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Nicotine Administration Enhances Negative Occasion Setting in Adolescent Rats

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Abstract

Substantial research has established that exposure to nicotine during adolescence can lead to long-term changes in neural circuitry and behavior. However, relatively few studies have considered the effects of nicotine use on cognition *during* this critical stage of brain development. This is significant because the influence of nicotine on cognitive performance during adolescence may contribute to the development of regular nicotine use. For example, improvements in cognitive functioning may increase the perceived value of smoking and facilitate impulses to smoke. To address this, the present research tested the effects of nicotine on a form of inhibitory learning during adolescence. Specifically, adolescent rats were exposed to nicotine as they were trained in a negative occasion setting paradigm, in which successful performance depends on learning the conditions under which it is, or is not, appropriate to respond to a target stimulus. Here, we found that nicotine administration enhances negative occasion setting in adolescents. In addition, nicotine increased the amount of orienting behavior directed toward the inhibitory stimulus, suggesting that improvements in this form of behavioral inhibition may be attributed to nicotine-induced increases in attentional processing. These results may help elucidate the factors that contribute to the onset as well as continued use of products containing nicotine during adolescence and provide insight to increase the effectiveness of interventions targeted at reducing the prevalence of adolescent smoking.

Keywords

Nicotine; Adolescence; Inhibition; Behavior; Learning

Adolescence is a critical developmental period characterized by significant behavioral and neurobiological changes. During this time, individuals often forgo appropriate behaviors, especially in the face of reward, resulting in impulsive decisions and heightened risk taking behavior compared to any other age group [1]. For example, adolescents have an increased vulnerability to use and abuse drugs, including tobacco [2, 3]. Indeed, although the prevalence of tobacco use in the United States has decreased over the past decade, a

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significant percentage of adolescents still experiment with cigarettes and the use of smokeless tobacco products is rapidly escalating [4].

To date, most research on nicotine use during adolescence has focused on how exposure to nicotine during this critical stage of brain development can lead to long-term changes in neural circuitry and behavior later in life [5, 6]. By comparison, relatively few studies have considered the influence of nicotine on cognitive performance *during* adolescence. This is an important issue because substantial research suggests that adolescents are highly sensitive to the rewarding properties of nicotine [7, 8], which may contribute to the development of regular nicotine use during adolescence. To address this, we tested the effect of nicotine on adolescent rats as they were trained in a negative occasion setting paradigm. In this procedure, rats are presented with trials in which a “target” stimulus is presented by itself and followed immediately by the delivery of food reinforcement. On other trials, a “feature” stimulus is presented just before the target and on those trials, food is not delivered. Thus, rats must learn the conditions under which it is, or is not, appropriate to respond to the target stimulus. In this way, negative occasion setting reflects an essential aspect of adaptive behavior that is particularly relevant to the adolescent period, when individuals must learn the significance of cues in the environment in order to appropriately regulate behavior. Our prior studies have shown that adolescent rats exhibit difficulties using negative occasion setters to guide behavior compared to adults [9]. Here, we hypothesized that nicotine administration would enhance negative occasion setting in adolescents, perhaps contributing to the propensity of adolescents to use nicotine-containing products.

Sixteen male Long Evans rats were obtained from Harlan Laboratories (Indianapolis) at 21 days of age. Rats were housed and maintained as described previously [9] and in compliance with the Association for Assessment and Accreditation of Laboratory Animal Care guidelines and the Dartmouth College Institutional Animal Care and Use Committee. After acclimating to the colony, body weights were reduced to 85% of the daily weight of free-feeding age-matched controls, and rats received intraperitoneal injections of vehicle (sterile 1× phosphate buffered saline) for four days to acclimate them to the injection procedures. Behavioral training subsequently began on post-natal day (PND) 35 and continued for 20 days. Vehicle solution or (−) nicotine hydrogen tartrate (equivalent of 0.35 mg/kg free-base nicotine, Sigma Aldrich Co., St. Louis, MO, USA) was prepared daily and administered 10 min before each training session [10]. The behavioral procedures were carried out in standard conditioning chambers as described previously [9]. Briefly, each 68-min daily conditioning session consisted of four reinforced and 12 non-reinforced presentations (5-sec in duration) of a 1500 Hz, 78 dB tone (target stimulus). During reinforced trials the tone was followed immediately by the delivery of two food pellets (Bioserv). On non-reinforced trials, a 2.8 W white panel light (feature stimulus) was presented for 5 sec, followed by a 5 sec empty period, and then a 5 sec presentation of the tone, after which no food was delivered.

The primary variable of interest was the number of sessions that were required until rats exhibited successful discrimination between reinforced and non-reinforced presentations of the tone. As described previously [9], this was assessed by recording the amount of time that a photobeam located across the entry to food cup was broken during the presentation of the

tone. The difference in responding during the tone on the two trial types was calculated and Z-scores were generated by dividing the difference by the SEM of the difference in responding. Successful discrimination between the two trial types was defined as a greater amount of time spent in the food cup during presentation of the tone on reinforced trials than during non-reinforced trials (a Z-score of at least 2.325, $P < 0.01$) for 3 consecutive daily sessions, as in prior studies [9, 10]. In addition, the difference in responding between trial types was subjected to a repeated-measures analysis of variance (ANOVA).

The amount of time spent with the head in the food cup during the tone on reinforced and non-reinforced trials is illustrated in (Figure 1). Adolescents that received nicotine discriminated between reinforced and non-reinforced trial types sooner than vehicle-treated rats. Specifically, nicotine-injected rats required only 11 sessions ($Z = 2.89$, $p < 0.005$) to exhibit significantly different responding during the two trial types and this discrimination was maintained for the duration of training. In contrast, vehicle-injected rats failed to reach criterion for differential responding during the 20 training sessions. A multivariate ANOVA indicated that exposure to nicotine did not influence overall levels of conditioned responding [$F(2,13) = 2.1$, $p = 0.2$]. Indeed, the average time spent in the food cup was similar for both groups during reinforced trials (2.0 ± 0.3 s for nicotine-treated rats, 2.0 ± 0.1 s for vehicle-treated rats; $p > 0.9$) and during non-reinforced trials (1.6 ± 0.2 s for nicotine-treated rats, 1.8 ± 0.1 for vehicle-treated rats; $p > 0.4$).

The average difference scores across the 20 training sessions for each group are shown in Figure 2. A repeated measures ANOVA indicated a significant main effect of training [$F(1,19) = 6.07$, $p < 0.001$] indicative of differential responding between trial types for all rats. The analysis did not support a main effect of drug [$F(1,14) = 2.98$, $p > 0.1$], indicating that across the 20 training sessions the discrimination magnitude was not significantly different between vehicle-treated rats and nicotine-treated rats. However, there was a significant interaction between time and drug [$F(1,19) = 1.71$, $p < 0.05$] indicating that the magnitude of discrimination between trial types increased faster in nicotine-treated rats compared to vehicle-treated rats.

To test for potential drug-induced changes in baseline responding or motivation, we also measured the amount of time spent with the head in the food cup during the 5-sec period immediately before any stimuli were presented (Pre-stimulus epoch) and the 5-sec period immediately after food was delivered on reinforced trials (Post-Tone epoch), respectively. A one-way multivariate ANOVA revealed that nicotine did not significantly influence Pre-stimulus responding [$F(2,13) = 1.90$, $p > 0.1$]; the mean amount of time spent in the food cup during the Pre-stimulus epoch was very low for both groups and did not differ between reinforced trials (0.18 ± 0.02 sec for nicotine-treated rats, 0.28 ± 0.05 sec for vehicle-treated rats) or non-reinforced trials (0.23 ± 0.03 sec for nicotine-treated rats, 0.3 ± 0.04 sec for vehicle-treated rats). In addition, nicotine did not alter amount of time spent in the food cup after food was delivered [$F(2,13) = 0.27$, $p > 0.7$]. The Post-Tone food cup behavior on reinforced trials was comparably high in both groups (3.2 ± 0.3 for nicotine-treated rats, 3.8 ± 0.3 for vehicle-treated rats). Thus, drug treatment did not appear to affect primary motivation for the food reinforcer or the ability to obtain the reinforcer from the cup.

Another variable of interest was orienting behavior during presentation of the light on non-reinforced trials. Orienting was defined as rearing on the hind legs with both forepaws off the ground and was assessed by measuring the amount of time that photobeams mounted just under the light stimulus were broken. Orienting behavior is an often-used measure of attentional processing of a stimulus [11] and previous work has shown that nicotine may enhance inhibition of responding to the target stimulus on non-reinforced trials by increasing attention to the feature stimulus [10]. As shown in Figure 3, nicotine-treated rats exhibited significantly higher levels of rearing behavior [$t(14) = -5.6$, $p < 0.001$] during presentation of the light compared to vehicle-treated. Importantly, baseline (Pre-stimulus) rearing behavior was comparably low in nicotine-treated rats (0.12 ± 0.03 s) and vehicle-treated rats (0.07 ± 0.02) and did not differ significantly [$t(14) = -1.69$, $p > 0.1$].

To summarize, the present study tested the effects of nicotine on a form of inhibitory learning during adolescence in order to inform our understanding of the psychosocial factors that contribute to the initiation and/or continuation of smoking during this developmental period. The results indicate that exposure to nicotine during adolescence enhances learned inhibition that is manifest in negative occasion setting. Indeed, nicotine-treated rats discriminated between reinforced and non-reinforced presentations of the target stimulus in fewer sessions than vehicle-treated rats. Furthermore, the magnitude of the discrimination increased at a faster rate as a result of nicotine treatment. Importantly, overall levels of conditioned responding were comparable in both groups, suggesting that the observed differences in discrimination were not likely due to nicotine-induced changes in motivation or general activity.

Previous research has implicated the cholinergic system in attentional effort, orienting behavior, and the detection of behaviorally significant stimuli [12]. Related to this, a second major finding of the present experiment was that nicotine-treated rats exhibited more orienting behavior during presentation of the feature stimulus, indicative of increased attentional processing of that cue. Thus, the nicotine-induced facilitation of negative occasion setting may reflect an increase in attention directed to the feature, which may enhance the ability to withhold responding during the tone on the non-reinforced trials.

Relatedly, nicotine may enhance negative occasion setting in adolescence by influencing functions mediated by prefrontal cortex. We have previously shown that negative occasion setting is dependent on the prefrontal cortex [13]. Structural and functional maturation of prefrontal cortex continues through the adolescent period [14, 15] and nicotine exposure during adolescence has been shown to influence the induction of plasticity associated genes, particularly in the prefrontal cortex, and thereby affect prefrontal network development and function [16, 17]. This may at least partially explain why the early use of cigarettes during adolescence has been associated with heightened risk for later dependence [18].

Improvements in cognitive functioning may influence the perceived value of smoking, and expectancies likely impact smoking-specific risk-taking behavior by facilitating impulses to smoke a cigarette when the anticipated consequences of smoking are positive. This may be especially apparent during adolescence, when positive expectancies develop as a result of heightened sensitivity to rewards during this period [19]. Nicotine may augment learning

during negative occasion setting by influencing mechanisms involved with the incentive processing of the target cue. Indeed, alterations in neural activity associated with adolescent nicotine exposure are particularly evident in several reward-related regions, including ventral striatum, basolateral amygdala, and ventral tegmental area [8, 20]. In particular, neural responses in ventral striatum markedly decreased during reward anticipation in adolescent smokers [21]. Conversely, repeated exposure to nicotine has also been shown to enhance the incentive salience of concurrently available reinforcers as well as increasing instrumental responses directed towards obtaining reinforcers [22, 23]. Follow up studies will be needed to address whether manipulating target-cue salience through either of these mechanisms influences negative occasion setting.

Finally, these data are consistent with previous findings from our laboratory indicating that administration of nicotine enhances negative occasion setting in adult rats [10], suggesting that the effects in adolescents may be mediated by similar neurobiological mechanisms. However, although cholinergic innervation of regions that are necessary for negative occasion setting (e.g., prefrontal cortex) are present by adolescence [24], more recent behavioral evidence suggests the *functional* capacity of this system remains underdeveloped for much longer [25]. Furthermore, previous research has established differences between adolescent and adult rats in sensitivity to nicotine as well as the specific loci that nicotine influences brain activity most [26]. As a result, nicotine exposure during adolescence may be particularly influential with regards to improving cognitive control. Future studies should address whether adolescent rats are more or less sensitive to the effects of nicotine on occasion setting than adults.

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Highlights

- We test the effects of nicotine on a form of inhibitory learning in adolescent rats
- Nicotine improved behavioral inhibition in a negative occasion setting paradigm
- Improved cognitive functioning may contribute to the adolescent nicotine use

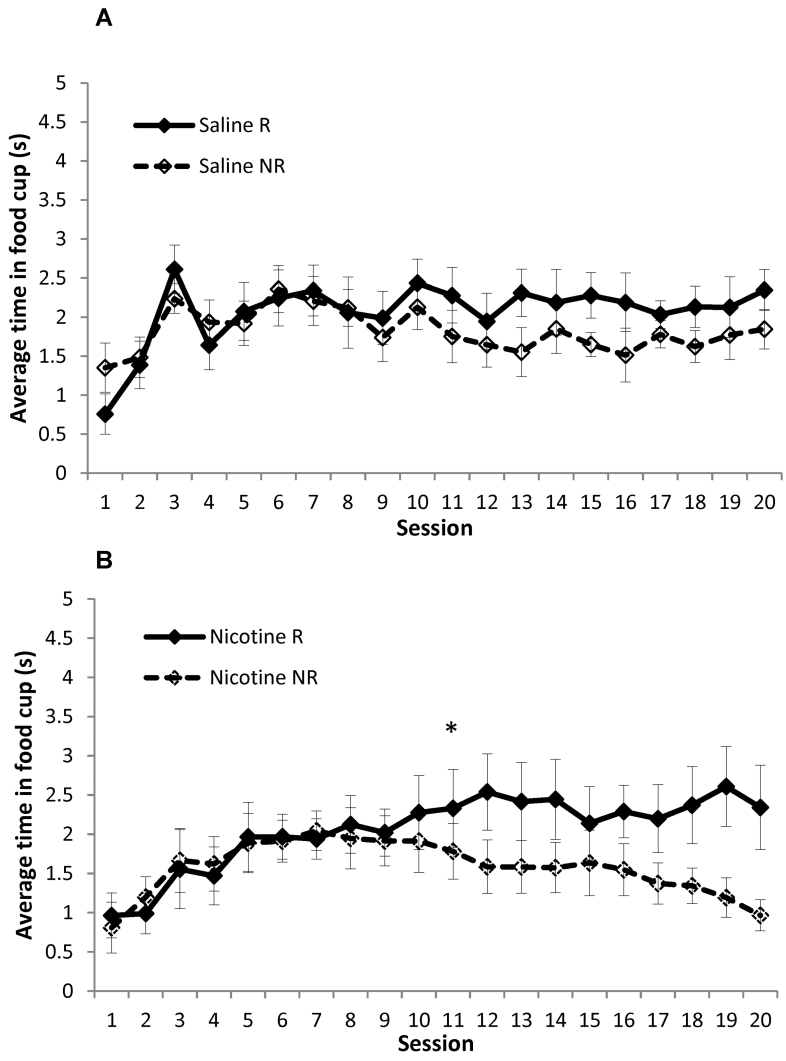

Figure 1.

Food cup behavior during presentation of the tone on reinforced (R) and non-reinforced (NR) trials in saline-treated (panel A) and nicotine-treated (panel B) rats. Nicotine-treated rats learned to discriminate between trial types on session 11, while saline-treated rats did not reach the criterion for successful discrimination at any point during training. *$p < 0.005$. Data are means ± *SEM*.

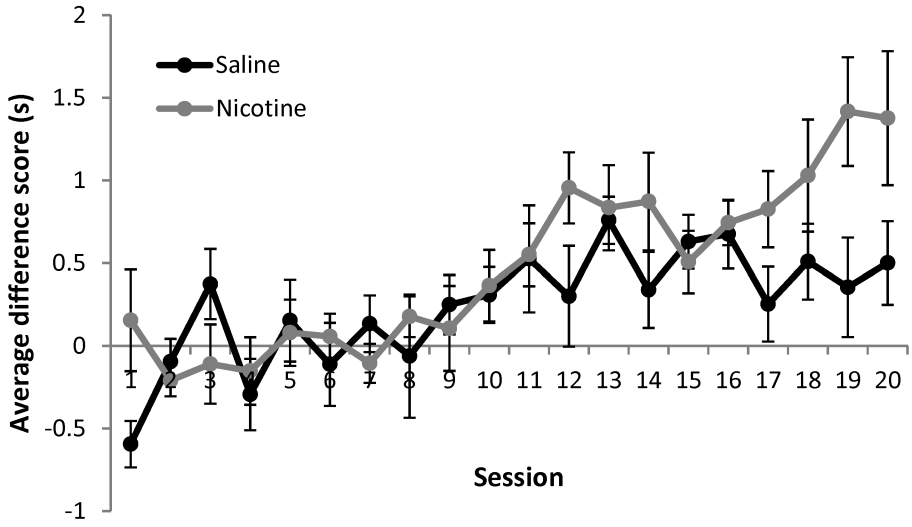

Figure 2.

Average difference in the time spent in the food cup during the presentation of the tone on the two trial types. Data are means ± *SEM*.

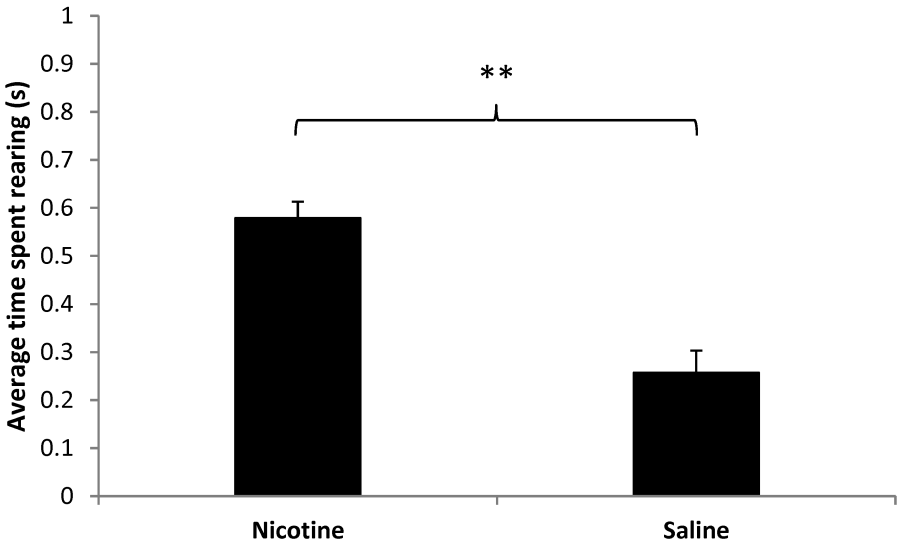

Figure 3.

Average time spent rearing during the presentation of the light on non-reinforced (NR) trials. **p < 0.001. Data are means ± *SEM*.