



Influence of reinforcer magnitude and nicotine amount on smoking's acute reinforcement enhancing effects



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ABSTRACT

Background: Nicotine's acute effects on enhancing reinforcement from sensory rewards, shown in animal models, appear to occur with smoking in humans. These effects may vary due to reinforcer magnitude and amount of acute smoke intake (dose).

Methods: In a fully within-subjects design, dependent smokers ($n = 23$) participated in 3 sessions. Each session followed overnight abstinence and involved 4 trials to assess responding via progressive ratio (PR 50%) for sensory reinforcement from high, moderate, or low preference music, or no reward (counter-balanced, 30-s/reinforcer). Sessions differed in smoking prior to each trial: 8 puffs on arrival and 2 puffs/trial ("8 + 2"), 2 puffs/trial only ("0 + 2"), or no smoking. Puffs were consumed via CRSS (Clinical Research Support System) to control topography, and smoking involved own brand to ensure palatability and increase generalizability of results.

Results: Reinforced responding was influenced by main effects of smoking condition ($p < .05$) and music reward type ($p < .001$). Compared to no smoking, responding for music was increased after smoking 8 + 2/trial puffs ($p < .005$), but not after 0 + 2/trial puffs. Smoking condition significantly increased reinforced responding only for the high preference music ($p = .01$), and not for moderate or low preference music, or for no reward. Withdrawal did not differ between the two smoking sessions, ruling out withdrawal relief as an explanation for differential reinforcement enhancement.

Conclusions: Our findings confirm that just one cigarette after abstinence is sufficient for reinforcement enhancing effects and suggest that such enhancement is greater as magnitude of a reward's reinforcing efficacy increases.

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1. Introduction

In addition to nicotine's primary and secondary reinforcing effects, research with animal models indicates that nicotine has a third reinforcing function, that of enhancing reinforcement from rewards *not* directly associated with nicotine intake (Caggiula et al., 2001; Palmatier et al., 2012). Some of this research suggests nicotine's reinforcement enhancing effects may be specific to certain classes of rewards, such as visual stimuli or others "sensory" in nature (e.g., Weaver et al., 2012). However, nicotine may not enhance reinforcement from primary rewards, perhaps such as food, but this selectivity of nicotine effects may stem from other factors (e.g., Caggiula et al., 2009; Raiff and Dallery, 2008). Even if limited in breadth, nicotine's enhancement of sensory rewards

common to the environment (e.g., Fowler, 1971) could help explain the persistence of nicotine intake in humans via tobacco smoking.

Very few human studies have directly examined nicotine's reinforcement enhancing effects, particularly for sensory rewards. We recently tested reinforcement enhancing effects of nicotine via smoking, compared with denicotinized smoking, on rewards varying in sensory and other characteristics (e.g., negative vs. positive reinforcer; Perkins and Karelitz, 2013). We found that nicotine enhanced responding for a positively reinforcing sensory reward (highly preferred music), but not for a positively reinforcing non-sensory reward (money), a negatively reinforcing sensory reward (termination of aversive noise), or no reward (control for non-specific behavior). Nicotine's reinforcement enhancing effect was similar between nondependent and dependent smokers, indicating a response to nicotine that was not due to dependence or withdrawal relief.

Because overall amounts of reinforced responding were similar for the money versus music rewards, our reinforcement enhancing results cannot be explained by differential magnitude of reinforcing efficacy. Yet, nicotine's reinforcement enhancing effects may differ by the degree of a sensory reward's reinforcing efficacy

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(Palmatier et al., 2012). Moreover, we found that modest smoking of roughly half a nicotine cigarette (6 puffs) before each trial produced enhancement of music reinforcement that was equal whether this smoking followed overnight abstinence or no abstinence (i.e., ad lib. smoking before the session; Perkins and Karelitz, 2013). Thus, such enhancement of reinforcement may occur after very minimal nicotine intake, well below that typically self-administered by smokers from a full cigarette.

The current study used a fully within-subjects design to examine differences in reinforced responding for a sensory reward due to: (1) two different modest amounts of acute nicotine intake via cigarette smoking after overnight abstinence, and (2) three different degrees of preference for a music reward, or no reward. As in our prior research, reinforced responding was assessed on a progressive ratio schedule using a simple operant computer task (e.g., Perkins et al., 2013; Perkins and Karelitz, 2013). However, here we employed subjects' preferred brand of cigarettes to increase generalizability and ensure palatability (i.e., avoid or lessen differences in taste or other non-nicotine cigarette characteristics that could cause variable responding between smokers).

2. Methods

2.1. Participants

Study participants were 23 dependent smokers (14 M, 9 F) who smoked at least 10 cigarettes per day for at least one year and met DSM-IV criteria for nicotine dependence (APA, 1994), according to a structured interview updated from Breslau et al. (1994). Mean (\pm SD) smoking characteristics were 14.5 ± 3.6 cigarettes/day, 4.1 ± 1.7 on the Fagerstrom Test of Nicotine Dependence (FTND; Heatherton et al., 1991), 1.0 ± 0.2 mg nicotine yield of preferred brand, and 70% were non-menthol smokers. Participants, recruited from the surrounding community, were 25.8 ± 7.1 years of age and self-identified mostly as Caucasian (82.6%), with 17.4% African-American. Men and women did not differ on any of these smoking characteristics or on age or ethnicity. Excluded were those currently taking medications to treat serious psychological problems (e.g., psychosis, major depression).

2.2. CO, withdrawal measures

During the three study sessions, expired-air carbon monoxide (CO) was assessed upon arrival via Breathco CO monitor (Lenexa, KS) to confirm overnight (≥ 12 h) smoking abstinence ($\text{CO} \leq 10$ ppm; SRNT Subcommittee, 2002). Nicotine withdrawal was assessed by the Minnesota Nicotine Withdrawal Scale (Hughes and Hatsukami, 2007) using the following 6 items: depressed mood/sad, irritable/angry/frustrated, anxious/nervous, difficulty concentrating, restless/impatient, and drowsiness. Items were each rated on a 0 ("not at all") to 100 ("extremely") visual analog scale (VAS) and averaged across symptoms to get a total withdrawal score. CO and withdrawal were obtained at the end of each session to compare effects of the different amounts of intermittent smoking exposure.

2.3. Reinforcement task

As described in our prior research (Perkins et al., 2009, 2013; Perkins and Karelitz, 2013), reinforced responding was assessed with a modified version of a simple operant computer task ("Applepicker"; Norman and Jongerius, 1985). It involved looking for "apples" on a monitor by moving a cursor around a "field" and pressing a button when the cursor landed on one of the "trees." When an "apple" was found, a red symbol briefly lit up, indicating a unit of the music reward designated for that trial had been earned (i.e., one reinforcer). The number of responses required to find an "apple" constituted the reinforcement schedule, which in our current version of this task (Perkins et al., 2013) is a progressive ratio incrementing by 50% after each completed ratio (i.e., PR50%), starting with an FR10.

Each of the four trials per session differed in the preference level of music reward that was available as a reinforcer over the 15-min of task responding: high, moderate, or low preference music, or no reward (control for nonspecific responding), obtained and validated as described below in Section 2.4. Each earned reinforcer resulted in the immediate playing of 30 s of the designated music reward, which was not identified before the trial began but only upon earning the first reinforcer and listening to the resulting music via headphones. The experimenter was not in the room during task trials, and playing of music reward was initiated by the computer immediately after a reinforcer was earned. Trials with these different levels of reward were presented within sessions in counter-balanced order between subjects. Upon earning a reinforcer, subjects could continue responding on the task without interruption, to earn additional units of the reinforcer (i.e., extend the continuous time of music, until the PR incremented to higher schedules). They were free to stop responding at any point and read available magazines (intentionally

routine in nature) or simply wait for the end of the 15-min task period. However, to eliminate availability of other reinforcers, they were not allowed to bring any of their own reading or other material to sessions.

2.4. Procedure

Participants were first screened by phone on smoking and health history and scheduled for an introductory session in the laboratory to obtain written informed consent, verify eligibility, and obtain their preferred cigarette brand and their different preference levels of music reward. They were instructed to bring with them an unopened pack of their own brand and at least one compact disc (CD) of their favorite music. The pack was used to provide cigarettes for the two experimental sessions involving intake of smoke puffs (see below). Using the CD, they were instructed to listen and select their 5 most highly preferred "tracks", with 4 tracks each rated at least 75 on a 0–100 VAS of "liking" identified as the high preference music reinforcer. From a library of music compiled by the experimenters, they then listened to additional music tracks (based on their ratings of general preference for different music genres) and rated them on the same 0–100 VAS of "liking". The moderate preference music comprised 4 tracks rated 40–60, and the low preference music was 4 tracks rated 0–20. For these participants, mean (SD) VAS "liking" ratings were 89.7 ± 5.8 , 51.9 ± 7.7 , and 7.9 ± 6.2 for their high, moderate, and low preference music, respectively. Each grouping of 4 tracks totaled at least 10 min of music, the maximum duration of listening possible from responding for music throughout a 15-min trial. They were then briefly introduced to the Applepicker computer task without reinforcement to become familiar with it.

All subsequently completed three 2-h experimental sessions, each following overnight smoking abstinence (confirmed upon arrival by $\text{CO} \leq 10$ ppm). Sessions differed only in the acute smoking condition in effect: (1) 8 puffs on arrival (after CO check) and 2 puffs prior to each trial ($8 + 2$ /trial puffs), (2) no smoking on arrival but 2 puffs prior to each trial ($0 + 2$ /trial puffs), or (3) no smoking at all throughout the session (0 puffs). Thus, on one session (" $8 + 2$ "), they took 8 puffs over 4 min (one every 30 s) on one cigarette after providing initial CO. Then, on both of the smoking sessions ($8 + 2$, $0 + 2$), participants self-administered two puffs over 60 s prior to each of the 4 task trials. These two smoke amounts provided just over half a full cigarette (10 puffs) versus a small fraction of a cigarette (2 puffs) prior to the first task trial of responding for music reward, and they totaled a full cigarette (16 puffs) versus a half cigarette (8 puffs) by the end of the respective session (e.g., Hatsukami et al., 1990). The order of these smoking conditions across sessions was counter-balanced between subjects, and sessions were separated by at least one day. All smoking during sessions involved their preferred cigarettes, unblinded and provided by the experimenter. This smoking was done via the portable Clinical Research Support System ("CReSS Pocket"; Borgwaldt KC, Inc., Richmond VA; www.plowshare.com), which assesses puff volume (in ml; Lee et al., 2003; Perkins et al., 2012). Exact puff timing and duration were guided by computer-presented puffing instructions to standardize intake at about 60 ml per puff (comparable to ad lib. puffing; e.g., Perkins et al., 2012), as in prior studies of controlled smoke exposure (Zacny and Stitzer, 1986), including with the CReSS (Perkins et al., 2010).

During each trial, participants were instructed they were free to work as much or as little as they wanted on the task for the designated music reward (high, moderate, low preference, or no reward) until the end of the 15-min task period. Consistent with the subjective "liking" ratings used to identify each music reward preference type during the introductory session (see above), the mean (SD) duration of task responding per 15-min trial was 6.3 ± 2.8 , 4.3 ± 3.7 , 1.8 ± 2.1 , and 2.0 ± 2.4 min for high, moderate, and low preference music, and no music reward, respectively. Thus, duration of participant responding was a function of the preference level of music reward, as expected, and they discontinued responding prior to the end of trials. The different orders of music reward across trials were counter-balanced between subjects but remained constant across the three sessions within subjects. Trials lasted 25 min each, to provide time for controlled intake of 2 puffs, completion of the task period, and brief rest until the next trial. Withdrawal and CO were obtained after the last trial of each session to gauge effects and exposure from these intermittent smoking conditions compared to no smoking. This study protocol was approved by the University of Pittsburgh Institutional Review Board.

2.5. Data analyses

All analyses were conducted using IBM SPSS 20.0. The primary dependent measure was number of responses on the Applepicker task (i.e., reinforcement), and the independent measures were the smoking condition per session following overnight abstinence and the music reward preference level per trial (high, moderate, and low, as well as no reward). Preliminary analyses showed no effects of smoking condition order across sessions, and so data for the three sessions were collapsed across orders in subsequent analyses. In these completely within-subjects analyses of variance (ANOVAs), which greatly increased statistical power (e.g., Cohen, 1988), the factors were smoking condition (no smoking, 0 puffs + 2 puffs/trial, 8 puffs + 2 puffs/trial) and type of music reward. Significant effects were followed up with paired comparisons of responses using Fisher's LSD *t*-test (Huitema, 1980). Because we previously found enhancement of high preference music reinforcement due to nicotine via smoking (Perkins and Karelitz, 2013), we specifically examined responding for each

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