N-methyl-D-aspartate-type glutamate receptor modulators and related medications for the enhancement of auditory system plasticity in schizophrenia

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ABSTRACT

Deficits in N-methyl-D-aspartate-type (NMDAR) function contribute to cognitive deficits in schizophrenia, particularly dysfunction in neuroplasticity, defined as reduced learning during training on exercises that place implicit, increasing demands on early sensory (auditory and visual) information processing. Auditory mismatch negativity (MMN) can be both a target engagement biomarker for the NMDAR and a proxy measure of neurophysiological plasticity. This review covers the evidence for using NMDAR modulator and related compounds for enhancement of cognition, with a particular focus on early auditory processing/plasticity. Compounds covered include glycine site agonists, glycine and system A-type transporter inhibitors, D-amino acid oxidase inhibitors, memantine and nicotinic alpha-7 acetylcholine receptor agonists. As opposed to daily treatment studies focusing on schizophrenia in general, intermittent, non-daily treatment combining NMDAR modulators with neuroplasticity-based paradigms, using MMN as target-engagement biomarkers show promise as treatments to both remediate plasticity deficits and overall functional deficits.

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1. Introduction: NMDAR agonists to enhance auditory neuroplasticity in schizophrenia

Schizophrenia is a major public health problem associated with core cognitive deficits that are amongst the strongest predictors of impaired functional outcome (Green et al., 2012; Keefe et al., 2017). While cognitive processes that are proximal to daily functioning, such as memory, social cognition and executive functioning are individually impaired, these deficits may be secondary to related learning process deficits, termed "cortical neuroplasticity" (Fisher et al., 2016). In turn, plasticity deficits can lead to reduced ability to benefit from various forms of cognitive remediation (Goff et al., 2011; Kantrowitz et al., 2016c), particularly when using programs that place implicit, increasing demands on early sensory (auditory and visual) information processing (Fisher et al., 2016). In the present review, the rationale for using N-methyl-D-aspartate-type glutamate receptor (NMDAR) modulator and related compounds for enhancement of cognition is presented, with a particular focus on early auditory processing/plasticity. The evidence for use of auditory mismatch negativity as a biomarker for both a neurophysiological

proxy of plasticity and a measure of NMDAR target engagement (Sections 2.1 and 2.2) is reviewed, followed by a discussion of the strengths and weakness of individual NMDAR modulator compounds and recommendations for future studies.

Multiple independent groups have demonstrated relationships between sensory processing, neuroplasticity impairments and more complex forms of information processing dysfunction, including global cognition (Green et al., 2012; Thomas et al., 2017), reading (Revheim et al., 2014), working memory (Keefe et al., 2011; Kern et al., 2011; McCleery et al., 2015), auditory emotion recognition (Corcoran et al., 2015; Gold et al., 2012; Kantrowitz et al., 2015b; Kantrowitz et al., 2013), perceptual music disorders (Hatada et al., 2014; Kantrowitz et al., 2014b) and theory of mind (Kantrowitz et al., 2014a; Kern et al., 2009; Leitman et al., 2006). Improved sensory processing may facilitate gains in complex cognitive processes (Medalia et al., 2016). Thus, remediating neuroplasticity represents an unmet clinical need.

In recent proof of concept studies, NMDAR modulators have increasingly been shown to facilitate neuroplasticity both in studies of psychiatric patients (Goff, 2012; Heresco-Levy et al., 2005; Ori et al., 2015) and healthy volunteers (Levin et al., 2015). This review will focus on the study of NMDAR modulators and related compounds, adjunctive to antipsychotics, for the enhancement of cognition, with a particular focus on early auditory processing/plasticity (Table 1/Fig. 1). Enhancing visual

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Table 1
Summary of the relative advantages, disadvantages, and proposed biomarkers of the compounds and targets covered in this review.

	Relation to NMDAR target	Evidence for/advantages	Evidence against/disadvantages	Proposed biomarkers	Section
D-Cycloserine	Partial agonist at the NMDAR glycine modulatory site	FDA approved; Extensively studied; Well-established safety profile	Narrow therapeutic window; Antagonist at higher doses	^{1}H MRS; high-frequency visual stimulation	3.1
D-Serine	Full agonist at the NMDAR glycine modulatory site	Positive meta-analysis; positive studies in plasticity and in early psychosis	Positive studies were generally small; limited experience at doses >60 mg/kg	Adaptive tone-matching; MMN; event-related oscillation responses	3.2.1–3.2.4
Glycine	Full agonist at the NMDAR glycine modulatory site	Positive small studies; improves MMN acutely	Ideal dose is ~60 g/day, limiting tolerability, less potent than D-serine	MMN	3.2.5
Selective glycine transport inhibitors	Block GlyT1 transport, preventing removal of glycine from the synaptic cleft	Positive target engagement study; Positive study for bitopertin	Negative Phase III studies for Glycine type-1 transport inhibitors;	MMN; Positron emission tomography; visual long-term potentiation; P300	3.3
Non-selective glycine transporters	Block System A-type and GlyT1 transport, preventing removal of glycine from the synaptic cleft	Multiple positive studies with sarcosine	Positive studies were generally small; lack of approval in U.S.	^{1}H MRS	3.4
D-Amino acid oxidase inhibitors	Inhibits of DAAO, increasing the levels of D-serine	Two positive studies with benzoate	Positive studies were generally small; lack of approval in U.S.	None published	3.4
Memantine	Uncompetitive NMDAR partial antagonist of low affinity; possible NMDAR agonist or dopaminergic competent	Positive meta-analysis	Dose dependent paradoxical effect on MMN	MMN	3.5
N-Acetylcysteine	Redox/glutathione sensitive site of the NMDAR	Positive small study	Limited follow-up after initial studies	MMN	3.6
Nicotinic alpha-7 acetylcholine (nα_7)	Indirectly modulate NMDAR via nα_7 induced release of GABA	Positive small studies	Initial results not replicated in Phase III studies; desensitization with direct agonist	MMN; P50	3.7

Abbreviations: N-methyl-D-aspartate-type glutamate receptor; ^{1}H MRS: proton magnetic resonance spectroscopy; MMN: mismatch negativity; GlyT1: Glycine type-1; DAAO: D-amino acid oxidase.

plasticity (Contreras et al., 2017; Jahshan et al., 2017; Kantrowitz et al., 2009) is also under active study, but will not be specifically covered.

As previously reviewed (Kantrowitz and Javitt, 2010b), NMDAR are crucial for plasticity (Burgos-Robles et al., 2007; Sotres-Bayon et al., 2007). NMDAR's function through both non-linear and linear (voltage-dependent ensemble selection) mechanisms (Kantrowitz and Javitt, 2010a). Thus, as proposed previously (Fig. 2) (Kantrowitz et al., 2016a; Leitman et al., 2010), dysfunction across multiple levels of the neuroaxis, not only in auditory sensory regions, but also in "top-down" cognitive control regions are consistent with NMDAR distributed hierarchical models of schizophrenia. While NMDAR are crucial for both

critical period and experience-dependent plasticity, this review focuses on experience-dependent plasticity.

NMDAR induced plasticity occurs across different phases – an *acquisition phase* that occurs over minutes, secondary to a NMDAR-induced increase in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPAR) receptor mobilization, followed by a *consolidation phase* that occurs over hours, secondary to a delayed increase in NMDAR synthesis and trafficking that occurs over hours to days (Watt et al., 2004). Longer-term plasticity improvements require sustained improvements in distributed cortical networks (Table 2).
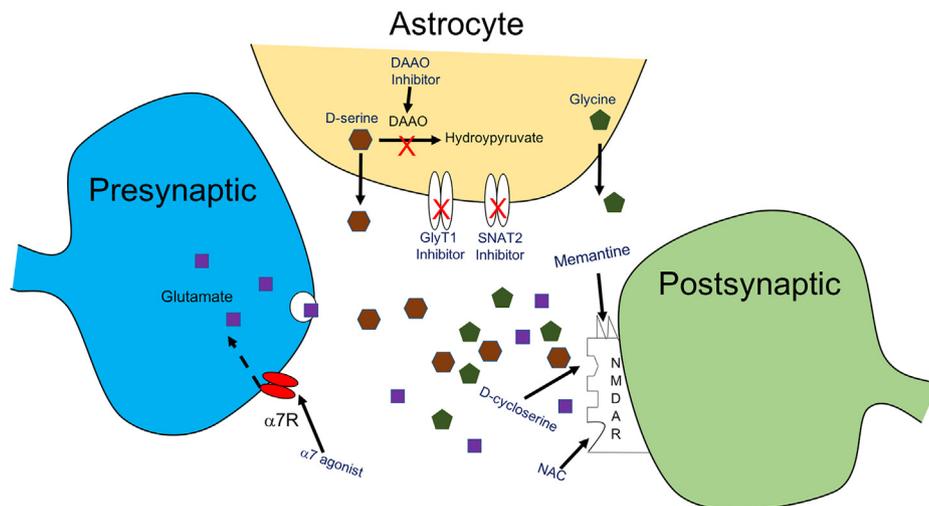

Fig. 1. Schematic model of N-methyl-D-aspartate-type glutamate receptor (NMDAR) modulator targets covered in this review, modified from Kantrowitz and Javitt (2010b) and Broide and Leslie (1999). Both physiological and non-physiological targets are shown, including D-serine: glycine: ⬢, glutamate: ■, selective glycine ■ type-1 (GlyT1) transport inhibitors, nicotinic alpha-7 acetylcholine (α₇), system A-type-2 glycine transporters (SNAT2), D-amino acid oxidase inhibitors (DAAO-I), memantine, N-acetylcysteine (NAC) and D-cycloserine. Potential drugs discussed in the review are shown in blue.
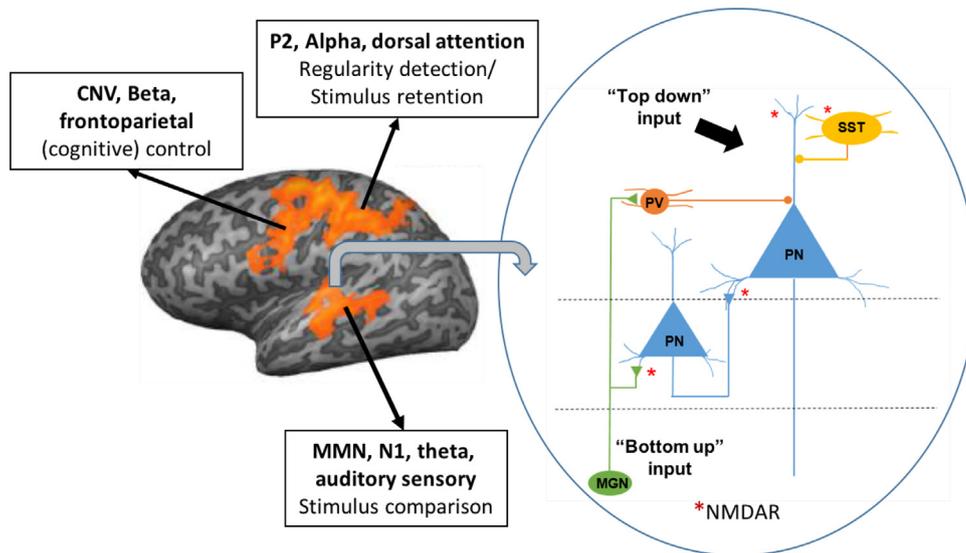
Fig. 2. Schematic of the distributed hierarchical *N*-methyl-ᴅ-aspartate-type glutamate receptor (NMDAR) related model of auditory plasticity in schizophrenia, originally published in Kantrowitz et al. (2016a). An auditory cortex pyramidal cell receives bottom-up input from the thalamic medial geniculate nucleus (MGN), parvalbumin (PV), and somatostatin (SST) interneurons (Womelsdorf et al., 2014), which in-turn receive top-down input from intraparietal or frontoparietal neurons (inset). NMDAR, noted by the red "*" are involved in multiple levels.

As opposed to treatment for schizophrenia in general, NMDAR modulator treatment for plasticity appears to be most beneficial when used non-daily (Goff, 2012; Javitt, 2013), as tachyphylaxis may develop after more frequent dosing (Parnas et al., 2005), potentially due to NMDAR internalization (Nong et al., 2003). While more frequent dosing might be intuitively expected to lead to greater enhancement, consistent with most cognitive remediation programs requiring 2 or more sessions per week, NMDAR modulator studies (see Sections 3.1 and 3.2.1) provide proof of concept for intermittent (weekly) dosing. Effects appear to be largest when NMDAR modulator treatment is given on the first session (Gottlieb et al., 2011; Kantrowitz et al., 2016a), which allows for action during both the acquisition and consolidation phases, and the "priming" effect of an increase in AMPAR and NMDAR trafficking.

2. Early auditory plasticity as a target engagement biomarker for NMDAR

NIMH experimental medicine initiatives (Insel, 2015) require the inclusion of target-engagement biomarkers to assist in "Fast-Fail" type treatment development (Javitt et al., 2018a; Javitt et al., 2011; Paul et al., 2010). "Target" refers to a factor that an intervention is intended to modify, leading to improvement in symptoms, and target engagement biomarkers are a measure of the ability of the intervention to "engage" the target. For this review, the focus is on the NMDAR target, and the primary target engagement biomarker discussed is auditory MMN. Additional biomarkers are discussed in the context of individual studies.

2.1. MMN and NMDAR

Glutamatergic models of schizophrenia specifically account for impairments not only in cognition, but also in the generation of early auditory processing measures. MMN (Naatanen et al., 2014) is a neurophysiological response elicited by a sequence of repetitive standard stimuli that is interrupted infrequently by a physically different oddball stimulus. Deviants may differ from standards in one or more physical and/or abstract dimension, most commonly frequency or duration. Deficits in auditory MMN generation in schizophrenia have been replicated extensively since the 1990's (Erickson et al., 2016; Friedman et al., 2012; Light et al., 2015; Umbricht and Krljes, 2005). Recent formulations of MMN conceptualize it as the "prediction error" evoked when the deviant differs from the standard stimulus (Friston, 2005), and thus MMN can be seen as a neurophysiological proxy of plasticity.

Links between NMDAR and MMN are supported by a meta-analysis of challenge studies with the NMDAR antagonist ketamine (Rosburg and Kreitschmann-Andermahr, 2016). Across studies, antagonizing the NMDAR with ketamine produces a moderate effect size deficit in MMN (pooled standard mean difference, SMD: 0.490). In addition, MMN has also been linked to glutamatergic functioning by a recent study involving serial measurement of verbal working memory, MMN and ^{1}H MRS of glutamate (Rowland et al., 2016). In this study, MMN was found to be an intermediate biomarker of glutamatergic function, and significantly related to both the ^{1}H MRS measured ratio of glutamine to glutamate and auditory cognition. By contrast, challenge studies with typical or atypical antipsychotics (Umbricht et al., 1998, 1999) minimally impact MMN, suggesting relative specificity for glutamatergic vs. dopaminergic mechanisms.

2.2. MMN and neuroplasticity

MMN deficits are tied to poor functional outcome (Biagianti et al., 2017; Jahshan et al., 2013; Javitt and Freedman, 2015; Kantrowitz et al., 2015b; Perrin et al., 2018; Wynn et al., 2010), as recently

Table 2
Summary of NMDAR related plasticity phases and MMN.

	Acquisition	Consolidation	Maintenance
Time course	Minutes	Hours–days	Days–months
Mechanism	↑ AMPAR insertion	↑ NMDAR trafficking	↑ connectivity between sensory and higher cortical regions
NMDAR modulator effect	Immediate	After repeat dosing only	Repeat dosing?
Effects on MMN	Immediate	Delayed	Sustained
Relevant reference	Greenwood et al., 2018	Kantrowitz et al., 2016a	Kantrowitz et al., 2018

AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; NMDA: *N*-methyl-ᴅ-aspartate-type glutamate receptor; MMN: mismatch negativity.

confirmed in a large, 1415 subject cross-sectional study of schizophrenia (Thomas et al., 2017). In this study, early auditory processing ERP (MMN, P300 and reorienting negativity) predicted cognition (β = 0.37, p < 0.001), while cognition itself directly predicted negative symptoms (β = −0.16, p < 0.001) and indirectly predicted functional outcome. The indirect effect of early auditory processing on functional outcome was independently significant (β = 0.14, p < 0.001). Of the three early auditory processing ERP that were measured, MMN was the largest individual predictor (β = −0.77, p < 0.001). Furthermore, MMN has robust test-retest reliability (Javitt et al., 1996; Light and Swerdlow, 2015), and is highly predictive of response to auditory cognitive remediation (Biagianti et al., 2017; Perez et al., 2017). Thus, MMN is useful as both a target engagement biomarker for NMDAR and cognitive treatment development, useful for studying multiple stages of plasticity/learning (Table 2), including acute changes during the acquisition phase (Greenwood et al., 2018), delayed changes during the consolidation phase (Kantrowitz et al., 2016a), and more potentially sustained changes during maintenance (Kantrowitz et al., 2018; Perez et al., 2017).

3. NMDAR modulators to enhance plasticity

3.1. D-Cycloserine

Because of its FDA approval for tuberculosis and extensive safety data dating back to the 1950's, most studies of NMDAR enhancement of neuroplasticity have been with D-cycloserine. D-Cycloserine cross reacts with the NMDAR glycine modulatory site, which regulates channel opening time and desensitization rate in the presence of glutamate (Mayer et al., 1989; Vornov and Coyle, 1991). Meta-analysis of preclinical learning studies (Norberg, 2008) demonstrate highly significant, large effect size (p < 0.001, d = 1.2) improvements favoring D-cycloserine. In human clinical studies, meta-analysis for efficacy in enhancing extinction learning in anxiety disorders are less robust (Mataix-Cols et al., 2017), showing significant, but small effect size improvements (d = 0.25).

In addition to studies focusing on cognition in general, Cain et al. (2014) provided proof of concept for specific improvement in auditory plasticity in a 32 subject, 8 week, parallel, placebo controlled study of once weekly D-cycloserine 50 mg. Using a paradigm of rapidly-presented frequency-modulated sweeps separated by a short interstimulus interval (ISI) (Fisher et al., 2009), significant, between group improvement favoring D-cycloserine was seen on this task (p = 0.01). However, the plasticity improvement was not generalizable to general cognition, with improvements on the MATRICS consensus cognition battery (MCCB) composite (Nuechterlein and Green, 2006) seen only in the placebo group.

No studies have looked at the effects of D-cycloserine on MMN, but in one recent study (Forsyth et al., 2017), the effect of acute of D-cycloserine (100 mg) on visual EEG biomarkers (high-frequency visual stimulation) and working memory was assessed in 45 schizophrenia patients in a double-blind, between-group design. While no significant overall effects of D-cycloserine were seen, D-cycloserine was superior to placebo in a post-hoc, subgroup analysis of subjects performing above chance on the working memory task.

3.1.1. Limitations

Use of D-cycloserine is limited by its pharmacology. D-cycloserine is a partial agonist at the NMDAR glycine modulatory site, and has a dose-related modulation of NMDAR function (Hood et al., 1989; Lanthorn, 1994). Low doses (≤100 mg) potentiate NMDAR function, but higher doses (>500 mg) function as a net NMDAR antagonist, with ketamine-like effects on ^{1}H MRS (Kantrowitz et al., 2016b) and potential efficacy in depression (Heresco-Levy et al., 2013; Kantrowitz et al., 2015a). Although studies in schizophrenia have generally used low dose (50 to 100 mg) D-cycloserine, the potential for NMDAR antagonism with

repeated D-cycloserine doses may result in psychosis or tachyphylaxis (Parnas et al., 2005), potentially due to NMDAR internalization (Nong et al., 2003). Even at low dosages, D-cycloserine is a low potency agonist (Hood et al., 1989).

3.2. Glycine site agonists (D-serine and glycine)

D-Serine and glycine are endogenous brain amino acids, and direct agonists at the glycine modulatory site (Balu and Coyle, 2015). While both amino acids activate the same target, D-serine is more potent than glycine (Sasabe et al., 2012; Vanoni et al., 1997).

3.2.1. D-Serine

As a higher potency, full agonist, D-serine has putative advantages over D-cycloserine, but was not available for use in the United States until the completion of dose-finding studies (Kantrowitz et al., 2010). Moreover, the shorter half-life (Kantrowitz et al., 2010) (tmax ~30–90 min) of D-serine allows for practical administration (~30 min before sessions), thus allowing for assessment during peak levels.

The majority of studies with D-serine have used a dose of 30 mg/kg (~2 g/d), with significant, but small (SMD = −0.3) beneficial effects on positive and negative schizophrenia symptoms across studies (Cho et al., 2016), including cognitive improvement on the Wisconsin Card Sorting Task (Tsai et al., 1998). Higher dose (60 mg/kg/d, ~4 g/d) may be even more effective than lower doses, finding significant dose effects for cognition in an open label study (Kantrowitz et al., 2010), as well as significant, moderate-size clinical beneficial effects in a study of patients at clinically high risk for schizophrenia (Kantrowitz et al., 2015c). Despite a negative multicenter study of 30 mg/kg D-serine (Weiser et al., 2012), an updated meta-analysis including higher dose studies continues to demonstrate significant clinical effect with moderate-large (d = 0.7) effect size for negative symptoms (Kantrowitz et al., 2018).

3.2.2. Intermittent D-serine and behavioral plasticity

Cognitive/plasticity outcomes have been assessed less frequently with D-serine. An initial attempt to enhance plasticity showed no significant effects (D'Souza et al., 2013) across 104 schizophrenia subjects in a double-blind placebo-controlled study. However, the trial was potentially limited by the use of low dose D-serine (30 mg/kg), the use of a non-neuroplasticity based program (Chen et al., 1997) and daily treatment.

More recently, the efficacy of intermittent, high dose D-serine (60 mg/kg) on behavioral plasticity was evaluated utilizing a simple, neuroplasticity-based auditory remediation program (Ahissar et al., 2006) in which participants are presented with paired tones, and were asked to indicate which tone is higher in pitch (frequency). Twenty-one schizophrenia patients received three auditory remediation sessions separated by 1-week intervals, paired with either D-serine or placebo. 13 controls completed one session without D-serine augmentation. After the 1st session, there were no significant between treatment effects for the patient groups (D-serine vs. placebo). However, over subsequent sessions, a significant effect of treatment order was seen, reflecting a significant D-serine effect (p = 0.044), driven primarily by a large effect size improvement in behavioral plasticity only for those subjects who received D-serine in two consecutive sessions (p = 0.016, d = 1.03, Fig. 3A). Furthermore, following just two D-serine treatments, schizophrenia outcomes for behavioral plasticity were normalized vs. controls (Fig. 3B).

By contrast, schizophrenia subjects showed non-significant worsening if they received either placebo followed by D-serine or D-serine followed by placebo. This finding is consistent with D-cycloserine studies (Gottlieb et al., 2011), suggesting efficacy only when an NMDAR modulator is given on the first session, along with rodent investigations, suggesting that greatest effects are on consolidation rather than acquisition phases of long term potentiation (LTP) (Liu et al., 2014; Quartermain et al., 1994; Santini et al., 2001).
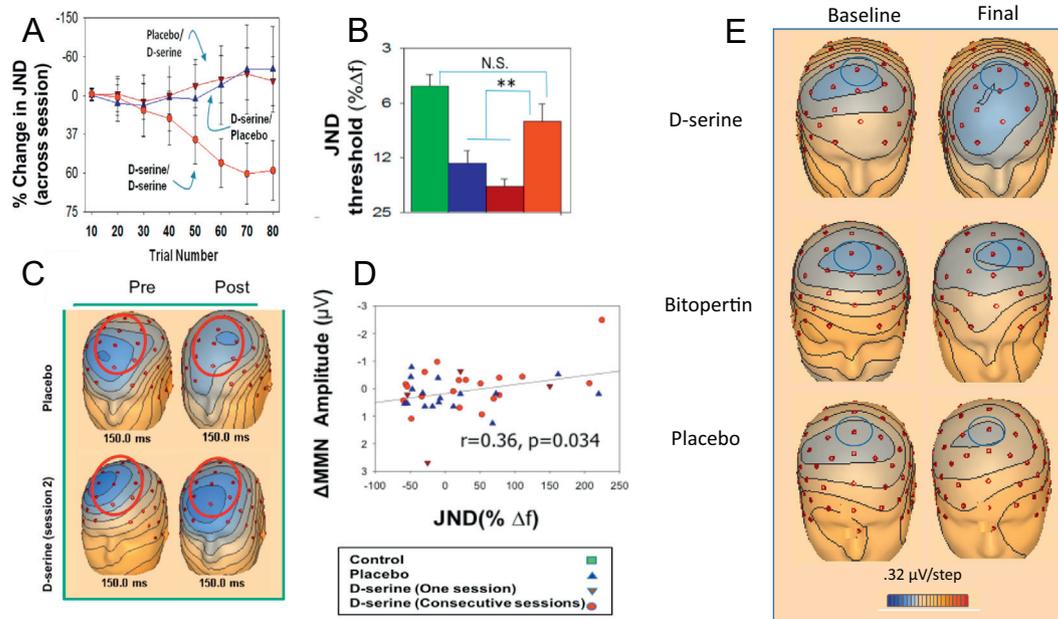
Fig. 3. A. Line graph of % change in behavioral plasticity on auditory remediation across sessions for the indicated treatment orders. B. Bar graph of behavioral plasticity on auditory remediation for controls and for schizophrenia patients receiving indicated treatments. C. Voltage topography maps for mismatch negativity (MMN) for indicated group for Pre training (left) and post training (right) shown at peak latencies. Analyzed electrode noted by red circles. D. Scatter plot for % change in behavioral plasticity on auditory remediation vs. change in MMN amplitude to the trained tone. E. Voltage topography maps for D-serine (top), bitopertin (middle) and placebo (bottom) subjects for MMN, shown at peak latencies. Analyzed electrode noted by blue circle (Fz). Modified from Kantrowitz et al. (2016a) and Kantrowitz et al. (2018). Error bars indicate standard error of the mean; ***p < 0.001.

3.2.3. Intermittent D-serine and neurophysiological plasticity (MMN)

In addition to behavioral plasticity assessment, MMN was used as a target engagement biomarker and an assessment of neurophysiological plasticity. Across all subjects, behavioral plasticity correlated with post-training MMN (r = 0.25, p = 0.04), driven by a trend level correlation for the consecutive sessions of D-serine group (r = 0.43, p = 0.066), but not controls (r = −0.25, p = 0.42). Schizophrenia patients receiving two consecutive weekly sessions of D-serine had a significantly larger pre-post change in MMN than those receiving placebo (p = 0.02, d = 0.7, Fig. 3C), demonstrating target engagement of D-serine. By contrast, and consistent with prior studies (Perez et al., 2017), groups receiving neuroplasticity-based auditory remediation without NMDAR modulator co-treatment showed tendency toward worsening in MMN. Across schizophrenia patients, a relationship between improvements in plasticity and MMN was seen (r = −0.34, p = 0.034, Fig. 3D).

In addition to MMN findings, a significant D-serine effect was seen in event-related oscillation responses during the plasticity paradigm within the θ (p = 0.043) and β ranges (p = 0.011). Changes in θ correlated significantly with plasticity improvements (r = −0.39, p = 0.002). θ changes may be related to MMN, and may be more sensitive than ERP to early auditory deficits (Javitt et al., 2018b; Lee et al., 2017), while β activity changes are related to frontoparietal control networks (Bickel et al., 2012; Dias et al., 2013). θ and β may also be potential target engagement biomarkers for the NMDAR target.

3.2.4. Daily D-serine and neurophysiological plasticity (MMN)

Complementing findings of plasticity improvements with non-daily treatment, this report (Kantrowitz et al., 2018) assessed the effects of six weeks of daily D-serine vs. placebo treatment on neurophysiological target engagement/plasticity (MMN) across 16 schizophrenia subjects. A significant, large effect size improvement vs. placebo for MMN (p = 0.001, d = 2.3, Fig. 3E) was seen, along with improvements in clinical symptoms. D-Serine treated subjects showed intercorrelated improvement in both symptoms and MMN. Additionally, improvement in early auditory processing was seen on the tone-matching task

(Kantrowitz et al., 2014a), with a trend toward improvement during D-serine (p = 0.06, d = 0.67), but not during placebo (p = 0.41, d = 0.30) treatment. However, the between treatments difference for the tone-matching task was not significant (p = 0.41, d = 0.37).

3.2.5. Glycine

While glycine showed initial efficacy (Kantrowitz and Javitt, 2012), promising early results were not replicated in a large multicenter study (Buchanan et al., 2007). Use of glycine is limited by tolerability of glycine 60 g/day, particularly in outpatients. More recent work suggests that similar to D-serine, glycine can improve MMN, including a preclinical study showing reversal of PCP-induced MMN deficits (Lee et al., 2018). Moreover, in a small randomized, double blind study, 22 schizophrenia subject received glycine (0.6 mg/kg: mean = 54.9 g/day, range = 30.3 g–87.8 g) or placebo (Greenwood et al., 2018). Significant acute improvement in MMN was seen after a single dose of glycine (d = 1.22). There was no significant MMN effect after six weeks, and no assessment of cognition or plasticity in this study.

3.3. Selective glycine transport inhibitors

As opposed to direct agonists like D-serine or glycine, selective glycine type-1 (GlyT1) transport inhibitors are akin to the selective serotonin reuptake inhibitors (SSRIs) of the glycine system, and function by preventing removal of glycine from the synaptic cleft, leading to indirect stimulation of the NMDAR (Javitt et al., 1997). The largest GlyT1 inhibitor trials have been conducted with bitopertin, focusing on predominant negative symptoms and suboptimal treatment response. Bitopertin showed significant beneficial effects in a phase-II study for persistent negative symptoms (Umbricht et al., 2014a), but follow-up phase II and III studies for bitopertin and other selective GlyT1 inhibitors have been mixed (Bugarski-Kirola et al., 2016; Dunayevich et al., 2017; Schoemaker et al., 2014), and without significant cognitive benefits. Selective GlyT1 inhibitors have not been assessed in plasticity paradigms.

3.3.1. Target engagement biomarkers and plasticity for selective GlyT1 inhibitors

Two recent studies have looked at potential cognitive biomarkers of selective GlyT1 inhibitors (Johannesen et al., 2015; Kantrowitz et al., 2017). The first (Johannesen et al., 2015) http://grantome.com/grant/NIH/UH2-TR000960-01 studied PF-03463275 and has only been published in abstract form. Dose-related increases in target occupancy (positron emission tomography), visual LTP, and P300 ERP amplitude were reported for 9 subjects.

The second study (Kantrowitz et al., 2017) tested bitopertin 10 mg using similar neurophysiological methods to the D-serine study described in Section 3.2.3 (Kantrowitz et al., 2018). In contrast to D-serine, bitopertin did not significantly affect either symptoms or MMN. This suggests that bitopertin failed because of inadequate target engagement (as measured by MMN, Fig. 3E, middle), and moreover, that MMN may have negative, as well as positive, predictive value in predicting efficacy of NMDAR agonists.

3.4. Other indirect NMDAR modulators: sarcosine and D-amino acid oxidase inhibitors

Sarcosine is a naturally occurring non-selective inhibitor of glycine transport (Tsai et al., 2004). In contrast to bitopertin, sarcosine inhibits glycine transport via both GlyT1 and system A-type-2 glycine transporters (SNAT2) in brain (Javitt et al., 2005). SNAT2 has been implicated in clozapine's efficacy (Javitt et al., 2005). In addition, benzoate, an inhibitor of D-amino acid oxidase (DAAO-I) can increase the levels of D-serine (Van den Berghe-Snorek and Stankovich, 1985). As noted in Section 3.2, D-serine is more potent than glycine, providing a potential advantage of DAAO-I over sarcosine.

Cognitive outcomes using these compounds have not been assessed until recently. In the first assessment of benzoate (Lane et al., 2013), 52 subjects with schizophrenia stable on antipsychotic medications for at least 3 months were randomized to six weeks of adjunctive benzoate (1 g/day) or placebo. Along with large effect size improvements in clinical symptoms, significant, moderate effect size improvements for the MCCB composite ($p = 0.04$, $d = 0.67$) and the Speed of Processing ($p = 0.03$, $d = 0.65$) and Visual Learning ($p = 0.02$, $d = 0.7$) domains were seen.

In a follow-up, 3-arm study (Lin et al., 2017), 63 subjects with schizophrenia stable on antipsychotic medications for at least 2 months were randomized to 12 weeks of adjunctive sarcosine (2 g/day) plus benzoate (1 g/day) vs. sarcosine alone (2 g/day) vs. placebo. While no significant between group effects were seen on clinical symptoms, the combined sarcosine plus benzoate group had significant effects on the MCCB composite vs. placebo ($p = 0.009$, $d = 0.68$) and the benzoate alone group ($p = 0.03$, $d = 0.45$). By contrast, the sarcosine alone group was not significantly better vs. placebo.

There have been no assessments of sarcosine or benzoate effects on MMN or plasticity, but decreased levels of glutamate and glutamine measured by ^{1}H MRS was recently found to be a biomarker of symptomatic response to sarcosine (Strzelecki et al., 2015a; Strzelecki et al., 2015b), but not specifically in relation to cognition or plasticity. Decreased glutamate and glutamine after sarcosine activation of the NMDAR conforms with studies showing increased glutamate and glutamine after NMDAR antagonism (Javitt et al., 2018a). Neither of these compounds is available in the US.

3.5. NMDAR partial antagonists

By contrast to the other NMDAR modulating compounds discussed so far, memantine is an uncompetitive NMDAR partial antagonist (Gardoni and Di Luca, 2006). Although ketamine and memantine are both considered NMDAR antagonists, and thus might both be expected to have detrimental effects on MMN, cognition and plasticity, memantine differs from ketamine by being a partial antagonist of low

affinity, producing only 30% NMDAR occupancy (More et al., 2008). In this way, memantine may be more similar to D-cycloserine than ketamine, with lower doses having more of an NMDAR agonist effect and higher doses having more of an NMDAR antagonist effect. This dose-related modulation of NMDAR function is supported by preclinical studies suggesting that while high dose memantine has a detrimental effect on MMN, lower doses do not (Tikhonravov et al., 2010).

Although meta-analyses (Kishi et al., 2017; Matsuda et al., 2013; Zheng et al., 2017), suggest that memantine may have modest, but significant subchronic benefits on cognition, it has inconsistent, potentially detrimental effects on cognition in schizophrenia (Bhakta et al., 2016) during acute administration. The acute effects of memantine on MMN were recently tested in 43 controls and 41 subjects with chronic psychotic disorder in a double-blind crossover design, comparing either: (1) placebo vs. 10 mg of memantine or (2) placebo vs. 20 mg memantine. A dose dependent paradoxical effect on MMN (Swerdlow et al., 2016) was seen. Lower doses (10 mg) produced a small effect size worsening ($d = -0.09$), while higher doses (20 mg) ($d = 0.19$), produce small effect size enhancements across groups, with enhancing effects most prominent in healthy controls. In a separate study (Korostenskaja et al., 2007), even larger MMN improvements were seen in healthy controls at 30 mg ($d = 0.87$). Improvements were also seen in an electrophysiological measure of sensorimotor gating (prepulse inhibition: PPI).

A review of preclinical studies suggests that memantine's effects on MMN may not be as paradoxical as they appear. The plasma levels of MMN impairing doses in preclinical studies (Beconi et al., 2011) are much higher than those produced by clinically used doses by in humans, e.g. 10 to 20 mg (Periclou et al., 2006). By contrast, plasma levels produced by MMN sparing doses in preclinical studies are similar to clinically used doses. This suggests that at clinical used doses, memantine may not be an NMDAR antagonist. Other preclinical studies suggest that the MMN enhancing effects of memantine may be due in part to dopaminergic stimulation (Mancini et al., 2016).

3.6. Redox site agonists

In addition to the glycine modulatory site, the NMDAR contains a well-characterized redox/glutathione sensitive site that is modulated by the oxidized form of glutathione (GSH) (Lipton et al., 2002; Sucher and Lipton, 1991). Studies testing this mechanism have utilized N-acetylcysteine (NAC), a glutathione precursor. In a 24-week, double-blind trial of 2 g/day of NAC vs. placebo, significant moderate effect size clinical improvements were seen (Berk et al., 2008). While there have been no direct assessments of NAC's effects on behavioral plasticity or cognition in schizophrenia, a small, 11 patient, 2 month, randomized, cross-over of NAC (2 g/day) vs. placebo for 60 days each (Lavoie et al., 2008) assessed effects on MMN. Treatment with NAC significantly improved MMN generation compared with placebo ($d = 1.6$). The study was limited by a small number of completers ($n = 7$). Despite these promising results, there has been limited follow-up studies of NAC.

3.7. Nicotinic

Activation of nicotinic alpha-7 acetylcholine (α_7) receptors can indirectly modulate the glutamate system (Broide and Leslie, 1999). α_7 activation allows for the release of GABA, which activates presynaptic inhibitory gamma-aminobutyric acid-type B (GABA$_B$) receptors on the excitatory inputs to NMDAR receptors on pyramidal cells.

The largest nicotinic agonist studies have been completed with encenicline, a partial agonist of the α_7 receptor. Efficacy for adjunctive encenicline was demonstrated in a 319 subject Phase II study (Keefe et al., 2015), finding a significant, but small effect size improvement vs. placebo ($d = 0.26$, $p = 0.03$) for cognition. Recently completed phase III clinical trials were negative, and development of encenicline has been suspended. Phase II studies of other α_7 receptor partial

agonists (Freedman et al., 2008; Haig et al., 2016; Lieberman et al., 2013; Umbricht et al., 2014b; Walling et al., 2016) have shown mixed results on cognitive outcomes.

Thus far, only encenicline has been assessed with MMN (Preskorn et al., 2014), finding a dose dependent increase in MMN, along with improvements in P50, P300 and N100 in a small study. In contrast to D-serine studies, increases in MMN with encenicline were not related to clinical or cognitive improvement. This is consistent with a recent study of healthy controls suggesting that nicotine's enhancement of MMN may be independent of NMDAR modulation (Hamilton et al., 2018).

An ongoing issue with α_7 receptor agonist development is that the receptor is quickly desensitized in the presence of agonists (Kem et al., 2018)). A possible solution to this is the use of positive allosteric modulators (PAMs) at the α_7 receptor, which are only active in the presence of acetylcholine and thus less likely to cause desensitization. AVL-3288, a α_7 receptor PAM was recently tested in a Phase I study in healthy controls (Gee et al., 2017), finding small/moderate effect size improvements in cognition (d = 0.49). The first schizophrenia biomarker study with AVL-3288 is ongoing (NCT2978599).

4. Conclusions

Treating cognitive and plasticity deficits in schizophrenia remains an important challenge to be solved. Although using NMDAR modulating drugs as a treatment for schizophrenia itself has produced mixed results, combining intermittent use of NMDAR modulators with neuroplasticity-based paradigms using MMN as target-engagement biomarkers warrant further study. Of the individual drugs discussed, the strongest effects have been seen with direct agonists at the NMDAR complex, such as D-serine. For immediate study, D-serine appears to be ideal because it balances efficacy, availability and safety. Selective GlyT1 inhibitors, such as bitopertin, failed target engagement studies vs. D-serine, D-cycloserine and memantine are partial agonists or antagonists, and thus not ideal. α_7 receptor agonists await study of allosteric modulators. Other alternatives, such as SNAT2's are DAAO-I's promising, but are presently unavailable in the US.

As opposed to daily treatment combined with cognitive remediation programs, intermittent use of NMDAR modulators appears most effective. Fast-Fail drug development programs (Javitt et al., 2018a; Javitt et al., 2011; Paul et al., 2010) could utilize the methods described here as a "screening" paradigm for assessing the efficacy of novel NMDAR modulating drugs, using D-serine effects as the "gold-standard".

While most intermittent programs have used 1× weekly spacing, further investigations into the most effective timing of NMDAR-based intervention relative to plasticity-based treatment (e.g. 1× vs. 2× week) are also of interest. In addition to specific compounds, MMN has shown to have negative, as well as positive, predictive value as a target engagement/plasticity biomarker of NMDAR modulating treatment.

Contributors
Dr. Kantrowitz takes sole responsibility for this review.

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