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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 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 × 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.

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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

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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., 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 revision; 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.

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 1500 Hz with 5 ms rise and fall times and had a 75 ms 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

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] Smoking 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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