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Does nicotine alter what is learned about non-drug incentives?

Thesis submitted in partial fulfillment of Honors.

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## Abstract

Nicotine is one of the most addictive drugs known to man, yet it has limited reinforcing effects in humans and non-human animals when it is not self-administered in tobacco products. One hypothesis for these paradoxical effects of nicotine is that the effects of the drug in the brain alter acquisition of incentive learning. The hypothesis for this study is that nicotine will increase the value of cues paired with a reward. To test this hypothesis, 26 Sprague Dawley Male rats were randomly assigned to one of three groups Pre-NIC (the critical experimental group), Post-NIC and SAL. Each group received a subcutaneous injection 15 min prior to testing and another injection 1-3 h after testing. For the Pre-NIC group, nicotine (0.4 mg/kg base) was injected 15 min before test sessions; placebo was administered after testing. For the Post-NIC group the order of injections was reversed, and this manipulation controls for total exposure to nicotine. The SAL groups received placebo injections before and after testing. Rats were shaped to respond for 10% sucrose for pressing an illuminated nose-key (Experiment 1) or 0.2% saccharin for pressing a lever (Experiment 2). Responding in the Pre-NIC group was higher than all other groups in Experiment 2 (saccharin reward); however, responding in the three groups was similar in Experiment 1 (sucrose reward). This paradigm highlights how nicotine can increase motivation for rewards, but that the facility of operant behaviors and caloric value of the reward may mask this effect.

## Introduction

Nicotine is a quaternary nitrate found in high concentrations in tobacco, and tobacco smoke is considered to be the addictive ingredient in tobacco. Nicotine is a psychomotor stimulant that acts on the reward pathways of the brain by increasing the release of dopamine. Dopamine is a neurotransmitter associated with reward and when nicotine is administered it distributes quickly to perfuse central nervous system tissues and increase the level of dopamine available to the surrounding cells, reaching the height of its influence approximately ten-seconds after inhalation.

This effect, however, is transient and smoking behavior increases to produce the same sense of pleasure once again. The alteration this elicits in the brain chemistry of long-time tobacco users is not a minor thing. Persistent exposure to the effects of nicotine result in changes dopaminergic receptors in the brain. These receptors become assimilated to the increased levels of dopamine to be had. Natural dopamine production decreases as a result of nicotine influencing its production, such that when nicotine is not actively in use dopamine production is limited. This change in chemistry regarding the receptors explains in part the occurrence of withdrawal symptoms.

Those tobacco users who are actively trying to quit are faced with feelings of irritability, depression, lessened quality of sleep and cognitive impairment due to an inability to focus. These symptoms of withdrawal will eventually these negative non-pleasurable experiences decrease the likelihood that a tobacco user will successfully discontinue tobacco use. By understanding the above changes in brain chemistry it comes as no surprise that people are setup for failure in smoking cessation attempts. This is compounded when reports by The World Health Organization (2013) cite that tobacco related deaths account for 6-million deaths per year and of

those deaths 600,000 are due to secondhand exposure.

Despite these very real consequences, and despite the fact that the CDC reports that tobacco related deaths are the number one preventable deaths in the US, people continue to use tobacco. This would suggest that nicotine is a very potent drug that reinforces smoking behavior; however, nicotine is not all that reinforcing despite the neurobiological changes it can elicit (Palmatier, et al. 2007). An important effect of nicotine piece of the puzzle comes from the cues associated with nicotine (e.g. tastes and smells of tobacco) which are powerful motivators in smokers.

Nicotine through the dopaminergic reward pathway has the ability to influence the environment and behaviors surrounding the use of tobacco which increases these behaviors. Nicotine not only smoking behavior in general, it increases associated with paired stimuli that people engage in while smoking. For example, if tobacco use coincides with social drinking, the pleasure one derives from social drinking will be increased. In essence nicotine is changing what is learned about these paired cues.

Our data suggests that nicotine is actively influencing the reward pathway of the brain and changing what is learned about the cues associated with the reception of nicotine. Our studies have indicated that nicotine supports low rates on operant behavior in pre-clinical models of nicotine dependence such as rodent self-administration. However, nicotine administered when its administration coincides with the receiving of another reward. Moreover, this change in behavior continues after nicotine has been removed and is replaced with placebo. This data illustrates that nicotine is acting on the reward pathways of the brain in an observable and measurable way demonstrating the psychopharmacological consequences of nicotine use.

Previous studies have shown intravenous injections of nicotine support operant

responding in non-human animals. This behavior can be reduced by substituting something else for nicotine, such as saline, or by injecting the subject with an agent that blocks nicotine's effects on receptors. (Goldberg, Spealman, and Goldberg, 1981) Thus, showcasing that nicotine is indeed acting on the nervous system in an observable and measureable way.

The effect that nicotine has on the learning areas of the brain, through nicotinic acetylcholine receptors (nAChR's) throughout the basal ganglia, is highlighted in a study by Havekes, Abel, and Van der Zee (2011). This system is especially important for procedural learning; the ability to learn a task and recall it which is crucial in developing sensory motor skills. The researchers indicated that nicotine, which acts nAChRs, can facilitate the release of dopamine and by doing so increase the firing of dopaminergic neurons and increase dopamine release in the ventral striatum. The reward pathway in the brain, which is activated by dopamine when rewards are introduced, would have an increase in activity with nicotine in the system. This activity would produce an increased level of to pursue a reward which has been paired with nicotine. The areas of the brain associated with this type of learning, the ventral striatum and the hippocampus, are activated when a rat is learning a task. The levels of acetylcholine (ACh) in these areas increase during the period when a rat is learning the task. These areas are both influenced by ACh release which can be facilitated by nicotine (Havekes, et al 2011).

Nicotine is an addictive drug, and as with any addictive drug the use of nicotine can be facilitated by cues in the environment. Stimuli associated with nicotine increase the probability of smoking nicotine again by evoking craving and approach behaviors. This is shown in a study conducted by Kuhn and Gallinat (2011) who studied the areas of the brain that are activated by cues associated with past experience with nicotine, specifically in the ventral striatum. In this study, they examine how nicotine changes what is learned in the acquisition of a reward by

acting on the biological pathway associated with those behaviors. The researchers were able to show areas of the brain that were activated by nicotine associated 'cues' (e.g. viewing someone smoking or seeing a lit cigarette in an ashtray). Activity in the ventral striatum was positively correlated with self-reported craving for nicotine. This reaction to the cues for nicotine identifies areas in the brain that are affected by drug dependency including the ventral striatum (Kuhn, et al 2011).

Nicotine induces positive reinforcing effects in animals - in the mesolimbic dopamine pathway by working on nicotinic acetylcholine receptors- and increases the production of dopamine in this area causing pleasure and thus promoting repeated use of the drug (Mederdichian, Rees, Wayne and Connolly, 2007). However, the paradoxical weakness of nicotine as a primary reinforcer and inducer of pleasure (Palmatier et. al, 2006) and the potent effects of nicotine-associated cues on behavior suggest that memory is affected by nicotine- specifically in the ventral striatum, cortex, and hippocampus. These areas are saturated with acetylcholine receptors and nicotine can act on these receptors affecting memory associated with the intake of nicotine, and the activities one participates in when doing so (Robinson, Platt and Riedel, 2011).

All of the aforementioned studies add up to nicotine playing an active role in altering learning and memory in ways we do not understand fully. Further research is then needed to better grasp the affects of nicotine in these areas of the brain and on the behaviors they control. By comprehending the biological effects of nicotine we could increase our understanding of just how nicotine works in the brain and the responses it elicits which would be very helpful in the treatment and prevention of nicotine and tobacco addiction.

The objective of this experiment was to investigate whether nicotine altered the

acquisition of rewards during incentive learning procedures. Palmatier's previous findings show that prior exposure to nicotine increases a rat's sensitivity to reward associated cues. The rats that learn to associate a response with the reward (sucrose) under the influence of nicotine may be more motivated to receive the reward when compared to those that did not receive nicotine (control group), or did not receive nicotine overlapping with the learning experience to obtain the reward (Post-NIC group). We were interested in determining at what point the rats' exposure to nicotine affected their motivated behavior. For many years nicotine and its effects on behavior and learning have been under serious review because of the drug's addictive affects and the changes it produces in people who smoke, not to mention the increased probability of serious diseases such as heart attack and stroke. To better understand these affects and nicotine's role in behavior modification we investigated varying exposure times to nicotine and the responses and changes in behavior, it elicited.

### Method

*Subjects.* Male Sprague-Dawley rats (n=26) varying in weight from 220-280 grams, were supplied by Charles River (Portage, ME USA). The rats were housed in single-occupant cages under constant temperature (20-21 °c) and a controlled 12/12 hour reversed light-dark cycle (light on at 3 a.m. and off at 3 p.m.) the rats were allowed to assimilate to this environment for 7 days. The rats had free access to food and water during this period before being restricted to 100% body weight for the duration of operant conditioning procedures.

### Materials and Procedure

*Drugs.* Nicotine ditartrate was dissolved into sterile physiological saline, and neutralized to a pH of 7.0. Nicotine was injected subcutaneously (0.4 mg/kg base). Sterile physiological saline was also injected subcutaneously in the role of placebo.



*Procedures:*

*Experiment 1:* The rats were placed in transparent operant conditioning boxes inside of sound attenuated chambers outfitted with a white noise fan to decrease external sound. The rats were allowed to assimilate to the operant conditioning boxes before the rats were shaped to make nose-poke responses for sucrose. The trial consisted of conditioning the rats to respond for 10% sucrose when paired with discriminative stimulus – illuminated nose-key. Their responses –nose pokes- were monitored and recorded using a PC running MedPC software (MedAssociates Inc., USA) that also recorded the amount of sucrose deliveries the rat received in the receptacle for the dipper.

*Experimental Design:*

The male rats were randomly assigned into one of three groups (n=8/group) SAL, Pre-NIC, and Post-NIC. All groups received 2 injections per day, one injection 15 minutes prior testing and one injection 3 hours after testing. The SAL group was only exposed to saline (both injections placebo), and serves as a group that shows basal responding for sucrose rewards. A second group (Post-NIC) received an injection of saline 15 minutes before testing and an injection of nicotine (0.4 mg/kg base) approximately 3 hours after the test sessions. This group controlled for total exposure of nicotine. The experimental group (Pre-NIC) received an injection of nicotine (0.4 mg/kg base) 15 minutes prior to testing sessions and an injection of placebo (physiological saline) 3 hours after testing.

*Experiment 2:* The rats were placed in transparent operant conditioning boxes inside of sound attenuated chambers outfitted with a white noise fan to decrease external sound. The rats were allowed to assimilate to the operant conditioning boxes before the rats were shaped to respond on

levers for 0.2% saccharin. The trial consisted of conditioning the rats to respond for 0.2% saccharine when paired with discriminative stimulus – a magazine light turning on. Their responses –pressing a lever- were monitored and recorded using a PC running MedPC software (MedAssociates Inc., USA) that also recorded the amount of time the rat spent with their head in the receptacle for the dipper.

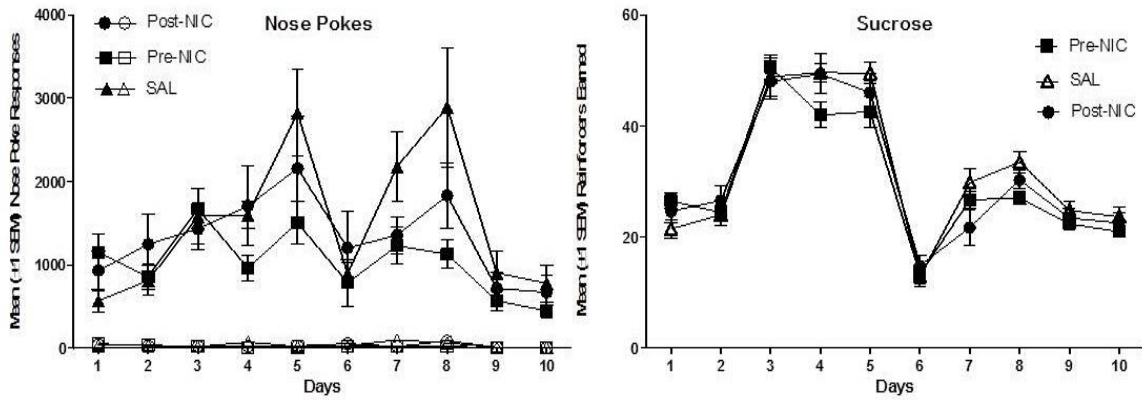
*Experimental Design:*

The male rats were randomly assigned into one of three groups SAL, Pre-NIC, and Post-NIC. All groups received 2 injections per day, one injection 15 minutes before testing and one injection 3 hours after testing. The SAL group was only exposed to saline (both injections are placebo), and serves as a comparison group that shows basal responding for sucrose rewards. A second group (Post-NIC) received an injection of saline 15 minutes before testing and an injection of nicotine (0.4 mg/kg base) approximately 3 hours after the test sessions. This group controlled for total exposure of nicotine. The critical experimental group (Pre-NIC) received an injection of nicotine (0.4 mg/kg base) 15 minutes prior to testing sessions and an injection of placebo (physiological saline) 3 hours after testing.

Results:

*Experiment 1:*

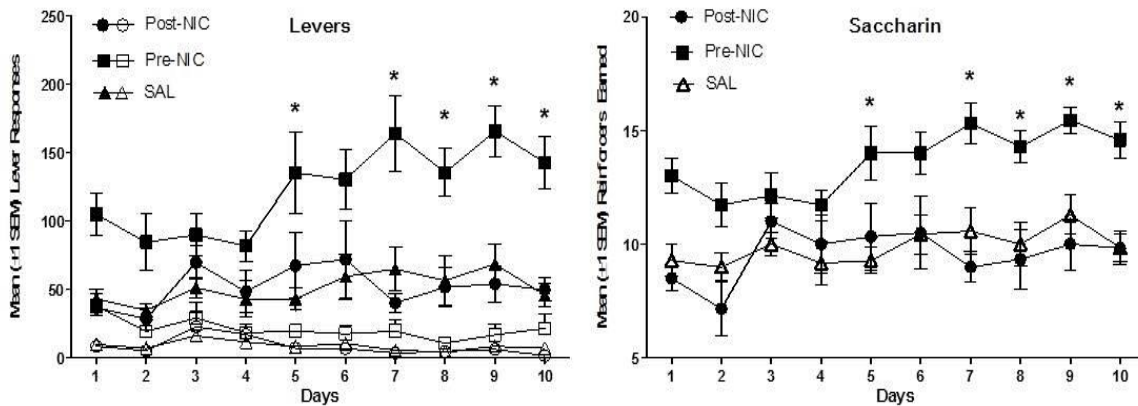
**Fig. 1**



**Figure 1.** The left panel illustrates average responses on the active and inactive nose-keys across the first 10 test sessions. The right panel illustrates the number of reinforcers earned (10% sucrose) on each of these test days. As illustrated in the figures, there were no significant differences between groups ( $p \geq 0.92$ ) on either measure of reinforcement.

**Experiment 2:**

**Fig. 2**



**Figure 2.** The left panel illustrates average responses on the active and inactive levers across the first 10 test sessions. The right panel illustrates the number of reinforcers earned (0.2% saccharin) on each of these test days. Pretreatment with nicotine increased responding for saccharin, as indicated by significant main effects of Group, Session, and a significant Group x Session interaction ( $p < 0.01$ ) for both active lever responses (left panel) and reinforcers earned (right panel). There were no significant differences in inactive lever responses ( $p \geq 0.24$ ). Follow-up analyses confirmed that rats in the Pre-NIC group responded more for saccharin and earned more saccharin reinforcers than rats in the SAL group on sessions 5 and 7-10. \* indicates Pre-NIC different from SAL,  $p < 0.05$ .

### Discussion:

This study investigated the role of nicotine on acquisition behavior in male Sprague-

Dawley rats operating under a Pavlovian conditioned reinforcement paradigm. The first experiment (operant responding for sucrose) was confounded by the rats becoming satiated by the caloric load of the sucrose. The rats did not exhibit significant levels of responding for the rewards despite being on an optimal weight restriction diet (Fig. 1 left). This satiation correlated to a decrease in the rats' behavior of responding for the reward while under the influence of nicotine as seen by their responding for sucrose (Fig. 1 right). Responding on the nose-pokes allowed for a decrease in effort to obtain the reward also contributing to the satiation of the rats. Thus, nicotine did not enhance responding for sucrose, this may be due to the previously mentioned confound of the caloric load of sucrose. To account for these confounds the experimental design was changed in two ways for the second experiment. First, the sucrose was replaced by a zero-calorie sweetener (saccharin) which removed the caloric load of the reward, but still kept the rewarding sweet taste. The easily operated nose-poke buttons were replaced by levers that required the rats to work a bit harder to obtain the reward.

The second experiment (operant responding for saccharine) exhibits that exposure to nicotine prior to being conditioned to respond for a discriminative stimulus paired reinforcer increased the motivation as shown by responses for saccharin (Fig. 2 right) to pursue a reward that has been paired with the drug.

## Conclusion:

Nicotine is a very potent drug that affects learning and acquisition behavior. Low doses of nicotine are correlated with increased responding for a paired incentive reward in pre-clinical rat paradigms. This increase in responding for the reward which is overlapped with a subcutaneous nicotine injection suggests that nicotine is impacting the reward centers of the brain; namely the ventral striatum and ventral tegmental areas. Our research was aimed at determining if nicotine did impact incentive learning. This was investigated over the course of two experiments. The first experiment for operant responding for the paired cue of an illuminated nose-poke key and the delivery of a sucrose reward showed no significant differences in responding across the three groups. This could be due to the role of the sucrose as a calorie dense reward. The rats on a 100% body weight restriction diet would have increased motivation to obtain the reward; particularly those in the SAL group would be susceptible to increasing response for caloric rewards. Rats across the groups gained considerable amounts of weight despite being on the restricted diet. The easily operated illuminated nose-key also played a role in increasing the delivery of the sucrose and this can be illustrated by referring to **Figure 1 Nose Pokes** which shows that responders pressed the key three thousand times with outliers reaching nearly four thousand presses. The rats sucrose deliveries are also high showing at the height of responding fifty deliveries of sucrose across the groups. The expectation that nicotine rats would respond at a higher rate than the saline pre-treated control and the post-nicotine groups turned out to be not true. This could be due in part to the anorectic effects of nicotine acting as an appetite suppressant on the group that received injections overlapping testing sessions [Pre-NIC]. Although nicotine did not enhance responding for the reward in the first experiment it potently enhanced responding for saccharin a zero-calorie sweetener in experiment two. Saccharin keeps

the rewarding sweet taste of the reinforcer but does not provide a dense caloric load and thus did not fuel weight gain of the rats in experiment two. Switching to the lever presses from the illuminated nose-keys lowered the deliveries of the reward and responding on the levers. The effect of nicotine on acquisition learning in rats injected with nicotine prior to testing sessions was significant and correlated with an increase in responding for the cues and delivery of the reward. Nicotine increases the level of dopamine available to nervous system tissues. Given that dopamine is associated with pleasurable feelings and stimulates the reward centers of the brain this indicates nicotine is acting on these structures; increasing the meaning of the reward for the nicotine pretreated group over that of either the control group or the post-nicotine group. Nicotine may specifically increase the motivation to obtain sensory reinforcers by increasing the pleasure associated with receiving these reinforcers. Nicotine is a very diverse drug that affects the nervous system in a myriad of ways and only through continued study can the role of nicotine be further assessed.

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