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The effects of nicotine on conditioning, extinction, and reinstatement in humans

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HIGHLIGHTS

- We examined the effects of nicotine on conditioning to a virtual room paired with M & M food rewards.
- Nicotine enhanced the strength of food-reward conditioning in participants with at least some level of nicotine dependence.
- Nicotine promoted the reinstatement of an extinguished conditioned place preference for a food reward after priming.
- Enhanced reward sensitivity by nicotine may play a role in addiction by promoting drug-seeking habits that increase relapse.

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ABSTRACT

Nicotine has been shown to enhance the reinforcement and reward-responsiveness of non-nicotine stimuli. To determine whether nicotine enhances the strength of conditioning to context, undergraduate participants with varying levels of nicotine dependence were recruited for a two-day study and tested on a virtual reality (VR) conditioned place preference (CPP) paradigm. On day one, participants explored two virtual rooms where they received multiple pairings of M & M rewards in one room and no rewards in the other room, followed by a free-access test session with no rewards. On day two, participants received three test sessions to assess extinction. Subsequently, participants received M & Ms. in a novel context and were then tested for reinstatement. Prior to testing on each day, subjects were administered either nicotine (4 mg) or placebo lozenges, in a between-subjects, four-group, 2 × 2 design (nicotine or placebo on days 1 and 2). After conditioning on day one, only participants who received placebo exhibited a CPP by spending significantly more time in the room previously-paired with M & Ms. Contrary to our hypothesis, nicotine-treated participants did not display a significant CPP, and there were no significant differences between treatment groups. However, post hoc analysis indicated that in a subset of participants with greater nicotine dependence, the nicotine group displayed a CPP by rating the M & M-paired room as significantly more enjoyable than those who received placebo. Additionally, while neither treatment group showed significant place preferences during the first two extinction sessions on Day 2, individuals who received nicotine on Day 1 or placebo on Day 2 spent significantly more time in the M & M-paired room during the final extinction session. Finally, those who received nicotine on Day 2 exhibited significantly greater reinstatement compared to placebo-treated participants. These results partially support preclinical evidence that nicotine can affect learning, extinction, and reinstatement.

1. Introduction

In addition to acting as a primary reinforcer (Caggiula et al., 2009; Henningfield, Miyasato, & Jasinski, 1983; Le Foll & Goldberg, 2009), nicotine is believed to enhance the incentive value of non-pharmacological stimuli conditioned through Pavlovian associations (Di Chiara, 2000; Palmatier et al., 2006; Sayette & Tiffany, 2013). Nicotine has also been shown to enhance responding for other reinforcers in a non-associative manner (Attwood, Penton-Voak, & Munafo, 2009; Buffalari et al., 2014; Caggiula et al., 2009; Chaudhri et al., 2007; Donny et al., 2003; Guy & Fletcher, 2013; Perkins & Karelitz, 2013). In other words, nicotine enhances the incentive, motivational value of a non-nicotine stimulus without requiring a temporal or causal relationship between nicotine and either the stimulus or the behavior. For example, Donny

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et al. (2003) showed that nicotine enhanced operant responding for a reinforcing visual stimulus in rats regardless of whether the drug was infused over a 1-hour period, contingent upon responding for the visual stimulus, or non-contingently, independent of operant responding. They concluded that nicotine enhanced behavior maintained by unconditioned reinforcers, independent of the temporal relationship with the stimulus or the behavior (Rupprecht et al., 2015). Another study showed that environmental cues can be classically conditioned to cigarette smoking (Lazev, Herzog, & Brandon, 1999). In this study, reactivity to environmental cues, as measured by self-report of urge and pulse rate, significantly increased across CS + trials paired with smoking, compared to responses in the CS- trials not paired with smoking.

The finding that nicotine enhances reinforcement and reward-responsiveness has been replicated across a range of doses, routes of administration, schedules of reinforcement, and reinforcing stimuli, including conditioned reinforcers (Chaudhri et al., 2006; Palmatier et al., 2006). To date, however, most of these studies have employed operant behavioral paradigms (Buffalari et al., 2014; Thiel, Sanabria, & Neisewander, 2009), rather than classical conditioning models, and none have examined nicotine's effects on the expression of conditioned place preferences (CPP) in humans. Thus, in conducting this research, we hope to elucidate the role of nicotine in enhancing human conditioned place preference by providing a solid foundation for future studies that aim to identify reward mechanisms that underlie risks for maintaining nicotine use and relapse. To do this, the present study sought to examine the ability of nicotine to enhance reward in humans by increasing the preference for an environment paired with a chocolate food reward, using a novel virtual CPP task. We also sought to determine whether nicotine slows the rate of extinction for previous conditioning in humans as it appears to do in nonhuman species (Brenhouse & Andersen, 2008; Elias, Gulick, Wilkinson, & Gould, 2010), and whether it increases reward-primed reinstatement after extinction (de Wit & Stewart, 1981; Le Foll & Goldberg, 2004; Brenhouse & Andersen, 2008). Additionally, Day 1 drug treatment was used to investigate Day 2 effects to determine whether nicotine during acquisition influences subsequent conditioned responses. Finally, nicotine dependence was explored as a moderating factor to determine whether conditioning differs among those with higher versus lower levels of dependence.

We hypothesized that, during the first test immediately after conditioning on Day 1, participants who received nicotine would demonstrate a stronger conditioned place preference (CPP) as measured by both the amount of time spent in each room, and the subjective ratings of how much they liked the room previously paired with chocolate reward. We also hypothesized that those who received nicotine on Day 2 would extinguish their responses more slowly as measured by sustained higher time and ratings of the food-paired room compared to the placebo group, and that this effect would be magnified in those who also received nicotine on Day 1. Finally, we hypothesized that nicotine on Day 2 would enhance reward-primed reinstatement after extinction as evidenced by increased time and ratings CPP measures relative to the placebo group.

2. Materials and methods

2.1. Participants

Ninety-six University of Connecticut undergraduates were recruited from introductory psychology classes. All participants in this study were pre-existing nicotine users with varied levels of dependence; however, we did not differentially recruit high and low nicotine users. Methods of nicotine consumption were not recorded. Nicotine-naïve participants were not used for the study as they are more likely to experience negative side effects of nicotine use. Participants were instructed to abstain from eating and from using nicotine for 6 h prior to the sessions. Participants with cardiac conditions, or who were pregnant, were excluded. We also excluded participants who were unwilling to eat chocolate during the study. Participants received class credit for their participation. 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 seated at the computer navigated through the virtual environments by manipulating a joystick. A speaker connected to the computer was used to provide auditory feedback and a Med Associates Inc. ENV-203IR pellet dispenser was used to dispense M & Ms. into a tray for the participant to consume. Throughout the experiment, participant position within the virtual environment was written to a data file at 20 Hz.

2.3. Procedure

This was a two-day study using a between-subjects 2 × 2 design where nicotine or placebo was administered during the Day 1 acquisition session and/or during the Day 2 extinction session. Overall, there were 4 groups based on whether they received Placebo (P) or Nicotine (N) on Day 1 or Day 2 (i.e., P/P group, P/N group, N/P group and N/N group). Participants were not counterbalanced based on age, sex, nicotine consumption level, or any other factors, but instead every four participants were pseudorandomly assigned to one of the four conditions in order to maintain counter-balancing.

On each day, participants arrived in the morning between 8:30 and 10:30 AM after at least 6 h fasting and abstaining from cigarettes. Consent was obtained on Day 1. Breath samples were obtained using a CoVita Smokerlyzer carbon monoxide sensor. While individual CO readings were not recorded, participants with CO readings of PPM > 10 were rescheduled (Perkins, Karelitz, & Jao, 2012). On Day 1, women were tested for pregnancy via a urine test. On a pre-test questionnaire, participants completed questions regarding age, sex, when they last ate, when they last used nicotine, how many nicotine-containing products they used weekly, and their level of hunger on a 1–10 scale (1 being “not at all,” 10 being “extremely”). Participants also completed the Fagerstrom Test for Nicotine Dependence (FTND; Fagerstrom, 1989), one of the most widely used, standardized instruments for assessing the intensity of physical dependence to nicotine (Chabrol, Niezborala, Chastan, & de Leon, 2005; Diaz et al., 2005; Fagerstrom, 1989; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991; Heatherton, Kozlowski, Frecker, Rickert, & Robinson, 1989; Piper, McCarthy, & Baker, 2006). It contains six items that evaluate the quantity of cigarette consumption and the compulsion to use. In scoring the FTND, yes/no items are scored from 0 to 1, and multiple-choice items are scored from 0 to 3. The items are summed to produce a total score of 0–10, where a higher score defines a more intense physical dependence on nicotine. A score of zero indicates no dependence, and a score of 6 is the standard cutoff for the presence of high nicotine dependence (Fagerstrom, Heatherton, & Kozlowski, 1991).

Participants were then randomly assigned to receive either a 4 mg nicotine lozenge or a similar-tasting placebo (Altoids Wintergreen mint) on Day 1. An Altoids mint was used as a placebo since it is similar in both appearance and taste to the nicotine lozenge. The 4 mg lozenge was chosen as a dose and route of nicotine administration because it results in blood nicotine levels that are 4-fold higher than other smokeless nicotine products across a 1-hour timeline, with levels peaking approximately15-minutes after administration (McEwen, West, & Gaiger, 2008). Participants were instructed to place the lozenge in their mouth, occasionally moving it from side to side to allow it to slowly dissolve over the course of 15 min. They were told to minimize swallowing, and not to chew or swallow the lozenge.

Fifteen minutes after administration of the lozenge or placebo, participants received a 90-second practice session in which they were placed in a single, barren, never-to-be-seen-again virtual reality (VR)