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ORIGINAL INVESTIGATION

Nicotine enhances auditory processing in healthy and normal-hearing young adult nonsmokers

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Abstract

Rationale Electrophysiological studies show that systemic nicotine narrows frequency receptive fields and increases gain in neural responses to characteristic frequency stimuli. We postulated that nicotine enhances related auditory processing in humans.
Objectives The main hypothesis was that nicotine improves auditory performance. A secondary hypothesis was that the degree of nicotine-induced improvement depends on the individual's baseline performance.
Methods Young (18–27 years old), normal-hearing nonsmokers received nicotine (Nicorette gum, 6mg) or placebo gum in a single-blind, randomized, crossover design. Subjects performed four experiments involving tone-in-noise detection, temporal gap detection, spectral ripple discrimination, and selective auditory attention before and after treatment. The perceptual differences between posttreatment nicotine and placebo conditions were measured and analyzed as a function of the pre-treatment baseline performance.
Results Nicotine significantly improved performance in the more difficult tasks of tone-in-noise detection and selective attention (effect size = − 0.3) but had no effect on relatively easier tasks of temporal gap detection and spectral ripple discrimination. The two tasks showing significant nicotine effects further showed no baseline-dependent improvement.
Conclusions Nicotine improves auditory performance in difficult listening situations. The present results support future investigation of nicotine effects in clinical populations with auditory processing deficits or reduced cholinergic activation.

Keywords Acetylcholinergic systems · Auditory processing · Nicotine · Selective attention · Spectral ripple discrimination · Tone in noise detection · Temporal gap detection

Introduction

Nicotine is known to affect muscular, neuronal, cardiovascular, gastrointestinal, and other systems' activities and functions. In the mouse auditory cortex, a systemic nicotine injection increases the gain and shortens latency near the center of a neuron's receptive field while decreasing the gain at the edges of the receptive field (Askew et al. 2017; Intskirveli and Metherate 2012; Kawai et al. 2011). This "sharpening" in the receptive field by nicotine may also act as a "stimulus filter" to enhance attentional gain to task-relevant stimuli while reducing the gain to task-irrelevant stimuli (Kassel 1997). Physiological studies in both the visual and auditory systems support this stimulus-filter model (Disney et al. 2007; Metherate et al. 2012).

In comparison, only a few human studies found enhanced selective attention by nicotine in nonsmoking healthy human subjects (e.g., Behler et al. 2015; Heishman et al. 2010; Knott et al. 2009; Lawrence et al. 2002). The present study attempts to bridge the knowledge gap between perceptual effects of nicotine on sensory processing in humans and the established physiological effects of nicotine in animals. We designed four experiments to probe the effect of nicotine on four different aspects of auditory perception, including (1) central gain in tone-in-noise detection, (2) temporal resolution in gap detection, (3) spectral resolution in spectral ripple discrimination, and (4) reaction time in selective attention. A group of young healthy nonsmokers participated in the study by consuming

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either 6mg nicotine chewing gum or a non-nicotine placebo gum having the same flavor as the nicotine gum. Our main hypothesis was that compared with the placebo gum, the nicotine gum would improve auditory performance. A secondary hypothesis was that those with the lowest baseline performance would produce the most improvement from nicotine (Knott et al. 2014a, 2015; Newhouse et al. 2004).

Materials and methods

Subjects

Eighteen individuals were recruited, and a total of 14 subjects participated in the study (age range = 18–27 years, mean ± std. = 21 ± 3 years; 9 males; 12 right-handed). All subjects gave written informed consent approved by the University of California, Irvine's Institutional Review Board. All subjects received monetary compensation for their participation. An online survey facilitated initial subject screening to ensure no known hearing dysfunction, medical or mental health illness including drug dependency, diabetes mellitus, renal failure, cardiovascular disease, neurological disease, psychiatric disorder, central nervous system disorder or regular use of prescription medication (excluding oral contraceptives), and low nicotine dependence via use and exposure consisting of a score of 0–2 out of 10 maximum on the Fagerström index of smoking dependency (Bramer and Kallungal 2003; Heatherton et al. 1991). Twelve subjects had no smoking history, i.e., smoked no more than 100 cigarettes in their lifetime and none in the past year (Knott et al. 2014a), and two smoked socially, i.e., smoked no more than one cigarette per week or four per month. To avoid chemical interactions, all subjects were asked to abstain from the following prior to testing: (1) drug use for ≥3 days, (2) alcohol consumption for 24 h, and (3) food consumption ≥1 h. To avoid caffeine withdrawal in regular caffeine consumers, one half cup of a caffeine-containing beverage ≥1 h was permitted (Lawrence et al. 2002). At the beginning of each session, female subjects took a pregnancy test to confirm negative results for continued participation. Eligible subjects had audibility ≤20dB HL (decibels Hearing Level) at octave frequencies between 0.125 and 8kHz, bilaterally. Data from four individuals were excluded from further analysis due to elevated audibility (1 subject) or incomplete treatment sessions (3 subjects), leaving 14 subjects whose data were analyzed.

Experimental protocol

All experiments took place in a double-walled, sound-attenuated booth. The tone-in-noise detection experiment measured the central gain of the stimulus-filter model, which would predict lower or better tone detection thresholds with the nicotine treatment. We chose two pure tones at 2000 and 4000Hz and a pink noise as a masker, since it would produce a similar degree of masking between the tones (Fletcher 1938). The pink noise had a center frequency of 2828Hz, a bandwidth of five octaves and was fixed at 50dB SPL. All stimuli had a duration of 500ms, including 2.0ms linear rise-fall times. A three-interval, three-alternative, forced choice adaptive procedure was used to measure the tone-in-noise detection threshold. During each trial, two of the three intervals contained the noise alone, and a randomized interval contained the tone embedded in noise. Subjects had to select the interval in which they perceived the tone. The tone threshold was measured with two different starting levels at 45 and 70dB SPL. A two-down, one-up decision rule was used to estimate the 71% correct performance level.

The gap detection experiment measured temporal resolution within the same perceptual channel or between two different channels (Phillips et al. 1997). For the within-channel condition, a temporal gap was marked by two tones of the same frequency (2 or 4kHz). For the between-channel condition, the temporal gap was marked by two tones of different frequencies (2:4kHz or 4:2kHz). Gap detection thresholds were measured for tones presented at 45 and 70dB SPL or ~10 and 40dB SL in the presence of 50dB SPL pink noise. The pink noise was used to minimize spectral splatter and would not interfere with gap detection. The duration of the two tones varied between 125 and 250ms, depending on the gap duration, to produce a total stimulus duration of 500ms. The abovementioned adaptive procedure was used to estimate the gap detection threshold.

The spectral-temporally modulated ripple test (Aronoff and Landsberger 2013) measured dynamic spectral resolution in terms of ripples per octave. The reference stimulus had 20 ripples per octave. The ripple test threshold was the number of ripples per octave that could be just discriminable from the reference stimulus. The modulation depth was set to 20Hz, and the ripple repetition rate was set to 5Hz. All ripple stimuli had a duration of 500ms with 100ms linear ramps. The same adaptive procedure, except for a one-down, one-up decision rule, was used to estimate the ripple discrimination threshold.

The test of attention in listening measured the reaction time required to discriminate between two tones that were presented sequentially and had same or different frequencies or locations (Zhang et al. 2012). In the different frequency condition, the frequencies of the two tones were drawn randomly between 476 and 6188Hz with the constraint that the two frequencies had to differ by ≥2.1 equivalent rectangular bandwidths. The tone could be located in either the left or the right ear. One test condition was to detect a frequency difference, while the tone location served as the distractor, in which the subject heard two tones presented randomly to the left or right ear and had to indicate as quickly as possible whether the two tones had the same or different frequencies. The other

condition was to detect a location difference, while the tone frequency was the distractor, in which the subject heard two tones of same or different frequencies and had to indicate whether the two tones were presented to the same or different ears. Each condition had four possible stimulus combinations, same frequency same location, same frequency different location, different frequency same location, and different frequency different location, resulting in a total of eight data points for the subjects. The subjects could perform this selective attention task accurately with an average error rate of 5%. We also ran a control condition where neither frequency nor location was task-relevant, and the subjects were instructed to press a button as soon as they heard the second tone. In all conditions, tone level varied between 70 to 85dB SPL, and tone duration varied between 100 and 300ms. The silent interval between the two tones was fixed at 300ms. All subjects used their dominant hand to press the response button. Before testing each experimental condition, subjects completed five practice trials with the option to repeat the practice as many times as needed to become familiar with the task. Reaction times longer than 2s or shorter than 100ms, which suggested lapsed attention and interrupted performance or premature responses, were excluded (~20% trials) from calculations.

Study design

Figure 1 shows the study design in a flow chart. Sessions occurred between 8:30 am and 2:00 pm, with the majority starting before noon and taking place during a consistent time across sessions to avoid confounding arousal and attention effects. At least 1 day preceding each session, subjects were reminded of abstinence instruction, and verbal compliance was confirmed before testing commenced. In Session 1, audiograms were first measured, and then the pre-treatment baseline performance in the four experiments was measured. After pre-treatment testing, subjects received either nicotine or placebo gum in a randomized design. The protocol was repeated with either nicotine or placebo treatment, adhering to a single-blind intra-subject design. In Session 2, ≥48h after Session 1 to allow for treatment clearance, the subjects completed the same tests, except for audiogram, in the same order as Session 1. Subjects participated in a minimum of two treatment options (nicotine and placebo) in one experiment, with the possibility of completing all four experiments. The order of drug administration was counterbalanced over subjects.

Nicotine was delivered in the form of two pieces of mint-flavored Polacrilex gum (4mg and 2mg; Nicorette®, Johnson & Johnson, Inc). The total 6mg dose produced a nicotine plasma concentration of 15–30ng/ml, i.e., the approximate blood concentration after smoking one, medium nicotine yield, cigarette (Hukkanen et al. 2005). This dose was selected based on the previous studies with nonsmokers showing drug tolerance without any significant adverse side effects resulting in terminated participation (Knott et al. 2014a, b). The placebo administration consisted of two pieces of commercially available mint-flavored gum (Eclipse®), resembling the nicotine gum in size, shape, color, and texture. Subjects wore a blindfold during treatment administration to mask any potential visual differences between placebo and nicotine gum. A drop of Tabasco sauce was added to each gum piece to disguise

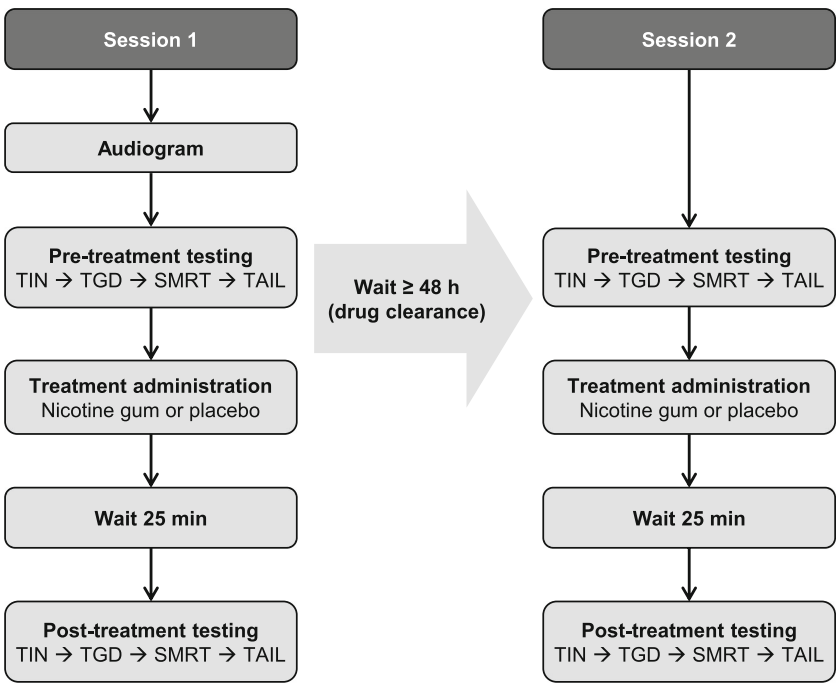

Fig. 1 Study design. In Session 1, subjects were first tested with audiogram and then completed pre-treatment testing in order of TIN (tone-in-noise detection), TGD (temporal gap detection), SMRT (spectral-temporally modulated ripples test), and TAIL (test of attention in listening). The subjects were then treated with either nicotine or placebo and waited for 25min before the posttreatment testing in the same order. The four experiments usually took 0.5–1h to complete. In Session 2, ≥48 h after Session 1 to allow for treatment clearance, the subjects completed the same tests, except for audiogram, in the same order as Session 1

taste bias (Thiel and Fink 2007). Pulse rate was measured via pulse oximetry before and after treatment (Choice MMed America Co; Thiel and Fink 2007). Mood and side effects were also monitored before and after treatment (Harkrider and Hedrick 2005; Lawrence et al. 2002; Parrott et al. 1996). To regulate drug administration and minimize side effects, subjects followed manufacturer guidelines to chew the gum for 25min, biting twice per minute and "parking" the gum between teeth and cheek between bites when cued by an auditory signal. Following 25min and prior to blind fold removal, subjects removed the treatment gum and chewed a commercially available, cinnamon-flavored gum for 2min at the same pace as before to mask any remaining taste differences between treatments (Knott et al. 2014a). This "wash" method disguised treatment in 7 out of 10 subjects who participated in multiple experiments and 30% of the time (9 out 32 times polled). In some subjects, however, changes in mood and/or side effects from nicotine could have biased the treatment administered. Posttreatment testing began 30min from the beginning of treatment administration considering oral nicotine exhibits peak blood nicotine concentrations 30min after nicotine gum chewing (Hukkanen et al. 2005). All experiment protocols could be completed in 30–60min, which is well within the time course of the 120min nicotine elimination half-life (Hukkanen et al. 2005).

Data analysis

To test our main hypothesis that nicotine improves auditory performance, we used a one-sample t-test to compare the difference in posttreatment performance between nicotine and placebo data. We would accept the hypothesis if the difference was significantly less than zero at the $p < 0.05$ level. We also calculated the effect size in terms of dividing the mean difference between the posttreatment nicotine and placebo conditions by the standard deviation of their joint distribution. Furthermore, we used linear regression between the nicotine-placebo difference and the baseline performance to test whether those with the lowest baseline performance would benefit the most from the nicotine treatment (Knott et al. 2015; Newhouse et al. 2004). We would accept this secondary hypothesis if significant positive linear regression existed between the nicotine-placebo difference and the baseline performance at the $p < 0.05$ level. The baseline performance was the average of the two sets of pre-treatment data from the nicotine and placebo conditions. The average was justified because no significant difference was found between these two pre-treatment conditions in any of the four experiments (the Kolmogorov-Smirnov test, $p = 0.57$, 0.80, 0.73, and 0.80 for the tone-in-noise detection, gap detection, ripple discrimination, and selective attention experiment, respectively).

Results

Pulse oximetry

Nicotine increased the pulse rate from a pre-nicotine level of 73.2 ± 1.5 (beats per min) to a post-nicotine level of 80.5 ± 1.2 ($n = 10$; paired t-test, $p < 0.01$), whereas the placebo produced no significant change in the pulse rate (pre-placebo = 72.3 ± 1.8; post-placebo = 72.5 ± 1.6; $n = 10$, $p > 0.05$). The present nicotinic effect on pulse rate was consistent with previous reports using oral nicotine (Smucny et al. 2015; Thiel and Fink 2007) and provided evidence that nicotine had indeed entered the bloodstream during the experiments.

Mood changes and side effects

All subjects provided subjective, pre-, and posttreatment ratings using a 9-category mood profile and a 5-point side effects scale (Harkrider and Hedrick 2005). Ratings were averaged across all four experiments. While nicotine increased mood ratings of energy, contentedness, and focus ($p < 0.05$), placebo also increased ratings of relaxation, calmness, energy, alertness, and hunger ($p < 0.05$). Subjects rated nicotine's side effects on a scale from 1 = none (no symptoms) to 5 = severe (jittery, dull or pounding headache, nausea, vomiting) (Harkrider and Hedrick 2005). Side effects increased with nicotine ($p < 0.01$), but not placebo ($p > 0.05$). Although no subject reported nicotine side effects higher than 3 (jittery, dull headache), the significant side effects rating in the present nonsmokers further verified nicotine entry into the blood. Of the four subjects that did not complete the study, only one subject decided to discontinue participation based on nicotine side effects.

Tone-in-noise detection

Ten subjects participated in the tone-in-noise detection experiment. Figure 2a shows the individual subjects' threshold difference between the nicotine and placebo posttreatment performance as a function of the pre-treatment baseline performance (the individual data being displayed as circles: red for 2000Hz and blue for 4000 Hz). The mean difference (thick dashed horizontal line) was −0.63dB, which was significantly lower from the 0dB effect (thin solid horizontal line; $p = 0.03$) and consistent with the main hypothesis that nicotine improved tone-in-noise detection. Dividing the −0.63dB mean difference by the 2.01dB standard deviation produced a small-to-medium effect size of −0.32. Linear regression (thick dotted line) just missed the significance level ($r^2 = 0.09$; $p = 0.05$), providing only a trend in support of the secondary hypothesis.

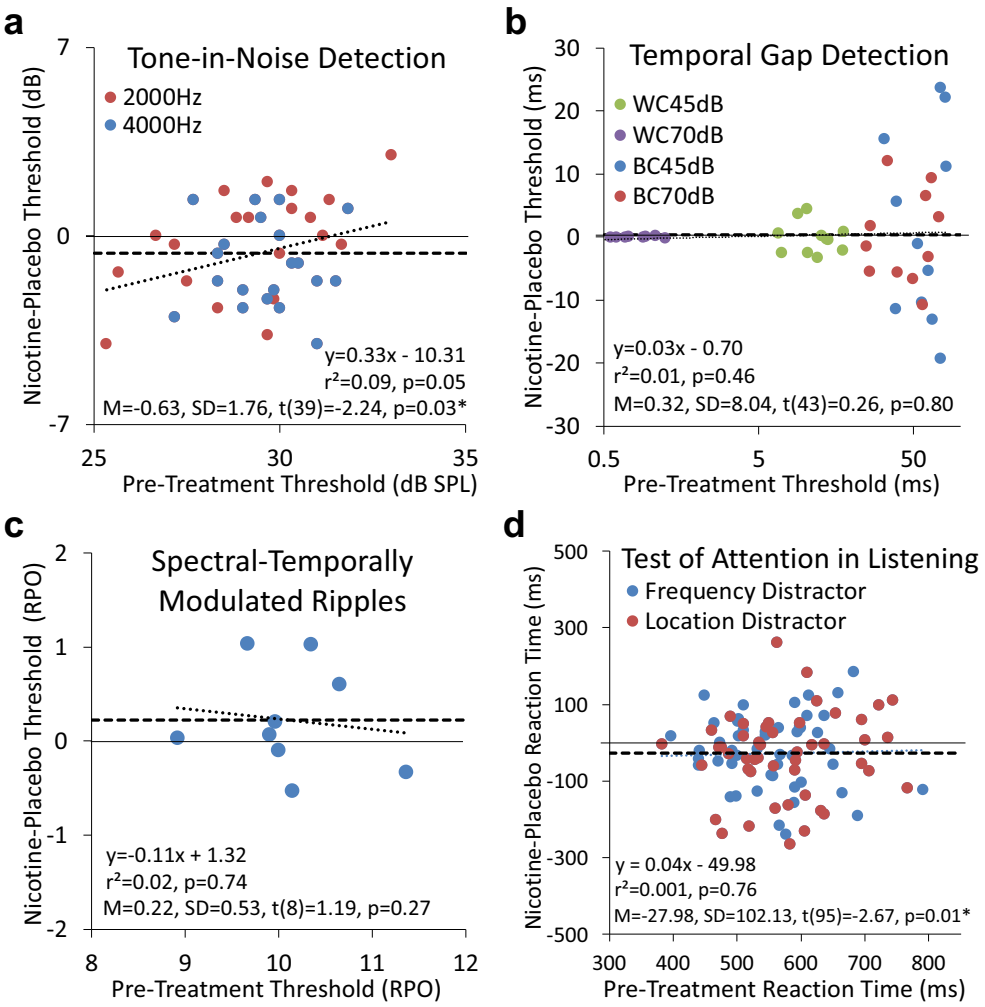

Fig. 2 Posttreatment placebo and nicotine difference as a function of pre-treatment baseline performance in four auditory experiments. (**a**) Tone-in-noise detection. Individual data are represented by circles (red for 2000Hz and blue for 4000Hz). The mean difference is represented by the thick dashed horizontal line. The regression line is represented by the dotted line. The text box shows the linear regression equation (top), r^2 and p value (middle), the mean difference, the standard deviation, and the one-sample t-test result (bottom). The same convention is applicable to panel **b**, **c**, and **d**. (**b**) Temporal gap detection. WC = Within-Channel, BC = Between-Channel. (**c**) Spectral-temporally modulated ripple discrimination. RPO = Ripples Per Octave. (**d**) Selective attention

Temporal gap detection

Eleven subjects participated in the gap detection experiment. Figure 2b shows both the individual (circles) and mean (thick dashed horizontal line) nicotine-placebo difference data as a function of pre-treatment baseline performance. Consistent with the previous result (Phillips et al. 1997), the nicotine-placebo variability increased from the within-channel (WC) to the between-channel (BC) condition and decreased with the stimulus level. We found neither a significant nicotine effect (mean = 0.32ms; effect size = 0.01; $p = 0.80$) nor a significant regression ($r^2 = 0.01$; $p = 0.46$; the regression line virtually overlaps with the mean difference line).

Spectral-temporally modulated ripples

Nine subjects participated in this spectral ripple discrimination experiment. Figure 2c shows both the individual (circles) and mean (thick dashed horizontal line) nicotine-placebo difference data as a function of pre-treatment baseline performance. Again, we found neither a significant nicotine effect (mean = 0.22 ripples per octave; effect size = 0.29; $p = 0.27$) nor a significant regression ($r^2 = 0.02$; $p = 0.74$; the dotted line).

Test of attention in listening

Twelve subjects participated in the selective attention experiment. In the control condition where the subjects did not have to pay any attention to sound frequency or location but simply pressed the response button as soon as they heard the second tone, there was no significant difference between the posttreatment nicotine and placebo performance (290 ± 73 vs. 282 ± 67ms; $p = 0.53$). Figure 2d shows both the individual (circles) and mean (thick dashed horizontal line) nicotine-placebo difference data as a function of pre-treatment baseline performance. First, compared with the control condition, the attention task, regardless of treatment, significantly slowed the reaction time (566 ± 83ms; $p < 0.0001$). Second, compared with the placebo treatment, the nicotine treatment significantly shortened the reaction time by 28ms (effect size = −0.31; $p = 0.01$). Third, there was no significant regression between the nicotine-placebo difference and the baseline performance

($r^2 = 0.001$; $p = 0.76$; the regression line virtually overlaps with the mean difference line).

Discussion

The present study tested the hypotheses that nicotine improves auditory processing in terms of (1) central gain, (2) temporal resolution, (3) spectral resolution, and (4) selective attention. Our results partially supported this hypothesis by showing significantly improved nicotine over placebo performance in the central gain and selective attention experiments but not in temporal and spectral resolution experiments. We found minimal evidence for the secondary hypothesis that those with lower baseline performance would benefit more from the nicotine treatment, with only a statistical trend in the central gain results.

Comparisons with previous studies

Relative to extensive animal literature, nicotine studies on human auditory processing are scarce. Harkrider and colleagues (Harkrider and Champlin 2001a, b; Harkrider et al. 2001) found that nicotine administered via a transdermal patch (7mg/24h) to nonsmokers produced no effect on otoacoustic emissions but enhanced auditory brainstem and cortical responses. In a combined behavioral and electrophysiological study involving both four smokers and ten nonsmokers, Harkrider and Hedrick (2005) found nicotine produced no symptoms in one third of these smokers and nonsmokers but a variety of symptoms from itchiness in the patch area to headache and nausea correlated in the remaining two thirds of the subjects. They also found a task-dependent result, showing that not only did the severity of nicotine symptoms correlate with consonant-vowel discrimination in quiet for nonsmokers, but nicotine improved consonant-vowel discrimination in noise for both smokers and nonsmokers.

The previous results were partially consistent with the present study, showing improved performance by nicotine in the tone-in-noise and selective attention tasks but no effect on the more basic temporal and spectral resolution measurements. The discrepancy between the previous and present results cannot be explained by participant characteristics, as both studies tested young, normal-hearing nonsmokers. Instead, this discrepancy may be related to differences in task difficulty, suggesting that nicotine produces a significant effect in difficult listening situation only.

Peripheral and central mechanisms

The previous and present findings are likely a result of central rather than peripheral mechanisms. Physiologically, Harkrider et al. (2001) found no nicotine effect on otoacoustic emissions, a peripheral phenomenon related to outer hair cells in the cochlea. Instead, nicotine effects were observed in the auditory midbrain and cortex that may reflect enhanced receptive field (Askew et al. 2017). Similarly, human imaging studies have shown that nicotine enhances neural responses in hippocampus, sensory, and motor cortices in healthy nonsmokers (Smucny et al. 2015) while decreasing hyperactivity in such brain areas in schizophrenic patients (Smucny et al. 2016). Although significant nicotine effects are observed in the brain, relationship of these physiological effects to perceptual effects remains unclear and understudied (Hong et al. 2011). Finally, the baseline-dependent nicotinic effect is likely due to central mechanisms (Baschnagel and Hawk 2008; Knott et al. 2014a, b, 2015; Newhouse et al. 2004). However, we found minimal evidence for the baseline-dependent nicotinic effect on the present auditory processing experiments.

Limitations and future directions

First, the present study limited testing to a small number of healthy, normal-hearing young adults. The inclusion of both female and male subjects in the present study likely increased data variability and further reduced the power because sex hormones influence nicotine metabolism (Benowitz et al. 2006). In addition, the present study did not test other populations such as children, elderly, hearing-impaired individuals, or clinical patients. Future nicotine treatment could, instead, be given to special populations whose acetylcholinergic systems are either impaired or underdeveloped, for example, in Alzheimer's patients (Levin et al. 2006; Sarter et al. 2009) or in children (Dwyer et al. 2009). Second, the present study limited testing to basic auditory processing tasks, requiring relatively low cognitive demand. Future studies should employ tasks varying in cognitive load, e.g., using an active three-stimulus auditory oddball paradigm (Knott et al. 2014a). Third, the present acute study using a single dosage had a severe time constraint which precluded a sensitive measure of within-subject variability (Zhang et al. 2012). This time constraint was related to oral nicotine administration, which might have produced insufficient nicotine serum concentration to significantly change perception as reflected by mild, self-reported side effects. Additionally, the absolute absorption rate of nicotine from gum administration may be subjected to greater variability across individuals as compared to other routes of administration, such as the transdermal patch. With oral administration, a quantity of nicotine can be swallowed and subject to first-pass metabolism rather than becoming fully absorbed via oral mucosa. Also, some of the drug may be retained within the gum instead of entering the subject's blood stream (Hukkanen et al. 2005). To potentially produce a higher nicotine concentration or retain the drug's effects over a longer time course while minimizing nicotinic

side effects, future studies may consider varying the nicotine dosage, altering the administration route (e.g., gum, patch or inhaler), or introducing a chronic treatment condition (Myers et al. 2008; Newhouse et al. 2012).

Conclusion

The present study assessed the acute effect of oral nicotine administration on auditory processing in a group of young-adult, normal-hearing nonsmokers. Compared with the placebo result, we found that nicotine significantly improved performance in tone-in-noise detection and selective attention tasks but produced no effect on relatively easy temporal and spectral resolution tasks. In the two tasks showing significant nicotinic improvement, we found little evidence for the baseline-dependent improvement. The present result supports the previous hypothesis that nicotine enhances auditory gating function, especially in difficult listening conditions. The present result suggests that future studies be conducted in younger, older, or clinical populations, where nicotine treatment could be used to target deficits in their acetylcholinergic systems relative to healthy young adults.

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Compliance with ethical standards

Conflict of interest F.G.Z. owns stock in Axonics, Nurotron, Syntiant, and Velox Biosystems. The other authors declare no competing interests.

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