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SENSORY REINFORCEMENT ENHANCING EFFECTS OF NICOTINE VIA SMOKING

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Abstract

As in animal research, acute nicotine in humans enhances reinforcement from rewards unrelated to nicotine intake, but this effect may be specific to rewards from stimuli that are “sensory” in nature. We assessed acute effects of nicotine via smoking on responding for music or video (“sensory”) rewards, for monetary (“non-sensory”) reward, or for no reward (control), to gauge the generalizability of nicotine’s reinforcement enhancing effects. Using a fully within-subjects design, dependent smokers (N=20) participated in three similar experimental sessions, each following overnight abstinence (verified by CO<10 ppm) and varying only in the smoking condition. Sessions involved no smoking or smoking denicotinized (0.05 mg) or nicotine (0.6 mg) Quest^R brand cigarettes in controlled fashion prior to responding on a simple operant computer task for each reward separately, using a progressive ratio schedule. The reinforcing effects of music and video rewards, but not money, were significantly greater due to the nicotine versus denicotinized cigarette (i.e. nicotine per se), while there were no differences between the denicotinized cigarette versus no smoking (i.e. smoking behavior per se), except for no reward. These effects were not influenced by withdrawal relief from either cigarette. Results that generalize from an auditory to a visual reward confirm that acute nicotine intake per se enhances the reinforcing value of sensory rewards, but its effects on the value of other (perhaps non-sensory) types of rewards may be more modest.

Keywords

nicotine; smoking; reinforcement enhancement; sensory reward

Animal models have shown acute effects of nicotine in enhancing reinforcement from rewards that are available independent of nicotine intake (e.g. Caggiula, Donny, Palmatier, Liu, Chaudhri, & Sved, 2009; Chaudhri, Caggiula, Donny, Palmatier, Liu, & Sved, 2006; Raiff & Dallery, 2009). This reinforcement enhancing effect of nicotine, recently also demonstrated with humans (Perkins & Karelitz, 2013a; 2013b), is separate from nicotine’s primary and secondary reinforcing effects (e.g., Caggiula, et al., 2009; LeFoll & Goldberg 2006; Rose, Salley, Behm, Bates, & Westman, 2010). Yet, the magnitude of nicotine’s

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reinforcement enhancing effect may depend on the nature of the available rewards, rather than being a nonspecific influence of nicotine on increasing the reinforcing value of all rewards. For example, rewarding stimuli involving some sensory systems (visual, auditory, etc.) are enhanced by nicotine in animal studies, while other types of rewards are not enhanced (see Caggiula, et al., 2009). Broadly dividing these systems into “distal” senses (e.g. auditory, visual) and “proximal” senses (e.g. touch, taste), as outlined by Wise (2002), may aid understanding of the parameters under which nicotine enhances reinforcement.

In 52 dependent and non-dependent smokers, we recently demonstrated acute effects of smoking nicotine versus denicotinized cigarettes in enhancing immediate positive reinforcement from one type of sensory reward (music, i.e. auditory) but not from another type of reward (money, i.e. non-sensory; Perkins & Karelitz, 2013a). The rewards were equal in reinforcing efficacy, lack of differences between denicotinized cigarettes versus no smoking ruled out simple effects of smoking behavior per se, and comparable nicotine effects in non-dependent versus dependent smokers argued against withdrawal relief as the explanation (Perkins & Karelitz, 2013a). We have also found enhanced responding for music reward by nicotine intake in other research (Perkins, Karelitz, Jao, & Stratton, 2013; Perkins & Karelitz, 2013b), while at least one study by others also reported no effect of nicotine (via inhaler) on behavior reinforced by money (McGrath, Barrett, Stewart, & Schmid, 2012), indicating some reliability of nicotine’s effects in enhancing responding for music reward but not monetary reward.

The degree to which nicotine’s reinforcement enhancing effects generalize to other kinds of sensory reward is unclear but important for determining how often these effects may be experienced by smokers and, thus, the extent to which these effects may contribute to smoking maintenance. Other daily sensory rewards frequently associated with smoking behavior include those consisting primarily of visual stimuli, such as watching TV or movies, internet viewing, or other sources (Hatsukami, Morgan, Pickens, & Champagne, 1990; Raiff, Jarvis, & Rapoza, 2012; Van Gucht, Van den Bergh, Beckers, & Vansteenwagen, 2010). Although human research of nicotine’s effects on actual responding that is reinforced by such rewards is lacking, nicotine increases responding for visual stimuli in animals (Barrett & Bevins, 2012; Donny, Chaudhri, Caggiula, Evans-Martin, Booth, Gharib, Clements, & Sved, 2003; Raiff & Dallery 2009). Perhaps relevant here is that nicotine via smoking increases subjective attractiveness ratings of viewed faces (Attwood, Penton-Voak, & Munafo, 2009) and self-reported pleasure from watching movie clips (Dawkins, Acaster, & Powell, 2007), consistent with the notion that nicotine may also enhance sensory reinforcement from visual rewards in humans.

Given how common these types of rewards are in the natural environments of most people (e.g. Fowler 1971; Raiff, et al., 2012), an additional factor in explaining smoking’s persistence may be nicotine’s ability to enhance positive reinforcement from sensory rewards, particularly stimuli that are auditory (e.g. music) or visual (e.g. video) in nature. Recent evidence suggests that early lapses in quit attempts often occur during “leisure” activities, including while enjoying “TV/music” (Deiches, Baker, Lanza, & Piper, 2013). Thus, cigarette smoking may be very hard to quit partly because the acute intake of nicotine makes many routinely enjoyable activities even more pleasurable (i.e. reinforcing).

The current study followed up our earlier work demonstrating nicotine's reinforcement enhancing effects with music reward (auditory stimuli) by examining whether these effects generalize to video reward (visual stimuli), perhaps supporting the notion that nicotine enhances sensory reinforcement. Using a within-subjects design involving overnight abstinence prior to each of 3 sessions, we compared smoking nicotine versus denicotinized cigarettes to determine nicotine effects per se on reinforced responding, and compared smoking denicotinized cigarettes versus no smoking to gauge nonspecific effects of any smoking behavior per se. We hypothesized that nicotine would increase reinforced responding for the available music and video sensory rewards, but not for monetary (non-sensory) reward or no reward (control for nonspecific responding). We also expected smoking behavior alone would not enhance reinforced responding, based on our prior findings (Perkins & Karelitz, 2013a).

Method

Participants

Study participants (N=20; 9 men, 11 women) were those who smoked 10 cigarettes per day for at least one year and met DSM-IV criteria for nicotine dependence (APA 1994), based on a structured interview updated from Breslau, Kilbey, and Andreski (1994). Respective mean ($\pm$ SD) smoking characteristics for men vs. women were 15.0 ± 4.3 vs 15.4 ± 4.4 cigarettes/day and 4.2 ± 1.6 vs 4.6 ± 1.4 on the Fagerstrom Test of Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991). The respective nicotine yield of their preferred brand was 1.1 ± 0.1 vs 1.0 ± 0.3 mg, 44% vs 55% were non-menthol smokers, and they were 24.7 ± 7.1 vs 24.1 ± 6.4 years of age. Men and women did not differ on these smoking characteristics or age. Participants were recruited from the surrounding community and most self-identified as Caucasian (85.0%), with 5.0% African American, 5.0% American Indian, and 5.0% Asian. Those currently taking medications to treat serious psychological problems (e.g. psychosis, major depression) were excluded.

CO, Withdrawal

Expired-air carbon monoxide (CO) was assessed via Breathco CO monitor (Vitalograph; Lenexa, KS). Upon arrival to each session, overnight (>12 hr) smoking abstinence was confirmed by $\text{CO} < 10$ ppm (SRNT Subcommittee, 2002). Nicotine withdrawal was assessed by the Minnesota Nicotine Withdrawal Scale (MNWS; Hughes & Hatsukami, 1986), with items each rated on a 0 ("not at all") to 100 ("extremely") visual analog scale (VAS) and averaged to get a total withdrawal score.

Cigarettes

Subjects remained abstinent throughout one session and smoked intermittently during the other two sessions. One session involved a moderate "nicotine" brand, Quest^R 1 (yield of 0.6 mg nicotine, 9 mg tar), and the other a denicotinized brand, Quest^R 3 (yield < 0.05 mg nicotine, 9 mg tar), formerly sold commercially by Vector Group, Ltd. (Miami, FL). Menthol-preferring smokers (n=10) received menthol Quest; non-menthol smokers (n=10) received non-menthol Quest. All Quest cigarettes had identifiable markings covered and

subjects were kept blind to brand. See control and assessment of puff topography in the Procedures, below.

Reinforcement Task

Reinforced responding was assessed with a modified version of a simple computer task (“Applepicker”; Norman & Jongerius, 1985) used in many prior studies by us and others (e.g., Epstein, Bulik, Perkins, Caggiula, & Rodefer, 1991; Perkins, Epstein, Grobe, & Fonte, 1994; Perkins, Grobe, & Fonte, 1997), and described in more detail in our recent studies documenting nicotine’s reinforcement enhancing effects on music reward (Perkins & Karelitz 2013a; 2013b). Briefly, subjects use the arrow keys to move a cursor on a monitor around a “field” and press a button (a “pick”) when the cursor lands on one of the “trees” to look for “apples.” (These task features are intentionally displayed with rudimentary graphics to minimize the “entertainment” value of responding). Number of responses, or “picks,” required to find an “apple” (and thus earn one reinforcer; see below) constitutes the reinforcement schedule, which was 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 reward available over the 15-min trial of task responding. The 4 reward conditions (and amount of each earned reinforcer) were: 1) music (playing 30 sec of preferred music from participant’s compact disc through headphones), 2) video (playing 30 sec of preferred video from among high rated alternatives, e.g. short comedy clips; see Procedures below), 3) money (counter on monitor incrementing by \$.10), and 4) no reward (control). The reward for the current trial was displayed on the monitor as the trial began, and the four reward trials were presented in counter-balanced order between subjects. No one else was in the room with participants during task trials; the computer automatically initiated the playing of the music or video rewards immediately after a reinforcer was earned. Upon earning a reinforcer, subjects could continue responding on the task without interruption to earn more reinforcers (i.e. further increment money counter, extend the time of music or video playing). “Earnings” for each respective reward trial averaged 4.0 mins of music, 3.9 mins of video, and \$0.80 for money, or 8 reinforcers for each reward trial, showing equal overall earnings for these three rewards (and comparable reinforcing efficacy; see Honig & Staddon, 1977).

All subjects were instructed they could stop responding at any point prior to the end of the 15-min task period and simply wait quietly or read the available magazines. (The latter were intentionally of mundane interest so they would not serve as alternative reinforcers. Also, subjects could not bring their own material to sessions so we could eliminate any other alternative reinforcers that might compete with the reward designated for each trial.) Virtually all discontinued responding on the task during each trial, as mean (SE) duration of responding per trial was 6.3 ± 0.4 min (8.2 ± 0.8 min for money, 7.5 ± 0.6 min for music, 7.5 ± 0.5 min for video clips, and 2.2 ± 0.5 min for no reward). These durations indicate that maximal responding for reward was reached well before the end of each 15-min trial, as planned, and further confirm equal reinforcing efficacy of the rewards.

Procedure

After being screened by phone on smoking and health history, prospective participants were scheduled for an introductory laboratory session to obtain written informed consent and verify eligibility. As in our prior studies of nicotine's enhancement of music reward (Perkins & Karelitz 2013a; 2013b; Perkins et al., 2013), subjects also brought with them a compact disc of their own preferred music for use as the music reward in experimental sessions. They were instructed to rate each of the "tracks", and 4–8 tracks rated at least 75 on a 0–100 VAS of "liking" were selected as the music reinforcers. These tracks totaled more than 10 mins of music per session to ensure sufficient rewards if responding persisted throughout the 15-min trial. Also, and new to this study, subjects briefly viewed video clips from genres they reported enjoying and were instructed to rate them on the 0–100 VAS "liking" scale in the same manner as the music tracks. Video clips rated 75 or higher were selected as video reinforcers, again so that they totaled more than 10 mins of video per session. (Most were standup comedy routines.) Subjects were then introduced to the Applepicker task without reinforcement to become familiar with it during subsequent experimental sessions.

Participants completed three 2-hr experimental sessions, each after abstaining overnight and differing only in the acute smoking condition in effect: nicotine (Quest 1) or denicotinized (Quest 3, "denic") cigarettes presented under blind conditions, or no smoking. The order of these smoking conditions across the three sessions was counter-balanced between subjects and separated by at least one day. Upon arrival to each session, participants completed the withdrawal and CO measures. Before each of the 4 task trials on the 2 smoking sessions, participants self-administered six puffs over 3 mins, one puff every 30 sec, on the cigarette assigned for that session. All smoking was done via the portable Clinical Research Support System ("CReSS Pocket"; Borgwaldt KC, Inc., Richmond VA), which assesses puff volume (in ml; Lee, Malson, Waters, Moolchan, & Pickworth, 2003; Perkins, Karelitz, Giedgowd, & Conklin, 2012). Exact timing and duration of each puff inhalation were guided by computer-presented instructions to standardize intake at about 60 ml per puff (consistent with ad lib puffing; e.g. Perkins et al., 2012), as in our prior studies of controlled smoke exposure, including with the CReSS (Perkins, Karelitz, Conklin, Sayette, & Giedgowd, 2010; Perkins & Karelitz 2013a). Withdrawal was again assessed at the end of each session to gauge differences due to intermittent puffs on the nicotine and denicotinized Quest cigarettes vs. no smoking.

Prior to each trial, subjects were instructed that they were free to work on the task for as long as they wanted the designated reward (music, video, money, no reward). The different orders of rewards across trials were counter-balanced between subjects but remained constant across sessions within subjects. Trials lasted 25 mins each, to provide time for controlled intake of 6 puffs, completion of the 15-min task period, and 5-min brief rest until the next trial. This study protocol was approved by the University of Pittsburgh Institutional Review Board.

Data Analyses

All analyses were conducted using IBM SPSS 21.0. The main dependent measure was reinforced behavior, i.e. number of task responses for the various available rewards, one per

trial. With a sample of 20 subjects, we first analyzed the 6 possible orders for the 3 rewards across trials (ignoring no reward), and found no order effects. These preliminary analyses also showed no effects of smoking condition order across the three sessions, and so data were collapsed across orders in subsequent analyses. In the primary analyses of variance (ANOVAs) of these responses for rewards, the factors were smoking condition (no smoke, denicotinized cigarette, nicotine cigarette sessions) and type of reward trial (4), both within-subjects factors that greatly increased statistical power (e.g. Cohen, 1988). A priori pairwise comparisons (Huitema, 1980) of each reward were done for differences in reinforced responding between the nicotine vs. denic cigarette conditions, to isolate nicotine effects per se, and between the denic cigarette vs no smoking conditions, to isolate the effects of smoking behavior per se. Effects of nicotine, but not smoking behavior, were expected to be significant for music and video rewards, and not significant for monetary reward. No differences were significant due to the main or interaction effects of sex (all $F_s < 1$), or due to the main ($F(1,18) = 1.83$, $p = .19$, ns) or interaction effects of menthol preference ($F_s < 1$), and so these between-subjects factors are not addressed further. Effect sizes for reinforced responding results of particular interest are presented by partial eta-squared values (η_p^2), which indicate the percent of variance explained.

Results

Withdrawal

Overnight smoking abstinence prior to each session was confirmed, as mean (SE) CO upon arrival was 4.3 ± 0.5 ppm. Consequently, mean (SE) withdrawal was initially similar across sessions and then declined in consistent fashion due to intermittent smoking of the nicotine (from 36.9 ± 4.0 to 22.1 ± 3.3) or denicotinized cigarette (from 37.9 ± 4.5 to 25.8 ± 3.8), in contrast to remaining elevated during the no smoking session (from 35.3 ± 4.0 to 38.0 ± 4.4). Thus, as expected, the smoking condition $\times$ time interaction was significant, $F(2,36) = 10.65$, $p < .001$.

Control of puff behavior

Mean puff volume from the 6 puffs on each trial was greater on the denicotinized vs nicotine cigarette smoking sessions, 346 ± 22 vs 300 ± 17 ml, respectively, $F(1,19) = 5.27$, $p < .05$. Yet, there was no main effect of reward type (range of 313 ml for video to 327 ml for music; $F(3,57) = 1.26$, n.s.) and no interaction of nicotine/denicotinized cigarette $\times$ reward on puff volume, $F(3,57) < 1$, ns. Therefore, as in prior research with these cigarettes (e.g. Perkins & Karelitz 2013a), smoke intake was greater for the denicotinized cigarette but consumption did not differ by reward type, demonstrating good control of puff topography across trials.

Reinforcing value of rewards

Mean (SE) responding for each reward is shown in Figure 1 by the 3 smoking conditions. Overall responding for rewards during the sessions was significantly influenced by the main effects of smoking condition, $F(2,38) = 16.69$, $p < .001$, $\eta_p^2 = .468$, and of reward type, $F(3,57) = 27.65$, $p < .001$, $\eta_p^2 = .593$, but not the smoking $\times$ reward interaction, $F(6,114) < 1$, ns. In the a priori planned comparisons, as indicated in the figure, reinforced responding for music reward increased by 210 ± 98 during the nicotine vs the denicotinized cigarette,

$t(19) = 2.15, p < .05$. The denicotinized cigarette vs. no smoking conditions did not differ from each other, $t(19) = 0.17, p = .87$, indicating that nicotine intake per se, and not simply smoking behavior in general, enhanced reinforced responding for music reward. Similarly, for video reward, responding increased by 221 ± 92 for the nicotine vs denicotinized cigarette, $t(19) = 2.42, p < .05$, while responding was only marginally greater, by 159 ± 79 , for the denicotinized cigarette vs. no smoking, $t(19) = 2.02, p < .10$. By comparison, responding for monetary reward was not significantly increased either by the nicotine vs. denicotinized cigarette, or by the denic cigarette vs. no smoking, t 's (19) = 1.52 and 1.69, respectively, both $p > .10$. Finally, while responding for no reward was uniformly low on each session, as expected (Figure 1), it tended to be greater for the nicotine vs. denicotinized cigarette, $t(19) = 1.77, p < .10$, and unexpectedly was increased, if only by 65 ± 22 , for the denicotinized cigarette vs. no smoking, $t(19) = 3.02, p < .01$.

Discussion

Very consistent with our prior research (Perkins & Karelitz, 2013a), reinforced responses for music, and now also for video reward, were significantly enhanced by smoking of nicotine cigarettes, compared to smoking denicotinized cigarettes or no smoking, which generally did not differ. Consequently, these reinforcement enhancing effects are due to acute nicotine intake per se and not general responses to smoking behavior. Nicotine intake did not significantly increase responding for monetary reinforcement, arguing for the notion of specificity in the types of reinforcers enhanced by these nicotine effects and against a broad nonspecific nicotine effect on enhancing reinforcement from all available reinforcers.

More specifically, nicotine may particularly enhance reinforcement from “sensory” types of rewards. With the three types available in our study, nicotine significantly enhanced the sensory rewards of music and video but not the non-sensory reward of money, again as with other recent findings (Perkins & Karelitz, 2013a). We found very similar overall amounts and duration of responding for the music, video, and money rewards, ruling out any differential magnitude of reinforcing efficacy as an explanation for this specificity of nicotine effects on the robustness of responses by reward type (and consistent with Perkins & Karelitz, 2013b; see also Palmatier, Matteson, Black, Liu, Caggiula, Craven, Donny, & Sved, 2007). Additional research is needed to further confirm this apparent specificity of reinforcement enhancing effects of nicotine in humans and extend the findings from animal research that nicotine enhances reinforcement from certain types of rewarding stimuli but not others (Caggiula, et al., 2009). Research should also assess reinforcement enhancing effects of acute nicotine intake in humans via means other than tobacco smoking (e.g. McGrath et al., 2012) to further verify that nicotine per se influences reinforced responding for sensory rewards.

Our results also confirm earlier work showing that relief of withdrawal due to overnight abstinence is not an explanation for these nicotine effects (Perkins & Karelitz 2013a, 2013b; Perkins et al., 2013). Relief was virtually identical from smoking the nicotine and denicotinized cigarettes and much greater than in the no smoking session, while responding for music and video rewards differed between the cigarette conditions but generally not between the denicotinized cigarette and no smoking sessions. Yet, responding for no reward

curiously was greater for the denic smoking versus the no smoking sessions, which necessarily could not be compared in blind fashion. Such responding was uniformly very low, as expected, and our prior studies, with larger N's, have not shown differential responding on this task for no reward due to smoking conditions (Perkins & Karelitz, 2013a; 2013b), perhaps pointing to a Type 1 error here.

Potential mechanisms that can explain these particular nicotine effects remain uncertain, and future research should carefully relate the reinforcement enhancing effects to changes in brain activation due to acute nicotine (Klinkenberg, Blokland, Riedel, & Sambeth, 2013; Paterson, 2009). Notably, nicotine's effects on striatum may be critical, as visual (Aharon, Etcoff, Ariely, Chabris, O'Connor, & Breiter, 2001; Lahnakoski, Salmi, Jaaskelainen, et al. 2012), auditory (Blood & Zattore, 2001; Fedorenko, McDermott, Normal-Haignere, & Kanwisher, 2012; Klinkenberg et al. 2013), and other (Erk, Spitzer, et al. 2002) sensory characteristics of rewards may differentially activate striatum when compared to rewards less clearly sensory in nature, such as monetary reinforcement (e.g., Thut, Schultz, et al. 1997). Results could help clarify nicotine's influences in processing of immediate auditory, visual, and other types of stimuli (e.g., Lloyd, Kausch, Gancarz, Beyley, & Richards, 2012; Metherate, Intskirveli, & Kawai, 2012). In addition, other stimulants or similar drugs may comparably enhance reinforcement from non-drug rewards (e.g. Palmatier, Levin, Mays, Donny, Caggiula, & Sved, 2009; Sheppard, Gross, Pavelka, Hall, & Palmatier, 2012), including sensory types (Lloyd et al., 2012; Perkins et al. 2013).

Despite reinforcement enhancing effects of nicotine being independent of withdrawal relief, they could have clinical implications, since nicotine via smoking could increase enjoyment from many common rewarding activities that involve sensory stimuli during hours of "leisure" time each day (e.g., Hatsukami et al., 1990; Raiff et al., 2012; van Gucht et al., 2010). Removing this enhanced sensory reinforcement by abstaining from smoking, either temporarily or during a quit attempt, could help explain smoking persistence beyond the substantial impacts of the primary and secondary reinforcing effects of nicotine. Moreover, the modest exposure to nicotine after overnight abstinence here suggests that just a single smoking "lapse" could rapidly enhance reinforcement from these sensory-related rewarding activities, consistent with our recent study of some parameters of enhanced music reward from smoking (Perkins & Karelitz, 2013b). This observation could help explain why smoking lapses may be especially reinforcing after a period of abstinence and how lapses commonly foster full blown relapse (e.g., Shadel, Martino, Setodji, Cervone, Witkiewitz, Beckjord, Scharf, & Shih, 2011).

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Figure 1.

Mean±SE number of responses for reinforcers, by reward type and smoking condition (N = 20). A priori paired comparisons between the nicotine vs. denic cigarette isolated effects of nicotine per se, while comparisons between the denic cigarette vs. no smoking isolated effects of smoking behavior per se. Music and video reward, but not money or no reward, were significantly increased by nicotine intake. No reward, but not the other rewards, was increased by smoking behavior. * $p < .05$, ** $p < .01$