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Publication Date

2018

DOI

10.1016/j.schres.2017.06.040

Peer reviewed

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Author manuscript

Schizophr Res. Author manuscript; available in PMC 2019 January 01.

Published in final edited form as:

Schizophr Res. 2018 January ; 191: 87–94. doi:10.1016/j.schres.2017.06.040.

Interactive effects of an N-methyl-D-aspartate receptor antagonist and a nicotinic acetylcholine receptor agonist on mismatch negativity: implications for schizophrenia

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Abstract

N-methyl-D-aspartate glutamate receptor (NMDAR) hypofunction has been implicated in the pathophysiology of schizophrenia, including auditory processing abnormalities reflected by the mismatch negativity (MMN) event-related potential component. Evidence suggesting cognitive benefits from nicotine administration, together with the high rate of cigarette use in patients with schizophrenia, has stimulated interest in whether nicotine modulates NMDAR hypofunction. We examined the interactive effects of ketamine, an NMDAR antagonist that produces transient schizophrenia-like neurophysiological effects, and nicotine, a nicotinic acetylcholine receptor (nAChR) agonist, in 30 healthy volunteers to determine whether nicotine prevents or attenuates

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Contributors

Drs. Mathalon, D'Souza, and Ford and Mr. Roach were responsible for the design of the study and the supervision of data collection. Dr. Hamilton took the lead on writing the manuscript in consultation with all authors. All authors contributed to and approved the final manuscript.

Conflicts of Interest

Deepak C. D'Souza has in the past 3 years received or currently receives research grant support administered through Yale University School of Medicine from Astra Zeneca, Abbott Laboratories, Eli Lilly Inc., Organon, Pfizer Inc., and Sanofi; he is a consultant for Bristol Meyers-Squibb. Mohini Ranganathan has received in the past 3 years or currently receives research grant support administered through Yale University School of Medicine from Insys Therapeutics and Pfizer Inc. Daniel H. Mathalon reports that he is a consultant for Boehringer Ingelheim, Alkermes, and Upsher-Smith Laboratories. Holly K. Hamilton, Judith M. Ford, Brian J. Roach, Naomi S. Kort, Kyung-Heup Ahn, and Savita G. Bhakta declare that they do not have any potential conflicts of interest.

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MMN abnormalities. Secondary analyses compared the profile of ketamine and schizophrenia effects on MMN using previously reported data from 24 schizophrenia patients (Hay et al., 2015). Healthy volunteers completed four test days, during which they received ketamine/placebo and nicotine/placebo in a double-blind, counterbalanced design. MMN to intensity, frequency, duration, and frequency+duration double deviant sounds was assessed each day. Ketamine decreased intensity, frequency, and double deviant MMN amplitudes, whereas nicotine increased intensity and double deviant MMN amplitudes. A ketamine x nicotine interaction indicated, however, that nicotine failed to attenuate the decrease in MMN associated with ketamine. Although the present dose of ketamine produced smaller decrements in MMN than those associated with schizophrenia, the profile of effects across deviant types did not differ between ketamine and schizophrenia. Results suggest that while ketamine and schizophrenia produce similar profiles of MMN effects across deviant types, nicotinic agonists may have limited potential to improve these putative NMDAR hypofunction-mediated impairments in schizophrenia.

Keywords

mismatch negativity; electroencephalography; schizophrenia; NMDAR hypofunction; ketamine; nicotine

1. Introduction

A cornerstone of the glutamatergic N-methyl-D-aspartate receptor (NMDAR) hypofunction model of schizophrenia is evidence that NMDAR antagonists such as ketamine induce symptoms, neurocognitive deficits, and neurophysiological abnormalities similar to those observed in schizophrenia (Krystal et al., 2003; Moghaddam and Javitt, 2012; Moghaddam and Krystal, 2012). Therefore, NMDAR antagonists provide an elegant pharmacological model of NMDAR-mediated abnormalities in schizophrenia. Given that dopaminergic antipsychotic medications do not improve neurocognitive or neurophysiological abnormalities in schizophrenia (Buchanan et al., 2007; Ford et al., 1994; Keefe et al., 2007; Umbricht et al., 1998, 1999), there is interest in identifying novel pharmacological targets with potential to improve these abnormalities, directly or via amelioration of NMDAR hypofunction. One possible target is nicotinic acetylcholine receptor (nAChR) augmentation, which has been shown to improve cognition (Newhouse et al., 2004; Rezvani and Levin, 2001; Swan and Lessov-Schlaggar, 2007) and associated neurophysiological measures (Polich and Criado, 2006; Pritchard et al., 2004). Accordingly, we examined whether pharmacological augmentation of nAChRs can attenuate the neurophysiological consequences of NMDAR hypofunction induced by ketamine. We focused on the mismatch negativity (MMN), an event-related potential (ERP) component that is reduced by schizophrenia (see Erickson et al., 2016) and NMDAR antagonists (see Rosburg and Kreitschmann-Andermahr, 2016).

MMN is an auditory ERP elicited by infrequent deviant sounds interspersed among frequent “standard” sounds. MMN has been considered to reflect auditory echoic memory (Näätänen et al., 2005; Näätänen and Kähkönen, 2009; Näätänen et al., 2004) and predictive coding in the auditory system (Friston, 2005; Garrido et al., 2009; Stephan et al., 2006; Stephan et al.,

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2009). Although MMN is elicited pre-attentively (Näätänen and Kähkönen, 2009), it correlates with higher-order cognition and functional outcomes in schizophrenia patients (Baldeweg et al., 2004; Hamilton et al., in press; Light and Braff, 2005; Wynn et al., 2010) and healthy individuals (Light et al., 2007).

MMN amplitude is reduced in schizophrenia (Erickson et al., 2016; Umbricht and Krljes, 2005). Moreover, NMDAR antagonists reduce MMN in animal (e.g., Ehrlichman et al., 2008; Javitt et al., 1996) and human (Gunduz-Bruce et al., 2012; Heekeren et al., 2008; Knott et al., 2012; Kreitschmann-Andermahr et al., 2001; Schmidt et al., 2013; Umbricht et al., 2000) studies. A recent meta-analysis showed ketamine to significantly reduce MMN amplitude in most human studies (Rosburg and Kreitschmann-Andermahr, 2016), despite some failures to demonstrate these effects (Mathalon et al., 2014; Oranje et al., 2000; Roser et al., 2011). Conversely, some have shown nAChR agonists, principally nicotine, to enhance MMN amplitude in healthy individuals (Baldeweg et al., 2006; Dunbar et al., 2007; Harkrider and Hedrick, 2005; Martin et al., 2009), although others failed to demonstrate this enhancement (Inami et al., 2005; Inami et al., 2007; Knott et al., 2011; Martin et al., 2009; Mathalon et al., 2014). Some have shown enhancement of MMN by nAChR agonists only in subgroups of individuals with low MMN amplitudes at baseline (Impey et al., 2015; Knott et al., 2015; Knott et al., 2014; Smith et al., 2015). In schizophrenia, the effects of nicotine have also been mixed (see Dulude et al., 2010; Fisher et al., 2012; Inami et al., 2007). Mixed results may partly depend on the type of deviance used to elicit MMN in specific studies, arguing for use of multi-deviant paradigms within a single study (Näätänen et al., 2004).

Several mechanisms may explain potential nAChR agonist enhancement of neurocognitive and neurophysiological function. Nicotinic agonists facilitate glutamatergic neurotransmission in rat prefrontal cortex (Gioanni et al., 1999; Lambe et al., 2003) and hippocampus (Radcliffe et al., 1999), possibly via presynaptic nAChRs (McGehee et al., 1995) or GABA interneurons (Alkondon et al., 1999; Ji and Dani, 2000). Importantly, nicotine has been shown to attenuate or reverse NMDAR antagonist-induced memory and attentional deficits in rats (Levin et al., 1998; Rezvani and Levin, 2003), whereas NMDAR antagonists can block nicotinic enhancement of memory consolidation in mice (Ciamei et al., 2001). In a study examining the interaction of ketamine and nicotine in healthy humans, ketamine reduced frequency deviant MMN, but co-administration of nicotine blocked this effect in a subgroup prone to sub-threshold delusional/hallucinatory experiences (Knott et al., 2012). Previously, we failed to replicate these effects on duration deviant MMN (Mathalon et al., 2014), although we may have lacked sufficient power given the study's small sample size.

Accordingly, the present placebo-controlled study examined the interactive effects of ketamine and nicotine on MMN in a relatively large sample of healthy volunteers. We hypothesized that 1) ketamine alone would reduce MMN amplitude, 2) nicotine alone would increase MMN amplitude, and 3) nicotine combined with ketamine would attenuate ketamine's disruptive effects on MMN. Given inconsistent effects of ketamine and nicotine on MMN as a function of the type of auditory deviance used, we implemented a multi-deviant paradigm to simultaneously examine drug effects on intensity, frequency, duration, and frequency+duration double deviant MMN.

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Because we used the identical paradigm in a previous study documenting MMN amplitude deficits in 24 early illness schizophrenia patients relative to healthy controls (Hay et al., 2015), we conducted a secondary analysis comparing the z-score profile of ketamine effects (relative to placebo norms) in the current sample with the z-score profile of schizophrenia effects (relative to healthy control norms) across MMN deviant types.

2. Methods

2.1 Ketamine-Nicotine Study Participants

Participants were 30 healthy individuals (see Table 1) representing a subgroup from a previous report of ketamine-nicotine effects on neurocognitive measures (for full description of inclusion/exclusion criteria, see D'Souza et al. (2012)). Participants had no personal lifetime or family history of a major Axis I disorder based on structured interview (First et al., 2002) and were medically healthy based on physical exam and clinical laboratory testing. Participants were instructed to refrain from consuming illicit drugs, prescription medications not approved by the research team, and alcohol for two weeks before and throughout participation. Participants were also instructed not to smoke cigarettes after midnight before each test day. Heavy tobacco users (>15 cigarettes per day) were excluded from participation to prevent nicotine withdrawal precipitated by test day abstinence, which could be difficult for heavy smokers to tolerate (see D'Souza et al., 2012). A minority of subjects described themselves as current smokers, and daily tobacco use ranged from none (n = 20) to 15 (n = 1) cigarettes per day.

2.2 Early Schizophrenia Study Participants

Data from a prior study (Hay et al., 2015) of 24 early illness schizophrenia spectrum patients (ESZ), defined as being within five years of first hospitalization or initiation of antipsychotic treatment (age M=23.95, SD=5.17), and 21 healthy controls (age M=22.89, SD=4.26), were used to compare effects of ketamine on MMN to the effects schizophrenia. Sample characteristics and results, which demonstrated reduced MMN amplitudes across deviant types in ESZ compared to healthy controls, are described in Hay et al. (2015).

Both studies were approved by the Institutional Review Boards of the Veterans Affairs Connecticut Healthcare System and Yale University School of Medicine. All participants provided written informed consent.

2.3 MMN Paradigm

MMN was elicited using a variant of the "Optimum-1" multi-deviant paradigm (Näätänen et al., 2004) presented through Etymotic ER-3A insert earphones. Four types of auditory deviants (intensity, frequency, duration, frequency+duration double; each 12.5%) were presented in pseudorandom order within a sequence of standard tones (50%), totaling 2640 tones. The standard tone comprised of 3 sinusoidal partial frequencies of 500, 1000, and 1500Hz with 5ms rise and fall times and had a 75ms duration. These partials were presented at 75 dB SPL, 72 dB SPL, and 69 dB SPL, respectively. Deviant tones were identical to the standard tone except for the specified deviant feature: intensity deviant tones were either 10 dB higher (50% of intensity deviants) than the standard tone or 10 dB lower (50%);

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frequency deviant tones had either sinusoidal partials 10% higher (50%) than the frequency of the standard tone or 10% lower (50%); duration deviant tones were 125ms in duration (i.e., 50ms longer than the standard tone); and frequency+duration double-deviant tones were 125ms in duration and additionally had either sinusoidal partials 10% higher (50%) or 10% lower (50%) than the standard tone. Tones were presented with a 500ms stimulus onset asynchrony. The paradigm was presented in 4 blocks of approximately 5 minutes each, and the first 15 tones in each block were all standard tones. To minimize the influence of attention on MMN, participants were instructed to ignore auditory stimuli while performing a picture-name verification task (Perez et al., 2012).

2.4 Electroencephalographic data acquisition and preprocessing

Electroencephalography (EEG) data were recorded using Neuroscan Synamps amplifiers and acquired using a 0.05–200Hz band pass filter with a 1000Hz sampling rate from a 22-channel EasyCap (Brain Products GmbH), with an FPz ground electrode and linked earlobes as a reference channel. Vertical and horizontal electro-oculograms (VEOG and HEOG) were recorded to correct for eye blink and eye movement artifacts. Electrode impedances were maintained at <10kΩ, with most sites <5kΩ.

Data were segmented into 1000ms epochs time-locked to auditory stimulus onset (−500 to 500ms) and were baseline corrected (−50 to 0ms). VEOG and HEOG channels were used to correct for ocular artifacts using a regression-based algorithm (Gratton et al., 1983). Outliers were identified for each electrode and epoch and replaced by interpolated values using a previously published automated EEG data cleaning routine (Nolan et al., 2010). Epochs containing amplitudes greater than ±75μV were rejected. ERP averages were determined using a sorted averaging method as previously described (Hay et al., 2015; Perez et al., 2014; Rahne et al., 2008). Resulting mean waveforms were low-pass filtered at 30Hz, and deviant-standard difference waves were calculated for six frontocentral electrodes (F3, Fz, F4, C3, Cz, C4). MMN amplitude was identified at each electrode as the most negative peak between 90–290ms, or 160–290ms for duration deviant MMN because of its later peak latency. Participants' data were excluded from analysis for a given test day if they had <100 trials for one or more deviant type (n=3 test days excluded).

2.5 Study Design and Procedure

This study was a double-blind, randomized, placebo-controlled, counterbalanced crossover 2x2 design (active ketamine or placebo-ketamine and active nicotine or placebo-nicotine), over 4 test days, with a minimum of 3 days between each test session. Participants fasted overnight and received a standard breakfast prior to testing. Breath carbon monoxide (CO) testing was performed on the morning of each test day to verify abstinence from cigarette smoking, and expired CO levels ≥10ppm resulted in cancellation of the test day. For expired CO levels between 10ppm and 14ppm, subjects were retested after two hours and the test day was cancelled if the repeated CO level remained ≥10ppm. Vital signs were assessed regularly throughout testing. Ketamine and nicotine blood levels were assessed before and throughout drug administration, and methodological details and results of these assays have been previously presented (D'Souza et al, 2012). MMN was assessed 70 minutes after initial

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infusion, following cognitive and behavioral testing, the results of which were previously published (D'Souza et al., 2012).

Ketamine was administered intravenously as a 0.23mg/kg bolus over 1 minute, followed by an initial maintenance infusion at .58mg/kg/hour for 30 minutes, followed by a reduced infusion rate of 0.29mg/kg/hour for 64 minutes, a protocol used previously to achieve stable ketamine plasma levels (Anticevic et al., 2015; Driesen et al., 2013) and at similar doses administered in previous studies of ketamine effects on MMN (see Rosburg and Kreitschmann-Andermahr, 2016). Nicotine was infused intravenously with a loading dose of 13.5μg/kg over 10 minutes followed by a constant infusion of 31.02μg/kg over 85 minutes to achieve and maintain nicotine levels of 10ng/mL throughout the ketamine infusion. For the placebo conditions, normal saline (sodium chloride 0.9%) was administered in a manner identical to the active drug conditions.

2.6 Statistical Analysis

MMN data were fitted using a mixed effects model with a compound symmetric variance-covariance matrix and p-values adjusted for Analysis of Variance (ANOVA) type statistics to include 5 participants who did not complete all test days (2 with 1 day, 1 with 2 days, 2 with 3 days). In this model, ketamine (active vs. placebo-ketamine), nicotine (active vs. placebo-nicotine), deviant type (intensity, frequency, duration, frequency+duration double), frontocentral lead (frontal, central), and lateral lead (left, midline, right) were within-subjects factors, sequence (i.e., test day order) was a between-subjects factor, and participant was a random factor. Post-hoc contrasts with Bonferroni correction were used to parse higher order interactions.

For secondary analyses comparing ketamine effects with previously reported schizophrenia effects (Hay et al., 2015) on the MMN deviant type profiles, MMN peak amplitudes at the Fz electrode, where MMN is maximal, were converted to z-scores for each deviant type, expressing MMN amplitudes as deviations, in standard units, from the control condition/group used in each study. For ketamine participants, z-scores were calculated by subtracting the placebo-ketamine day group mean MMN amplitude from each participant's ketamine day MMN amplitude and dividing by the placebo-ketamine day standard deviation (excluding both nicotine days). For ESZ participants, z-scores were calculated by subtracting the healthy control group mean MMN amplitude from each ESZ participant's MMN amplitude and dividing by the healthy control group standard deviation. An ANOVA model with a between-subjects factor of group (ketamine vs. schizophrenia), a within-subjects factor of deviant type, and a random factor of participant directly compared ketamine z-scores to ESZ z-scores. Bonferroni correction was applied to post-hoc contrasts.

3. Results

3.1 Effects of Ketamine and Nicotine on MMN

Grand average ERP waveforms and scalp topography maps are presented in Figure 1. MMN amplitude means are presented in Figure 2. MMN amplitudes appear attenuated (i.e., less negative) during ketamine compared to saline, whereas during nicotine, MMN appears

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enhanced (i.e., more negative) compared to saline. During ketamine+nicotine, MMN generally appeared attenuated relative to saline but comparable to ketamine alone.

Results of the mixed effects model are presented in Table 2. There was a main effect of ketamine, indicating an overall reduction of MMN amplitude by ketamine relative to placebo-ketamine. There was also a main effect of nicotine, indicating an overall increase in MMN amplitude by nicotine relative to placebo-nicotine. A main effect of deviant type was also evident, indicating largest MMN amplitudes for double followed by intensity, frequency, and duration deviants. These main effects were qualified by ketamine x nicotine, ketamine x deviant type, and nicotine x deviant type interactions. Examination of the nicotine effect during ketamine and placebo-ketamine demonstrated that nicotine, relative to placebo-nicotine, increased MMN amplitudes during placebo-ketamine but not ketamine infusion. Examination of the ketamine effect during nicotine and placebo-nicotine revealed that ketamine, relative to placebo-ketamine, attenuated MMN amplitudes during both nicotine and placebo-nicotine infusions.

Follow-up contrasts parsing the ketamine x deviant type interaction showed that ketamine, relative to placebo-ketamine, reduced intensity, frequency, and double deviant MMN, but not duration deviant MMN. Parsing of the nicotine x deviant type interaction showed that nicotine, relative to placebo-nicotine, increased MMN amplitude only for intensity and double deviants.

Additionally, a frontocentral lead effect indicated larger MMN amplitudes at frontal relative to central leads. Finally, a lateral lead effect indicated larger MMN amplitudes at midline relative to right and left hemisphere leads, as well as at right relative to left leads.

3.2 Comparison of Ketamine and Schizophrenia Effects on MMN

Figure 3 shows the mean ketamine effect and schizophrenia effect z-score profiles across MMN deviant types. A main effect of group ($F(1,50)=5.77$, $p=0.020$) indicated that schizophrenia produced a larger decrement in MMN than the current dose of ketamine across deviant types. There was also a main effect of deviant type ($F(3,150)=3.10$, $p=0.029$), with post-hoc contrasts revealing significantly smaller MMN decrements across groups to duration deviants compared to frequency deviants ($p=.008$). The group x deviant type interaction was not significant ($F(3,150)=0.61$, $p=0.61$), indicating that the profiles of ketamine and schizophrenia effects on MMN did not differ by deviant type.

4. Discussion

The present study investigated the effects of intravenous nicotine, an nAChR agonist, on reductions in MMN induced by ketamine, an NMDAR antagonist, in a relatively large sample of healthy volunteers. Given inconsistencies in ketamine and nicotine effects on MMN in the prior literature, our use of a multi-deviant paradigm allowed us to investigate differential drug effects on various dimensions of auditory deviance simultaneously in the same sample. As expected, ketamine produced a reduction in MMN, particularly for intensity, frequency, and frequency+duration double deviant types.

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Although nicotine alone enhanced MMN amplitudes for intensity and frequency+duration double deviants, it did not prevent MMN amplitude reduction induced by ketamine. Consistent with our prior small study showing that nicotine did not enhance MMN when combined with ketamine (Mathalon et al., 2014), as well as the previously reported results from the current study showing that nicotine failed to mitigate the deleterious cognitive and behavioral effects of ketamine (D'Souza et al., 2012), results suggest that nicotinic agonists may not be able to overcome impairments produced by acute NMDA receptor blockade. Results do contrast with one report of MMN augmentation by nicotine gum during ketamine administration in healthy individuals (Knott et al., 2012); however, this study used a lower dose of ketamine than the present study and nicotine effects were limited to a "psychosis-prone" subgroup.

While unable to mitigate the effects of ketamine, nicotine alone increased intensity and frequency+duration double deviant MMN, but not frequency or duration deviant MMN. Previous studies have also shown nicotine to enhance MMN for some deviant types but not others, but effects are not consistent across prior studies. Some of these inconsistencies may arise from pharmacokinetic and pharmacodynamic variability associated with different routes of nicotine administration, including intravenous (current study), gum (Baldeweg et al., 2006; Dulude et al., 2010; Impey et al., 2015; Knott et al., 2014; Martin et al., 2009; Smith et al., 2015), and transdermal patch (Harkrider and Hedrick, 2005; Inami et al., 2005; Inami et al., 2007), affecting time to onset of action and peak levels achieved.

The reduction of MMN amplitudes by ketamine is consistent with previous reports (see Rosburg and Kreitschmann-Andermahr, 2016) and parallels work demonstrating other schizophrenia-like neurophysiological, cognitive, and behavioral effects of ketamine in healthy individuals (e.g., see Cho et al., 2008; D'Souza et al., 2012; Kort et al., 2017; Mathalon et al., 2014). Our results further corroborate the role of glutamate NMDAR neurotransmission in the neurophysiological mechanisms of MMN, and given the well-established reduction of MMN amplitude in schizophrenia, they support the NMDAR hypofunction model and its theorized role in mediating MMN deficits.

The comparison of ketamine and schizophrenia effects on MMN suggest that the present dose of ketamine produced smaller MMN decrements than did schizophrenia. Overall, both produced MMN deficits and the difference in effects would likely be eliminated by using a higher dose of ketamine. More importantly, the profile of MMN deficits across deviant types did not differ between ketamine and schizophrenia. Interestingly, both ketamine and schizophrenia appeared to produce a relatively smaller deficit in duration deviant MMN relative to other deviant types, especially frequency deviants, despite prior evidence suggesting that duration deviant MMN may be most sensitive to schizophrenia (e.g., see Umbricht and Krljes, 2005), particularly in the early phase of illness (Todd et al., 2008). Likewise, we did not find a significant reduction in duration deviant MMN by ketamine, which has similarly been reported by prior studies (Gunduz-Bruce et al., 2012; Mathalon et al., 2014; Oranje et al., 2000; Roser et al., 2011). Indeed, a meta-analysis did not find evidence that duration deviant MMN is more affected by ketamine than frequency deviant MMN (Rosburg and Kreitschmann-Andermahr, 2016). Taken together, these results suggest

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that when presented in the same paradigm, ketamine produces a similar pattern of MMN deficits as schizophrenia that may not significantly depend on the eliciting deviant type.

The present study is limited by the use of a single ketamine dose, precluding the examination of dose-response effects on MMN. Nonetheless, our ketamine dosing and infusion protocol was chosen because it has been frequently used in prior studies to induce psychotomimetic effects and neurocognitive deficits resembling schizophrenia (Anticevic et al., 2015; DeLorenzo et al., 2015; Driesen et al., 2013; Gunduz-Bruce et al., 2012; Krystal et al., 2006). In addition, our sample included some light smokers, raising the possibility that nicotine's effects were limited by baseline occupancy of nAChRs and that pro-cognitive effects of nicotine were confounded by the effects of reversal of nicotine withdrawal in our smoking participants. Unfortunately, we did not have enough smokers and non-smokers in our sample to permit a direct analysis of interactions with smoking status. Nonetheless, we believe such effects were minimized in our sample by exclusion of heavy smokers, and further, it is important to note that prior studies have shown nicotine to enhance MMN in smokers (Baldeweg et al., 2006; Harkrider and Hedrick, 2005; Martin et al., 2009). In addition, given the high prevalence of smoking among individuals with schizophrenia, confining our sample to non-smokers would have significantly limited the generalizability of our results to the schizophrenia population.

Despite these limitations, the present findings suggest differential effects of nAChR and NMDAR systems on MMN, with the dominance of the detrimental consequences of NMDAR blockade when combined with augmentation of nAChR activity. Furthermore, results imply that nAChR neurotransmission does not significantly alter the effects of acute NMDAR antagonism, suggesting that nicotinic agonists may have limited potential to ameliorate putative NMDAR hypofunction-mediated impairments in schizophrenia.

Acknowledgments

Role of funding source

This study was supported by a grant from AstraZeneca to Deepak C. D'Souza, and National Institute of Mental Health Grants R01 MH076989 and MH058262, and T32 MH089920. AstraZeneca and NIMH had no further role in the study design; in the collection, analysis, and interpretation, of data; in the writing of the report; and in the decision to submit the paper for publication.

This study was supported by AstraZeneca, the Department of Veterans Affairs and the Yale Center for Clinical Investigation. Holly K. Hamilton is supported by the Department of Veterans Affairs Office of Academic Affiliations Advanced Fellowship Program in Mental Illness Research and Treatment and the Sierra-Pacific Mental Illness Research, Education, and Clinical Center. We also thank Angelina Genovese, R.N.C., M.B.A.; Elizabeth O'Donnell, R.N.; Sonah Yoo, R.Ph.; Rachel Galvan, R.Ph.; and Willie Ford of the Neurobiological Studies Unit at the Veterans Affairs Connecticut Healthcare System, West Haven Campus for their central contributions to the success of this project.

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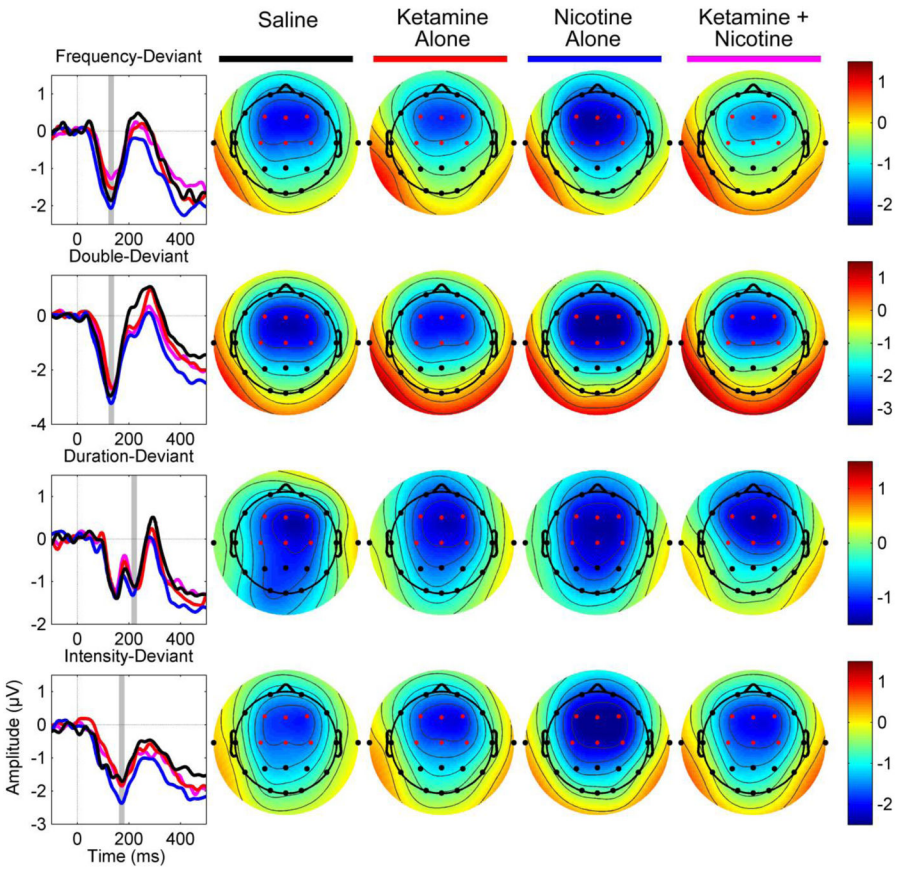

Figure 1.

Mismatch negativity (MMN) for each drug condition and deviant type. Event-related potential (ERP) difference waveforms averaged across electrodes F3, Fz, F4, C3, Cz, and C4 for each deviant type are shown for each drug condition (left). Scalp voltage topography maps of MMN amplitudes are shown for Saline, Ketamine Alone, Nicotine Alone, and Nicotine+Ketamine in columns from left to right for each MMN deviant type. MMN topography maps show the group means of MMN amplitudes around the peak latency ±10 ms (indicated by gray bars in ERP difference waveform plots).

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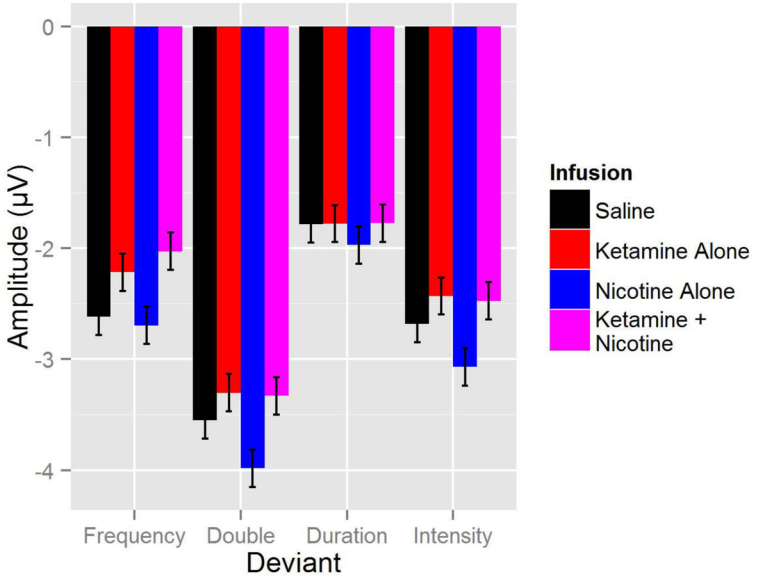

Figure 2.

Mean MMN peak amplitudes (averaged over electrodes F3, Fz, F4, C3, Cz, and C4) for each drug condition. Error bars represent standard errors.

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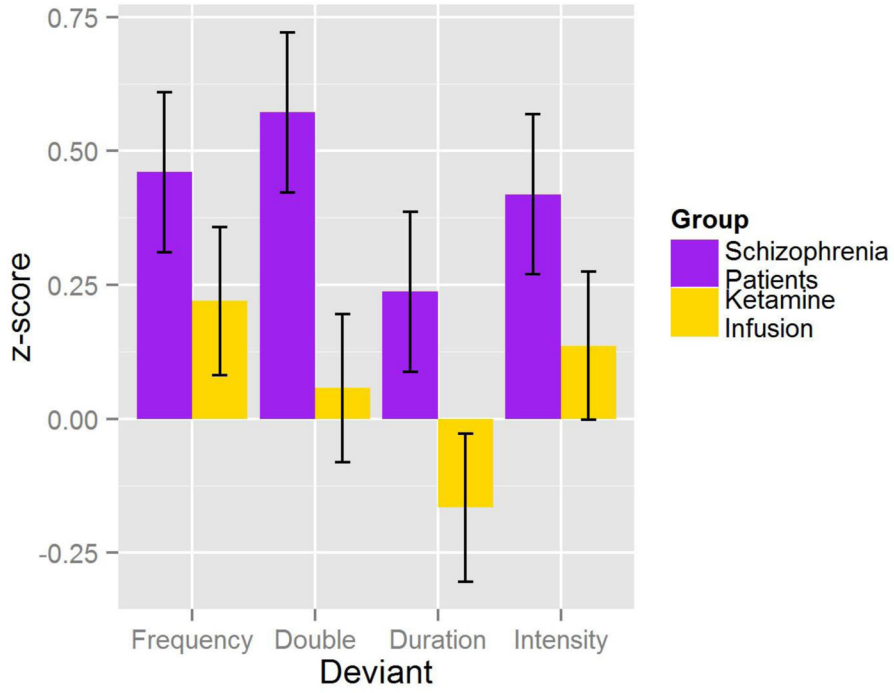

Figure 3.

MMN amplitudes of schizophrenia patients z-scored to the MMN amplitudes of healthy control subjects (purple), and MMN amplitudes during ketamine infusion z-scored to the MMN amplitudes during saline infusion (yellow).

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Table 1

Demographic data of ketamine-nicotine study participants (n=30).

Variable	Number of Subjects
Gender (male/female)	16/14
Smoking status (smoker/non-smoker) [a]	10/20
Handedness (right/left)	27/3
	Mean (SD)
Age (years)	26.0 (6.1)
Education (years)	15.4 (2.5)

[a]Smoker status defined by any cigarette smoking, ranging from (<1 cigarette/week to 15 cigarettes /day). Of the individuals who reported current smoking, 2 participants reported smoking 10–15 cigarettes/day, while the rest reported light or social smoking (i.e., 2 reported smoking 3–4 cigarettes/day, 3 reported 1 cigarette/day, 1 reported 5–6 cigarettes/week, and 2 reported <1 cigarette/week).

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Table 2

Mixed effects model of ketamine and nicotine effects on MMN amplitudes.

Effect	df	F	*p*	Direction of Effect
Ketamine (Ketamine vs. Placebo-Ketamine)	1,26	85.11	<0.0001	Placebo-Ketamine < Ketamine
Nicotine (Nicotine vs. Placebo-Nicotine)	1,26	8.83	0.0063	Nicotine < Placebo-Nicotine
Deviant Type	3,87	322.19	<0.0001	Double < Intensity < Frequency < Duration [a]
Frontocentral Lead	1,29	71.79	<0.0001	Frontal < Central
Lateral Lead	2,58	17.22	<0.0001	Midline < Right < Left [b], Midline < Left [a]
Frontocentral Lead x Lateral Lead	2,58	1.57	0.2172	
Frontocentral Lead x Ketamine	1,26	3.69	0.0657	
Lateral Lead x Ketamine	2,52	0.00	0.9972	
Frontocentral Lead x Lateral Lead x Ketamine	2,52	0.07	0.9300	
Frontocentral Lead x Nicotine	1,26	0.03	0.8688	
Lateral Lead x Nicotine	2,52	0.28	0.7559	
Frontocentral Lead x Lateral Lead x Nicotine	2,52	0.71	0.4972	
Ketamine x Nicotine	1,22	13.97	0.0011	
Nicotine effect during Placebo-Ketamine	*1,22*	*22.66*	*<0.0001*	*Nicotine < Placebo-Nicotine*
Nicotine effect during Active Ketamine	*1,22*	*0.61*	*0.6099*	
Ketamine effect during Placebo-Nicotine	*1,22*	*15.92*	*0.0006*	*Placebo Ketamine < Ketamine*
Ketamine effect during Active Nicotine	*1,22*	*81.72*	*<0.0001*	*Placebo-Ketamine < Ketamine*
Frontocentral Lead x Ketamine x Nicotine	1,22	0.00	0.9935	
Lateral Lead x Ketamine x Nicotine	2,44	0.31	0.7367	
Frontocentral Lead x Lateral Lead x Ketamine x Nicotine	2,44	0.01	0.9921	
Frontocentral Lead x Deviant Type	3,87	1.53	0.2134	
Lateral Lead x Deviant Type	6,174	0.19	0.9781	
Frontocentral Lead x Lateral Lead x Deviant type	6,174	0.10	0.9965	
Ketamine x Deviant Type	3,78	5.73	0.0014	
Ketamine effect for Intensity-Deviant	*1,78*	*27.77*	*<0.0001*	*Placebo-Ketamine < Ketamine*
Ketamine effect for Frequency-Deviant	*1,78*	*44.36*	*<0.0001*	*Placebo-Ketamine < Ketamine*
Ketamine effect for Duration-Deviant	*1,78*	*1.54*	*0.2204*	
Ketamine effect for Double-Deviant	*1,78*	*31.47*	*<0.0001*	*Placebo-Ketamine < Ketamine*
Frontocentral Lead x Ketamine x Deviant Type	3,78	0.43	0.7322	
Lateral Lead x Ketamine x Deviant Type	6,156	0.12	0.9941	
Frontocentral Lead x Lateral Lead x Ketamine x Deviant Type	6,156	0.02	1.0000	
Nicotine x Deviant Type	3,78	2.77	0.0470	
Nicotine effect for Intensity-Deviant	*1,78*	*7.24*	*0.0088*	*Nicotine < Placebo-Nicotine*
Nicotine effect for Frequency-Deviant	*1,78*	*0.47*	*0.4949*	
Nicotine effect for Duration-Deviant	*1,78*	*1.35*	*0.2504*	
Nicotine effect for Double-Deviant	*1,78*	*8.29*	*0.0051*	*Nicotine < Placebo-Nicotine*
Frontocentral Lead x Nicotine x Deviant Type	3,78	0.23	0.8747	
Lateral Lead x Nicotine x Deviant Type	6,156	0.39	0.8861	

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Effect	df	F	*p*	Direction of Effect
Frontocentral Lead x Lateral Lead x Nicotine x Deviant Type	6,156	0.05	0.9996	
Ketamine x Nicotine x Deviant Type	3,66	0.34	0.7994	
Frontocentral Lead x Ketamine x Nicotine x Deviant Type	3,66	0.05	0.9839	
Lateral Lead x Ketamine x Nicotine x Deviant Type	6,132	0.21	0.9728	
Frontocentral Lead x Lateral Lead x Ketamine x Nicotine x Deviant Type	6,132	0.02	0.9999	
Sequence	19,10	0.69	0.7682	

Note. Follow-up analyses to parse significant interactions are shown in italics and survive Bonferroni adjustment for multiple comparisons.

[a] *p*s < .0001.

[b] *p*s < .01.