* **2014**, *39*, 625-637.

[98] Aura, J.; Riekkinen, M.; Riekkinen, P., Jr Tetrahydroaminoacridine and D-cycloserine stimulate acquisition of water maze spatial navigation in aged rats. *Eur. J. Pharmacol.,* **1998**, *342*(1), 15-20. [http://dx.doi.org/10.1016/S0014-2999(97)01512-4] [PMID: 9544787]

[99] Pitkänen, M.; Sirviö, J.; MacDonald, E.; Ekonsalo, T.; Riekkinen, P., Sr The effects of d-cycloserine, a partial agonist at the glycine binding site, on spatial learning and working memory in scopolamine-treated rats. *J. Neural Transm. Park. Dis. Dement. Sect.,* **1995**, *9*(2-3), 133-144. [http://dx.doi.org/10.1007/BF02259655] [PMID: 8526998]

[100] Pitkanen, M; Sirvio, J; MacDonald, E; Niemi, S; Ekonsalo, T; Riekkinen, P, Sr The effects of D-cycloserine and MK-801 on the performance of rats in two spatial learning and memory tasks. *Eur. Neuropsychopharmacol.,* **1995**, *5*, 457-463.

[101] Ressler, K.J.; Rothbaum, B.O.; Tannenbaum, L.; Anderson, P.; Graap, K.; Zimand, E.; Hodges, L.; Davis, M. Cognitive enhancers as adjuncts to psychotherapy: use of D-cycloserine in phobic individuals to facilitate extinction of fear. *Arch. Gen. Psychiatry,* **2004**, *61*(11), 1136-1144. [http://dx.doi.org/10.1001/archpsyc.61.11.1136] [PMID: 15520361]

[102] Norberg, M.M.; Krystal, J.H.; Tolin, D.F. A meta-analysis of D-cycloserine and the facilitation of fear extinction and exposure therapy. *Biol. Psychiatry,* **2008**, *63*(12), 1118-1126. [http://dx.doi.org/10.1016/j.biopsych.2008.01.012] [PMID: 18313643]

[103] Grillon, C. D-cycloserine facilitation of fear extinction and exposure-based therapy might rely on lower-level, automatic mechanisms. *Biol. Psychiatry,* **2009**, *66*(7), 636-641. [http://dx.doi.org/10.1016/j.biopsych.2009.04.017] [PMID: 19520359]

[104] Kuriyama, K.; Honma, M.; Koyama, S.; Kim, Y. D-cycloserine facilitates procedural learning but not declarative learning in healthy humans: a randomized controlled trial of the effect of D-cycloserine and valproic acid on overnight properties in the performance of non-emotional memory tasks. *Neurobiol. Learn. Mem.,* **2011**, *95*(4), 505-509. [http://dx.doi.org/10.1016/j.nlm.2011.02.017] [PMID: 21402164]

[105] Otto, M.W.; Basden, S.L.; McHugh, R.K.; Kantak, K.M.; Deckersbach, T.; Cather, C.; Goff, D.C.; Hofmann, S.G.; Berry, A.C.; Smits, J.A. Effects of D-cycloserine administration on weekly nonemotional memory tasks in healthy participants.

Psychother. Psychosom., **2009**, *78*(1), 49-54. [http://dx.doi.org/10.1159/000172620] [PMID: 19018157]

[106] Onur, O.A.; Schlaepfer, T.E.; Kukolja, J.; Bauer, A.; Jeung, H.; Patin, A.; Otte, D.M.; Shah, N.J.; Maier, W.; Kendrick, K.M.; Fink, G.R.; Hurlemann, R. The N-methyl-D-aspartate receptor co-agonist D-cycloserine facilitates declarative learning and hippocampal activity in humans. *Biol. Psychiatry,* **2010**, *67*(12), 1205-1211. [http://dx.doi.org/10.1016/j.biopsych.2010.01.022] [PMID: 20303474]

[107] Kalisch, R.; Holt, B.; Petrovic, P.; De Martino, B.; Klöppel, S.; Büchel, C.; Dolan, R.J. The NMDA agonist D-cycloserine facilitates fear memory consolidation in humans. *Cereb. Cortex,* **2009**, *19*(1), 187-196. [http://dx.doi.org/10.1093/cercor/bhn076] [PMID: 18477687]

[108] Feld, GB; Lange, T; Gais, S; Born, J Sleep-dependent declarative memory consolidation--unaffected after blocking NMDA or AMPA receptors but enhanced by NMDA coagonist D-cycloserine. *Neuropsychopharmacology,* **2013**, *38*, 2688-2697.

[109] Nitsche, MA; Jaussi, W; Liebetanz, D; Lang, N; Tergau, F; Paulus, W Consolidation of human motor cortical neuroplasticity by D-cycloserine. *Neuropsychopharmacology,* **2004**, *29*, 1573-1578.

[110] Heckers, S. Neuroimaging studies of the hippocampus in schizophrenia. *Hippocampus,* **2001**, *11*(5), 520-528. [http://dx.doi.org/10.1002/hipo.1068] [PMID: 11732705]

[111] Reichenberg, A.; Harvey, P.D. Neuropsychological impairments in schizophrenia: Integration of performance-based and brain imaging findings. *Psychol. Bull.,* **2007**, *133*(5), 833-858. [http://dx.doi.org/10.1037/0033-2909.133.5.833] [PMID: 17723032]

[112] Minzenberg, M.J.; Laird, A.R.; Thelen, S.; Carter, C.S.; Glahn, D.C. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. *Arch. Gen. Psychiatry,* **2009**, *66*(8), 811-822. [http://dx.doi.org/10.1001/archgenpsychiatry.2009.91] [PMID: 19652121]

[113] Cornblatt, B.; Obuchowski, M.; Roberts, S.; Pollack, S.; Erlenmeyer-Kimling, L. Cognitive and behavioral precursors of schizophrenia. *Dev. Psychopathol.,* **1999**, *11*(3), 487-508. [http://dx.doi.org/10.1017/S0954579499002175] [PMID: 10532621]

[114] Niendam, T.A.; Bearden, C.E.; Rosso, I.M.; Sanchez, L.E.; Hadley, T.; Nuechterlein, K.H.; Cannon, T.D. A prospective study of childhood neurocognitive functioning in schizophrenic patients and their siblings. *Am. J. Psychiatry,* **2003**, *160*(11), 2060-2062. [http://dx.doi.org/10.1176/appi.ajp.160.11.2060] [PMID: 14594759]

[115] Holt, D.J.; Coombs, G.; Zeidan, M.A.; Goff, D.C.; Milad, M.R. Failure of neural responses to safety cues in schizophrenia. *Arch. Gen. Psychiatry,* **2012**, *69*(9), 893-903. [http://dx.doi.org/10.1001/archgenpsychiatry.2011.2310] [PMID: 22945619]

[116] Holt, D.J.; Lebron-Milad, K.; Milad, M.R.; Rauch, S.L.; Pitman, R.K.; Orr, S.P.; Cassidy, B.S.; Walsh, J.P.; Goff, D.C. Extinction memory is impaired in schizophrenia. *Biol. Psychiatry,* **2009**, *65*(6), 455-463. [http://dx.doi.org/10.1016/j.biopsych.2008.09.017] [PMID: 18986648]

[117] Manoach, D.S.; Cain, M.S.; Vangel, M.G.; Khurana, A.; Goff, D.C.; Stickgold, R. A failure of sleep-dependent procedural learning in chronic, medicated schizophrenia. *Biol. Psychiatry,* **2004**, *56*(12), 951-956. [http://dx.doi.org/10.1016/j.biopsych.2004.09.012] [PMID: 15601605]

[118] Wamsley, E.J.; Tucker, M.A.; Shinn, A.K.; Ono, K.E.; McKinley, S.K.; Ely, A.V.; Goff, D.C.; Stickgold, R.; Manoach, D.S. Reduced sleep spindles and spindle coherence in schizophrenia: mechanisms of impaired memory consolidation? *Biol. Psychiatry,* **2012**, *71*(2), 154-161. [http://dx.doi.org/10.1016/j.biopsych.2011.08.008] [PMID: 21967958]

[119] Skelley, S.L.; Goldberg, T.E.; Egan, M.F.; Weinberger, D.R.; Gold, J.M. Verbal and visual memory: characterizing the clinical and intermediate phenotype in schizophrenia. *Schizophr. Res.,* **2008**, *105*(1-3), 78-85. [http://dx.doi.org/10.1016/j.schres.2008.05.027] [PMID: 18617370]

[120] Waltz, J.A.; Gold, J.M. Probabilistic reversal learning impairments in schizophrenia: further evidence of orbitofrontal dysfunction. *Schizophr. Res.,* **2007**, *93*(1-3), 296-303. [http://dx.doi.org/10.1016/j.schres.2007.03.010] [PMID: 17482797]

[121] Floresco, S.B.; Zhang, Y.; Enomoto, T. Neural circuits subserving behavioral flexibility and their relevance to schizophrenia. *Behav. Brain Res.,* **2009**, *204*(2), 396-409. [http://dx.doi.org/10.1016/j.bbr.2008.12.001] [PMID: 19110006]

[122] Goff, D.C.; Cather, C.; Gottlieb, J.D.; Evins, A.E.; Walsh, J.; Raeke, L.; Otto, M.W.; Schoenfeld, D.; Green, M.F. Once-weekly D-cycloserine effects on negative symptoms and cognition in schizophrenia: an exploratory study. *Schizophr. Res.,* **2008**, *106*(2-3), 320-327. [http://dx.doi.org/10.1016/j.schres.2008.08.012] [PMID: 18799288]

[123] Chatburn, A.; Lushington, K.; Kohler, M.J. Complex associative memory processing and sleep: a systematic review and meta-analysis of behavioural evidence and underlying EEG mechanisms. *Neurosci. Biobehav. Rev.,* **2014**, *47*, 646-655. [http://dx.doi.org/10.1016/j.neubiorev.2014.10.018] [PMID: 25452112]

[124] Gottlieb, J.D.; Cather, C.; Shanahan, M.; Creedon, T.; Macklin, E.A.; Goff, D.C. D-cycloserine facilitation of cognitive behavioral therapy for delusions in schizophrenia. *Schizophr. Res.,* **2011**, *131*(1-3), 69-74. [http://dx.doi.org/10.1016/j.schres.2011.05.029] [PMID: 21723096]

[125] Martineau, M.; Baux, G.; Mothet, J.P. D-serine signalling in the brain: friend and foe. *Trends Neurosci.,* **2006**, *29*(8), 481-491. [http://dx.doi.org/10.1016/j.tins.2006.06.008] [PMID: 16806506]

[126] Cohen, S.M.; Tsien, R.W.; Goff, D.C.; Halassa, M.M. The impact of NMDA receptor hypofunction on GABAergic neurons in the pathophysiology of schizophrenia. *Schizophr. Res.,* **2015**, *167*(1-3), 98-107. [http://dx.doi.org/10.1016/j.schres.2014.12.026] [PMID: 25583246]

[127] Laruelle, M.; Abi-Dargham, A. Dopamine as the wind of the psychotic fire: new evidence from brain imaging studies. *J. Psychopharmacol. (Oxford),* **1999**, *13*(4), 358-371. [http://dx.doi.org/10.1177/026988119901300405] [PMID: 10667612]

[128] Martin-Facklam, M; Pizzagalli, F; Zhou, Y; Ostrowitzki, S; Raymont, V; Brasic, JR; Parkar, N; Umbricht, D; Dannals, RF; Goldwater, R; Wong, DF Glycine transporter type 1 occupancy by bitopertin: a positron emission tomography study in healthy volunteers. *Neuropsychopharmacology,* **2013**, *38*, 504-512. [http://dx.doi.org/10.1038/npp.2012.212]

[129] Preskorn, S.H.; Baker, B.; Kolluri, S.; Menniti, F.S.; Krams, M.; Landen, J.W. An innovative design to establish proof of concept of the antidepressant effects of the NR2B subunit selective N-methyl-D-aspartate antagonist, CP-101,606, in patients with treatment-refractory major depressive disorder. *J. Clin. Psychopharmacol.,* **2008**, *28*(6), 631-637. [http://dx.doi.org/10.1097/JCP.0b013e31818a6cea] [PMID: 19011431]

[130] Goff, D.C.; Henderson, D.C.; Evins, A.E.; Amico, E. A placebo-controlled crossover trial of D-cycloserine added to clozapine in patients with schizophrenia. *Biol. Psychiatry,* **1999**, *45*(4), 512-514. [http://dx.doi.org/10.1016/S0006-3223(98)00367-9] [PMID: 10071726]

[131] Javitt, D.C.; Duncan, L.; Balla, A.; Sershen, H. Inhibition of system A-mediated glycine transport in cortical synaptosomes by therapeutic concentrations of clozapine: implications for mechanisms of action. *Mol. Psychiatry,* **2005**, *10*(3), 275-287. [http://dx.doi.org/10.1038/sj.mp.4001552] [PMID: 15278098]

[132] Duffy, S; Labrie, V; Roder, JC D-serine augments NMDA-NR2B receptor-dependent hippocampal long-term depression and spatial reversal learning. *Neuropsychopharmacology,* **2008**, *33*, 1004-1018.

[133] Tsai, G.; Yang, P.; Chung, L-C.; Lange, N.; Coyle, J.T. D-serine added to antipsychotics for the treatment of schizophrenia. *Biol. Psychiatry,* **1998**, *44*(11), 1081-1089. [http://dx.doi.org/10.1016/S0006-3223(98)00279-0] [PMID: 9836012]

[134] Moskal, J.R.; Burch, R.; Burgdorf, J.S.; Kroes, R.A.; Stanton, P.K.; Disterhoft, J.F.; Leander, J.D. GLYX-13, an NMDA receptor glycine site functional partial agonist enhances cognition and produces antidepressant effects without the psychotomimetic side effects of NMDA receptor antagonists. *Expert Opin. Investig. Drugs,* **2014**, *23*(2), 243-254. [http://dx.doi.org/10.1517/13543784.2014.852536] [PMID: 24251380]

[135] Miyazaki, M.; Noda, Y.; Mouri, A.; Kobayashi, K.; Mishina, M.; Nabeshima, T.; Yamada, K. Role of convergent activation of glutamatergic and dopaminergic systems in the nucleus accumbens in the development of methamphetamine psychosis and dependence. *Int. J. Neuropsychopharmacol.,* **2013**, *16*(6), 1341-1350. [http://dx.doi.org/10.1017/S1461145712001356] [PMID: 23195702]

[136] Jimenez-Sanchez, L; Campa, L; Auberson, YP; Adell, A The role of GluN2A and GluN2B subunits on the effects of NMDA receptor

antagonists in modeling schizophrenia and treating refractory depression. *Neuropsychopharmacology,* **2014**, *39*, 2673-2680.

[137] Suryavanshi, P.S.; Ugale, R.R.; Yilmazer-Hanke, D.; Stairs, D.J.; Dravid, S.M. 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.,* **2014**, *171*(3), 799-809. [http://dx.doi.org/10.1111/bph.12518] [PMID: 24236947]

[138] Rosse, R.B.; Fay-McCarthy, M.; Kendrick, K.; Davis, R.E.; Deutsch, S.I. D-cycloserine adjuvant therapy to molindone in the treatment of schizophrenia. *Clin. Neuropharmacol.,* **1996**, *19*(5), 444-450. [http://dx.doi.org/10.1097/00002826-199619050-00008] [PMID: 8889288]

[139] Goff, D.C.; Tsai, G.; Manoach, D.S.; Flood, J.; Darby, D.G.; Coyle, J.T. D-cycloserine added to clozapine for patients with schizophrenia. *Am. J. Psychiatry,* **1996**, *153*(12), 1628-1630. [http://dx.doi.org/10.1176/ajp.153.12.1628] [PMID: 8942463]

[140] Heresco-Levy, U.; Javitt, D.C.; Ermilov, M.; Silipo, G.; Shimoni, J. Double-blind, placebo-controlled, crossover trial of D-cycloserine adjuvant therapy for treatment-resistant schizophrenia. *Int. J. Neuropsychopharmacol.,* **1998**, *1*(2), 131-135. [http://dx.doi.org/10.1017/S1461145798001242] [PMID: 11281957]

[141] Heresco-Levy, U.; Javitt, D.C.; Ermilov, M.; Mordel, C.; Horowitz, A.; Kelly, D. Double-blind, placebo-controlled, crossover trial of glycine adjuvant therapy for treatment-resistant schizophrenia. *Br. J. Psychiatry,* **1996**, *169*(5), 610-617. [http://dx.doi.org/10.1192/bjp.169.5.610] [PMID: 8932891]

[142] Evins, A.; Amico, E.; Posever, T.; Toker, R.; Goff, D. D-cycloserine augmentation of risperidone in the deficit syndrome of schizophrenia. *Schizophr. Res.,* **2002**, *56*, 19-23. [http://dx.doi.org/10.1016/S0920-9964(01)00220-1] [PMID: 12084415]