



Original Investigation

Genetic and Depressive Traits Moderate the Reward-Enhancing Effects of Acute Nicotine in Young Light Smokers

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Abstract

Introduction: Rates of light smoking have increased in recent years and are associated with adverse health outcomes. Reducing light smoking is a challenge because it is unclear why some but not others, progress to heavier smoking. Nicotine has profound effects on brain reward systems and individual differences in nicotine's reward-enhancing effects may drive variability in smoking trajectories. Therefore, we examined whether a genetic risk factor and personality traits known to moderate reward processing, also moderate the reward-enhancing effects of nicotine.

Methods: Light smokers ($n = 116$) performed a Probabilistic Reward Task to assess reward responsiveness after receiving nicotine or placebo (order counterbalanced). Individuals were classified as nicotine dependence 'risk' allele carriers (rs16969968 A-allele carriers) or non-carriers (non-A-allele carriers), and self-reported negative affective traits were also measured.

Results: Across the sample, reward responsiveness was greater following nicotine compared to placebo ($p = 0.045$). For Caucasian A-allele carriers but not non-A-allele carriers, nicotine enhanced reward responsiveness compared to placebo for those who received placebo first ($p = 0.010$). Furthermore, for A-allele carriers but not non-A-allele carriers who received nicotine first, the enhanced reward responsiveness in the nicotine condition carried over to the placebo condition ($p < 0.001$). Depressive traits also moderated the reward-enhancing effects of nicotine ($p = 0.010$) and were associated with blunted reward responsiveness following placebo but enhanced reward responsiveness following nicotine.

Conclusion: These findings suggest that individual differences in a genetic risk factor and depressive traits alter nicotine's effect on reward responsiveness in light smokers and may be important factors underpinning variability in smoking trajectories in this growing population.

Implications: Individuals carrying genetic risk factors associated with nicotine dependence (rs16969968 A-allele carriers) and those with higher levels of depressive personality traits, show more pronounced increases in reward learning following acute nicotine exposure. These findings suggest that genetic and personality factors may drive individual differences in smoking trajectories in young light smokers by altering the degree to which nicotine enhances reward processing.

Clinical trial registration: NCT02129387 (pre-registered hypothesis: www.clinicaltrials.gov)

Introduction

Although rates of heavy smoking across the general population have declined, the proportion of young light smokers has increased in recent years.¹ Approximately 25% of smokers in the U.S. report smoking fewer than 5 cigarettes/day, and these individuals tend to be under 30 years of age.² Young light smokers display highly varied smoking trajectories; over two years, 7–32% will quit, 21–35% will increase their use, and the rest will maintain their baseline smoking frequency.³ Relative to non-smoking, light smoking confers a 3- to 5-fold increased risk of lung cancer and a 3-fold increased risk of death from cardiovascular disease.⁴ Accordingly, understanding the factors that influence smoking trajectories in this population is critical for reducing smoking-related morbidity and mortality.

Questionnaire and interview-based studies on smoking motivations indicate that light smokers smoke to reduce negative affect and to improve concentration (for a review, see⁵). However, self-report measures of smoking motivation have several well-documented limitations, including a lack of sensitivity to the immediate cognitive/affective and physiological effects of acute nicotine.^{6,7} Given these limitations, the National Cancer Institute published a monograph concluding that behavioral and physiological endophenotypes, including those quantified using laboratory-based nicotine challenge studies, are needed to better characterize individual differences in nicotine's effects.⁸

Effects of Nicotine on Reward Processing

Mounting evidence indicates that acute nicotine enhances reward processing. Studies using the Probabilistic Reward Task (PRT)⁹ – a well-validated behavioral measure of reward learning – have shown that in rodents with chronic nicotine exposure and humans with nicotine dependence, nicotine enhances the ability to learn from prior rewards.^{10–12} Reward learning is reliant on phasic striatal dopamine signaling,^{13,14} and increases in reward learning following acute nicotine exposure are consistent with nicotine's ability to amplify reward-related striatal dopamine activity.¹⁵

Opposite findings have been observed during nicotine withdrawal. Nicotine-dependent individuals who have undergone a period of abstinence show reduced reward learning on the PRT¹⁰ that correlates with craving intensity.¹⁶ In rats with chronic nicotine exposure, the deficit in reward learning is reversed following nicotine re-exposure.¹⁰ This suggests that in the context of nicotine dependence, a decrease in reward learning during withdrawal and remediation of this decrease by nicotine re-exposure is likely a key factor that maintains smoking. However, less is known about the role of reward processing in light smokers. Many light smokers easily abstain from smoking beyond the initial period of nicotine withdrawal, so smoking to alleviate withdrawal symptoms cannot fully explain continued smoking behavior in this population. An alternate possibility is that pre-existing factors that moderate the effects of nicotine on reward processing may determine individual differences in smoking trajectories among light smokers.

Potential Moderating Influence of Genetic Factors

Nicotine dependence is highly heritable, for a review, see,¹⁷ suggesting that genetic factors may contribute to variability in smoking trajectories. In support of this, Genome-Wide Association Studies have identified a consistent link between the single-nucleotide polymorphism (SNP) rs16969968 of the nicotine acetylcholine receptor (nAChR) alpha-5 subunit gene (*CHRNA5*) or its proxy (rs1051730)

and increased smoking frequency.^{18–20} The rs16969968 SNP encodes an Asp398Asn polymorphism resulting in an aspartic acid (G-allele) change to asparagine (A-allele).^{21,22} Expression of the A-allele reduces nAChR function.²¹ Reduced nAChR function is proposed to facilitate the development of nicotine dependence via impacting dopamine-mediated reward signaling²¹ (although a separate theory posits that A-allele carriers smoke to remediate cognitive deficits²³). Indeed, prior work has shown that the A-allele was associated with a pleasurable “buzz” when recalling reactions to smoking one's first cigarette,²⁴ suggesting that this genetic marker may moderate nicotine's reward-enhancing effects. Variation in nAChR function has also been suggested to alter nicotine intake by disrupting the inhibitory signaling in the habenula, which is responsible for the aversive effects of high doses of nicotine.²⁵

Potential Moderating Influence of Negative Affective Traits

Smoking plays an important role in regulating negative affect²⁶ and individual differences in negative affective traits may moderate the reward-enhancing effects of nicotine in light smokers. Depression and anxiety are highly comorbid with smoking and have been linked to multiple stages of the smoking trajectory, including smoking initiation,²⁷ progression to regular smoking,²⁸ development of nicotine dependence²⁹ and risk for smoking cessation failure.³⁰ These same traits have been associated with impaired reward processing. For example, individuals with major depressive disorder (MDD; particularly those with high levels of anhedonia),^{9,31} remitted MDD,³² as well as individuals exposed to acute stress,³³ show disrupted reward learning on the PRT. However, this deficit is normalized in remitted³⁴ and acutely depressed³⁵ individuals who smoke. These findings suggest that negative affective traits may promote greater smoking because nicotine temporarily remediates pre-existing reward processing deficits. However, studies testing this hypothesis in light smokers are lacking.

The Present Study

Individual differences in genetic risk and negative affective traits may provide a key source of variability in smoking trajectories. The aim of this study was to provide the first empirical test of whether rs16969968 allelic variation and negative affective traits moderate changes in reward learning following acute nicotine in young light smokers. We hypothesized rs16969968 risk allele carriers, as well as individuals with greater negative affective traits, would show greater increases in reward learning following nicotine relative to placebo. Consistent with prior links between rs16969968 allelic variation, negative affective traits, and disrupted striatal dopamine function,²¹ we predicted that nicotine would have a normalizing effect on reward learning in these individuals.

Method

Participants

Young light smokers ($n = 123$) aged 18–24 were recruited as part of a broader study (see *Supplement*). Participants smoked 5–35 cigarettes/week for the past 3 months with no previous smoking level exceeding 35 cigarettes/week. History of smoking and drug use was evaluated using modified sections from the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA)^{36,37} and the Timeline Follow-back for tobacco and other nicotine use.³⁸ Participants were excluded if they

used psychoactive drugs, including smokeless tobacco (e.g., vaping), on a weekly basis [exceptions to this were alcohol (<30 drinks per week), marijuana (<3 uses per week), and caffeine (any amount)], if they met criteria for a mood, anxiety or psychotic disorder on the Structured Clinical Interview for DSM-IV-TR (SCID-Research Version),³⁶ if they reported a history of head injury with loss of consciousness for greater than 10 minutes, current significant medical or neurological illness, were pregnant, breastfeeding, had motor impairment preventing task completion or cognitive or intellectual impairment. All participants were asked to refrain from smoking for at least 12 hours before each testing session. Procedures were approved by the Southern Illinois University Human Subjects Committee and all participants gave written informed consent before participating.

Quantified Smoke Delivery System (QSDS)

Author DG developed the QSDS which produces reliable standard doses of smoke-delivered nicotine with a low variation of plasma nicotine concentration.³⁹ This system delivers smoke into the participant's mouth by means of a motorized syringe. Relative to placebo (ultra-low nicotine but normal "tar"), QSDS-delivered nicotine produces the same electroencephalographic, hormonal,^{40,41} mood,⁴² and cognitive performance enhancements⁴⁰ as ad-lib smoking, yet with lower variability in blood nicotine concentration. This allows for improved characterization of individual differences in nicotine-related effects.

Cigarettes

Cigarettes were Camel Lights™ with an FTC-procedure estimated machine-delivered 0.8mg nicotine and Quest3™ (0.05mg nicotine [ultra-low nicotine placebo]).

Measures of Nicotine Dependence and Negative Affective Traits

Nicotine dependence was assessed using the Hooked on Nicotine Checklist (HONC),⁴³ which assesses diminished autonomy over smoking and is considered especially well-suited for use in light smokers.⁴⁴ Anhedonia was measured using the Fawcett-Clark Pleasure Capacity Scale,⁴⁵ which is a 36-item self-report measure of capacity for pleasure (higher scores indicate greater pleasure/less anhedonia). Depressive and anxious personality traits were measured using the Depressive and Anxious facet scales of the NEO Personality Inventory-Neuroticism subscale,⁴⁶ and participant's tendency to smoke in response to negative emotions was measured using the Smoking Motivation Questionnaire's Negative Affect Reduction subscale.⁴⁷

Probabilistic Reward Task (PRT)

Reward learning was assessed using the Probabilistic Reward Task (PRT).⁹ On each trial of this computerized task, participants are presented with schematic faces with two eyes and a nose. Next, a horizontal line mouth is presented quickly (100ms) and participants indicate whether the mouth was long (11mm) or short (10mm). The task consists of three blocks of 100 trials, and on 40% of correct trials, participants receive a monetary reward ("Correct! You won 20 cents"). Long and short mouths are presented at equal frequency, however, unbeknownst to participants, correct identification of one mouth ("rich stimulus") is rewarded three times more frequently than the other ("lean stimulus"). Among healthy controls, this asymmetrical reinforcement ratio induces a behavioral response

bias toward the rich stimulus,⁹ reflective of an individual's sensitivity to reward. Prior studies show that nicotine significantly enhances response bias.¹¹ To avoid practice effects, two task versions were administered: one where the mouth length varied and another where the nose length varied (order counterbalanced). The PRT was administered approximately 5 minutes after nicotine (or placebo) administration, and nicotine and placebo sessions occurred at least 24 hours apart.

PRT Data Reduction

Aligning with prior studies that have used the PRT,⁹ a quality control assessment was first carried out. Specifically, trials where the reaction time (RT) was <150ms or >2500ms were excluded, along with trials in which the RT fell $\pm 3SD$ from the mean. Subjects were excluded from analyses if more than 10% of trials were reaction time outliers. Subjects were also required to perform above chance accuracy ($\geq 55\%$) to ensure that they were exposed to the intended asymmetrical (3 : 1) reinforcement schedule.

Next, signal detection analysis⁴⁸ was used to calculate response bias and discriminability (the ability to distinguish between the mouth sizes) for each block of the task using the formulae:

$$\text{Response bias : } \log b = \frac{1}{2} \log \left(\frac{Rich_{correct} * Lean_{incorrect}}{Rich_{incorrect} * Lean_{correct}} \right)$$

$$\text{Discriminability : } \log d = \frac{1}{2} \log \left(\frac{Rich_{correct} * Lean_{correct}}{Rich_{incorrect} * Lean_{incorrect}} \right)$$

To compute values for cases that had a zero in the formula, 0.5 was added to every cell in the matrix. Although discriminability is commonly the key outcome of interest in signal detection tasks, response bias was the key outcome of interest in this study because it provides a measure of the degree to which the participant implicitly learns to alter their behavior as a function of the asymmetrical reinforcement schedule. Hence, response bias provides a behavioral readout of an individual's responsivity to reward.

Genetic Information

DNA extraction and genotyping were completed by the Hope Center DNA/RNA Purification Core at Washington University School of Medicine. DNA was extracted from saliva samples collected using Oragene DNA Self-Collection Kits (DNA Genotek, Ottawa, Canada). Single nucleotide polymorphism (SNP) genotyping assays for rs16969968 were run in duplicate using the KBiosciences Competitive Allele-Specific PCR SNP genotyping system (KASPar). Alleles (A = minor, G = major) were coded to test a dominant genetic model, i.e., comparing carriers with at least one copy of the risk allele (A/A or A/G) to those without (G/G).

Statistical Analyses

The effects of nicotine on response bias and discriminability were analyzed with a 2 (*Drug*: placebo, nicotine) \times 3 (*Block*: 1, 2, 3) \times 2 (*Order*: placebo first, nicotine first) analysis of variance (ANOVA). *Drug* and *Block* were within-subjects factors and *Order* was a between-subjects factor. Order was included given prior evidence showing that order of nicotine administration may moderate nicotine's effects on reward learning.¹¹

Genetic effects were examined using a 2 (*SNP*: A-allele carrier, non-A-allele carrier) \times 2 (*Drug*) \times 2 (*Order*) \times 3 (*Block*) ANOVA.

SNP was a between-subjects factor. Given that allele frequency is known to differ in Caucasian individuals relative to individuals of other races,²⁴ we ran this analysis both in the whole sample and in Caucasians alone. Finally, the moderating effects of negative affective traits were examined with regression models for repeated-measures data using the xtreg procedure in STATA 13.0 that included effects of *Drug*, *Order*, and *Block*, along with *Trait* and *Drug × Trait* terms.

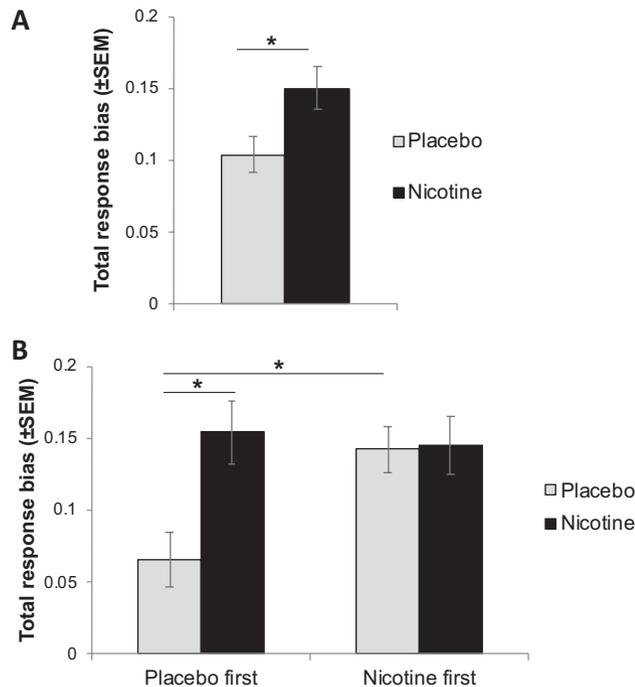


Figure 1. Results showed a main effect of *Drug* (A), where averaged across blocks and order, response bias was significantly higher in the nicotine relative to the placebo condition. There was also a trend-level *Drug × Order* interaction (B), which was driven by higher response bias in the nicotine relative to the placebo condition in those who received the placebo first, but not in those who received nicotine first. Furthermore, response bias in the placebo condition was higher for those who received nicotine first relative to those who received the placebo first. * $p < 0.05$.

Tests for moderating effects of *Sex* were also examined and are reported in the *Supplement*.

Results

Sample Characteristics

In total, 116 participants completed the PRT, and 106 had valid data for both the placebo and the nicotine conditions (all participants retained in the analysis had a minimum of 80% valid trials; Mean \pm SD = 294 \pm 10). Of the 10 participants who were excluded, 4 were A-allele carriers and 6 were non-A-allele carriers. $n = 115$ participants provided a saliva sample for genotyping, therefore one individual was not included in the genetic subgroup analysis. Sample characteristics are shown in [Table 1](#).

Effects of Nicotine on Response Bias

A main effect of *Block* emerged from the ANOVA, $F(2,208) = 36.12$, $p < 0.001$, $\eta_p^2 = 0.26$, where averaged across drug conditions, response bias in blocks 2 and 3 was significantly higher than in block 1 (both p s < 0.001), indicating that the task was effective at inducing a response bias toward the more frequently rewarded stimulus. Furthermore, a main effect of *Drug* emerged, $F(1,104) = 4.11$, $p = 0.045$, $\eta_p^2 = 0.04$, where averaged across blocks, response bias was significantly higher in the nicotine relative to the placebo condition ([Fig. 1A](#)). Finer-grained analyses showed that this was due to nicotine increasing correct identification of the rich stimulus on trials following non-rewarded trials (see [Supplement and Fig. S1](#)).

There was also a trend-level *Drug × Order* interaction, $F(1,104) = 3.52$, $p = 0.06$, $\eta_p^2 = 0.03$, which was further explored in light of prior findings.¹¹ Bonferroni-corrected post hoc tests showed that this interaction was driven by higher response bias (averaged across blocks) in the nicotine compared to the placebo condition, but only for those who received the placebo condition first (placebo first: $p = 0.01$; nicotine first: $p = 0.91$; [Fig. 1B](#)). Furthermore, response bias in the placebo condition was higher for those who received nicotine first compared to those who received placebo first ($p = 0.003$). We confirmed that the effects were specific to reward processing, as the key findings remained significant when controlling for the effects of

Table 1. Sample characteristics

	Whole sample ($n = 106$)	A-allele carriers ($n = 52$)	Non-A-allele carriers ($n = 53$)	Test	df	p
Age, M (SD)	20.32 (1.93)	20.29 (1.94)	20.28 (1.88)	$t = 0.02$	103	0.99
Male, N (%)	68 (64.2)	33 (63.5)	35 (66.0)	$\chi^2 = 0.12$	1	0.73
Education, M (SD)	3.13 (0.90)	3.08 (0.93)	3.13 (0.79)	$t = 0.33$	103	0.74
Caucasian, N (%)	79 (74.5)	44 (84.6)	34 (64.2)	$\chi^2 = 5.50$	1	0.02
Hispanic, N (%)	13 (12.3)	8 (15.4)	5 (9.4)	$\chi^2 = 0.93$	1	0.34
Age 1 st smoke, M (SD)	16.22 (2.14)	16.48 (1.72)	15.92 (2.47)	$t = 1.34$	103	0.19
Years smoked, M (SD)	3.35 (2.33)	3.23 (1.97)	3.42 (2.66)	$t = 0.40$	103	0.69
HONC, M (SD)	3.59 (2.86)	3.58 (2.96)	3.58 (2.81)	$t = 0.01$	103	0.99
Smoking Pros, M (SD)	22.55 (6.67)	23.96 (6.91)	21.26 (6.23)	$t = 2.10$	103	0.04
Smoking Cons, M (SD)	25.54 (7.91)	24.88 (8.49)	26.15 (7.40)	$t = 0.82$	103	0.42
Fawcett, M (SD)	141.60 (18.04)	141.79 (19.41)	141.13 (16.82)	$t = 0.19$	103	0.85
NEO-Dep, M (SD)	14.45 (5.77)	14.44 (6.10)	14.45 (5.47)	$t = 0.01$	103	0.99
NEO-Anx, M (SD)	16.03 (4.65)	15.96 (4.78)	16.09 (4.57)	$t = 0.15$	103	0.89
SMOQ-Neg, M (SD)	68.62 (22.97)	68.60 (21.60)	68.64 (24.46)	$t = 0.01$	103	0.99

Note. M = Mean; SD = Standard deviation; HONC = Hooked on Nicotine Checklist; Smoking Pros = measure assessing positive attitudes to smoking; Smoking Cons = Measure assessing negative attitudes to smoking; Fawcett = Fawcett-Clarke Pleasure Scale; NEO-Dep = Depression facet of the NEO Personality Inventory Neuroticism Scale; NEO-Anx = Anxious facet of the NEO Personality Inventory Neuroticism Scale; SMOQ-Neg = Smoking Motivations Questionnaire-Avoid negative emotions subscale. One individual did not provide a saliva sample for genotyping and was therefore not included in the genetic subgroup analysis.

nicotine on discriminability (a measure of overall task performance; see *Supplement*).

Moderating Effects of rs16969968

Although A-allele carriers ($n = 52$) did not differ from non-A-allele carriers ($n = 53$) on nicotine dependence severity on the HONC, $t(103) = 0.01$, $p = 0.99$, or the age at which they first smoked, $t(103) = 1.34$, $p = 0.19$, A-allele carriers scored higher than non-A-allele carriers on a measure evaluating positive attitudes towards smoking, $t(103) = 2.10$, $p = 0.04$, consistent with this risk allele's link with increased risk for nicotine dependence. The groups showed similar levels of negative affective traits (all $ps > 0.80$).

Whole Sample

When considering the entire sample, neither the main effect of *SNP* ($p = 0.73$) nor the *SNP* \times *Drug* interaction ($p = 0.97$) was significant.

Caucasians Only

There were 78 Caucasian individuals, of whom 44 were A-allele carriers and 34 were non-A-allele carriers. Although the main effect of *SNP* ($p = 0.93$) and the *SNP* \times *Drug* interaction ($p = 0.69$) were not significant, a significant *SNP* \times *Drug* \times *Order* interaction emerged, $F(1,74) = 5.40$, $p = 0.02$, $\eta_p^2 = 0.07$ (Fig. 2). This 3-way interaction was unpacked by examining all possible 2-way interactions. First, analyses showed that the *SNP* \times *Drug* interaction differed at levels of *Order*, with the interaction being significant for those who received nicotine first, $F(1,43) = 4.30$, $p = 0.045$, $\eta_p^2 = 0.09$, but not for those who received placebo first, $F(1,31) = 1.67$, $p = 0.21$, $\eta_p^2 = 0.05$. However, none of the post hoc tests of simple effects that comprised this interaction survived Bonferroni correction (all $ps > 0.05$). Second, analyses showed that the *Drug* \times *Order* interaction also differed at levels of *SNP*, with the interaction being significant for the A-allele carriers, $F(1,42) = 10.76$, $p = 0.002$, $\eta_p^2 = 0.20$, but not the non-A-allele carriers, $F(1,32) = 0.10$, $p = 0.76$, $\eta_p^2 = 0.003$. In this case, several post hoc tests of simple effects were significant after Bonferroni correction. Specifically, for A-allele carriers, response bias (averaged across blocks) was significantly higher in the nicotine

relative to the placebo condition for those who received the placebo first ($p = 0.01$), whereas response bias was trend-level lower in the nicotine relative to the placebo condition for those who received nicotine first ($p = 0.06$). Similarly, for A-allele carriers, response bias was higher in the placebo condition for those who received nicotine first relative to those who received placebo first ($p < 0.001$), whereas there was a trend for response bias to be lower in the nicotine condition for those who received nicotine first relative to those who received placebo first ($p = 0.08$). These findings suggest that in Caucasian individuals carrying a genetic polymorphism linked to increased risk for nicotine dependence, nicotine produced a higher response bias relative to placebo, and the ability for prior nicotine exposure to influence reward processing in the placebo condition was stronger (see *Tables S1 and S2* for ANOVA tables).

Competing theories posit that rather than influencing reward function specifically, nicotine may enhance cognitive function in A-allele carriers.²³ To test this, we conducted the same analysis using the PRT discriminability scores. Discriminability measures more general task performance that is unrelated to the asymmetrical reinforcement schedule and therefore provides a proxy measure of reward-independent cognitive functioning. Results showed no main effects or interactions involving *SNP* for discriminability either in the whole sample or when examining Caucasian participants separately (all $ps > 0.10$). This suggests that our effects were likely specific to reward processing and not cognitive functioning.

Moderating Effects of Mood and Negative Affect Traits

We fitted regression models to examine whether two moderators related to mood (anhedonia and the tendency to smoke in response to negative emotion) and two moderators related to negative affective traits (depressive and anxious traits) moderated the reward-enhancing effects of nicotine. A separate regression model was run for each moderator. To control for multiple testing, we used a Bonferroni-corrected alpha level of 0.05×4 moderators/tests = 0.0125. Of the four moderators examined, only the *Drug* \times *Depressive traits* interaction was significant [$B = 0.006$, 95% confidence interval (CI) = 0.001–0.011, $p = 0.010$]. As shown in Fig. 3A,

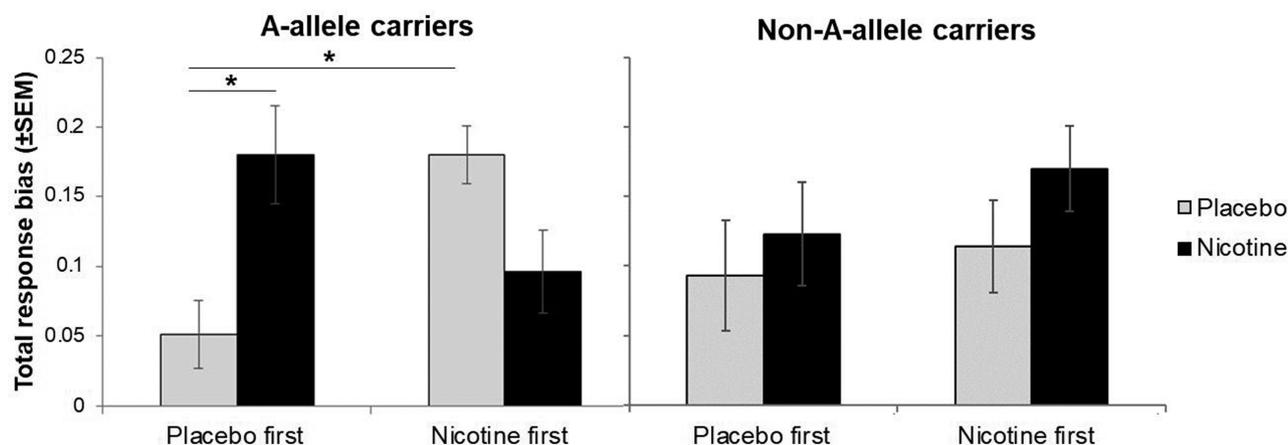


Figure 2. Figure shows the significant *SNP* \times *Drug* \times *Order* interaction in the Caucasian subset of the sample. The *Drug* \times *Order* interaction was significant in the A-allele carriers (left) but not in the non-A-allele carriers (right). Within the A-allele carriers, there was a significant increase in response bias in the nicotine relative to the placebo condition, but only for individuals who received the nicotine condition first. Furthermore, response bias in the placebo condition was higher for those who received nicotine first compared to those who received the placebo first. These findings suggest Caucasian young light smokers at increased genetic risk for nicotine dependence show greater increases in response bias following nicotine relative to a placebo and also show a greater propensity for prior nicotine exposure to influence reward processing following a placebo. * $p < 0.05$. *SNP*, single-nucleotide polymorphism.

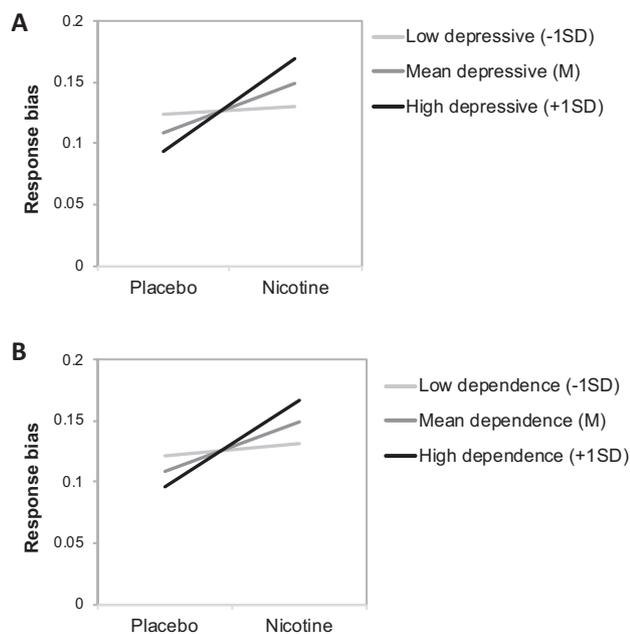


Figure 3. Figure shows the moderating effect of depressive traits (A) and nicotine dependence severity (B) on changes in response bias following nicotine relative to a placebo. For visualization purposes, predicted response bias for individuals with depressive trait scores and nicotine dependence scores at the mean (“Mean”), 1 SD above the mean (“High”) and 1 SD below the mean (“Low”) are plotted. The reward-enhancing effects of nicotine were stronger in young light smokers scoring higher on depressive personality traits and also in those reporting a greater sense of being “hooked” on nicotine.

the effects of nicotine on reward learning were stronger for individuals higher on depressive traits. These individuals showed a more blunted response bias following placebo, but potentiated response bias following nicotine.

Relationship to Nicotine Dependence

We fitted a final regression model to determine whether the reward-enhancing effects of nicotine were moderated by nicotine dependence on the HONC. The *Drug* × *HONC* interaction was significant [$B = 0.01$, $CI = 0.001-0.020$, $p = 0.03$]. As shown in Fig. 3B, a very similar pattern emerged for individuals scoring high on nicotine dependence as for individuals scoring high on depressive traits. Specifically, as dependence increased, the effects of nicotine on response bias became stronger.

Discussion

This study examined moderators of the reward-enhancing effects of acute nicotine in young light smokers. As predicted, relative to a placebo, exposure to acute nicotine enhanced reward responsiveness, evidenced by increased response bias on the PRT. This is consistent with prior studies showing that exposure to nicotine potentiates reward sensitivity,¹⁰⁻¹² likely via enhancing phasic striatal dopamine signaling.¹⁵ Furthermore, we observed order effects reported in prior studies,¹¹ wherein nicotine enhanced reward responsiveness even in the placebo condition for individuals who received the nicotine condition first, potentially via its effects on motivational salience. This also aligns with findings showing that in rodents, self-administration

of nicotine results in excitation of brain reward systems lasting up to 36 days after removal of nicotine availability⁴⁹ – a finding interpreted as evidence that nicotine may alter or “reset” the sensitivity of reward systems to a new, increased level.

The reward-enhancing effects of nicotine were also moderated by rs16969968 allelic variation. Specifically, in Caucasian participants carrying the A-allele, which is associated with increased risk for nicotine dependence,⁵⁰ nicotine produced a higher response bias relative to placebo, and this was not observed in non-A-allele carriers. Furthermore, the ability for prior nicotine exposure to influence response bias in the placebo condition was stronger in A-allele carriers than in non-A-allele carriers. These findings support prior work suggesting that the reductions in nAChR function evident in A-allele carriers may alter the effects of nicotine on striatal dopamine signaling.²¹ Although there are several purported mechanisms by which this allelic variation may impact striatal dopamine, compelling evidence suggests that it may reduce the negative effects of nicotine,⁵¹ thereby increasing nicotine’s pleasurable sensations. Competing theories suggest that A-allele carriers may smoke more to remediate cognitive deficits,²³ however our effects were specific to response bias and not discriminability (a measure of more general cognitive functioning).

The effects of acute nicotine on reward processing were also moderated by depressive traits. As predicted, individuals higher in depressive traits showed a more blunted response bias in the placebo condition, but an enhanced response bias following nicotine. This is consistent with prior studies showing blunted response bias in non-smokers with current and remitted MDD, but normative or increased response bias in smokers with these conditions.^{10,34} These findings indicate that young light smokers high on depressive traits may smoke to remediate deficits in reward processing. We observed highly similar effects when examining the moderating effects of nicotine dependence severity, indicating that depressive traits and nicotine dependence may moderate nicotine’s effects on the reward system in a similar manner.

These findings have several important implications for our understanding of how to reduce smoking behavior in young light smokers. First, it is clear that research focusing on the role of *CHRNA5* genetic variation on nicotine’s reward-enhancing effects may highlight avenues for novel treatment options in individuals with rs16969968 risk alleles. Furthermore, these findings emphasize the value of further research that examines the utility of pharmacogenetic optimization of smoking cessation interventions. Second, given that high levels of depressive traits may promote maintenance of smoking behavior because nicotine normalizes depression-related impairments in reward responsiveness, interventions aimed at enhancing reward deficits in these individuals may be beneficial in reducing the risk for ongoing smoking. These therapies may also be critical during smoking cessation attempts to minimize further reductions in reward responsiveness.

The order effects observed in the current study also warrant mention, as they further highlight the uniqueness of nicotine’s effects on the reward system relative to other drugs of abuse. To our knowledge, this study is now the third to observe a persistent amplification of reward sensitivity following acute nicotine exposure, which, unlike other reward-enhancing substances such as cocaine, extends beyond the early abstinence period. This effect has previously been observed in rodents, where the reward-enhancing effects of nicotine self-administration (measured via intracranial self-stimulation thresholds) persisted for 36 days

after nicotine intake had ceased.⁴⁹ The authors suggested that this may explain some of the unique properties of nicotine relative to other substances of abuse, such as why extended access to nicotine does not result in the same escalation of drug intake over time, as does extended access to cocaine.⁵² Similar order effects have also been observed in non-smoking, psychiatrically healthy humans using the same PRT used in the current study.¹¹ Aligning with our results, the authors found that exposure to acute nicotine via a transdermal nicotine patch resulted in increased reward responsiveness relative to placebo. However, reward responsiveness was also elevated following a placebo for those who received nicotine first, even though it had been at least 1 week since they had been exposed to the nicotine condition. Despite the consistency of these order effects across these three different studies, the interpretation of these effects is challenging and the possibility that they are partially driven by practice effects or Type I error cannot be ruled out. Further research is needed to test the robustness of these findings.

Some limitations of this study should be noted. This study was cross-sectional and longitudinal studies are needed to determine whether variability in the reward-enhancing effects of nicotine predicts individual differences in smoking trajectories long-term. Specifically, longitudinal studies could identify whether genetic and trait factors predispose certain individuals to initiate smoking, or whether they make smoking cessation more difficult. This is critical for evaluating whether efforts focused on reducing early experimentation or improving smoking cessation will be most effective at reducing the prevalence of light smoking. Finally, it is important to note that our genetic findings were in Caucasian individuals only, and we lacked the sample size to evaluate our effects in different race subgroups. Future studies should systematically evaluate these effects in individuals from different racial backgrounds.

In sum, our findings indicate that individual differences in the smoking trajectories of young light smokers may be associated with a genetic risk factor and personality traits that moderate nicotine's effects on reward processing. Accordingly, reducing rates of smoking in young light smokers may be improved by mitigating these effects using therapies that target the reward system, or by using these pre-existing factors to personalize treatment.

Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at <https://academic.oup.com/ntr>.

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Declaration of Interests

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