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Original Investigation

Nicotine enhances automatic temporal processing as measured by the mismatch negativity waveform

Laura F. Martin, Deana B. Davalos, & Michael A. Kisley

Abstract

Introduction: Cholinergic agonists and, more specifically, nicotine, have been found to enhance a number of cognitive processes. The effect of nicotine on temporal processing is not known. The use of behavioral measures of temporal processing to measure its effect could be confounded by the general effects of nicotine on attention. Mismatch negativity (MMN) has been used as a physiological measure of automatic temporal processing to avoid this potential confound.

Methods: A total of 20 subjects (11 nonsmokers and 9 smokers following 2 hr of abstinence) participated in a two-visit single-blind, placebo-controlled crossover study of the effect of nicotine on MMN indices in response to an interstimulus interval deviant.

Results: Nicotine-enhanced MMN amplitudes from baseline recording to postdrug recording greater than did the placebo condition. This enhancement was seen in both nonsmokers and smokers. Nicotine had no significant effect on MMN latency or N100 amplitude or latency.

Discussion: This is the first study to demonstrate a nicotine-related enhancement of MMN amplitude to an interstimulus interval duration deviant and confirms our hypothesis that nicotine enhances preattentive temporal processing. Nicotinic agonists may represent a potential therapeutic option for individuals with abnormalities in early sensory or temporal processing related to cholinergic system abnormalities. Methodologically, our paradigm of nicotine administration in abstinent smokers is important because it resulted in both minimal withdrawal symptoms and meaningful data that are not attributable solely to relief of withdrawal.

Introduction

In 2007, an estimated 20% of adults in the United States were current smokers. Disease associated with tobacco use is one of the leading preventable causes of death in the United States, and it is estimated that 5.1 million years of potential life have been lost due to tobacco-related deaths from 2000 to 2004. During the same timeframe, it is estimated that tobacco-related illness was associated with productivity losses of approximately U.S. $96.8 billion per year (Centers for Disease Control and Prevention, 2008). Nicotine is believed to be the addictive substance within cigarettes. Smoking behavior is often maintained as a result of fears of gaining weight with abstinence or a need to avoid withdrawal symptoms. Additionally, positive effects on mood, cognitive, and behavioral measures appear to occur with nicotine administration. For instance, strong evidence indicates that nicotine can improve sustained attention, processing speed, and simple motor functioning (Levin, MCClernon, & Rezvani, 2006; Sacco, Bannon, & George, 2004; R. J. West & Jarvis, 1986). There is also modest evidence that nicotine can improve selective attention and working memory (Sacco et al., 2004).

Little is known, however, about whether nicotine enhances temporal processing, a process important for the moment-to-moment timing of activities, the sequencing of behaviors, and attention (Volz et al., 2001). Deficits in temporal processing have been documented in schizophrenia (Davalos, Kisley, & Freedman, 2005; Todd, 2006) and healthy older adults (Kisley, Davalos, Engleman, Guinther, & Davis, 2005). Changes in the cholinergic system also are associated with these populations (Bartus, Dean, Beer, & Lippa, 1982; Berman, Talmage, & Role, 2007). Because nicotine is a cholinergic agonist, and because administration of this drug has been shown to improve other cognitive functions in these populations (Newhouse, Potter, &

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Singh, 2004), the present study was designed to test whether nicotine leads to improvements in temporal processing. This initial investigation was conducted with healthy younger adults.

Mismatch negativity (MMN) is an electrophysiological measure of the ability to detect automatically a change in the characteristics of a recurrent auditory stimulus (Naatanen, Teder, Alho, & Lavikainen, 1992). A benefit of MMN is that it is elicited in the absence of focused attention or motor response and therefore may better control for mediating cognitive processes (Naatanen & Winkler, 1999; Sussman, Winkler, & Wang, 2003). MMN has been used to assess the ability to detect changes in interstimulus interval duration, in the absence of other changes in stimuli such as tone frequency or duration (Naatanen, Jiang, Lavikainen, Reinikainen, & Paavilainen, 1993). These results suggest that MMN reflects accurate discrimination of auditory interstimulus interval durations (Kujala, Kallio, Tervaniemi, & Naatanen, 2001). Subsequent work has demonstrated that MMN amplitudes are associated positively with a greater degree of deviance (Kisley et al., 2004) and negatively with the number of errors made during a behavioral task involving the identification of interstimulus interval deviants (Davalos et al., 2005). Thus, greater ability to behaviorally discriminate between the standard and deviant intervals was associated with a larger MMN amplitude.

Nicotine and nicotinic receptor agonists have been shown to affect MMN latencies or amplitudes in response to changes in auditory tone characteristics. Nicotine decreased MMN latency to auditory tone frequency deviants in nonsmokers (Inami, Kirino, Inoue, & Arai, 2005; Inami, Kirino, Inoue, Suzuki, & Arai, 2007), reduced latency and increased MMN amplitude to frequency deviants in nonsmokers (Dunbar et al., 2007), and enhanced a combined MMN latency and amplitude measure elicited by a complex consonant–vowel deviant in a group of smokers and nonsmokers (Harkrider & Hedrick, 2005). In limited studies in which the stimuli of interest involved temporal auditory deviants, results have been mixed. Nicotine increased MMN amplitude elicited from a tone duration deviant in a group of smokers (Baldeweg, Wong, & Stephan, 2006) but had no effect on MMN amplitude or latency in smokers in a separate study (Knott, Scherling, et al., 2006).

We hypothesized that nicotine would improve the discrimination of changes in the interstimulus interval duration between auditory tones, our measure of temporal processing. Evidence for this improvement would be an increase in the MMN amplitude following the administration of nicotine but not placebo.

Methods

Participants

Participants consisted of 20 healthy volunteers. Subjects were screened for medical and psychiatric illness (Structured Clinical Interview for DSM-IV Axis I Disorders–Non-Patient Edition; First, Spitzer, Gibbon, & Williams, 1996), and individuals were excluded for any current cardiac illness, psychiatric illness, neurological disorders, or head trauma or for any personal or first-degree family member history of psychosis. All subjects gave written consent for participation, as approved by an appropriate institutional review board. A total of 11 subjects were nonsmokers (mean age = 30.0 years, $SD = 7.0$; $n = 4$ female). One of the nonsmokers was a former smoker with a 2.8 pack-year history. Another nonsmoker had smoked fewer than 20 cigarettes in her lifetime.

Nine subjects were smokers (mean age = 35.3 years, $SD = 11.1$; $n = 4$ female). Smokers smoked 14.4 cigarettes/day ($SD = 4.5$), had a mean carbon monoxide level of 8.5 ppm ($SD = 7.86$; after at least 2 hr of abstinence), a mean Fagerström nicotine dependence score of 3.2 ($SD = 1.48$), and a mean 7.5 pack-year ($SD = 6.05$) history. Age and gender distribution did not significantly differ between the two groups. Mental state was assessed using the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987) and the Minnesota Withdrawal Symptom Scale (MWSS; Hughes & Hatsukami, 1986).

Study design

Subjects participated in two nearly identical visits at least 4 days apart. Smoking subjects were asked to refrain from smoking for a period of 2 hr prior to arrival. An expired-air carbon monoxide measurement was taken to ensure that the subjects were compliant with this minimal amount of abstinence. If the level was higher than 15.0 ppm, the subject was asked to wait an additional hour before proceeding with the study. All subjects were asked to abstain from alcohol and illicit drugs for a period of 24 hr prior to arrival. A psychiatric diagnostic interview was performed first. A medical history and physical exam were performed to rule out any excluding illness. Subjects watched a closed-caption muted movie of their choice throughout the recording period. Baseline electrophysiological recordings were performed as outlined below. Subjects were allowed to relax for 45 min following the baseline recording to prevent habituation effects. Following an assessment for withdrawal symptoms, nicotine or placebo was administered as outlined below. Vital signs and any side effects were noted. Subjects were asked to rate on a scale from 0 (no symptoms) to 10 (the worst intensity one could imagine) the side effects of nausea, lightheadedness, increased heart rate, a sense of calmness, a sense of intoxication, mouth tingling, headache, and anxiety. A second electrophysiological recording was then performed. The PANSS was then administered. Subjects returned for a second visit approximately 1 week later; this visit was identical to the first, although subjects did not complete a diagnostic interview.

Nicotine gum administration

The nicotine gum consisted of two 2-mg pieces of Nicorette and one piece of mint gum administered as one large piece for nonsmokers and three 2-mg pieces of Nicorette and two pieces of mint gum administered as one large piece for smokers. The lower nicotine content was used for nonsmokers to prevent adverse events (Tregellas, Tanabe, Martin, & Freedman, 2005) and has been shown to result in nicotine levels of at least 9 ng/ml and a 15- to 20-min time window for peak nicotine levels (Harris et al., 2004). The placebo gum consisted of four pieces of nonmedicinal mint gum administered as one piece. Subjects were administered the gum with their eyes closed to maintain the single blind. Subjects chewed the gum for 10 min and were asked not to swallow their saliva but instead to expectorate every 2 min into a cup. Our laboratory has used this gum-chewing paradigm to shorten the amount of time necessary for gum administration from 25 to 10 min and to minimize nausea, which can interfere with study participation and data collection. Our

paradigm differs from the manufacturer guidelines in that individuals are asked to chew the gum slowly for 10 min, rather than to chew intermittently and then park the gum for 25 min. This protocol results in blood levels comparable with the typical gum administration directions (Harris et al., 2004). Administration of nicotine and placebo gum during the first session was counterbalanced.

MMN procedure and analysis

Gold-plated electrodes were attached to the following 10–20 scalp locations: Frontal (Fz), Central (Cz), Parietal (Pz), left mastoid, and right mastoid. Brain activity evoked by auditory stimuli was referenced to an electrode attached to the nose, bandpass filtered from 0.05 to 30 Hz, and digitally sampled at 1000 Hz. A ground electrode was attached to the forehead. Eye movements were monitored with electrodes attached above and directly lateral to the left eye. Headphones were used to binaurally present pure tones (1000 Hz, 50 ms in duration) to the subjects. Brain-evoked responses were collected in a "passive" condition. Subjects were asked to watch a closed-captioned movie of their choice. Participants were administered a total of 1,650 tones (per condition). The standard interval between tones was 500 ms, and a deviant interval of 150 ms occurred randomly, but on average every 16th interval. Continuously recorded signals were separated into 500-ms epochs with a 100-ms prestimulus interval relative to timing pulses. Tone onset served as time 0. Baseline correction involved subtracting average voltage of the 100-ms prestimulus interval and was applied to each single trial. Trials for which any channel exceeded ±75 μV were removed from further analysis. The entire group averaged 1,253.1 ± 175.38 trials and 89.8 ± 12.45 deviants. The nonsmoking group averaged 1,241.9 ± 151.03 trials and 88.8 ± 10.1 deviants. The smoking group averaged 1,266.8 ± 202.60 trials and 90.9 ± 14.89 deviants.

The number of sweeps remaining after artifact rejection for each baseline and postdrug condition did not differ significantly between smokers and nonsmokers for either standard (F = 0.381, df = 7, 72, p = .911) or deviant waveforms (F = 0.480, df = 7, 72, p = .846). Following rejection of artifact, standard and deviant evoked responses were averaged separately offline for each subject. Standard evoked response averages were subtracted from deviant evoked response averages, and the MMN amplitude was defined as the peak negativity between 140- and 210-ms poststimulus latency range in subtraction waveforms (deviant–standard). The N100 component also was detected and identified as the largest negative trough between 75 and 125 ms to determine whether any possible effects on MMN might be related to effects on N100.

Data analyses

A 2 (drug: nicotine and placebo) × 2 (session: baseline and postdrug) × 3 (site: Fz, Cz, Pz) × 2 (smoking status: smoker and nonsmoker) repeated measures analysis of variance (ANOVA) was used to assess the effect of nicotine on MMN amplitudes and latencies. The within-subject variables were drug, session, and site, and the between-subjects variable was smoking status. Pearson correlations were used to examine the relationship between the MMN indices, N100 indices, and symptom levels. Two-tailed Student's t tests and chi-square tests were used to assess, respectively, continuous and categorical characteristics of the smoking and nonsmoking groups.

Results

The grand averaged waveforms for MMN amplitudes before and after placebo and nicotine administration are shown in Figures 1 and 2. Nicotine enlarged MMN amplitudes from baseline (Table 1). The repeated measures ANOVA revealed no main effect of drug, session, or smoking status. It did reveal a drug × session effect (F = 17.869, df = 1, 18, p = .001), with nicotine significantly increasing the MMN amplitude from the first to the second recording. There also was a drug × session × site effect (F = 4.189, df = 2, 17, p = .033). Visual inspection revealed that although nicotine enhanced the MMN amplitude at each electrode site over time, there was a decrement in MMN amplitude over time at site Fz following the administration of placebo. There were no drug × smoking status, drug × session × smoking status, or drug × session × site × smoking status effects. At baseline, the largest MMN amplitudes were found at Cz. Individual subject values for baseline, postplacebo, and postnicotine MMN amplitudes are shown in Figure 3. A post-hoc analysis at this site found that the change in amplitude following the administration of nicotine (1.0 ± 0.98) was significantly larger than the change in amplitude following the administration of placebo (–0.32 ± 0.94; t = 4.341, df = 38, p < .001). The effect size (Cohen's d) for this effect at Cz was 1.4 (very large effect).

During the placebo visit day, subjects had baseline mean latencies of 171.1 ± 20.2 (Cz), 173.0 ± 17.9 (Fz), and 173.2 ± 20.4 (Pz). Following placebo administration, mean latencies were 164.5 ± 27.5 (Cz), 163.1 ± 26.5 (Fz), and 172.2 ± 26.4 (Pz). During the nicotine visit day, subjects had baseline mean latencies of 168.7 ± 27.3 (Cz), 167.8 ± 25.7 (Fz), and 171.6 ± 29.7 (Pz). Following the administration of nicotine, mean latencies were 164.5 ± 25.4 (Cz), 157.6 ± 22.9 (Fz), and 167.7 ± 28.0 (Pz). The repeated measures ANOVA revealed no significant drug, session, site, smoking status, or interaction effects on MMN latency.

To assess the specificity of nicotine effects on MMN, we evaluated the effects of nicotine on the N100 ERP. During the placebo visit day, subjects had baseline mean amplitudes of –1.15 ± 0.91 (Cz), –0.92 ± 1.07 (Fz), and –1.02 ± 0.56 (Pz). Following placebo administration, mean amplitudes were –0.99 ± 0.93 (Cz), –0.92 ± 0.92 (Fz), and –0.87 ± 0.64 (Pz). During the nicotine visit day, subjects had baseline mean amplitudes of –1.11 ± 1.08 (Cz), –0.92 ± 0.94 (Fz), and –0.81 ± 0.64 (Pz). Following nicotine administration, mean amplitudes were –1.26 ± 0.87 (Cz), –1.17 ± 0.99 (Fz), and –0.99 ± 0.59 (Pz). We found no significant effects of nicotine on the N100 amplitude. There was a site × session interaction for the N100 amplitude (F = 4.517, df = 2.17, p = .027). Visual inspection revealed that the N100 amplitude at Fz increased from the first recording to the second.

Concerning N100 latencies, baseline mean latencies during the placebo visit were 94.6 ± 12.1 (Cz), 96.2 ± 13.8 (Fz), and 95.8 ± 14.5 (Pz). Following the administration of placebo, mean latencies were 95.4 ± 14.4 (Cz), 95.8 ± 13.4 (Fz), and 96.9 ± 16.8 (Pz). Baseline mean latencies during the nicotine visit were 98.7 ± 13.6 (Cz), 99.6 ± 13.0 (Fz), and 96.9 ± 16.2 (Pz). Following the administration of nicotine, mean latencies were 98.1 ± 12.9 (Cz), 98.1 ± 14.3 (Fz), and 102.1 ± 18.0 (Pz). The repeated measures ANOVA revealed no significant drug, session, site, smoking status, or interaction effects on N100 latency.

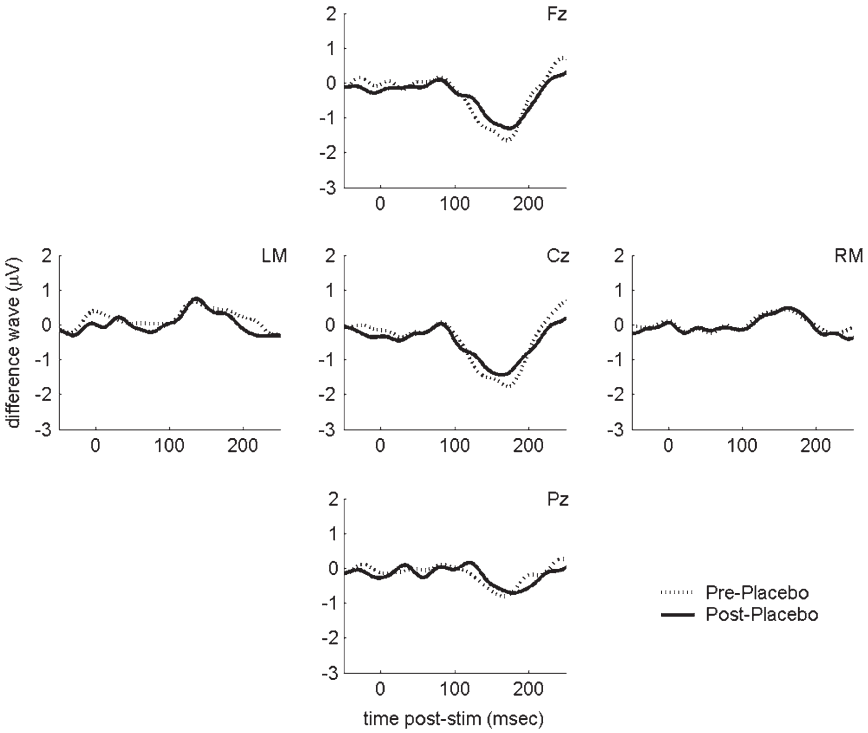

Figure 1. Grand averaged mismatch negativity (MMN) waveforms during the placebo visit. The dashed line represents baseline and the solid line represents MMN after the administration of placebo. LM, left mastoid; RM, right mastoid.

Subjects did not have significantly different psychopathology scores from visit 1 to visit 2. The smoking subjects had significantly more withdrawal symptoms (7.28 ± 4.2 vs. 1.0 ± 1.1; $t = –6.189$, $df = 18.973$, $p < .001$), higher total PANSS symptoms (32.17 ± 3.26 vs. 30.32 ± 0.84; $t = –2.344$, $df = 18.848$, $p = .03$), higher PANSS general subscale scores (18.06 ± 3.08 vs. 16.23 ± 0.61; $t = –2.481$, $df = 18.103$, $p = .023$), and higher PANSS depression scores (1.78 ± 1.40 vs. 1.00 ± 0.00; $t = –2.364$, $df = 17.000$, $p = .03$) than the nonsmokers. Within the smoking group, MWSS scores were significantly correlated with the PANSS total score ($p = .008$, $r = .600$), the PANSS general subscale symptoms ($p = .005$, $r = .629$), and a higher PANSS depression item score ($p = .017$, $r = .555$).

Concerning side effects, no subjects reported nausea. Average ratings for lightheadedness were as follows: smoker postnicotine, 0.7 ± 1.39; smoker postplacebo, 1.7 ± 3.24; nonsmoker postnicotine, 2.0 ± 2.64; and nonsmoker postplacebo, 0.3 ± 1.00. Average ratings for intoxication were as follows: smoker postnicotine, 1.1 ± 2.23; smoker postplacebo, 0.5 ± 1.41; nonsmoker postnicotine, 2.5 ± 3.28; nonsmoker postplacebo, 0.9 ± 2.02. Average ratings for mouth tingling were as follows: smoker postnicotine, 1.3 ± 2.23; smoker postplacebo, 1.1 ± 2.80; nonsmoker postnicotine, 1.9 ± 2.15; nonsmoker postplacebo, 0.8 ± 1.20. Smokers never reported a sense of calmness. However, nonsmokers reported an average change in calmness of 0.9 ± 2.67 following nicotine and 0.7 ± 1.99 following placebo. Smokers never reported anxiety. Nonsmokers reported no anxiety following placebo but did experience an average level of 0.9 ± 2.67 following nicotine. We found no significant differences between the two groups for the experience of side effects following nicotine administration. However, sample size may have limited the power to detect significant differences in the report of lightheadedness (Cohen's $d = 0.62$), a sense of calm (Cohen's $d = 0.49$), a sense of intoxication (Cohen's $d = 0.54$), and a sense of anxiety (Cohen's $d = 0.49$).

We found no significant relationships between psychopathology ratings and MMN or N100 indices. However, an increase in feeling intoxicated after chewing gum was correlated positively with the change in the MMN amplitude at Cz after chewing nicotine ($r = .432$, $p = .011$). Additionally, we found a negative correlation between the MWSS and the change in MMN amplitude at Cz ($r = –.358$, $p = .023$) such that individuals with lower MWSS scores had greater increases in their MMN amplitude at Cz. These correlations were driven by changes in MMN amplitude postnicotine administration (intoxication $r = .547$, $p = .023$; MWSS $r = –.513$, $p = .021$) and were not significant when explored in the nonsmoking and smoking groups.

Discussion

This study is the first to demonstrate a nicotine-related effect of an interstimulus interval duration deviant on MMN amplitude. Given the evidence that increases in MMN amplitude are associated with better discrimination (Davalos et al., 2005; Kisley et al., 2004), our hypothesis that nicotine enhances preattentive temporal processing is confirmed. This enhancement was not related merely to more efficient information processing or attentional mechanisms, given that there was no effect on MMN latency or N100 processing. Our finding extends the work of Baldeweg et al. (2006), who demonstrated an increase in MMN amplitude in response to nicotine using an auditory tone duration deviant to a temporal deviant (interstimulus interval duration) independent of auditory tone characteristics. This work

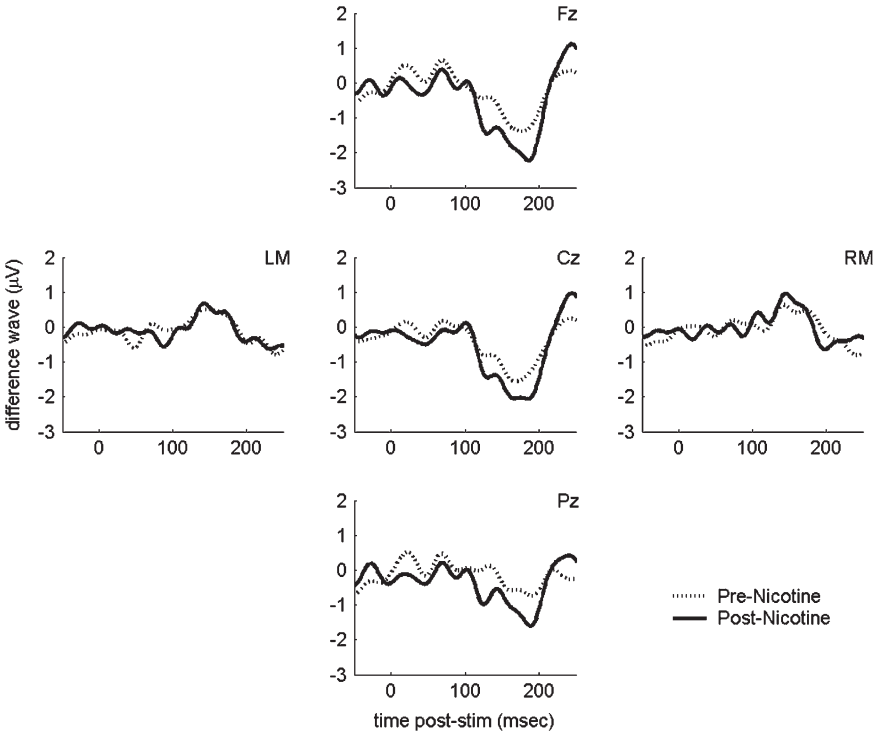

Figure 2. Grand averaged mismatch negativity (MMN) waveforms during the nicotine visit. The dashed line represents baseline and the solid line represents MMN after the administration of nicotine. LM, left mastoid; RM, right mastoid.

contributes to an increasing body of work implicating the cholinergic system, and specifically, the nicotinic system, in automatic sensory and temporal processing (Baldeweg et al., 2006; Harkrider & Hedrick, 2005; Inami et al., 2005). However, a negative study (Knott, Blais, et al., 2006) differed from the present study in its use of a dichotic listening task rather than merely an unattended stimulus train and the use of a smaller nicotine dose (4 mg) for the smokers.

Nicotine may enhance MMN through multiple mechanisms. Nicotine has been shown to enhance the release of glutamate (Vidal, 1994), an effect possibly mediated by either alpha4-beta2 (Lambe, Piccioto, & Aghajanian, 2003) or alpha-7 nicotinic receptors (Pérez de la Mora, Mendez-Franco, Salceda, Aguirre, & Fuxe, 1991). Enhancement of the glutamatergic system is most consistent with electrophysiological studies of MMN to date. Intracortical recordings in monkeys have revealed that the glutamatergic system, and specifically, N-methyl D-aspartate (NMDA) receptors, are integral to the generation of MMN (Javitt, Steinschneider, Schroeder, & Arezzo, 1996), implicating their involvement in the processing of repetitive stimuli as well as contributing to performance during a preattentive working memory task. MMN in healthy controls is impaired by the NMDA antagonist ketamine, although memantine has been shown to enhance MMN amplitudes in response to auditory tone deviants (Korostenskaja, Nikulin, Kicic, Nikulina, & Kaakkola, 2007; Kreitschmann-Andermahr et al., 2001; Umbricht et al., 2000). Finally, MMN is impaired in persons with schizophrenia, a disease involving not only cholinergic dysfunction but also glutamatergic dysfunction (Catts et al., 1995; Davalos, Kisley, & Ross, 2003; Javitt, Doneshka, Zylberman, Ritter, & Vaughan, 1993; Shelley et al., 1991).

Nicotine effects on interneuronal-mediated inhibition via gamma-aminobutyric acid (GABA) also may contribute to enhanced sensory cortex functioning as well as prefrontal gating of irrelevant stimuli. Nicotine is known to enhance cortical function through the presynaptic enhancement of GABA-mediated interneuronal inhibitory tone (Alkondon, Pereira, Eisenberg, & Albuquerque, 2000). This is consistent with previous evidence that benzodiazepines attenuate MMN (Nakagome et al., 1998; Rosburg, Marinou, Haueisen, Smesny, & Sauer, 2004) as well as findings that enhancement of interneuronal inhibition by nicotine enhances sensory gating, another task reliant on the filtering of irrelevant stimuli (Adler, Hoffer, Wiser, & Freedman, 1993).

It is less clear whether enhancement of the dopaminergic system may have contributed to our findings. Nicotine has been shown to enhance dopamine release (Summers & Giacobini, 1995; Westfall, Grant, & Perry, 1983), an effect mediated by both alpha-7 and non–alpha-7 nicotinic receptors (Summers, Kem, & Giacobini, 1997; Turner, 2004). These effects may occur at the synaptic terminal and by enhancing the excitation of dopaminergic neurons in the ventral tegmental area. This latter effect is mediated both by direct action at non–alpha-7 nicotinic receptors and by activation of NMDA receptors (Grillner & Svensson, 2000). Clinical studies to date, however, have not supported this hypothesis. The use of methylphenidate in hyperactive children had no effect on MMN indices (Winsberg, Javitt, & Shanahan/Silpo, 1997). Similarly, neither the administration of the D2 agonist bromocriptine nor the administration of the D1/D2 agonist pergolide has any effect on MMN (Leung, Croft, Baldeweg, & Nathan, 2007). Studies of haloperidol in healthy controls found an enhancement of MMN amplitude

Table 1. Mismatch negativity amplitudes

Variable	Entire group ($n = 20$)	Nonsmokers ($n = 11$)	Smokers ($n = 9$)
Cz amplitude			
Nicotine visit baseline	−1.37 ± 0.86	−1.10 ± 0.74	−1.69 ± 0.93
	−3.51 – −0.27	−2.86 – −0.27	−3.51 – −0.68
Postnicotine	−2.36 ± 1.05	−2.45 ± 1.22	−2.25 ± 0.85
	−4.47 – −0.72	−4.47 – −0.72	−3.62 – −1.36
Placebo visit baseline	−2.19 ± 1.34,	−2.39 ± 1.62,	−1.94 ± 0.92,
	−5.48 – −0.45	−5.48 – −0.45	−3.71 – −0.45
Postplacebo	−1.86 ± 1.27	−2.15 ± 1.60	−1.51 ± 0.61
	−5.07 + −0.03	−5.07 – −0.03	−2.08 – −0.44
Fz amplitude			
Nicotine visit baseline	−1.51± 0.90	−1.48 ± 0.89	−1.56 ± 0.96
	−3.49 – −0.44	−2.71 – −0.44	−3.49 – −0.47
Postnicotine	−2.25 ± 1.02	−2.34 ± 1.13,	−2.13 ± 0.94,
	−4.18 – −0.81	−4.18 – −0.81	−3.80 – −1.30
Placebo visit baseline	−1.85 ± 1.27	−2.18 ± 1.25	−1.45 ± 1.25
	−3.97 – −0.15	−3.90 – −0.15	−3.97 – −0.20
Postplacebo	−1.78 ±1.18	−2.17 ± 1.34	−1.29 ± 0.77
	−4.68 – −0.03	−4.68 – −0.03	−2.98 – −0.46
Pz amplitude			
Nicotine visit baseline	−0.99 ± 0.85	−0.90 ± 0.92	−1.11 ± 0.81
	−3.10 – 0.09	−3.10 – −0.06	−2.48 – 0.09
Postnicotine	−1.67 ± 0.82	−1.79 ± 0.97	−1.52 ± 0.63
	−4.03 – −0.60	−4.03 – −0.60	−2.40 – −0.68
Placebo visit baseline	−1.59 ± 1.03,	−1.78 ± 1.29,	−1.35 ± 0.57,
	−4.27 – −0.23	−4.27 – −0.32	−1.94 – −0.23
Postplacebo	−1.24 ± 1.02	−1.46 ± 1.10	−0.97 ± 0.88
	−3.43 – 0.34	−3.43 – −0.20	−2.56 – 0.34

Note. Results are reported as means with *SD* and range.

(Kähkönen et al., 2001), although a second study by the same group found no effect (Kähkönen et al., 2002), and a third study found an effect for frequency but not duration deviants on MMN latency (Pekkonen et al., 2002).

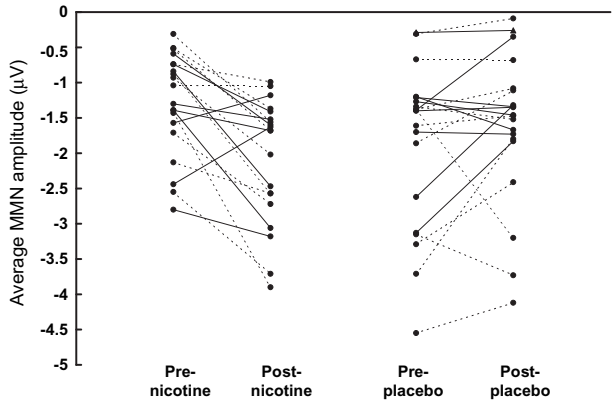

Figure 3. Change in mismatch negativity (MMN) amplitudes from baseline to postdrug recordings. Each circle represents an individual and each line represents that individual's change in amplitude from baseline to postdrug administration. Smokers are displayed with a solid line and nonsmokers with a dashed line.

In the present study, we found an effect in a combined sample of smokers and nonsmokers. The use of the nonsmoking group allowed us to draw the conclusion that the effects of nicotine on MMN are not related merely to the relief of withdrawal symptoms. The use of smoking subjects allowed us to demonstrate that our protocol for administering nicotine in smokers (Harris et al., 2004) results in both limited withdrawal symptoms and meaningful data that are not attributable solely to relief of withdrawal. Our smokers had higher levels of psychopathology than the nonsmokers. A greater degree of psychopathology in smokers compared with their nonsmoking peers is consistent with prior studies (Breslau, 1995; reviewed in Quattrocki, Baird, & Yurgelun-Todd, 2000). Given the association between withdrawal symptoms in the smokers and these psychopathology scores (which reflected functioning over the preceding week), one might question whether the use of a single withdrawal report in the present study might reflect the general psychopathology of the smokers rather than acute withdrawal per se. Furthermore, the level of withdrawal symptoms reported by the abstinent smokers was within the range reported by nonabstinent smokers in previous studies (R. West, Ussher, Evans, & Rashid, 2006).

A limitation of the present study is that we did not assess subjective and objective changes in withdrawal symptoms and mood symptoms prior to and following nicotine administration.

Research suggests that nicotine may increase arousal or improve mood, which also could contribute to changes in cognitive processes and neurophysiological responses (Waters & Sutton, 2000). In terms of mood, however, the findings are mixed and suggest that, in isolation from pharmacological intervention, there are minimal effects of changes in mood. In terms of arousal, the findings also are mixed. However, we cannot rule out that nicotine may increase arousal, which may result in increased sensitivity in the detection of stimulus change. Furthermore, we did not measure nicotine levels prior to and following nicotine gum administration. Finally, we did not assess formally whether our gum administration protocol was sufficiently blinded. It remains to be seen whether these acute effects of nicotine are maintained on a chronic basis by smokers or whether processes such as nicotinic receptor desensitization may limit the long-term effects of nicotine. Further, future studies are needed to determine which subtypes of nicotinic receptor are responsible for this effect.

Our finding of a nicotine-mediated enhancement of automatic temporal processing provides further support for the role of cholinergic processes in a broad range of cognitive processes. These positive effects (or worsening of these processes upon withdrawal) may be contributing to the difficulty many smokers have in quitting smoking. Additionally, nicotinic agonists may represent a potential therapeutic option for individuals with abnormalities in early sensory or temporal processing. Nicotine has been shown to enhance MMN amplitudes elicited by auditory tone variations in individuals with Alzheimer's disease (Engeland, Mahoney, Mohr, Ilivitsky, & Knott, 2002). Given the broad range of cognitive deficits present in schizophrenia, and specifically, impairment in temporal processing (Davalos, Kisley, Polk, & Ross, 2003; Davalos, Kisley, & Ross, 2003; Davalos et al., 2005), and the increasing evidence of the ability of nicotinic agonists to reverse these deficits (Olincy et al., 2006; reviewed in Martin & Freedman, 2007), a trial of a nicotinic agonist is warranted in persons with schizophrenia using an interstimulus interval duration deviant MMN paradigm.

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Declaration of Interests

LFM is a coinvestigator for a clinical trial funded by Pfizer and has attended an investigator's meeting for Lundbeck. DBD and MAK have no competing interests.

References

Adler, L. E., Hoffer, L. D., Wiser, A., & Freedman, R. (1993). Normalization of auditory physiology by cigarette smoking in schizophrenic patients. *The American Journal of Psychiatry*, *150*, 1856–1861.

Alkondon, M., Pereira, E. F. R., Eisenberg, H. M., & Albuquerque, E. X. (2000). Nicotinic receptor activation in human cerebral cortical interneurons: A mechanism for inhibition and disinhibition of neuronal networks. *The Journal of Neuroscience*, *20*, 66–75.

Baldeweg, T., Wong, D., & Stephan, K. E. (2006). Nicotinic modulation of human auditory sensory memory: Evidence from mismatch negativity potentials. *International Journal of Psychophysiology*, *59*, 49–58.

Bartus, R. T., Dean, R. L., III, Beer, B., & Lippa, A. S. (1982). The cholinergic hypothesis of geriatric memory dysfunction. *Science*, *217*, 408–417.

Berman, J. A., Talmage, D. A., & Role, L. W. (2007). Cholinergic circuits and signaling in the pathophysiology of schizophrenia. *International Review of Neurobiology*, *78*, 193–223.

Breslau, N. (1995). Psychiatric comorbidity of smoking and nicotine dependence. *Behavior Genetics*, *25*, 95–101.

Catts, S. V., Shelley, A.-M., Ward, P. B., Liebert, B., McConaghy, N., Andrews, S., et al. (1995). Brain potential evidence for an auditory sensory memory deficit in schizophrenia. *The American Journal of Psychiatry*, *152*, 213–219.

Centers for Disease Control and Prevention. (2008). Cigarette smoking among adults—United States, 2007. *Morbidity and Mortality Weekly Report*, *57*, 1221–1228.

Davalos, D. B., Kisley, M. A., & Freedman, R. (2005). Behavioral and electrophysiological indices of temporal processing dysfunction in schizophrenia. *Journal of Neuropsychiatry and Clinical Neurosciences*, *17*, 517–525.

Davalos, D. B., Kisley, M. A., Polk, S. D., & Ross, R. G. (2003). Mismatch negativity in detection of interval duration deviation in schizophrenia. *Neuroreport*, *14*, 1283–1286.

Davalos, D. B., Kisley, M. A., & Ross, R. G. (2003). Effects of interval duration on temporal processing in schizophrenia. *Brain and Cognition*, *52*, 295–301.

Dunbar, G., Boeijinga, P. H., Demazieres, A., Cisterni, C., Kuchibhatla, R., Wesnes, K. A., et al. (2007). Effects of TC-1734 (AZD3480), a selective neuronal nicotinic receptor agonist, on cognitive performance and the EEG of young healthy male volunteers. *Psychopharmacology*, *191*, 919–929.

Engeland, C., Mahoney, C., Mohr, E., Ilivitsky, V., & Knott, V. J. (2002). Acute nicotine effects on auditory sensory memory in tacrine-treated and nontreated patients with Alzheimer's disease. An event-related potential study. *Pharmacology, Biochemistry and Behavior*, *72*, 457–464.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1996). *Structured clinical interview for DSM-IV axis I disorders—Non-patient Edition (SCID-I/NP, Version 2.0)*. New York City: NYSPI/Biometrics Research Department.

Grillner, P., & Svensson, T. H. (2000). Nicotine-induces excitation of midbrain dopamine neurons in vitro involves ionotropic glutamate receptor activation. *Synapse*, *38*, 1–9.

Harkrider, A. W., & Hedrick, M. S. (2005). Acute effect of nicotine on auditory gating in smokers and non-smokers. *Hearing Research*, *202*, 114–128.

Harris, J. G., Kongs, S., Allensworth, D., Martin, L., Tregellas, J., Sullivan, B., et al. (2004). Effects of nicotine on cognitive

deficits in schizophrenia. *Neuropsychopharmacology*, *29*, 1378–1385.

Hughes, J. R., & Hatsukami, D. K. (1986). Signs and symptoms of tobacco withdrawal. *Archives of General Psychiatry*, *43*, 289–294.

Inami, R., Kirino, E., Inoue, R., & Arai, H. (2005). Transdermal nicotine administration enhances automatic auditory processing reflected by mismatch negativity. *Pharmacology, Biochemistry and Behavior*, *80*, 453–461.

Inami, R., Kirino, E., Inoue, R., Suzuki, T., & Arai, H. (2007). Nicotine effects on mismatch negativity in nonsmoking schizophrenic patients. *Neuropsychobiology*, *56*, 64–72.

Javitt, D. C., Doneshka, P., Zylberman, I., Ritter, W., & Vaughan, H. G., Jr. (1993). Impairment of early cortical processing in schizophrenia: An event-related potential confirmation study. *Biological Psychiatry*, *33*, 513–519.

Javitt, D. C., Steinschneider, M., Schroeder, C. E., & Arezzo, J. C. (1996). Role of cortical N-methyl-D-aspartate receptors in auditory sensory memory and mismatch negativity generation: Implications for schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*, *93*, 11962–11967.

Kähkönen, S., Ahveninen, J., Jääskeläinen, I. P., Kaakkola, S., Näätänen, R., Huttunen, J., et al. (2001). Effects of haloperidol on selective attention: A combined whole-head MEG and high-resolution EEG study. *Neuropsychopharmacology*, *25*, 498–504.

Kähkönen, S., Ahveninen, J., Pekkonen, E., Kaakkola, S., Huttunen, J., Ilmoniemi, R. J., et al. (2002). Dopamine modulates involuntary attention shifting and reorienting: An electromagnetic study. *Clinical Neurophysiology*, *113*, 1894–1902.

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, *13*, 261–276.

Kisley, M. A., Davalos, D. B., Engleman, L. L., Guinther, P. M., & Davis, H. P. (2005). Age-related change in neural processing of time-dependent stimulus features. *Cognitive Brain Research*, *25*, 913–925.

Kisley, M. A., Davalos, D. B., Layton, H. S., Pratt, D., Ellis, J. K., & Seger, C. A. (2004). Small changes in temporal deviance modulate mismatch negativity amplitude in humans. *Neuroscience Letters*, *358*, 197–200.

Knott, V. J., Blais, C., Scherling, C., Camarda, J., Millar, A., Fisher, D., et al. (2006). Neural effects of nicotine during auditory selective attention in smokers: An event-related potential study. *Neuropsychobiology*, *53*, 115–126.

Knott, V. J., Scherling, C. S., Blais, C. M., Camarda, J., Fisher, D. J., Millar, A., et al. (2006). Acute nicotine fails to alter event-related potential or behavioral performance indices of auditory distraction in cigarette smokers. *Nicotine & Tobacco Research*, *8*, 263–273.

Korostenskaja, M., Nikulin, V. V., Kicic, D., Nikulina, A. V., & Kaakkola, S. (2007). Effects of a NMDA receptor antagonist memantine on mismatch negativity. *Brain Research Bulletin*, *72*, 275–283.

Kreitschmann-Andermahr, I., Rosburg, T., Demme, U., Gaser, E., Nowak, H., & Sauer, H. (2001). Effect of ketamine on the neuromagnetic mismatch field in healthy humans. *Cognitive Brain Research*, *12*, 109–116.

Kujala, T., Kallio, J., Tervaniemi, M., & Naatanen, R. (2001). The mismatch negativity as an index of temporal processing in audition. *Clinical Neurophysiology*, *112*, 1712–1719.

Lambe, E. K., Piccioto, M. R., & Aghajanian, G. K. (2003). Nicotine induced glutamate release form thalamocortical terminals in prefrontal cortex. *Neuropsychopharmacology*, *28*, 216–225.

Leung, S., Croft, R. J., Baldeweg, T., & Nathan, P. J. (2007). Acute dopamine D1 and D2 receptor stimulation does not modulate mismatch negativity (MMN) in healthy human subjects. *Psychopharmacology*, *194*, 443–451.

Levin, E. D., MCClernon, F. J., & Rezvani, A. H. (2006). Nicotinic effects on cognitive function: Behavioral characterization, pharmacological specification, and anatomic localization. *Psychopharmacology*, *184*, 523–539.

Martin, L. F., & Freedman, R. (2007). Schizophrenia and the alpha-7 nicotinic acetylcholine receptor. *International Review of Neurobiology*, *78*, 225–246.

Naatanen, R., Jiang, D., Lavikainen, J., Reinikainen, K., & Paavilainen, P. (1993). Event-related potentials reveal a memory trace for temporal features. *Neuroreport*, *5*, 310–312.

Naatanen, R., Teder, W., Alho, K., & Lavikainen, J. (1992). Auditory attention and selective input modulation: A topographical ERP study. *Neuroreport*, *3*, 493–496.

Naatanen, R., & Winkler, I. (1999). The concept of auditory stimulus representation in cognitive neuroscience. *Psychological Bulletin*, *125*, 826–859.

Nakagome, K., Ichikawa, I., Kanno, O., Akaho, R., Suzuki, M., Takazawa, S., et al. (1998). Overnight effects of triazolam on cognitive function: An event-related potentials study. *Pharmacoelectroencephalography*, *38*, 232–240.

Newhouse, P. A., Potter, A., & Singh, A. (2004). Effects of nicotinic stimulation on cognitive performance. *Current Opinion in Pharmacology*, *4*, 36–46.

Olincy, A., Harris, J. G., Johnson, L. L., Pender, V., Kongs, S., Allensworth, D., et al. (2006). An alpha 7-nicotinic cholinergic agonist enhances cognitive function in schizophrenia. *Archives of General Psychiatry*, *63*, 630–638.

Pekkonen, E., Hirvonen, J., Ahveninen, J., Kähkönen, S., Kaakkola, S., Huttunen, J., et al. (2002). Memory-based comparison process not attenuated by haloperidol: A combined MEG and EEG study. *Neuroreport*, *13*, 177–181.

Pérez de la Mora, M., Mendez-Franco, J., Salceda, R., Aguirre, J. A., & Fuxe, K. (1991). Neurochemical effects of nicotine on

glutamate and GABA mechanisms in the rat brain. *Acta Physiologica Scandinavica*, *141*, 241–250.

Quattrocki, E., Baird, A., & Yurgelun-Todd, D. (2000). Biological aspects of the link between smoking and depression. *Harvard Review of Psychiatry*, *8*, 99–110.

Rosburg, T., Marinou, V., Haueisen, J., Smesny, S., & Sauer, H. (2004). Effects of lorazepam on the neuromagnetic mismatch negativity (MMNm) and auditory evoked field component N100m. *Neuropsychopharmacology*, *29*, 1723–1733.

Sacco, K. A., Bannon, K. L., & George, T. P. (2004). Nicotinic receptor mechanisms and cognition in normal states and neuropsychiatric disorders. *Journal of Psychopharmacology*, *18*, 457–474.

Shelley, A.-M., Ward, P. B., Catts, S. V., Michie, P. T., Andrews, S., & McConaghy, N. (1991). Mismatch negativity: An index of a preattentive processing deficit in schizophrenia. *Biological Psychiatry*, *30*, 1059–1062.

Summers, K. L., & Giacobini, E. (1995). Effects of local and repeated systemic administration of (-)nicotine on extracellular levels of acetylcholine, norepinephrine, dopamine, and serotonin in rat cortex. *Neurochemical Research*, *20*, 753–759.

Summers, K. L., Kem, W. R., & Giacobini, E. (1997). Nicotinic agonist modulation of neurotransmitter levels in the rat frontoparietal cortex. *Japanese Journal of Pharmacology*, *74*, 139–146.

Sussman, E., Winkler, I., & Wang, W. (2003). MMN and attention: competition for deviance detection. *Psychophysiology*, *40*, 430–435.

Todd, J. (2006). Impaired detection of silent interval change in schizophrenia. *Auditory and Vestibular Systems*, *17*, 785–789.

Tregellas, J. R., Tanabe, J. L., Martin, L. F., & Freedman, R. (2005). fMRI of response to nicotine during a smooth pursuit eye movement task in schizophrenia. *The American Journal of Psychiatry*, *162*, 391–393.

Turner, T. J. (2004). Nicotine enhancement of dopamine release by a calcium-dependent increase in the size of the readily releasable pool of synaptic vesicles. *The Journal of Neuroscience*, *24*, 11328–11336.

Umbricht, D., Schmid, L., Koller, R., Vollenweider, F. X., Hell, D., & Javitt, D. C. (2000). Ketamine-induced deficits in auditory and visual context-dependent processing in healthy volunteers. *Archives of General Psychiatry*, *57*, 1139–1147.

Vidal, C. (1994). Nicotinic potentiation of glutamatergic synapses in the prefrontal cortex: New insight into the analysis of the role of nicotinic receptors in cognitive functions. *Drug Development Research*, *31*, 120–126.

Volz, H., Nenadic, I., Gaser, C., Rammsayer, T., Hager, F., & Sauer, H. (2001). Time estimation in schizophrenia: An fMRI study at adjusted levels of difficulty. *Neuroreport*, *12*, 313–316.

Waters, A. J., & Sutton, S. R. (2000). Direct and indirect effects of nicotine/smoking on cognition in humans. *Addictive Behaviors*, *25*, 29–43.

West, R., Ussher, M., Evans, M., & Rashid, M. (2006). Assessing DSM-IV nicotine withdrawal symptoms: A comparison and evaluation of five different scales. *Psychopharmacology*, *184*, 619–627.

West, R. J., & Jarvis, M. J. (1986). Effects of nicotine on finger tapping rate in non-smokers. *Pharmacology, Biochemistry and Behavior*, *25*, 727–731.

Westfall, T. C., Grant, H., & Perry, H. (1983). Release of dopamine and 5-hdroxytryptamine from rat striatal slices following activation of nicotinic cholinergic receptors. *General Pharmacology*, *14*, 321–325.

Winsberg, B. G., Javitt, D. C., & Shanahan/Silpo, G. (1997). Electrophysiological indices of information processing in methylphenidate responders. *Biological Psychiatry*, *42*, 434–445.