Nicotine-enhanced responding for chocolate rewards in humans

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ABSTRACT

Despite an abundance of evidence illustrating the harmful effects of nicotine use, only a small percentage of users successfully quit (Messer et al., 2008). Moreover, current treatments for nicotine cessation produce only a slight increase in the likelihood of successfully quitting, which emphasizes the need for more effective strategies that facilitate smoking cessation (Hopkins et al., 2001). Several studies suggest that difficulty in controlling nicotine use behaviors results from nicotine's ability to enhance the motivating function of cues associated with obtaining rewards. In order to better understand the reward mechanisms that underlie the risk for becoming dependent, the aim of the current study was to examine nicotine's effects on conditioning, extinction, and reinstatement in humans. Using a novel virtual reality translation of the hallmark conditioned place preference paradigm to investigate the aforementioned objectives, our main findings suggest that nicotine (1) increases the sensitivity of reward properties by enhancing the strength of food-reward conditioning, (2) delays the rate of extinction of conditioned preferences, and (3) increases the reinstatement of previous conditioning.

1. INTRODUCTION

The conditioned place preference (CPP) task is a well-established behavioral paradigm traditionally used in nonhuman research to assess the rewarding or aversive effects of a substance. Using a novel virtual reality translation of the CPP task, the present experiment aimed to understand the behavioral and neuropharmacological mechanisms by which nicotine enhances responding for conditioned rewards in humans.

While most of the toxicity of nicotine use is related to the added components of nicotine-containing products, nicotine's actions as a reinforcer of drug-taking behavior are primarily responsible for the production and maintenance of the dependence. The actions of nicotine as a primary reinforcer are well characterized by self-administration studies (Le Foll & Goldberg, 2009). Nicotine has also been shown to influence associative learning as a result of Pavlovian conditioning where non-pharmacological stimuli paired with nicotine can elicit conditioned responses (DiChiara, 2000; Sayette & Tiffany, 2013). More recently, research has demonstrated that nicotine enhances non-associative responding for other reinforcers by increasing the incentive value of non-nicotine stimuli without requiring a temporal or causal relationship between nicotine and the stimulus or behavior (Perkins & Karelitz, 2013; Buffalari et al., 2014).

There is a paucity of literature regarding the relationship between nicotine and reward-paired stimuli, particularly in humans. Therefore, the present study examined nicotine's ability to increase sensitivity of reward properties in humans by enhancing preference for a virtual environment paired with a chocolate food reward using the CPP task. In addition to investigating nicotine's effects on the acquisition of conditioned behavior, this study aimed to determine whether nicotine slows the rate of extinction for previous conditioning in humans as suggested by several non-human studies (Brenhouse & Andersen, 2008; Elias et al., 2010). Finally, because nicotine has been shown to increase vulnerability to reward-primed reinstatement after extinction (de Wit & Stewart, 1981; Brenhouse & Andersen, 2008), the final aim was to determine whether nicotine will promote the reinstatement of an extinguished CPP.

2. METHOD

2.1 Participants

Ninety-six University of Connecticut undergraduates (avg. age = 19.5 yrs; SD = 1.18; 25 females) were recruited from introductory psychology classes. After exclusions due to ineligibility, Day 1 data from 72 participants (avg. age = 19.3 yrs; SD = 1.12; 16 females), and Day 2 data from 62 participants (avg. age = 19.3 yrs; SD = 1.19; 16 females; Day 1/Day 2: Nicotine/Nicotine, n = 20; Nicotine/Placebo, n = 38; Placebo/Nicotine, n = 22; Placebo/Placebo, n = 32) was used. On average, 10.6 (SD = 8.9) nicotine-containing products were used weekly. Participants were required to abstain from eating and from using nicotine for six hours prior to the experiment. Approval for this study was obtained from the University of Connecticut Institutional Review Board.

2.2 Apparatus

An IBM-compatible computer with a SVGA color monitor was used for testing. Participants navigated through the virtual environments by manipulating a joystick.

2.3 Procedure

This was a two day study with each daily session lasting approximately one hour. On Day 1, food-deprived participants arrived in the morning and consent was obtained. All participants blew into a CoVita Smokerlyzer carbon monoxide sensor to ensure they had not smoked within the last 6 hours (PPM <10). Female participants took a urinalysis pregnancy test that had to be negative. Participants were then randomly selected to receive either a 4mg nicotine lozenge or a similar-tasting placebo. While the lozenge or placebo dissolved, participants completed the Fagerstrom Test for Nicotine Dependence (Fagerstrom, 1989), a standard instrument for assessing the intensity of physical dependence to nicotine where a zero score indicates no dependence, a 1-5 score indicates low to moderate dependence, and anything greater than 5 indicates high dependence.

After completing the surveys, and 15-minutes after administration of the lozenge or placebo to maximize absorption (McEwan et al., 2008), participants were guided through a 90-second practice session in which they were placed in a barren VR room. To encourage exploration throughout the practice session (and in the later experimental sessions), a downward-facing arrow appeared periodically in random locations, and participants were required to locate and collide with it. Three to five M&Ms were dispensed during the practice session, and participants were instructed that throughout the experiment they are to eat the M&Ms as they were dispensed.

After completing the practice session, each participant completed six, 3-minute experimental pairing sessions in a VR environment. The environment consisted of two visually-distinct rooms connected by a neutral hallway (see Fig. 1). In each of the six experimental sessions, participants were confined to one of the two rooms and explored the environment using the joystick. One room was paired with real M&Ms for three sessions, while the opposing room was paired with no food for three sessions. The room paired with M&Ms and the order of the pairing sessions were counterbalanced. One M&M was dispensed periodically into a dish next to the participant during the M&M sessions, and the participant was instructed to eat the M&Ms as they were dispensed. Between 25-30 M&Ms total were dispensed over the course of the experiment. After all six pairing sessions were completed, a 10-minute break was given before the test session.

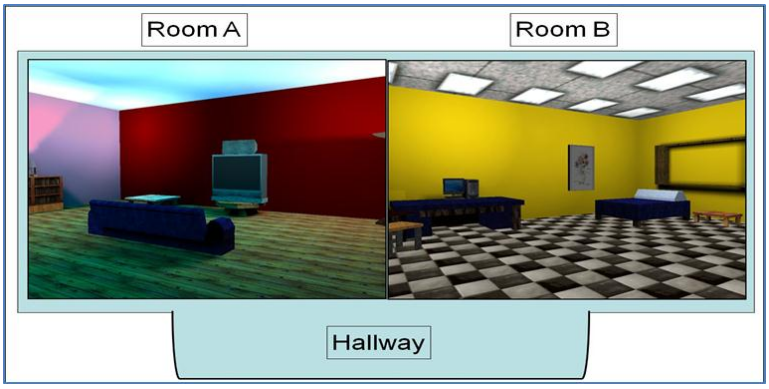

Figure 1. *Both rooms were identical in shape and size, but contained different items, colors and patterns.*

For the test session, participants were placed in the same VR environment and started in the neutral hallway. They had access to both rooms for the entire three-minute session. M&Ms were not dispensed during the test session. After the test, participants were given a survey. Questions asked which of the two rooms they preferred, how much they enjoyed each room on a scale of 0-100 (0 being "not at all"), and how much they enjoyed chocolate on a scale of 0-100 (0 being "not at all").

On Day 2, participants were again asked to complete the CO test and were then randomly selected to either receive a 4mg nicotine lozenge or the similar-tasting placebo. To test for extinction, the participant underwent three, 3-minute test sessions, as described on Day 1, in which they had unrestricted access to both VR rooms where no M&Ms were given. After the test sessions, participants underwent a 60-second reinstatement session where they received M&Ms in a neutral, novel VR room. After a 10-minute break, participants underwent a final test session to test for possible reinstatement. After the test, participants were given a survey asking the same subjective rating questions as on Day 1. The VR software recorded the amount of time spent in each of the virtual rooms on Day 1 and Day 2.

3. RESULTS

Conditioned place preference scores were calculated as difference scores by subtracting the amount of time spent in the non M&M-paired room from the amount of time spent in the M&M-paired room during the test session, such that any score greater than zero indicated a conditioned place preference for the M&M-paired room. Difference scores in ratings were also calculated this way.

In support of previous findings by our lab (Astur et al., 2014), placebo-treated participants demonstrated a significant CPP by spending significantly more time in the previously-paired M&M room on test day ($t(38) = 1.99$, $p = 0.04$). Nicotine-treated participants, however, did not display a significant CPP in terms of time ($t(33) = 0.67$, $p = 0.51$; Figure 2). In an attempt to determine whether individuals with greater nicotine dependence condition differently than those with lesser or no dependence, we specifically examined the 36 participants who scored greater than zero on the Fagerstrom questionnaire. For individuals with a Fagerstrom score greater than 0, the M&M-paired room was rated as significantly more enjoyable for the nicotine group compared to the placebo group ($F(1, 35) = 4.72$, $p = 0.04$; Fig. 2).

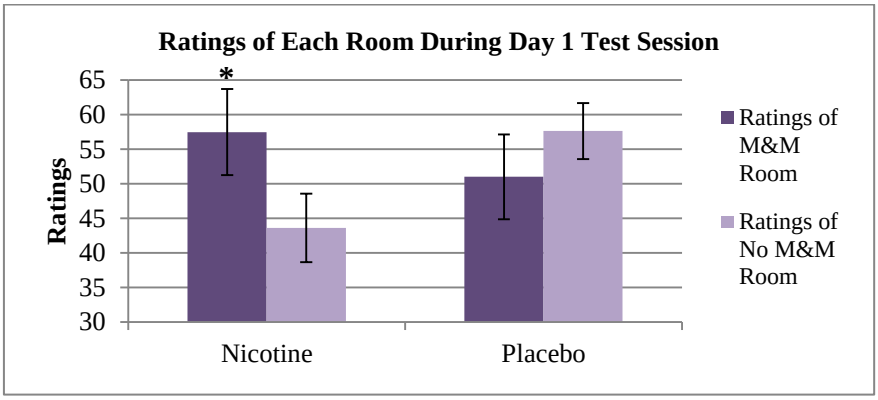

Figure 2. *Day 1 nicotine group rates M&M room more favorably than placebo group when Fagerstrom score greater than zero ($F(1, 35) = 4.72$, $p < 0.05$).*

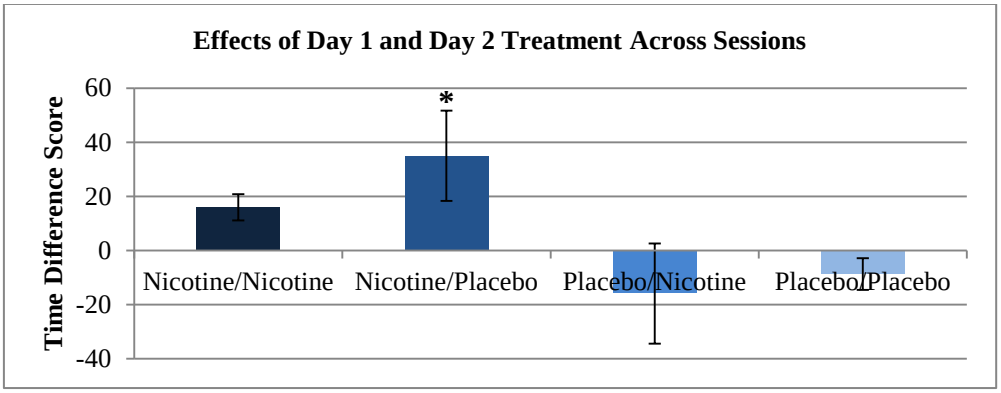

Figure 3. *Effects of Day 1 and Day 2 treatments where nicotine on Day 1 and placebo on Day 2 are most likely to result in a CPP during extinction.*

We next aimed to characterize the effects of nicotine on extinction and reinstatement. When examining extinction, it is worthwhile to analyze those who acquired a CPP on Day 1 since those who did not display a CPP may not have acquired the necessary learned associations needed to readily show extinction. Looking at Day 2 drug effects in nicotine-dependent participants who demonstrated a CPP on Day 1 (Fagerstrom > 0; CPP Difference Score > 0), those who received placebo on Day 2 showed a CPP during the third extinction session by

spending significantly more time in the M&M-paired room than Day 2 nicotine-treated participants ($F(1, 18) = 5.01$, $p = 0.04$; Fig. 3). What is more, individuals who received nicotine on Day 1 spent significantly more time in the M&M-paired room during the third extinction session than placebo-treated participants ($F(1, 18) = 13.7$, $p = 0.002$). Therefore, nicotine administration on Day 1 and placebo administration on Day 2 appear to be the most influential in determining whether the participant will demonstrate a conditioned place preference during the third extinction session.

Finally, while there were no significant differences between Day 1 treatments in terms of time during the reinstatement session ($F(1, 18) = 3.39$, $p = 0.83$), participants who received nicotine on Day 2 reinstated by a significantly greater change between the amount of time spent in the M&M-paired room during the last extinction session and the reinstatement session compared to placebo-treated participants ($F(1, 18) = 5.87$, $p = 0.03$).

4. CONCLUSIONS

The present experiments were undertaken to characterize the effects of nicotine on conditioned responses in humans using a virtual CPP paradigm. Overall, the present results demonstrate that nicotine does seem to enhance conditioning for a food reward during the virtual CPP task as evidenced by participants who are dependent on nicotine rating the M&M-paired room as significantly more enjoyable when they receive nicotine on Day 1. Nicotine also seems to make individuals more resistant to extinction since those who received nicotine on Day 1 revealed an increased preference for the M&M room in the last extinction session. Lastly, nicotine on Day 2 seems to promote reinstatement of the conditioned behavior following a small amount of M&Ms given in a neutral context after extinction.

The current study provides novel and informative data in understanding the role of nicotine in enhancing CPP preferences in humans using a virtual task. Furthermore, these data provide a foundation for future studies aimed at more thoroughly characterizing the reward mechanisms that underlie risks for maintaining nicotine use, as well as risks for relapse following cessation. Importantly, the current findings of our study will allow for better understanding and interpretation with regard to the mechanisms of nicotine dependence, and hopefully will provide insight into how treatments can be developed and implemented to treat nicotine abuse and dependence.

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