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Permalink

<https://escholarship.org/uc/item/1z08d1n8>

Journal

Biological Psychiatry Cognitive Neuroscience and Neuroimaging, 3(7)

ISSN

2451-9022

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Publication Date

2018-07-01

DOI

10.1016/j.bpsc.2018.02.002

Peer reviewed



HHS Public Access

Author manuscript

Biol Psychiatry Cogn Neurosci Neuroimaging. Author manuscript; available in PMC 2019 July 01.

Published in final edited form as:

Biol Psychiatry Cogn Neurosci Neuroimaging. 2018 July ; 3(7): 581–590. doi:10.1016/j.bpsc.2018.02.002.

Auditory system target engagement during plasticity-based interventions in schizophrenia: a focus on modulation of N-methyl-D-aspartate-type glutamate receptor function

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Abstract

Cognitive deficits are predictive of long-term social and occupational functional deficits in schizophrenia, but are currently without gold-standard treatments. In particular, augmentation of auditory cortical neuroplasticity may represent a rate-limiting first step prior to addressing higher-order cognitive deficits. We review the rationale for N-methyl-D-aspartate-type glutamate receptor (NMDAR) modulators as treatments for auditory plasticity deficits in schizophrenia, along with potential serum and electroencephalographic (EEG) target engagement biomarkers for NMDAR function. Several recently published NMDAR modulating treatment studies are covered, involving D-serine, memantine, and transcranial direct current stimulation (tDCS). While all three interventions appear to modulate auditory plasticity, direct agonists (D-serine) appear to have the largest and most consistent effects on plasticity, at least acutely. We hypothesize that there may be synergistic effects of combining pro-cognitive NMDAR modulating approaches with auditory cortical neuroplasticity cognitive training interventions. Future studies should assess biomarkers for target engagement and patient stratification, along with head to head studies comparing putative interventions and potential long term vs. acute effects.

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This review was previously presented in part as a symposium entitled “Neural Substrates of Auditory Plasticity” at the Society of Biological Psychiatry's 72nd Annual Scientific Meeting, May 18–20, 2017.

Financial Disclosures:

All other authors report no biomedical financial interests or potential conflicts of interest.

Keywords

plasticity; schizophrenia; treatment; MMN; cognition; biomarker; NMDA

Introduction

In addition to positive and negative symptoms (1), schizophrenia is associated with deficits in neurocognition (2–5) that represent a core feature of the disorder (6, 7). Schizophrenia patients show impairments across a large variety of cognitive domains; they also show related deficits in perceptual (auditory and visual) learning, sometimes termed ‘cortical neuroplasticity’ (8, 9), during training on exercises that place implicit, increasing demands on early perceptual processing (10). Remediating or ameliorating these impaired cortical neuroplasticity processes represents a rate-limiting first step prior to addressing higher-order cognitive domains that are more proximal to occupational or social functioning (e.g., verbal or working memory, executive functioning) (11, 12). Examples of available neuroplasticity programs include adaptive tone-matching (13)—a repeated series of tone pairs in which subjects respond whether the second tone is higher or lower in frequency. Other programs, developed by Posit science, train to detect brief, high frequency-modulated auditory transient sweeps. However, ~45% of schizophrenia patients demonstrate minimal improvement when remediation is used adjunctive to antipsychotics (14), suggesting that further refinement is needed.

Similarly, previous efforts to develop procognitive/plasticity-enhancing agents as adjuncts to antipsychotics have been mixed (15–20), potentially based on two important weaknesses. First, the medication trials were not conducted in the context of active cognitive interventions. Simply adding a putative procognitive drug to a daily antipsychotic regimen may not provide a sensitive test of its activity: drugs that enhance specific neurocognitive processes, e.g. working memory capacity, might not yield clinical benefits unless paired with interventions that access those domains, i.e. utilize/place demands on working memory. Second, schizophrenia is highly heterogeneous, and pro-cognitive medication trials in schizophrenia have suffered from the absence of target engagement biomarkers that could either identify "sensitive" clinical subgroups (21) or refine dosing and intervention strategies.

What measures could potentially serve as useful biomarkers for engagement of a meaningful cognitive target in schizophrenia? And what is the evidence to support such an approach? We first briefly review the rationale for focusing on N-methyl-D-aspartate-type glutamate receptor (NMDAR) function as a target for enhancing cognition in schizophrenia. We also discuss emerging evidence of putative electroencephalographic (EEG) target engagement biomarkers for NMDAR function. We then focus on a promising cognitive enhancing strategy in schizophrenia-- the augmentation of auditory cortical neuroplasticity via modulation of NMDAR. Finally, we review evidence suggesting that while using NMDAR modulators or plasticity training alone is of interest, there may be synergistic effects of combining pro-cognitive NMDAR agents or neuromodulation methods with well-defined

cognitive training interventions that target auditory cortical neuroplasticity, as well as patient stratification via the use of reliable biomarkers—a true personalized psychiatry approach.

Rationale and mechanism for NMDAR as a target for cognitive enhancement

Recent studies of NMDAR modulators have shown the ability to enhance neuroplasticity both in specific patient populations (22–26) and healthy volunteers (13, 27)—suggesting a potentially useful role in addressing cognitive deficits in schizophrenia, yet one which has not yet been translated into clinical practice. The use of NMDAR modulators stems from the well-characterized role of brain NMDAR function in both schizophrenia pathophysiology (28), and in learning and neuroplasticity (22–26), including acquisition, consolidation, and retrieval of perceptual information (29). NMDAR serve as critical triggers for long-term potentiation (LTP) and depression (LTD) (30–33). LTP occurs in two different phases – an initial NMDAR-induced increase in AMPAR trafficking that occurs over minutes (acquisition phase), followed by a delayed increase in NMDAR trafficking that occurs over hours (consolidation phase) (34).

Furthermore, in animals (35), intensive cognitive activity increases brain levels of D-serine, an endogenous, direct agonist at the NMDAR's glycine modulatory site (36). Furthermore, administration of low-dose D-serine improves recognition and working memory function (35). In humans, serum D-serine levels are generally found to be lower at baseline in people with schizophrenia compared to controls (37). In a recent study (Panizzutti et al, under review), mean serum D-serine and L-serine levels were found to be significantly lower in schizophrenia subjects (N=90) prior to intensive cognitive training of auditory processing, as compared to healthy control subjects (N=53). Schizophrenia subjects were then assigned 50 hours of either auditory training (N=47) or a computer games control condition (N=43), followed by repeat assessment of cognition and serum amino acids. While there were no significant changes in these measures at a group level after the intervention, in the active training group increased D-serine was significantly and positively correlated with improvements in global cognition and in verbal learning and memory. No such associations were observed after the control condition. Consistent with the animal literature, these results suggest that D-serine—and hence NMDAR function—is involved in the plasticity processes induced by intensive cognitive training in schizophrenia. The significant association between change in serum D-serine levels and training-induced cognitive gains indicates the presence of inter-individual variation.

Together, these results suggest two important directions for the field: 1) Pharmacologic strategies that modulate NMDAR functioning may provide a mechanism for enhancing the behavioral effects of intensive cognitive training; 2) The identification of target engagement biomarkers will support a precision psychiatry approach for identifying those individuals most likely to respond to this method of cognitive enhancement.

EEG Target Engagement Biomarkers for NMDAR Function

Event-related potential (ERP) and event-related oscillation (ERO or time-frequency) EEG responses hold particular promise as biomarkers for NMDAR function. ERP and ERO approaches are standardized reactions of the brain to a particular stimulus. Mismatch negativity (MMN) (38, 39) is an ERP elicited when a sequence of repetitive standard tones are interrupted infrequently by a physically different “oddball” stimulus, that differs in frequency, duration or location (40–42). The oddball typically produces a more negative signal on the ERP, and the difference between standard and oddball response is termed mismatch negativity.

Deficits in auditory MMN generation in schizophrenia were first demonstrated in the early 1990’s and have been extensively replicated (43–46). These deficits correlate extensively with poor premorbid function and impaired psychosocial outcome even following covariation for more general demographic and neurocognitive factors (43, 46–51). In addition, test-retest reliability of auditory MMN is high, showing an ICC of 0.9 (52), further encouraging its use as a neurophysiological biomarker (45, 53).

Links between NMDAR dysfunction and MMN is supported by a series of studies in which ketamine, an NMDAR antagonist, produces schizophrenia like deficits in MMN across non-human (54–56) and human (57–62) investigations. This was confirmed in a recent meta-analysis (62), and in studies showing that MMN deficits predict parallel deficits in proton magnetic resonance spectroscopy (^1H MRS) measured glutamate (63, 64). By contrast, MMN is relatively unaffected by treatment with antipsychotics (46, 65, 66), suggesting minimal impact of dopamine antagonism on MMN.

Pertinent to the present review, auditory MMN is increasingly conceptualized as reflecting the “prediction error” when the deviant differs from the standard stimulus (67), and is highly predictive of response to auditory cognitive training (68, 69), and thus can be considered a neurophysiological proxy of both target engagement for NMDAR-associated cortical plasticity and the integrity of early auditory information processing. This association permits some interesting predictions on the expected benefit of interventions that improve early auditory information processing as indexed by MMN response. Using structural equation modeling in 1415 schizophrenia patients, a recent study (10) determined that measures of early auditory information processing, particularly MMN, had a direct (mediating) effect on cognition ($p < 0.001$), that cognition had a direct effect on negative symptoms ($p < 0.001$), and that both cognition ($p < 0.001$) and negative symptoms ($p < 0.001$) had direct effects on functional outcome. Overall, early auditory information processing had a fully mediated effect on functional outcome, engaging general rather than modality-specific cognition. Explicitly, this model predicted that a $1 \mu\text{V}$ change in early auditory information processing (including MMN) will result in improvements of approximately $d = 0.78$ for cognition and $d = 0.28$ for psychosocial functioning (10).

ERO activity complements ERP data by assessing circuit-level functions. ERO activity is divided conventionally into discrete (e.g. θ (4–7 Hz), α (7–12 Hz) and β (12–30 Hz) bands, which reflect differential underlying local-circuit processes (21, 70–72). Within these bands,

ERO is further differentiated into those that reflect alterations in phase reset mechanisms, as reflected in intertrial coherence (ITC), vs. those that reflect alterations in single-trial power (e.g. 71, 73). ERO measurements complement early auditory processing ERP, such as MMN (74), which are typically associated with increases in both θ -ITC and power (75). By contrast, suppression of ongoing α and β activity (e.g., event-related desynchronization, ERD) has been tied to bringing regions “on-line” during cognitive processing (76–78). In this review, we will also discuss other measures of early auditory information processing, such as steady-state (ASSR) responses (21) and prepulse inhibition of startle (PPI). Although literature linking these measures to NMDAR dysfunction is less robust than for MMN, they are also widely used measures (21, 52) with potential clinical utility. Enhancing visual plasticity and visual ERP biomarkers (79–82) are also under active study, but will not be specifically covered.

The NMDAR agonist D-serine as a means of enhancing auditory cortical neuroplasticity

Two recently published studies investigated whether novel NMDAR agonists can differentially modify neurophysiological plasticity (auditory MMN), and whether changes in this neurophysiological measure has predictive value for efficacy. Studies utilized D-serine at a dose of 60 mg/kg/d, which may be more effective than earlier studies at 30 mg/kg (83, 84), along with a glycine type I (GlyT1) transport inhibitor (bitopertin). Bitopertin showed promise as a stand-alone treatment in an initial study (85), but subsequent studies for bitopertin (86, 87) and other selective GlyT1 inhibitors (88) were negative.

Subchronic D-serine administration

In this study (89), 16 schizophrenia patients were treated with D-serine or placebo daily for 6 weeks. Significant, large effect size improvement in auditory MMN ($d=2.3$) was seen as compared to placebo (Fig. 1A), along with a significant treatment effect for PANSS total ($d=0.80$) and negative symptoms ($d=0.88$). Specificity of D-serine’s effect on auditory MMN was suggested by a parallel study (86) of bitopertin. Using an identical paradigm to the D-serine study, no significant effect was seen for auditory MMN, nor for any other behavioral outcome. Moreover, in the D-serine study, baseline auditory MMN predicted change in total PANSS, whereas no relationship between outcome and MMN was seen in the bitopertin study. This suggests that bitopertin failed because of inadequate target engagement (as measured by the auditory MMN).

Acute D-serine administration

Following up on these findings of sub-chronic, daily treatment with D-serine, a recent study (8) utilized a well validated, brief neuroplasticity-based adaptive tone-matching program (auditory training) (13) to assess the efficacy of intermittent, weekly D-serine treatment. In addition to behavioral effects, participants were assessed on neurophysiological cortical plasticity biomarkers, including MMN and θ -ITC. 21 schizophrenia patients received three auditory training sessions separated by 1-week, paired with either D-serine 60 mg/kg or placebo. Analyses focused on effects of both initial and repeated D-serine administration, given 30 minutes before sessions to allow for assessment at peak serum D-serine levels (84).

While there were no significant treatment effects after the 1st session, over subsequent sessions, a highly significant improvement in cortical plasticity, as assessed by a smaller tone-matching threshold, was seen in subjects who received D-serine in two consecutive sessions ($d=1.03$, Fig. 1B). By contrast, subjects showed non-significant worsening in the second session if they received either placebo followed by D-serine ($d=-0.36$) or D-serine followed by placebo ($d=-0.30$).

As expected, schizophrenia patients had significant baseline deficits in auditory MMN generation compared to healthy controls. Similar to the behavioral results, schizophrenia patients receiving two consecutive sessions of D-serine+auditory training had a significant larger pre-post change in auditory MMN ($d=0.7$), demonstrating both target engagement of the NMDAR by D-serine and improvement in neurophysiological plasticity. By contrast, and consistent with prior studies (68), groups receiving placebo+auditory training showed a tendency toward worsening of the auditory MMN response. Across schizophrenia patients, a relationship between plasticity and functional target engagement was demonstrated by a significant correlation between changes in MMN and plasticity improvements (tone-matching threshold: $r=-0.34$, Fig. 1C).

In addition, significant overall statistical effects were observed for θ -ITC and β -power, driven primarily by significant differences between the consecutive session D-serine and the placebo groups. Similar to auditory MMN, θ -ITC during the motor-preparation interval correlated significantly with plasticity thresholds. Correlations remained significant after control for group status ($r=-0.32$).

A noteworthy result of this study is the observed large behavioral improvement following only 2 sessions of auditory training paired with D-serine, as opposed to following ~50 hours of training (90, 91). We hypothesize that two consecutive treatments allow for action during two phases of NMDAR-induced plasticity: the acquisition phase and the consolidation phase. Overall, these studies suggest that repeated administration of D-serine led to intercorrelated improvements in auditory plasticity as assessed by a behavioral measure and by auditory MMN generation.

The NMDAR uncompetitive antagonist memantine as a means of enhancing auditory cortical neuroplasticity

In contrast to D-serine, memantine is an uncompetitive NMDAR partial antagonist of low affinity (92), producing only 30% NMDAR occupancy (93). Along with its NMDAR modulating effects, memantine also activates dopaminergic (94) receptors. By contrast to the detrimental effects of ketamine, a non-competitive antagonist of the NMDAR, previous studies in healthy subjects have reported that acute administration of memantine significantly increases auditory MMN ($d=0.87$ for 30 mg) (95), as well as PPI (96).

In a series of recent studies using a placebo-controlled, within-subject cross-over design, statistically significant positive effects of memantine (20 mg) on auditory MMN, PPI and ASSR were detected (97, 98) in schizophrenia and healthy controls. In each case, one 20 mg pill of memantine significantly “moved” these measures in schizophrenia patients towards

“normal” values. These changes could not be explained on the basis of antipsychotic medication interactions, or other artifacts related to illness treatment or chronicity, as qualitatively similar changes were also detected in healthy controls. For PPI, these memantine-induced changes were somewhat less robust in healthy controls; for MMN, they were somewhat more robust in healthy controls; and for ASSR, they were roughly comparable in healthy controls and patients (Fig. 2A–D).

Recent meta-analyses (99–101), suggest that subchronic use of adjunctive memantine offers modest but statistically significant symptomatic benefits, along with cognitive benefits. One recent study did not demonstrate improvement in cognition after a single dose of memantine (102). Importantly, none of these previous studies utilized memantine in concert with a systematic cognitive training intervention, nor were any specific biomarkers used to stratify the cohort into memantine-sensitive and memantine-insensitive patient subgroups.

Plasticity as a biomarker for individualized treatment

Conceivably, the magnitude of the early auditory information processing response to memantine challenge might serve as such a “biomarker” of memantine sensitivity in schizophrenia patients. While statistically significant increases in early auditory processing measures were detected after memantine in both healthy controls and schizophrenia patients, there was heterogeneity in this memantine response, with some healthy controls and patients exhibiting robust increases after memantine, and others showing little change, or even reductions (Fig. 2E). This heterogeneity of response might provide a basis for stratifying patients into subgroups based on predicted treatment effects, and may be more specific than stratifying based on clinician rated symptom scales.

We propose that, by using a memantine “challenge” test, in the span of two office visits separated by one week, individuals with schizophrenia might be defined as “memantine-sensitive” vs. “memantine-insensitive”, based on their change in early auditory processing measures such as MMN, ASSR and PPI after a single dose of memantine vs. placebo. Although data is limited, similar challenge tests could be used for other NMDAR modulating agents. It is also conceivable that such patient subgroups might differ in cognition-relevant NMDAR circuitry, and hence represent neurobiologically distinct forms of this disorder, shedding important light on pathophysiologic mechanisms.

Transcranial Direct Current Stimulation effects on NMDAR function as a means of enhancing auditory cortical neuroplasticity

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation technique that applies low direct electrical current on the scalp to target underlying cortical regions (103–105). tDCS effects may be due in part to modifications of synaptic strength, mediated by NMDAR activity (106–108). The effects of tDCS are divided into two phases: online, when the current is active, and offline, during the post-stimulation period. During the online phase, the current is proposed to preferentially polarize pyramidal neurons resulting in intracellular voltage shifts. Cortical regions under the anodal or positive electrode undergo a slight depolarization where neurons are brought closer to their action potential threshold.

This depolarization is not sufficient to cause neuronal firing, but increases the probability of an action potential to occur. Conversely, cathodal stimulation hyperpolarizes the cell thereby decreasing the probability of neuronal firing (109–111). Once the tDCS current is turned off, intracellular voltages return to their baseline state but the effects of tDCS persist (103).

tDCS and NMDAR Function

tDCS appears to enhance plasticity through NMDAR mechanisms, as shown through studies that have focused on motor plasticity. tDCS of the motor cortex induces offline effects lasting 60–90 min after a single stimulation (112, 113). After anodal tDCS, amplitudes of motor evoked potential (MEP) are increased compared to pre-tDCS. Following cathodal tDCS, there is a decrease in MEP amplitudes (109, 114). In human studies, NMDAR antagonists abolish tDCS induced MEP changes (112, 113). A recent mouse study suggested that tDCS induces neuroplastic changes through modulation of NMDAR activity (115, 116). Given the putative association between NMDAR dysfunction and symptoms of schizophrenia, tDCS may have a role in helping to address aspects of the cognitive impairments seen in the illness (36, 73, 117). Indeed, a recent pilot study demonstrated that tDCS combined with working memory training in schizophrenia enhanced the behavioral gains, as compared to training alone (118).

tDCS and Auditory Mismatch Negativity

The neural effects of tDCS applied alone in non-motor systems such as auditory processes are less well characterized (119–121). In an initial study, tDCS was applied to the dorsal lateral prefrontal cortex of schizophrenia participants in a parallel, sham-controlled design. There was a large effect size ($d=0.95$) decrease in auditory MMN amplitude with anodal tDCS compared to sham (control condition) (122). This suggests that anodal tDCS facilitated neuroplastic changes as reflected by modulation of MMN amplitude. The decrease in amplitude was unexpected, as although polarity-specific effects in non-motor systems are less consistent (121), anodal tDCS has been associated with increased cortical activity during stimulation of the motor cortex. This tDCS-induced decrease in MMN does not appear to be a schizophrenia specific finding, as anodal tDCS of prefrontal regions in healthy controls also decreased MMN amplitude (123).

Based on findings that reduced MMN amplitudes in schizophrenia are associated with poorer cognitive status and greater functional impairments, we hypothesize that improved plasticity should be associated with increased MMN. However, these studies typically compare MMN deficits with chronic and stable functional impairments (68, 124, 125), and it may be possible that acute reduction in MMN represents increased neural efficiency.

tDCS and Tone Matching Task

In addition to neurophysiological measures such as MMN, auditory discrimination tasks may also corroborate auditory system target engagement by tDCS. In a static version of the adaptive tone-matching program (13), the Tone Matching Task (TMT) (126), subjects are presented with pairs of auditory tones and asked to determine if they are identical or differing in frequency. The early auditory processing deficits in schizophrenia contribute to

impairments in tone discrimination and patients perform worse than healthy controls (127–129).

In a within subject cross-over study (130), a single session of cathodal tDCS targeting the primary auditory cortex demonstrated significant improvement in TMT performance compared to sham. Anodal stimulation also improved TMT performance at a trend level. The improvement in tone discrimination suggested that tDCS is able to engage and modulate auditory processing. However, the improvement after both cathodal and anodal tDCS was unexpected. A post-hoc analysis revealed an interaction between negative symptoms and stimulation condition where TMT performance declined with greater negative symptom severity after cathodal stimulation. In contrast, higher negative symptom burden was associated with improved TMT performance after anodal stimulation (130). NMDAR dysfunction has been implicated in both auditory processing deficits and negative symptoms (131, 132). Therefore, a possible explanation of these results is that tDCS modulates NMDAR activity and produces variable effects that reflect individual patient variability in NMDAR dysfunction, consistent with the picture emerging from the other studies reviewed here.

Auditory Plasticity Training alone and NMDAR functioning

Recent studies examining the effects of auditory training interventions alone on ERP biomarkers have yielded mixed results (68, 124, 125). In a recent study by Perez et al., schizophrenia participants engaged in one hour of auditory perceptual training (68). Consistent with previous findings, training improved task performance (133, 134). However, there was a small, but statistically significant decrease in auditory MMN amplitude assessed immediately after the one-hour training. This decrease in MMN is similar to the acute effects seen after tDCS (122) and to placebo findings in the D-serine study (8).

Few studies have assessed plasticity intervention effects on MMN beyond the acute post-intervention period, so the longer-term effects on MMN are unknown. One possible consideration is that training induced changes to neural substrates continue to evolve beyond the acute time frame. Eventually, steady state is achieved at which time MMN amplitudes may look very different from the acute post-intervention period.

Menning et al. conducted a study of healthy controls undergoing multiple sessions of auditory training over three weeks and assessed mismatch field amplitudes (MMF, the neuromagnetic counterpart to MMN) during and post training. There was a significant increase in MMF amplitude midway through the three weeks of training. MMF was then assessed immediately at the conclusion of the three-week training, and three weeks after the conclusion of training. Illustrating the evolving nature of the mismatch response, the MMF at these two later time points had decreased compared to the midway findings and were no longer statistically different from baseline amplitudes (125).

Thus, there appear to be some interesting contrasts between the increases in auditory MMN observed after acute or sustained D-serine or memantine treatment, which act directly on NMDAR function, vs. the decreases that are observed immediately after tDCS and single

session cognitive training which act on distributed neural system function. Furthermore, findings from multiple training sessions suggests a dynamic pattern of change rather than a single static shift of amplitude in response to training. These findings deserve closer investigation, as they are likely to yield insights into the nature and timing of differing mechanisms of action that can be brought to bear on auditory cortical plasticity.

Conclusions

In this review, we have demonstrated that that deficient auditory plasticity, as measured by behavioral tone matching paradigms and neurophysiological measures (MMN) in schizophrenia patients – widely viewed to reflect fixed, heritable abnormalities in brain mechanisms regulating auditory information processing – can be significantly enhanced (i.e. brought significantly closer to normal values) via interventions targeting the NMDAR receptor in chronically ill schizophrenia patients. These findings demonstrate significant plasticity in brain mechanisms that are thought to contribute to “core” neurocognitive deficits in schizophrenia.

While D-serine, memantine and tDCS all appear to modulate auditory plasticity, the degree of modulation varies across studies. Agents that work directly on NMDAR functioning, particularly D-serine or glycine (135), appear to have the largest, most consistent and sustained effects in schizophrenia, while those that work at the circuit level (tDCS, auditory training) appear to decrease MMN (at least acutely). Head to head studies are warranted to assess potential differences between D-serine and memantine on plasticity, potential synergistic effects of pharmacological, brain stimulation and auditory training and potential long term vs. acute effects. In addition, the refinement of target engagement biomarkers such as MMN will support a precision psychiatry approach for patient stratification most likely to respond to this method of cognitive enhancement (see Fig. 2E). Finally, the auditory plasticity paradigms described appear to be well suited to be used as a “screening” paradigm for assessing the efficacy of a putative pharmacologic cognitive enhancers. For example, the effects of D-serine or memantine on the adaptive tone-matching task could be used as the “gold standard,” and used to test novel compounds such as non-selective inhibitors of glycine transport (136, 137), D-amino acid oxidase (DAAO) inhibitors (136, 138) or phosphodiesterase inhibitors (139, 140).

Acknowledgments

This work was supported in part by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant Number UL1 RR024156 and the Dr. Joseph E. And Lillian Pisetsky Young Investigator Award for Clinical Research in Serious Mental Illness to JTK; MH59803, MH94320 and the Brain & Behavior Research Foundation to NRS; and MH068725 to SV.

Dr. Kantrowitz reports having received consulting payments within the last 24 months from Krog & Partners Incorporated, Kinetix Group, Annenberg Center for Health Sciences at Eisenhower, Semantics MR LTD, Transperfect, and Cowen and Company. He has conducted clinical research supported by the NIMH, the Stanley Foundation, Taisho, Lundbeck, Boehringer Ingelheim, NeuroRX, Merck, and Lilly within the last 24 months. He owns a small number of shares of common stock in GlaxoSmithKline. Dr. Vinogradov is a site Investigator on an SBIR grant to Positscience Inc., a company with a commercial interest in cognitive training software. She is on the Scientific Advisory Board of Mindstrong and Alkermes.

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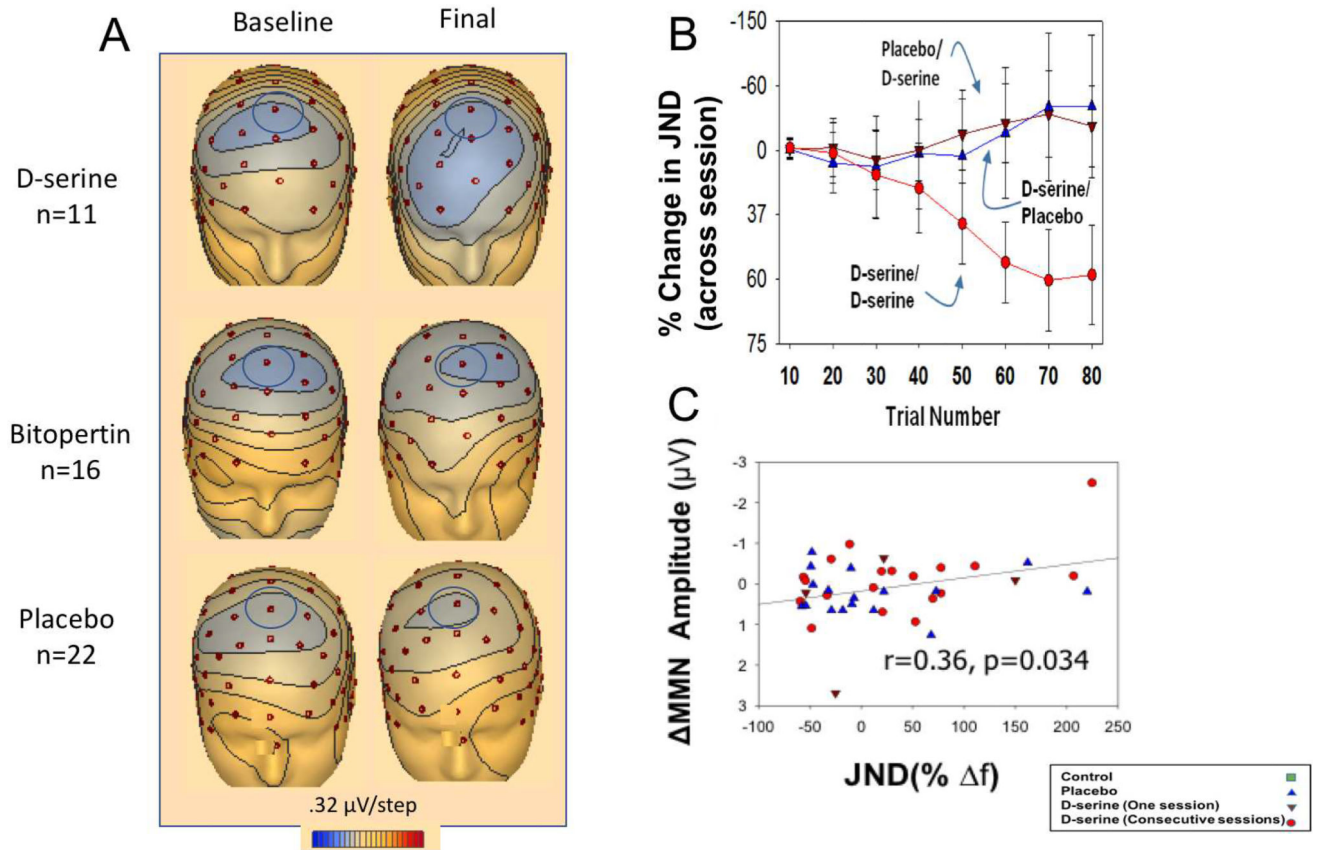
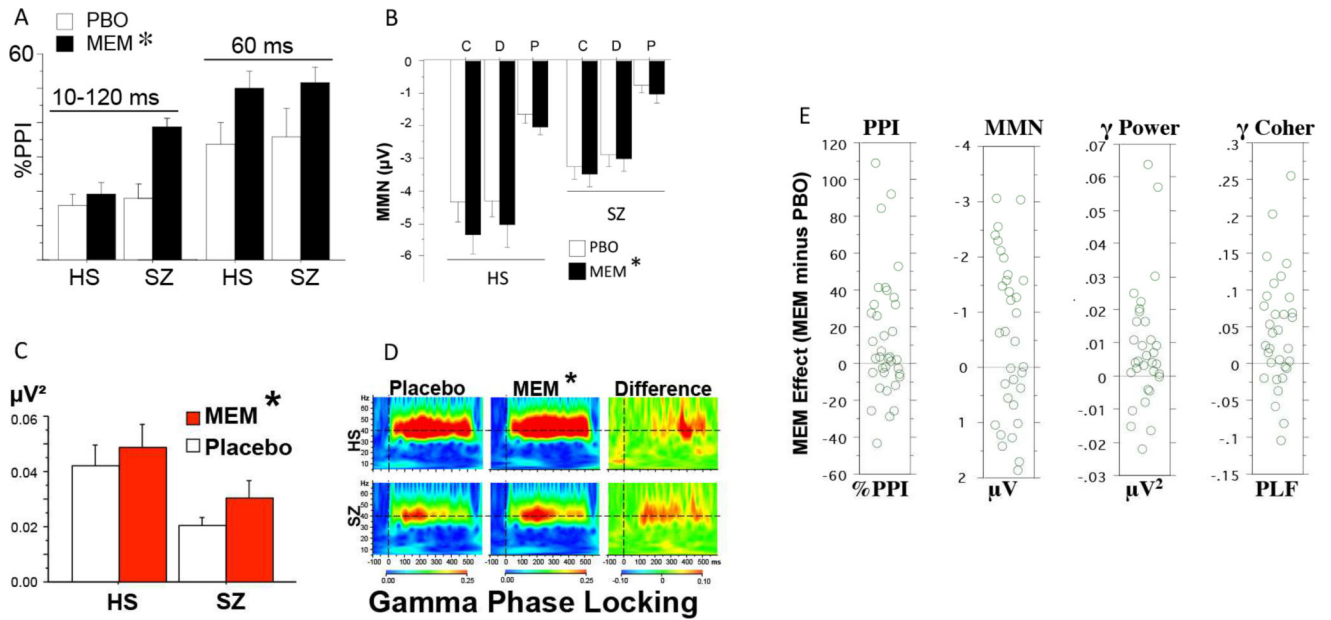


Figure 1.

A. 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). B. Line graph of % change in behavioral plasticity on the adaptive tone-matching task across sessions for the indicated treatment orders. C. Scatter plot for % change in behavioral plasticity on the adaptive tone-matching task vs. change in MMN amplitude to the trained tone. E. Modified from (8, 89). Error bars indicate standard error of the mean; *** $p < 0.001$

**Figure 2.**

Effects of memantine on A: PPI; B: MMN; C, D: ASSR in healthy subjects or schizophrenia patients. Patients and HS (n 's=42 & 42) were tested after placebo or memantine (10 or 20 mg p.m.; 20 mg shown here). Compared to healthy subjects, patients had deficits in MMN and ASSR. Memantine (20 mg) significantly enhanced PPI (A; $p < 0.04$ for 10–120 ms; $p < 0.01$ for 60 ms), MMN (B; $p < 0.014$; Duration; Pitch; Combined) and ASSR (C: evoked power, 40 Hz * $p < 0.025$; D: gamma phase locking, * $p < 0.002$). E. Distributions of “memantine effect” (memantine (20 mg) minus placebo) on early auditory processing performance, for (left to right): PPI (60 ms), MMN, gamma power and gamma coherence, in healthy subjects or schizophrenia patients (pooled, since there were no group differences in memantine effects) Modified from (97, 98).