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SPECIAL ARTICLE

Does mismatch negativity have utility for NMDA receptor drug development in depression?

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Rapid antidepressant effects associated with ketamine have shifted the landscape for the development of therapeutics to treat major depressive disorder (MDD) from a monoaminergic to glutamatergic model. Treatment with ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, may be effective, but has many non-glutamatergic targets, and clinical and logistical problems are potential challenges. These factors underscore the importance of manipulations of binding mechanics to produce antidepressant effects without concomitant clinical side effects. This will require identification of efficient biomarkers to monitor target engagement. The mismatch negativity (MMN) is a widely used electrophysiological signature linked to the activity of NMDA receptors (NMDAR) in humans and animals and validated in pre-clinical and clinical studies of ketamine. In this review, we explore the flexibility of the MMN and its capabilities for reliable use in drug development for NMDAR antagonists in MDD. We supplement this with findings from our own research with three distinct NMDAR antagonists. The research described illustrates that there are important distinctions between the mechanisms of NMDAR antagonism, which are further crystallized when considering the paradigm used to study the MMN. We conclude that the lack of standardized methodology currently prevents MMN from being ready for common use in drug discovery.
Clinical trial registration: This manuscript describes data collected from the following National Institutes of Health (NIH) and Veterans Affairs (VA) studies: AV-101, NCT03583554; lanicemine, NCT03166501; ketamine, NCT02556606.

Keywords: Mismatch negativity; NMDA-receptor; AV-101; ketamine; lanicemine mismatch negativity for NMDAR drug development

Introduction

The symptoms of major depressive disorder (MDD) appear to arise from broad systemic dysfunctions that disrupt processes such as salience monitoring, emotional affect regulation, anhedonia, and depressed mood.[1,2] The hypothesis concerning the biology of these dysfunctions has shifted in recent years from broad depletion of monoaminergic neurotransmitters to one focused on the regulation of the glutamate system. Glutamate is the primary excitatory neurotransmitter in the regulation of excitation/inhibition (E/I) balance in the central nervous system (CNS). Dysregulation of glutamate transmission would imply a reduction in synaptic plasticity and an impoverished degree of cognitive flexibility,[3] which would place the system at risk for the development of many depressive symptoms.

The discovery of the rapid antidepressant effects of the N-methyl-D-aspartate (NMDA) antagonist ketamine has been pivotal to this shift in perspective.[4-6] The consistent replication of antidepressant effects from sub-anesthetic intravenous ketamine (0.5 mg/kg) prompted detailed study into the mechanism of action, implicating the blockade of NMDA receptors (NMDAR) in the antidepressant effects.[7] Thus far the literature converges on a mechanism involving inhibition of NMDARs on gamma aminobutyric acid (GABA) interneurons and on glutamate neurons that results in changing the balance between concentration of glutamate and GABA. Blockade of NMDARs located on GABA interneurons in the prefrontal and temporal cortices[8,9] is believed to reduce release of GABA. GABAergic interneurons projecting to glutamate neurons inhibit the release of glutamate. Ketamine-induced lower GABA levels are believed to cause a surge

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of glutamate release within the prefrontal cortex, hippocampus, and nucleus accumbens, subsequently increasing the neural E/I ratio.[10-12] GABAergic and glutamate receptors project to primary pyramidal neurons. Blockade of NMDARs on pyramidal neurons results in activation of post-synaptic α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors, promoting enhanced neural signaling patterns within targeted regions.[13]

Glutamatergic neurotransmission plays an important role in the regulation of cortical excitability and is a critical component in the organization of interregional communication.[14] Animal studies of NMDAR antagonism demonstrate that the glutamate system is strongly associated with attention and memory,[15] learning,[16] cognitive control,[17] regional neural signaling patterns,[3] and the regulation of other neurotransmitter systems.[18]

Despite promising evidence, there are several drawbacks to ketamine as a primary antidepressant treatment. These include behavioral dissociation, psychotogenic effects, and elevated blood pressure, resulting in the requirement of a licensed health care provider to oversee administration. This has led to the development of alternative NMDAR modulators, which aim to preserve the antidepressant mechanism of ketamine while exploiting variations in receptor binding characteristics to curtail problematic side effects. The development of new NMDAR modulators requires, first, demonstration that the medication engages the NMDAR complex similarly to ketamine; and, second, demonstration that treatment response to the agent is directly related to this biological mechanism.

Markers for drug development

The ideal route for confirmation of effective transfer of a medication across the blood-brain barrier would be to measure metabolism of a related ligand at the target synapse pre- and posttreatment in combination with real-time monitoring of functional consequences of receptor engagement. This can be achieved with excellent spatial resolution using positron emission tomography (PET); however, this approach falls short of the ability to monitor acute temporal changes in response to the drug, which can provide crucial insight into the pharmacological mechanism of action. This can instead be achieved more effectively through electroencephalography (EEG).[19]

EEG and magnetoencephalography (MEG) can demonstrate neurotransmitter engagement by tapping into variation in E/I ratio.[20] MEG and EEG operate by detecting large electric field oscillations with a concomitant magnetic field resulting from synchronized neuronal communications based on neurotransmission dynamics.[21] Simple yet robust physiological markers, such as the auditory steady state response (ASSR)[22,23] and the mismatch negativity (MMN) have been repeatedly shown to be influenced by the neuropathological state of diseases such as schizophrenia,[22,23] which may be linked to hypoactivation of NMDARs.[24] Studies in animal models and healthy human volunteers have replicated disease states such as schizophrenia using NMDAR antagonists, thus implicating a functional role of glutamatergic signaling in these markers.[25-28]

In this article, we will review the use of the MMN in the study of NMDAR drug development, with a specific focus on depression. The MMN is a robust neurophysiological response that has been repeatedly linked to NMDAR function in both human[29] and animal research[30] through clinical[31] and pharmacological studies.[32] In the remainder of this review, we evaluate the utility of the MMN in the context of drug development from the perspective of the existing literature and from our own novel data.

What is the mismatch negativity?

The MMN is an event-related potential (ERP) measured with an oddball task that presents frequent standard stimuli and occasional deviant stimuli. The task can present either auditory or visual stimuli, but is most commonly performed as an auditory task. The MMN is estimated by taking the difference between the grand average of the deviant trials and the grand average of the standard trials (Figure 1). The MMN appears as a negative peak between 120 and 250 ms at fronto-central electrodes. Imaging and source reconstruction research supports primate studies that suggest the response is generated by multiple sources within the supra-granular layer of the primary and secondary auditory cortex.[30,33] More recently, this has been expanded to demonstrate bilateral temporal, parietal, and prefrontal engagement via functional connectivity,[34] supporting a cortical hierarchy model.

The basic framework for the MMN posits that it updates network activity regarding the monitoring and processing of a continuous stream of information.[35] When a deviant element is detected, the processing network is updated to signal the potential for a reallocation of resources. The strength of this output is believed to represent the plasticity of the system as well as the capacity for learning how to handle the deviant response.[35-37] Modern efforts focused on modelling this have expanded this theory to the realm of predictive coding. In this approach, the perceptual system makes predictions about upcoming sensory information based on the current context and neuronal adaptation to the train of stimuli (including repetition rate); the proto-object for sensory processing (standard stimulus) is then compared against the incoming information.[38] When the prediction is correct (another standard), no further response is necessary. However, when the prediction does not match the input (deviant stimulus), the system signals this by way of the MMN evoked potential.[39,40] In this context, the amplitude of the MMN has also been interpreted as a coded response to the strength of the match between the top-down and bottom-up systems, where a larger response indicates a more substantial error and thus a greater need to alter the allocation of processing resources.[41] It is therefore likely that the MMN represents implicit trial-by-trial encoding of prediction errors that depends on NMDAR-dependent plasticity at glutamatergic synapses.[42,43]

The relationship between NMDAR and the MMN

The mechanism by which NMDARs contribute to the generation of MMN is complicated and involves the

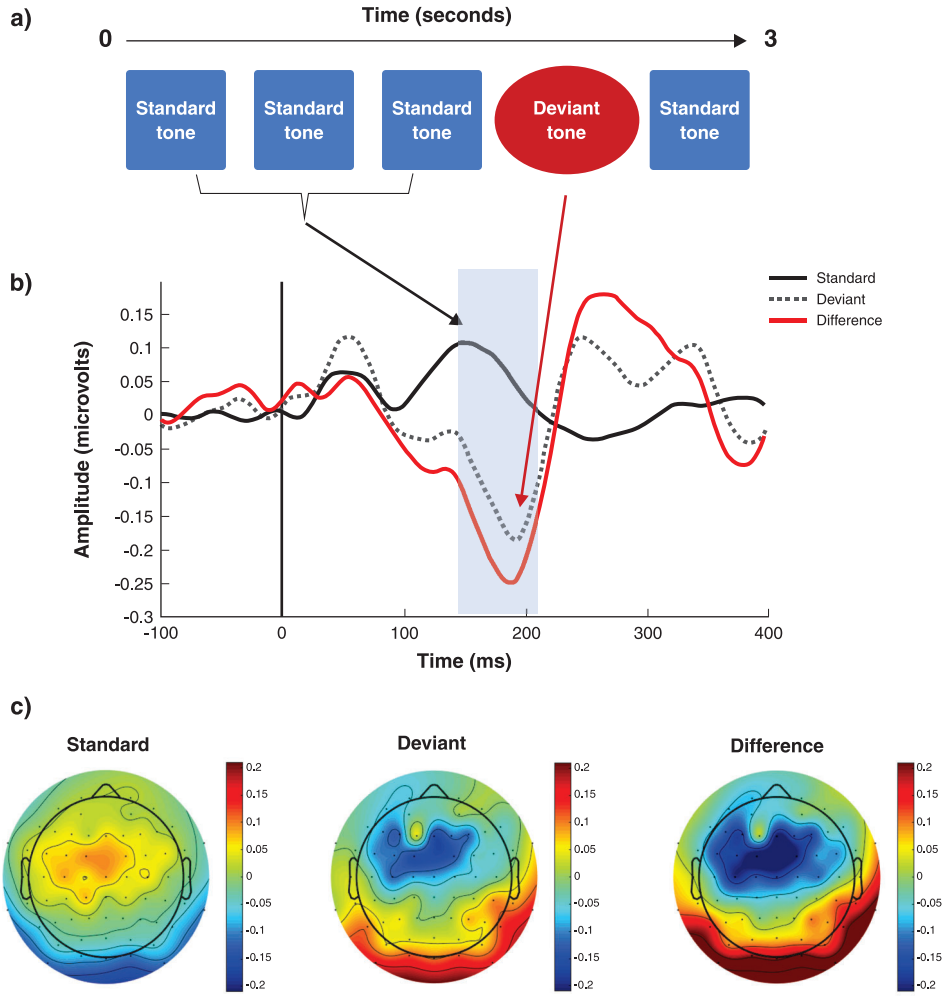

Figure 1 Outline of the cortical response to the generic mismatch negativity (MMN) paradigm. A) The schematic demonstrates the frequency and nature of an oddball stimulus over time. B) The solid black trace represents the grand average of the standard trials contrasted with the grand average of the deviant trials (dashed line) and the difference between them (deviant minus standard, solid red line). The MMN appears within the 150 to 220 ms window and reflects the extent of the deviation between the two conditions. C) Topographic response to each condition as recorded using a 64-channel EEG cap (10-20 montage).

balancing of processes that manipulate the extent of neuronal adaptation to the response in the primary auditory cortex (PAC), with changes (plasticity) along forward and backward connections between the PAC and the rest of the auditory processing hierarchy. The significance of NMDARs to the generation of the MMN can perhaps best be explained through the use of dynamic causal modelling (DCM).[40] Modelling of the synaptic communication in ketamine and control conditions demonstrated the propensity of ketamine to alter the plasticity of the neurons forming connections between the PAC and the superior temporal gyrus, but did not show ketamine to have an effect of the adaptiveness of neurons within the PAC. In the ketamine comparison, the distinction between effects on plasticity relative to adaptation suggests that NMDAR activity plays a crucial role in managing the connectivity profile at the heart of coordinating the response to deviance detection.

This interpretation consolidates earlier findings that demonstrate, in isolation, the important contributions of neuronal adaptation to a stimulus[44] and long-term potentiation (LTP).[45,46] Neuronal adaptation can be inferred by measuring spike frequency in response to a repeated stimulus. This is controlled by calcium-dependent potassium channels and is affected by NMDAR activation, which mediates intracellular calcium.[44] NMDARs are also critical for both LTP and long-term depression (LTD), mechanisms that may underlie learning and memory.[47] Pharmacological blockade of NMDARs in hippocampal neurons reduces pyramidal neuron spiking[48] and extracellular synaptic potentials,[45,46] indicating disruption of LTP.

Ketamine studies of deviance detection and insights from schizophrenia

Neurophysiological studies of ketamine have revealed that antidepressant response is associated with decreased parietal pyramidal neuron gain and reduced NMDA-mediated connectivity across important functional networks

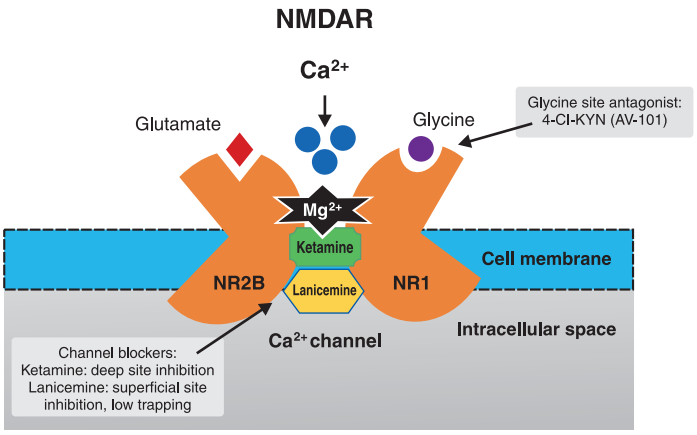

Figure 2 Schematic depiction of an NMDA receptor (NMDAR). Mechanisms of NMDAR antagonists can include blockade of subunits NR2B and NR1 (competitive antagonists), blockade of the glycine binding site (glycine antagonists), blockade of allosteric sites (noncompetitive antagonist), and blockade of the pore (uncompetitive channel blockers). The MMN appears to be affected by all types of NMDAR antagonists, indicating a generic role of NMDAR activation within its circuitry. Lanicemine and ketamine are channel blockers with different trapping block profiles. Ketamine exhibits the strongest and lanicemine the weakest trapping block. AV-101 (4-chlorokynurenine [4-Cl-KYN]) blocks NMDAR activity through competitive antagonism of the glycine-binding site.

implicated in affective cognition, including the frontal and default mode networks.[13] These effects occur within 1 hour of infusion, demonstrating a rapid effect on pyramidal neurons through activation of AMPA glutamate receptors. The maintenance of these effects over a longer period of time (24 hours, single infusion; 14 days, one infusion per week) might then be propagated by slower, more complex, downstream effects via increased brain derived neurotrophic factor (BDNF) release and upregulation of mammalian target of rapamycin (mTOR), critical factors in neural plasticity.[49,50]

Ketamine robustly reduces MMN amplitude across different stimulus paradigms (duration, frequency, and intensity deviance).[43,51-54] This effect is replicable in rats[28] and mice,[27] supporting the MMN as a translational biomarker of NMDA function. Reduced MMN amplitude has consistently been reported in patients with schizophrenia, animal models, and genetic models of NMDAR hypofunction,[55,56] leading to the hypothesis that NMDAR hypofunction may underlie this disorder.[57-59] Further, the substantial relationship between the degree of MMN disruption and cognitive decline in patients further supports deleterious effects of NMDAR hypofunction (e.g., Pochwat et al.[60]) on MMN.[39,40]

Studies of the oscillatory components of deviance detection in schizophrenia have more recently begun to emerge due to an inherent advantage over traditional ERP measurements for inferring circuit level activity. The fine-grained distinction between patterns of activity that occur at different timescales can inform us of discreet changes in the state of local neuron populations. In schizophrenia, the MMN has been associated with reduced theta (4-7 Hz) power and disturbed phase coherence,[61-63] emphasizing that deviance detection is additionally dependent upon the consistency of inputs across time. Theta reduction occurs in tandem with increased alpha activity (8-14 Hz) during standard stimulus trials,[62] suggesting that pathological distress within thalamocortical (alpha) and corticocortical (theta) projections are critical anatomical components of deviance detection, lending support to the DCM proposed by Schmidt et al.[40]

N-methyl-D-aspartate receptor structure and function

The NMDAR is a heterotetramer consisting of four subunits. Two subunits respond to glutamate occupancy of NMDAR subunit 1 (NR1) and two subunits respond to glutamate occupancy of subunit 2 (NR2A to NR2D) (Figure 2). NMDAR activation also requires simultaneous occupancy of glycine and multiple allosteric binding sites, in addition to the glutamate binding sites. NMDAR activation causes release of a magnesium ion from the NMDAR pore, allowing entry of calcium and generation of an action potential. Mechanisms of NMDAR antagonists can include blockade of subunits (competitive antagonists), blockade of the glycine binding site (glycine antagonists), blockade of allosteric sites (noncompetitive antagonist), and blockade of the pore (uncompetitive channel blockers).

Competitive (CGS-19755) and noncompetitive (phencyclidine [PCP]) NMDAR antagonists reduce MMN responses, showing a reduced neural response to deviant but not standard stimuli.[30] Reductions in MMN were also found using the NMDAR channel pore blocker MK-801.[47,64] Dose-dependent inhibition of the MMN by the selective GluN2B antagonist traxoprodil (previously CP-101,606) suggests that the effect on the MMN may be mediated by the NR2B subunit of the NMDAR.[65] In terms of NMDAR affinity, it was found that both moderate affinity antagonist memantine and high-affinity antagonist MK-801 bind to the NR2B subunit of the NMDAR at similar binding locations.[66] The varying presence of MMN effects across NMDAR blockade mechanisms suggests

that the contribution of glutamatergic signaling to the generation of MMN is broad and complex.

Impact of three NMDAR antagonists on the MMN: our findings

The findings of MMN manipulation in response to a broad variety of NMDAR antagonists present a clear case for the MMN as a target for drug development. Drug development to date has explored a number of different NMDAR binding sites and binding properties to replicate the antidepressant effects of ketamine while attempting to avoid the side effects discussed earlier. To move forward, it is important to study the specific physiological effects on cell behavior that stem from this. For example, a recent meta-analysis revealed that MMN amplitude is suppressed and, with a lower effect size, latency increases after ketamine administration in chronic schizophrenia patients.[29] However, there is also evidence to the contrary, in which the low-affinity NMDAR antagonist memantine increases MMN amplitude.[64] The findings from studies of memantine in both MMN and MDD contexts provide a strong example of the challenges faced in drug development for rapid acting antidepressants. Although the purpose of memantine is to act as an NMDAR antagonist, and one which is successfully used in the treatment of Alzheimer's dementia,[67] there are currently no successful placebo-controlled trials in MDD to demonstrate treatment efficacy.[5] It is possible to speculate that the mechanistic design of memantine, low affinity for NMDA and much more rapid trapping kinetics,[68] results in reduced potency at the 20 mg dose typically prescribed. In this case, we might interpret the failure to detect stereotypical effects of NMDAR blockade via the MMN as an indication of poor target engagement. A lesson to be learned in this instance is that proper comparison against placebo and a dose-response curve are imperative to determining the strength of a tool such as the MMN. To date, this is still an emerging technical area within research on the interplay between NMDAR antagonist design and MMN engagement.

Differences between drugs in receptor binding can alter the release of glutamate considerably through differentiation in how they manipulate sensitivity to Ca^{2+}. Manipulation of signaling has branching effects on the connectivity between the prefrontal and other systems being measured in the auditory and visual MMN. The basis of this is explored in the DCM study by Schmidt et al.,[40] which demonstrates the importance of these pathways and how their disruption scales with degradation in cognitive performance. However, the fine details of this are still unexplored. For drug development, targeting different binding sites and the different binding properties of drugs could have different effects on changing the E/I ratio, if the drugs have side effects on cognition, and on how effective drugs are as an antidepressant. The MMN could be used as a measure to test the reactivity of the NMDAR complex as a function of NMDAR binding site and binding properties.

As a demonstration of the first element for consideration (binding-site specifics), we describe the procedures and outcomes for three different NMDAR antagonists, each using the same duration deviance auditory oddball paradigm. The data presented are from three individual studies (AV-101, NCT03583554[66]; lanicemine, NCT03166501; ketamine, NCT02556606), each designed to test the MMN as a marker of NMDAR target engagement.

General methods

EEG was acquired using a 64 channel Brain Products GmbH, EasyCap, at a 1,000 Hz sampling rate. MMN was assessed at multiple time points relative to medication administration. To generate the MMN, we used a duration deviance oddball paradigm with 630 trials consisting of 50 ms standard tones (90 db., 1 kHz) presented 90% of the time, and 100 ms deviant tones (90 db., 1 kHz) that occurred in 10% of trials. To prevent adaptation effects, each deviant tone had a minimum of four standard trials preceding it. All trials had an interstimulus interval of 500 ms. Trials were presented passively and did not require activity from the participant.

Continuous data were filtered between 1 and 30 Hz and re-sampled to 250 Hz. Line noise at 60 Hz was removed using the CleanLine plugin for EEGLab.[69,70] Bad channels were identified using cap-wise thresholding, where z scores for kurtosis greater than 3 were excluded from analysis. Independent components analysis (ICA) was used to inform the estimation and removal of blinks, muscular activity, and other non-cortical artifacts from the data. The spatially filtered data were then segmented into epochs of length -100 to 400 ms. Bad trials were identified and removed using in-house functions for statistical thresholding. The MMN was measured as the difference between the deviant and standard grand averages for electrodes FZ and CZ, with the larger amplitude being carried forward for statistical analysis. Group analysis was performed using linear mixed models. Models were varied according to the study design, but each model consistently applied a random intercept and covaried for effects of assessment time. Findings are summarized in Figures 3, 4 and 5.

AV-101 (4-chlorokynurenine [4-Cl-KYN])

AV-101 is an oral pro-drug that acts through the kynurenine pathway, which is investigated as an agent to treat MDD and suicidality.[71] In the brain, AV-101 is converted to 7-chlorokynurenine by kynurenine aminotransferase (KAT)-rich astrocytes, reducing NMDAR activity through competitive antagonism of the glycine binding site[72] (Figure 2).

Methods

We explored the neurophysiological correlates of a single dose of AV-101 on NMDAR functioning in a recent Phase 1b clinical trial (please see https://clinicaltrials.gov/ct2/show/NCT03583554).[73] The aim of this trial was to define sensitive markers of NMDAR engagement at different

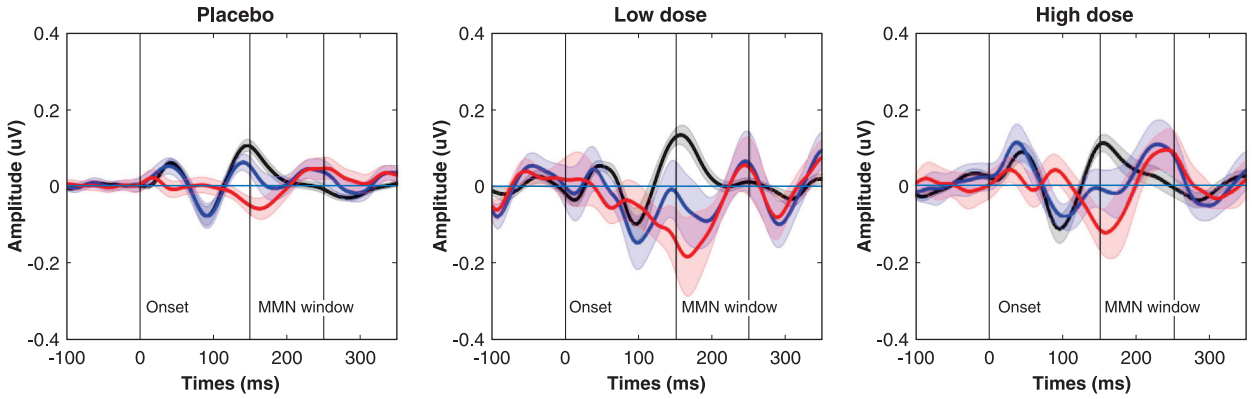

Figure 3 Summary of the mismatch negativity (MMN) findings from the AV-101 (4-chlorokynurenine [4-Cl-KYN]) investigation. The MMN is visualized as a waveform corresponding to the difference between the standard and the deviant event-related potential (ERP) waveforms (red). The plots show data averaged across the measurement time points for the placebo group, low-dose group, and high-dose group (right). Black = standard ERP; blue = deviant ERP.

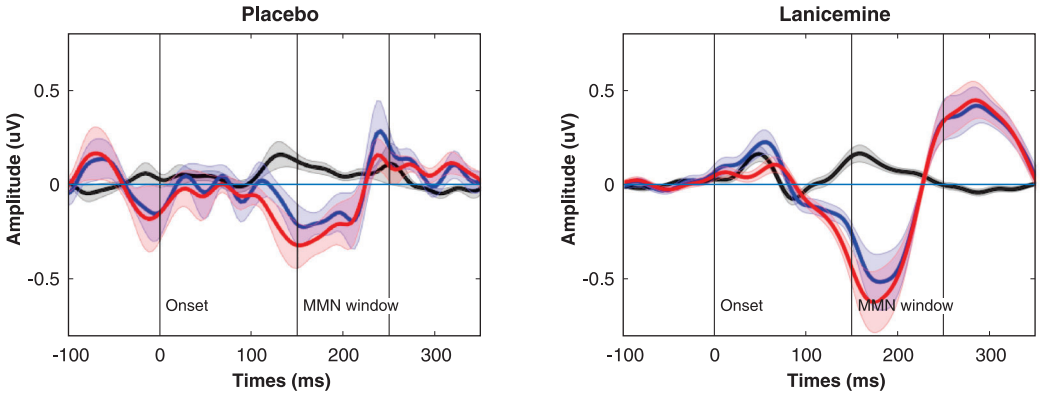

Figure 4 Summary of the mismatch negativity (MMN) findings from the lanicemine investigation. The MMN is visualized as a waveform corresponding to the difference between the standard and the deviant event-related potential (ERP) waveforms (red). The plots show data averaged across the measurement time points for the placebo group (left) and lanicemine group (right). Black = standard ERP; blue = deviant ERP.

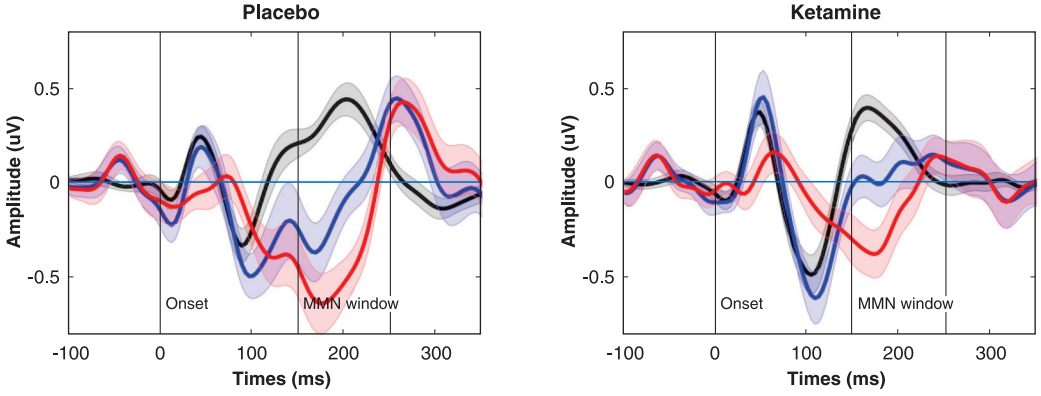

Figure 5 Summary of the mismatch negativity (MMN) findings from the ketamine investigation. The MMN is visualized as a waveform corresponding to the difference between the standard and the deviant event-related potential (ERP) waveforms (red). The plots show data averaged across the measurement time points for the placebo group (left) and ketamine group (right). Black = standard ERP; blue = deviant ERP.

individual doses of AV-101 relative to placebo. We recruited 12 healthy U.S. veterans (mean age = 32.6 years ± 6.11; n=1 female) and administered placebo, 720 mg AV-101, and 1,440 mg AV-101 on separate days in a randomized placebo controlled cross-over design. Visits were separated by a minimum of 1 week. Ten subjects completed all conditions and were included in the final analyses. At each visit, EEG was recorded 30 minutes prior to the dose, and then at hourly intervals after dosing up until 5 hours post-dose. We expected a dose-response effect on reducing MMN amplitude. In the linear mixed model, we used a fixed effect of time and dose, and a random effect of subject. The random effect takes into consideration the potential for individual variation in each data point and does not assume a common intercept. We used covariates of baseline measurement (pre-dose time point) and time to model a generalized effect of dose on changes in MMN amplitude and latency.

Results

Analysis of the fixed effects for AV-101 demonstrated that there was no significant impact of dose on MMN amplitude ($F = 0.89$, degrees of freedom [df] = 121.62, $p = 0.41$) and latency ($F = 0.94$, df = 122.88, $p = 0.39$) relative to placebo, falsifying the hypothesis.

Lanicemine (BHV-5500)

Lanicemine (BHV-5500, formerly AZD6765), a potent and selective NMDAR antagonist, is parenterally administered and is extensively studied in preclinical and early-phase clinical studies in patients with stroke, sleep apnea, and more recently in treatment-resistant depression (TRD) and post-traumatic stress disorders (PTSD). Lanicemine is an NMDAR channel blocker. In contrast to other NMDAR channel blockers such as ketamine and MK801, lanicemine is rapidly reversible (fast off-rate) and binds high in the NMDAR pore (52-59%),[74] properties associated with a favorable safety and tolerability profile.[75] At present, the primary focus of lanicemine research has been TRD, with our study being the first of its kind for PTSD. Earlier work demonstrates that NMDAR blockade with lanicemine produces an increase in EEG gamma power, a characteristic trait of NMDAR antagonism,[76] making it a suitable candidate to investigate in the context of the MMN.

Methods

In our Phase 1b, parallel-arm, randomized, double-blind, placebo-controlled study, we tested whether lanicemine affected NMDAR functioning in subjects with high stress reactivity measured as anxiety potentiated startle (APS) and significant PTSD symptoms as correlates of induction and expression of behavioral sensitization which involved changes in NMDAR functioning (please see https://clinicaltrials.gov/ct2/show/NCT03166501 for details). Participants received three 60-minute infusions of lanicemine (100 mg, n=12; mean age 41±10.8 years; n=6 females) or placebo (n=12; mean age 40.7±7 years; n=8 females) over a 5-day period. Of the patients, 83.3% had co-morbid MDD. We evaluated change in MMN amplitude from baseline to end of third infusion.[77] We used a linear mixed model to account for repeated measures, with a fixed effect of time and treatment group and a random effect of subject. The random effect takes into consideration the potential for individual variation in each time point and does not assume a common intercept. p-values < 0.05 were considered significant. Pre-infusion baseline values for both infusion days were used as covariates, and variance components were used as covariance structure. We hypothesized a reduction in MMN amplitude with lanicemine compared to placebo.

Results

Analysis of fixed effects of lanicemine demonstrated a trend effect on MMN amplitude decrease ($F = 3.919$, df = 24.84, $p = 0.059$), but no effect on latency ($F = 0.903$, df = 20.05, $p = 0.353$), suggesting a minimum effect of lanicemine on MMN. Lanicemine was well-tolerated and no serious adverse events were reported.

Ketamine

Ketamine is a non-competitive NMDAR antagonist. It occupies a binding site in the NMDAR channel pore below the binding site of the magnesium ion that blocks NMDAR activation in physiological conditions. In the aging population, the increased prevalence of major depressive episodes is a risk factor for dementia and increased mortality,[78] emphasizing a need for faster acting treatments than conventional antidepressants. Ketamine could be a viable option to rapidly treat depression in elderly populations. Limited clinical data are available in patients at advanced ages. We recently conducted a proof-of-concept dose-response clinical trial to assess the efficacy of ketamine in elderly U.S. veterans with TRD. The details of this trial are registered at ClinicalTrials.gov (NCT02556606) and in Mealing et al.[74]

Methods

We recruited 33 military veterans presenting with TRD. The study design compared single infusions of midazolam 0.03 mg/kg (active placebo), ketamine 0.1 mg/kg, ketamine 0.25 mg/kg, and ketamine 0.5 mg/kg on clinical and EEG recorded at intervals of 30 minutes pre-infusion, and 30, 60, 120, and 240 minutes relative to start of infusion. Randomization was achieved by using a Bayesian adaptive randomization strategy. Of the 33 subjects, 13 received midazolam (mean age 62.15 years ± 5.34; n=4 females), and 11 received 0.5 mg/kg ketamine (60.91 years ± 4.97; n=3 females). Due to the small number of subjects randomized to the 0.1 (n=4) and 0.25 mg/kg (n=5) conditions, only data from the midazolam and the 0.5 mg/kg groups were used for the final analysis. Consistent with prior studies with ketamine, we expected reduced MMN amplitude with ketamine. We used a linear mixed model to account for repeated measures

with a fixed effect of time and treatment group and a random effect of subject. The random effect takes into consideration the potential for individual variation in each time point and does not assume a common intercept. We used covariates of baseline measurement (pre-dose time point) and time to model a generalized effect of treatment on changes in MMN amplitude and latency.

Results

Analysis of the fixed effects of ketamine demonstrated no significant effects on MMN amplitude ($F = 0.03$, $df = 38.32$, $p = 0.86$), but did identify a significant increase in latency in the ketamine group relative to the control group ($F = 4.76$, $df = 47$, $p = 0.03$).

Discussion of findings

In the studies described, we identified varied effects on the MMN as a function of the specific mechanism of NMDAR blockade. At the doses investigated, it would appear that the variation in how NMDAR blockade occurs does not drastically affect the ability of the system to generate the mismatch response. The factor behind the lack of response is unknown; however, it could encompass a mixture of pharmacological and clinical factors. Importantly, the lack of change in MMN is similar for all compounds. For ketamine and lanicemine, this is supported by previous investigations of EEG gamma oscillations in response to therapeutically similar doses of each drug. Both resulted in similar increases in gamma power, suggesting that variations in receptor trapping do not affect the ceiling for plastic changes in cortical excitability.[75] If we consider this in the context of the model proposed by Schmidt et al.,[40] then the similar changes in cortical excitability could be an indication of shared manipulation of the plasticity of the feedback loop between the PAC and its functional connections.

An additional element to factor into this model is the latency of the MMN peak. We found that relative to the control group, ketamine increased the latency of the MMN response. This has previously been reported in a meta-analysis of ketamine findings in schizophrenia.[29] This may be specific to binding of an antagonist in the NMDAR pore, perhaps specific to the low binding site in the NMDAR pore or the slow off-rate, which could be compatible with the later MMN peaking time.

Functionally, the MMN latency represents the point at which the distinction between the standard and deviant stimuli is registered, which adds in a much stronger dependency on the generation of the early and mid-components of the standard and deviant auditory evoked potentials. There is a litany of factors linked with changes in latency, including stimulus presentation rate,[79] complexity of the stimuli,[80] and cognitive ability.[81] In the context of the Schmidt model,[40] this would point at changes in the flexibility of the PAC to adapt to incoming neural signals. However, without further investigation of the detailed parameters of the MMN stimuli and of how each of the evoked potentials interact this remains speculative.

It should be noted that each of these studies has a relatively small sample size. Further, in our ketamine study the advanced age of participants might contain effects specific to aging which mask the influence of ketamine on MMN amplitude; further the control substance used was the benzodiazepine midazolam and not an inert saline, which could ostensibly reduce the gap between the two groups in terms of systemic effects on the MMN (e.g., Forsyth et al.[82]). The results of our studies highlight the need for future work to break down the MMN task itself and assess the relationship between its cortical mechanics and the NMDA system. From a pharmacological standpoint, it will be important to consider how these can be understood using DCM, so that we can appreciate the nuanced effects of different antagonists on the interactions between nodes. The general conclusion based on our data is that the MMN amplitude may not be a sufficiently sensitive measure of NMDAR target engagement of a pharmacological intervention.

Findings of the MMN in major depressive disorder

MMN in MDD has been studied extensively and is widely reported to be impaired relative to healthy controls (Table 1). The difficulty with interpreting the literature is that the direction of effects shows much inconsistency between studies. This is due mostly to variations in study and paradigm design (we refer the reader to Takei et al.[83] for intimate details of paradigm variations and their effects on MMN morphology).

Amplitude effects

In studies that implemented a duration deviance paradigm, patients with MDD typically demonstrated a diminished MMN amplitude relative to controls,[83-86,89] while frequency and pitch deviance amplitude was enhanced in MDD.[26,83,90] The opposing effects of the different paradigms in MDD implies that the tuning parameters of the auditory cortex and the pre-attentive mechanisms of deviance detection consist of numerous overlapping and separate pathways which are affected differently by neuropathology. By extension, this further implies that any effects on NMDARs and their related counterparts occur in an anatomically specific fashion and are not distributed homogenously throughout the cortex.

Latency effects

In addition to the discrepancies in amplitude, several studies have also noted that MMN peak latency is increased in response to pitch deviance.[78,83,84] In ERP terms, the latency is often associated with the efficiency of information transfer or the conduction velocity. This has previously been associated with the concentration of glial cells following the effects of chronic stress on the cortex.[83,87,88,91] This could suggest that reductions in glial concentrations in MDD have disproportionate effects on subpopulations of neurons tuned for the coordination of pitch detection.[83,87]

Table 1 Summary of MMN findings by paradigm in MDD

Paradigm	Paradigm notes	Major findings	References
Duration deviance	Standard tone and deviant tons are presented for different lengths of time.		
Auditory	Example: Standard = 75 dB, 1,000 Hz, 100 ms Deviant = 75 dB, 1,000 Hz, 200 ms	MMN amplitude is reduced in MDD relative to HC; in some cases also reduced relative to BPD (which is also reduced relative to controls).	Bissonnette,[79] Kim,[80] Chen,[81] Forsyth[82]
Visual	Example: Standard = black square, 1 cm × 1 cm, 100 ms Deviant = black square, 1 cm × 1 cm, 200 ms	MMN amplitude was reduced in MDD, but only in response to longer duration deviants (150 vs. 50 ms).	Qiu[84]
Pitch/frequency deviance	Standard tone and deviant tone are presented at different frequencies. Everything else might remain constant.	MMN amplitude has been shown to depend on stimulus intensity (dB), with different studies showing effects in both directions.	He,[23] Bissonnette,[79] Restuccia[85]
	Example: Standard = 75 dB, 1,000 Hz, 100 ms Deviant = 75 dB, 2,000 Hz, 100 ms	MMN latency is increased in MDD relative to HC.	Bissonnette,[79] Restuccia,[85] Qiao[86]
Affective content	The standard and deviant differ in terms of affective information.		
Auditory	Example: Standard = five-word sentence in neutral tone Deviant = five-word sentence in sad tone	MMN was absent for sad deviant stimuli in MDD relative to controls. MMN amplitude and latency were similar between MDD and HC for neutral, happy, and angry prosody.	Pang[87]
Visual	Example: Standard = 10 cm × 10 cm, 100 ms, neutral face picture Deviant = 10 cm × 10 cm, 100 ms, angry face picture	Subcomponents of the MMN are differentially affected by MDD. The early MMN amplitude to all emotional faces was reduced relative to HC. The late MMN was absent.	Chang[88]

BPD = bipolar disorder; HC = healthy controls; MDD = major depressive disorder; MMN = mismatch negativity.

Information processing

In the majority of studies, the MMN paradigm is based on physical manipulations. In a recent study,[92] extension of the MMN to real-world information processing, such as emotional information, captured important insights into the generation of the MMN response. The authors adapted the auditory oddball paradigm to incorporate verbal prosody, which reflects more natural information processing at the everyday level. Given that a core feature of MDD is difficulty in accurately interpreting emotional information, the system should respond less effectively to emotional stimuli than neutrally presented stimuli. The authors found that sad stimuli failed to elicit an MMN in patients, while MMN for happy, angry, and neutral stimuli were unaffected. This bias partially replicates the results of a visual MMN study, which investigated emotional expressions on face-like targets.[93] In that study, the MMN data revealed early and late subcomponents within the temporal window of interest. In MDD patients, the early MMN amplitude was diminished in response to emotional stimuli relative to controls, while the late MMN amplitude was absent. However, when the stimuli were presented upside down, the MMN amplitude was decreased in controls but unaffected in MDD. What is apparent from both studies is that the architecture of deviance detection and its general effects in MDD are evident not only across sensory modalities, but also apply to more complex cognitive realms, including emotion. From the understanding that deficient prediction error processing may lead to disrupted learning and suboptimal inference on sensory inputs from environmental causes,[40] one could conclude that MMN would be a useful tool to reflect disrupted cognition in patients.

Patient heterogeneity

The concept of non-uniform dysfunction in MDD is more recently considered to be a major factor in issues such as low treatment remission rates and wildly heterogeneous symptom profiles.[1] From source imaging we understand that the MMN relies on a network of regions predominantly in the auditory, prefrontal, and parietal cortices,[94] and thus some discrepancies between MMN results in the past could reflect heterogeneity of the patients recruited. This is an important consideration which has gained traction in other aspects of MDD research such as predicting the likelihood of a therapeutic response to treatment with transcranial magnetic stimulation (TMS).[95,96] Studies in the context of repetitive TMS response have found that greater connectivity between the left dorsolateral prefrontal cortex (DLPFC) and the sub-genual[94] striatum and related frontal regions[92] predicted a better response to treatment. Presumably, this reflects the degree of intact communication required at the sensory cortex level to be able to entrain the frontal network responsible for interpreting emotional information. In a similar manner, several MMN studies show a correlation between

symptom severity and the amplitude of the P1 and P3 (for an example of the P1 [solid black line, peak at ~100 ms] and P3 [solid red line, peak at ~300 ms] components we refer the reader to the schematic depicted in Figure 1) components, but not the MMN.[85] While this would appear to exclude any processes encapsulated within the basic framework of the MMN, it does appear that there is evidence of disruption in some of the systems involved in the transfer of information between pre-attentive and attentive states associated with the severity of MDD. The lack of reported correlations between these variables suggests that the different MMN findings might be stable features of MDD and thus represent traits rather than symptom-driven state markers of neuropathology. As is to be expected, based on the history of the MMN findings described thus far, there remains significant variation in the symptom correlations associated with the paradigm used. Bissonnette et al.[79] found a significant negative correlation between the location-deviant MMN amplitude and the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D), whereas Naismith et al.[96] noted a correlation between pitch-deviant MMN amplitude and semantic fluency scores. It should be noted that in the latter of these examples, the MMN amplitudes were taken from temporal cortex electrodes in late-life depression patients, which raises the possibility that this correlation is driven by age-related deterioration, comorbid mild cognitive impairment, or both.

The efficacy of MMN as a marker of NMDA activity and directions for future research

The literature available suggests that the MMN is a promising tool that can aid with the development of NMDAR-focused pharmaceuticals for MDD. However, by assessing the effects of pharmacological mechanisms of different drugs and experimental design on the parameters of the MMN, we believe that more work is required before commercial application of the MMN could be relied upon. The general application of the MMN, to better understand NMDAR antagonism, reveals varying profiles of response between substances; however, careful dissection of the investigational methods highlights an inconsistent application of the MMN between studies. In its own right, the variation of the paradigm parameters provides useful insight into the nuances of NMDA antagonism between different patterns of neural circuitry. The drawback, however, is the limited supply of multivariate study designs that accurately capture the full range of the MMN (e.g., Bissonnette et al.[79]).

At present, we have the general understanding that the MMN is tied to the activity of NMDARs, and we have seen evidence that under certain conditions it has the sensitivity to detect physiological changes in these circuits in MDD. Future research should aim to report time and time-frequency domain analyses of the MMN from different paradigm variations (duration, pitch, stimulus type), so that we can create detailed models of the relationship between the mechanisms of action for different NMDA drugs and the MMN. The current lack of a rigorous standard for MMN experiments is the most critical factor holding back the efficacy of the MMN for this task.

As a final point of consideration for the future, it is worth to note the progress being made in the imaging of different receptor types. The successful application of the ligand [11C]K-2 to the study of AMPA receptors in the human brain[97] opens up new avenues to study the more complex elements in the mechanism of rapid antidepressant response seen in ketamine. This will improve the general understanding of up- and downstream mechanisms of response, and likely provide new clinical targets. As it becomes possible, these should be studied in tandem to gauge the full utility of NMDAR antagonism as a therapeutic, as well as to determine whether or not the MMN effects seen in the context of NMDARs can also reflect other critical mechanisms of antidepressant response.

Conclusions

The architecture of deviance detection contains different branching pathways that each account for different physical properties of the stimulus, whether that be pitch, duration, location, or tone, as well as for how regularly the stimulus is presented. In each case, the way the encoding of a mismatch is performed appears to be differently affected by MDD neuropathology. The extension of these findings into affective cognition further amplifies the sensitivity of the MMN as a tool for studying systemic manipulations in MDD. However, this sensitivity also presents some complications when considering the MMN as a clinical target for drug development. The findings reviewed in this article demonstrate that different variations of the MMN are not affected equally by NMDAR blockade. We believe that due to its passive nature, the MMN is a very simple and powerful tool, which can easily be incorporated into physiological studies of NMDAR blockade without any cognitive burden to the participant. However, we conclude that careful steps should be made to develop an MMN test battery so that manipulation of NMDARs can be studied with greater respect for the complex nuances of MMN generation.

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Disclosure

VistaGen Therapeutics provided the AV-101 and placebo capsules and analyzed AV-101 metabolites (AV-101 study).

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