Psychopharmacology (2002) 163:194–201
DOI 10.1007/s00213-002-1168-1

ORIGINAL INVESTIGATION

Kenneth A. Perkins · Lynette Jacobs · Mark Sanders · Anthony R. Caggiula

Sex differences in the subjective and reinforcing effects of cigarette nicotine dose

Received: 31 December 2001 / Accepted: 31 May 2002 / Published online: 13 July 2002

Abstract *Rationale:* Some research with novel nicotine delivery methods suggests that nicotine itself may be less reinforcing in women than in men. However, sex differences in the reinforcing effects of nicotine dose via cigarette smoking have received little attention. *Objectives:* Sex differences in the subjective and reinforcing effects of smoking were examined as a function of two cigarette nicotine "dose" levels (moderate – subjects' preferred brand, ≥0.7 mg yield; low – Carlton "ultra-light", 0.1 mg yield). *Methods:* Male and female smokers (n=30) participated in three sessions, the first two involving independent assessment (only one brand available), and the third involving concurrent assessment (both brands available), of subjective ratings (e.g. "liking") and reinforcement for the two cigarette brands. Subjects were blind to the brand of each cigarette, and subjects abstained overnight prior to each session. Reinforcement was determined by responses on a computer task to earn single puffs on the designated cigarette. *Results:* Subjective ratings differed between the low versus moderate cigarette nicotine dose under both independent and concurrent assessment conditions, as expected. Notably, this dose difference was smaller in women than in men (i.e. significant sex by dose interactions). The dose effect on smoke reinforcement also was smaller in women than men, but only under the independent and not concurrent assessment condition. *Conclusions:* These results indicate that cigarette nicotine dose is a less important influence on the subjective and, under some conditions, reinforcing effects of smoking in women than in men.

K.A. Perkins (✉) · L. Jacobs · M. Sanders
Department of Psychiatry,
University of Pittsburgh School of Medicine, 3811 O'Hara Street,
Pittsburgh, PA 15213, USA
e-mail: perkinska@msx.upmc.edu
Tel.: +1-412-6241716
Fax: +1-412-6246018

A.R. Caggiula
Department of Psychology, Langley Hall, University of Pittsburgh,
Pittsburgh, PA 15261, USA

Keywords Nicotine · Cigarette smoking · Sex differences · Reinforcement · Subjective effects

Introduction

Although men and women generally do not differ substantially in their patterns of smoking (USDHHS 2001), the relative influence of factors maintaining smoking behavior may differ between men and women. For example, the subjective and reinforcing effects of some non-nicotine cigarette stimuli (i.e. "cues") may be greater in women than in men (Perkins et al. 2001). By contrast, some research with novel nicotine delivery methods (i.e. other than smoking or other tobacco products) indicates that nicotine itself may be less reinforcing in women than in men (Perkins et al. 1999). In one study of smokers attempting to quit, ad lib self-administration behavior did not differ between women assigned double-blind to nicotine versus placebo nasal sprays, while self-administration of nicotine was twice as great as that of placebo in men (Perkins et al. 1996). This result is consistent with another study finding less nicotine gum self-administration in women versus men trying to quit (Killen et al. 1990). Other research has shown less acute self-administration of nicotine nasal spray in women versus men in a laboratory-based choice procedure (Perkins et al. 1997).

However, whether nicotine dose of cigarettes differentially influences smoking reinforcement in men versus women has not been directly examined. This question is important in order to determine whether the above-noted results with non-tobacco nicotine delivery methods are specific to those methods or may indicate a broader sex difference in the degree to which nicotine reinforces smoking behavior. We have found that men and women have generally similar subjective responses to nicotine dosing, whether by nasal spray or cigarette smoking, except women report greater selected pleasurable effects ("relaxed", "comfortable") from nicotine by smoking versus spray (Perkins et al. 1994). Other research also has

shown sex differences in subjective responses to smoking (e.g. Eissenberg et al. 1999), but the contribution of nicotine dose versus other aspects of smoking to these differences, and their relevance to smoking reinforcement, is not clear.

Virtually no other data are available by which to address sex differences in the reinforcing effects of cigarette nicotine dose. Only a few studies have cross-sectionally examined smoking behavior, exposure, or subjective ratings in men and women as a function of their preferred brand's yield, with mixed results. In each of two laboratory experiments, subjective ratings did not differ by sex, but some indices of puff topography increased with decreasing yield in women and not in men (Battig et al. 1982; Hofer et al. 1991). This result is contrary to the notion that nicotine dose is less influential of smoking behavior in women than men. However, subjects were not required to be abstinent prior to sessions, and the tendency for men in both studies to smoke more cigarettes before testing could have influenced the resulting topography during sessions. A third study, of 2754 smokers in the community, found a direct relationship between cotinine and yield of preferred brand among women but no relationship in men (Woodward and Tunstall-Pedoe 1993). This finding suggests that men fully alter smoking behavior to compensate for reduced nicotine yield and maintain a steady intake of nicotine regardless of their preferred brand's yield, while women do not (or do so to a lesser degree), consistent with nicotine being less influential of women's smoking behavior. Nevertheless, cross-sectional comparisons of smokers varying in the yield of their preferred brand confounds nicotine yield with other potential individual differences between smokers of these differing cigarette brands. These individual differences could obscure the influence of nicotine dose on smoking behavior, which perhaps can be more clearly examined by comparing the effects of different cigarettes within the same subjects.

The current study compared the subjective and reinforcing effects of a very low cigarette nicotine dose with those of the subjects' preferred brand to examine the influence of cigarette nicotine dose in men versus women. Because drug responses can vary depending on the specific testing procedures (e.g. Arnold and Roberts 1997), responses were assessed under two conditions: independent assessment, in which only one of the two cigarettes was available, and concurrent assessment, in which both cigarettes were available for comparison side-by-side. Past research has shown similar reinforcing effects of denicotinized versus standard nicotine cigarettes under the independent assessment condition, but much lower reinforcement from denicotinized cigarettes under the concurrent assessment condition (Shahan et al. 1999). Responding for denicotinized (or placebo) cigarettes, especially under the independent assessment condition, is thought to reflect conditioned reinforcement from the non-nicotine stimuli (i.e. "cues") accompanying this smoking (Shahan et al. 1999). Because we have previously found that reinforcement from nicotine intake via novel means may be less, and conditioned reinforcement of smoking may be greater, in women than in men (Perkins et al. 1999, 2001), we postulated that the difference in reinforcement due to cigarette nicotine dose would be smaller in women than in men, especially under independent assessment conditions.

Materials and methods

Participants

Participants were recruited from flyers posted in the nearby community and from ads placed in a university newspaper. Eligible subjects were those meeting DSM-IV criteria for tobacco dependence (APA 1994), who smoked at least 10 cigarettes per day, and whose preferred brand had a nicotine yield of at least 0.7 mg nicotine (to allow distinction from the very low nicotine comparison cigarette). Subjects included in the study totaled 30 healthy young nicotine-dependent smokers, 17 men and 13 women comparable on age (mean±SE=23.8±1.3 versus 22.3±1.0, respectively) and on smoking history characteristics of number of years smoking (6.6±1.0 versus 6.6±0.8), nicotine yield of preferred brand (0.9±0.1 versus 0.9±0.1 mg), and Fagerstrom Test of Nicotine Dependence (FTND) score (4.5±0.5 versus 3.6±0.4; Heatherton et al. 1991). However, men smoked more cigarettes per day (18.3±1.4) than did women (14.2±0.9) [$t(28)=2.30$, $P<0.05$].

Cigarettes

Two cigarette brands were used to manipulate cigarette nicotine dose: "moderate" (subject's own preferred brand; mean yield of 0.9±0.1 mg nicotine, 12.2±0.5 mg tar) and "low" (Carlton ultra-light; yield of 0.1 mg nicotine, 1 mg tar). We have previously used the Carlton ultra-light cigarette and subjects' preferred brand in research examining dose effects of nicotine via smoking and found equal dosing between men and women (Perkins et al. 1994). The preferred brand was selected as the moderate nicotine cigarette so that this comparison cigarette, by definition, would be well liked by subjects, rather than selecting a single brand for all that might be variably different from one's preferred brand across subjects (and perhaps different between men and women). The objective was to see how similar or different from the benchmark of the preferred brand were subjects' subjective and reinforcing responses to a very low nicotine cigarette to which they were blind.

The cigarettes had identifiable markings covered over and were labeled by a letter code ("A" or "B", with letter assignment counterbalanced between cigarettes). All smoking behavior was done according to computerized puffing instructions used in numerous other studies to standardize smoke intake (e.g. Perkins et al. 2001). These visual and auditory instructions indicated when to take a puff, when to inhale it, how long to hold it (2 s), and when to exhale. Research by us and others has demonstrated that smoking exposure differs in dose-dependent fashion between cigarettes varying widely in yield when standardized smoking conditions are imposed (Weinhold et al. 1988; Perkins et al. 1994), in contrast to exposure when smoking is uncontrolled (Benowitz 2001). Nevertheless, we also gauged smoking exposure via plasma nicotine (see below) to verify differential nicotine intake as a function of cigarette nicotine dose.

Subjective measures

Subjective responses to smoking were assessed primarily using the Rose Sensory Questionnaire items (see Westman et al. 1996). This questionnaire assesses subjective ratings of "like puffs" and "satisfying", as well as items asking "how high in nicotine" were

the smoke puffs. Each item in the Rose Questionnaire was rated on a 1 ("not at all") to 7 ("extremely") scale. This scale was completed following "sampling" puffs on each cigarette. In the concurrent assessment condition, we also asked subjects later to rate these items on 0–100 visual-analog scales (0=not at all; 100=extremely), for reasons noted in the Procedure. Participants were also asked the following: "How much would you pay to smoke another of the same type of cigarette right now?"(in US cents) and "How similar to your own brand were the puffs?" (rated on a 0–100 visual-analog scale similar to those above).

In addition, withdrawal was assessed by averaging across symptoms from the scale developed by Hughes and colleagues (Hughes et al. 1991), except that the "desire for a cigarette" item was examined separately. Each item was rated on a similar 0–100 scale.

Measure of smoking reinforcement

Smoking reinforcement was assessed using a computer task involving a varying response requirement for each reinforcer, one puff on the designated cigarette. This task was adapted from "Applepicker" (Norman and Jongerius 1985) and required operating a joystick to move a cursor across rows of "trees" in a "field" on the computer screen and picking on each tree to find an "apple". The response requirement was the number of "trees" needing to be picked before an "apple" could be found. Finding an apple was accompanied by a visual and auditory signal and indicated that one puff on the cigarette had been earned. The task was paused as the puff was immediately consumed, followed by a return to the task. Smoking reinforcement was measured by number of responses for a puff on the cigarette and total puffs earned.

Independent assessment

When smoking reinforcement was assessed independently (see below), subjects engaged in the task under standard progressive ratio (PR) conditions, with response requirements presented in an ascending order typical of the PR. Response requirements for each puff (i.e. finding an "apple") were 12, 28, 65, 152, 354, 620, and 886. The task ended when the subject failed to respond at all within a 5-min period (the end of which was signaled by a computerized warning after 4 min of no responding). All but one subject stopped responding at some point prior to completing the last, leanest schedule. This task is similar to other PR procedures (e.g. Comer et al. 1997).

Concurrent assessment

The assessment procedure was somewhat different when smoking reinforcement was assessed concurrently. Under this procedure, subjects were exposed to all of the response requirements available during the PR task in the independent condition, but they were presented once each in *random* rather than ascending order (due to difficulties in interpreting responses for two reinforcers across ascending schedules in a single PR). Each response requirement applied equally to both cigarettes (i.e. same number of responses for one puff on one or the other cigarette), to which subjects had equal but mutually exclusive access during this session. Thus, the task here was a concurrent choice procedure, with variable response requirements, and not a PR. Subjects were informed of the upcoming response requirement for the next puff and instructed to select which cigarette they wanted to work for by selecting the "A" or "B" screen. When the response requirement was met, a puff on the desired cigarette was provided, and subjects then proceeded to the next trial, involving a different response requirement. If subjects changed their mind about which cigarette they wanted, they could switch screens but had to start from the beginning of that response requirement. Subjects could opt to not complete the requirement for either cigarette by pushing a different computer key, which skipped that trial and resulted in a 5-min time-out period. This option was provided since stopping responding altogether, allowed with the PR task during independent assessment, was not an option during concurrent assessment.

These procedures for assessing smoking reinforcement independently and concurrently were adapted from those of Shahan et al. (1999).

Procedure

Subjects were told that the purpose of the study was to "evaluate the characteristics of different types of cigarettes and how much smokers like them." Subjects participated in three sessions, each following overnight smoking abstinence (defined as expired-air CO<13 ppm).

Independent assessment

In the first two sessions, subjects first completed the measures of withdrawal and desire to smoke. They then were introduced to only one of the two cigarettes (labeled as "cigarette A" or "cigarette B") and took four "sampling" puffs according to the computerized instructions. Subjects completed the Rose Sensory Questionnaire for that cigarette and the withdrawal and desire to smoke measures. After resting quietly for 10 min, subjects engaged in the PR task for single puffs on that same brand ("A" or "B"), smoking each puff immediately after earning it.

Concurrent assessment

In the third session, subjects rated withdrawal and desire to smoke at baseline. They then took two "sampling" puffs on cigarette A, completed the Rose Questionnaire and other measures, rested for 10 min, and then repeated this procedure for cigarette B. This modest exposure was designed to refamiliarize subjects with each cigarette brand (dose) prior to assessment of subjectives and reinforcement. After sampling and rating the second cigarette, subjects again completed the same items separately for each cigarette, but rated them on 0–100 VAS scales, as explained below. Finally, subjects engaged in the concurrent choice ratio procedure for puffs on one or the other cigarette, again smoking each puff immediately after earning it. Sessions ended at the same time, at least 30 min after the end of responding for smoke puffs, regardless of how long subjects engaged in the task, to discourage subjects from discontinuing responding in order to end the session and leave the laboratory to smoke their own cigarettes ad lib.

Rose Questionnaire items were re-assessed on 0–100 VAS scales after rating the second sampling cigarette because we were concerned that completing the very same questionnaire items on the same cigarettes just minutes apart would lead subjects to question this repeated assessment and also to respond with the same ratings they provided in the first rating of each cigarette. Yet, we wanted these second ratings, following sampling of both cigarettes, to reflect subjects' relative comparison of the two (i.e. concurrent ratings), which was not possible with the first ratings since the rating for the first cigarette could not be done taking the second cigarette's characteristics into consideration. Presenting the items as 0–100 VAS scales allowed them to appear as different items for subjects to rate, rather than repetitions of earlier items. For this reason, these later ratings were included in analyses, while the ratings immediately following each sampling were not. (Also, withdrawal and desire to smoke after each cigarette were not analyzed from day 3, since effects following the second sampled cigarette would be influenced by effects of the first sampled cigarette, and cigarettes were presented in counter-balanced order.)

Plasma nicotine analyses

Plasma nicotine was analyzed from days 1 and 2 to gauge nicotine exposure from the moderate and low nicotine cigarette. A blood sample was taken from the antecubital vein by venipuncture 30 min after the end of responding on the computer task and the corresponding intake of smoke puffs earned during the task. The sample was spun down and stored at –60°C for later analysis for nicotine concentration in the laboratory of Neal Benowitz (Jacob et al. 1981). (As with withdrawal and desire to smoke, plasma results from day 3 were not analyzed, since it was not possible for one end-of-session sample to differentiate nicotine intake from one versus the other concurrently available cigarette.)

Data analysis

Because of differences in the PR versus concurrent choice tasks and in the scaling of some of the self-report measures between the independent and concurrent assessment sessions, data from these sessions were analyzed separately. Thus, data from sessions 1–2 were analyzed to determine the influence of cigarette nicotine dose on responses of men versus women under the independent assessment condition, and data from session 3 were similarly analyzed to determine this influence under the concurrent assessment condition. Subjective responses to smoking were analyzed by analyses of variance (ANOVAs) of the responses to the initial "sampling" puffs, with dose (moderate, low) as a within-subject factor and subject sex as a between-subjects factor. The number of responses for each cigarette on the computer task, the measure of smoking reinforcement, was analyzed by similar ANOVAs. Follow-up comparisons to significant effects were made using Fisher's least significant difference *t*-test (Huitema 1980).

Results

Men and women did not differ on baseline desire to smoke, withdrawal, or CO at the start of each session, indicating equal smoking deprivation prior to assessments.

Independent assessment

As expected, end-of-session plasma nicotine levels were significantly different between the low and moderate cigarette nicotine doses, both for women (1.8±0.2 versus 4.3±0.5 ng/ml, respectively) and men (2.4±0.3 versus 6.5±1.0 ng/ml). The main effect of cigarette nicotine dose was highly significant [$F(1,28)=26.92$, $P<0.001$], but there were no significant main or interaction effects of sex, suggesting successful and comparable manipulation of cigarette nicotine dose between men and women. (Plasma nicotine levels were low, even after the moderate cigarette, because typical intake during sampling and the progressive ratio task was only about 7–9 puffs.)

Subjective responses

Ratings were significantly smaller for the low versus moderate cigarette nicotine dose on liking [$F(1,27)=20.92$, $P<0.001$], satisfied [$F(1,27)=29.67$, $P<0.001$], perceived nicotine content [$F(1,27)=54.06$, $P<0.001$], and similarity to own brand [$F(1,27)=24.05$, $P<0.001$], but there were no main effects of sex.

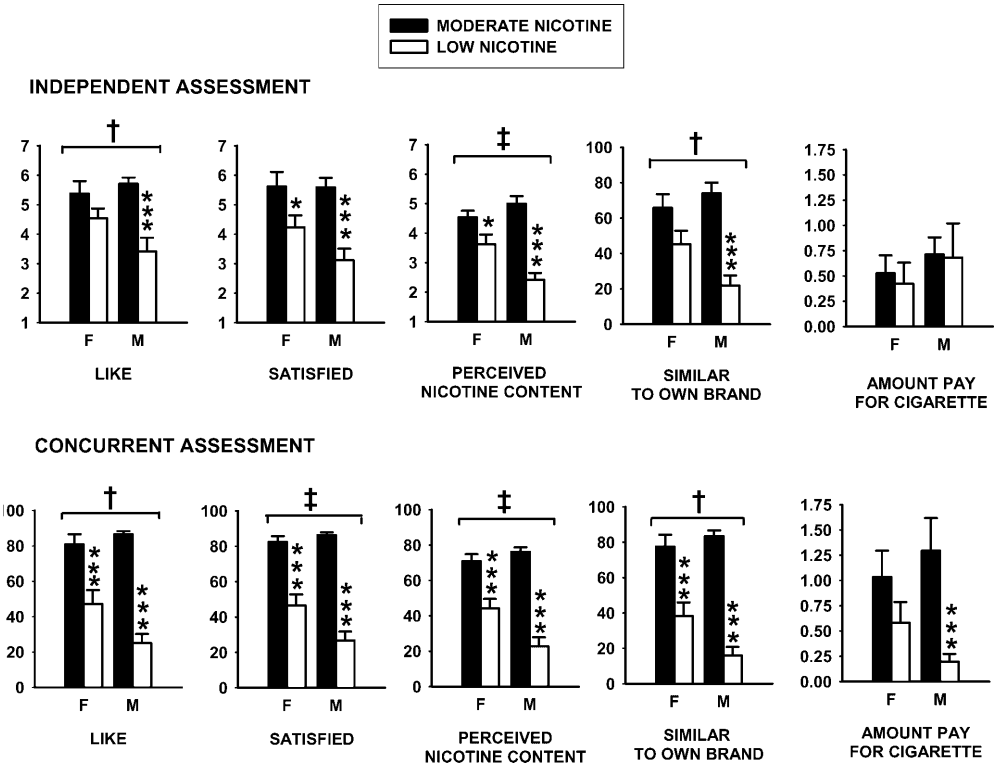

Fig. 1 Mean±SEM ratings for "subjective" measures of like, satisfied, perceived nicotine content, similarity to own brand, and amount pay (in US dollars) for another cigarette of this brand for the moderate and low nicotine cigarettes under independent (*top*) and concurrent (*bottom*) assessment conditions for women (*F*) and men (*M*). *Horizontal brackets* indicate a significant dose by sex interaction. +$P<0.05$, ++$P<0.01$ for the interaction. *$P<0.05$, ***$P<0.001$ for the comparison between moderate and low nicotine cigarettes within women or men

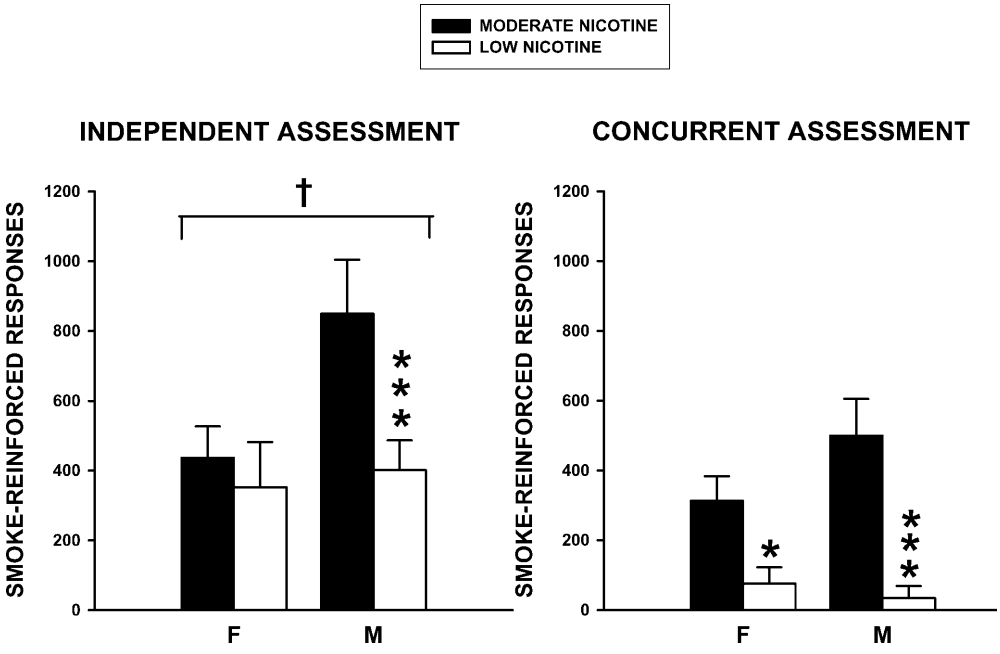

Fig. 2 Mean±SEM smoke-reinforced responding for the moderate and low nicotine cigarettes under independent (*left*) and concurrent (*right*) assessment conditions for women and men. *Bracket* and *symbols* as in Fig. 1

Moreover, as shown in Fig. 1 (top), there were significant interactions of cigarette dose by sex on each of these ratings, except satisfied, as the difference in ratings between doses was smaller in women than in men. However, ratings of "amount pay for a cigarette of this brand" did not differ as a function of dose or sex.

The decline in desire to smoke following sampling of the moderate nicotine cigarette (from 74.3 to 57.9 on 0–100 scale) was significantly greater than the decline following the low nicotine cigarette (73.3–64.1) [$F(1,28)=4.10$, $P=0.05$], but there were no main or interaction effects of sex. The decline in withdrawal was not significantly different between the moderate (from 22.7 to 16.5) and low (22.4 to 18.7) nicotine cigarettes, or as a function of sex.

Reinforcing effects

Consistent with the subjective ratings, the number of smoke-reinforced responses during the PR task was smaller for the low versus moderate nicotine dose [$F(1,27)=11.47$, $P<0.005$], and the difference between doses was not significant for women but was significant for men [i.e. sex by dose interaction; $F(1,27)=5.36$, $P<0.05$] [Fig. 2 (left)]. There were no main effects of sex. The number of puffs actually earned was similarly lower for the low versus moderate dose (3.5±0.3 versus 4.7±0.2, respectively [$F(1,27)=17.06$, $P<0.001$], but the interaction of sex by dose was not significant. Desire to smoke was still relatively high following the end of responding on the PR task for the low (62.8) and moderate (49.1) nicotine cigarettes, indicating that responding did not stop due to smoke satiation. There were no sex differences in post-task desire to smoke or withdrawal.

Concurrent assessment

Subjective responses

Ratings during concurrent assessment were very similar to those obtained during independent assessment, as the main effect of dose was highly significant for liking [$F(1,27)=71.57$, $P<0.001$], satisfied [$F(1,27)=124.99$, $P<0.001$], perceived nicotine content [$F(1,27)=77.76$, $P<0.001$], and similarity to own brand [$F(1,27)=87.97$, $P<0.001$], and there were no main effects of sex. Similarly, the interaction of sex by dose was significant for all measures, as the difference between doses again was smaller for women than men, as also shown in Fig. 1 (bottom). However, unlike during independent assessment, amount pay for a cigarette also was significantly different between doses [$F(1,28)=15.61$, $P<0.001$], but there were no main or interaction effects of sex.

Reinforcing effects

During concurrent assessment, puff-reinforced responding was highly significantly different as a function of cigarette nicotine dose [$F(1,27)=21.76$, $P<0.001$], as shown in Fig. 2 (right). However, the interaction of sex by dose was not significant [$F(1,27)=2.28$, $P>0.10$], unlike for reinforcement during the independent assessment. There was also no main effect of sex. Consistent with the strong influence of dose on puff-reinforced responding, the number of puffs actually earned was much lower for the low versus moderate dose [0.6±0.3 versus 3.7±0.3, respectively; $F(1,27)=36.59$, $P<0.001$]. The interaction of sex by dose was also significant [$F(1,27)=4.33$, $P<0.05$], as the difference in earned puffs

between the low versus moderate dose was smaller in women (1.2±0.5 versus 3.1±0.4) than in men (0.2±0.2 versus 4.2±0.3). As in the independent assessment, desire to smoke remained high after the end of the responding for smoke puffs (53.8) and did not differ by sex. Post-task withdrawal also did not differ by sex.

Re-analyses to examine influence of sex difference in cigarettes per day

On average, men smoked more cigarettes per day and tended to have higher FTND scores than did women. To control for these differences, we repeated all analyses for subjective and reinforcing effects of cigarette dose under both independent and concurrent assessment conditions using analyses of covariance (ANCOVAs), with cigarettes per day and FTND as covariates. Results were the same as in the ANOVAs above, except the sex by dose interaction was only marginally significant ($P<0.10$) for ratings of liking under the independent condition and similarity to own brand under the concurrent condition. We also redid the ANOVAs after dropping the three men who smoked more heavily than any of the women (25, 30, and 30 cigarettes per day), such that cigarettes per day were no longer different between men and women. This approach addressed the slightly different question as to whether sex influences responding among those with daily smoking rates in the same range (10–20 cigarettes per day). Results for all effects were unchanged from the ANOVAs above.

Discussion

In this study, differences in subjective and reinforcing effects between the moderate and low nicotine cigarettes were generally smaller in women than in men. Plasma nicotine levels were different between cigarette nicotine doses, as planned, but comparably so for men and women, ruling out differential nicotine intake between sexes as an alternative explanation for this difference in dose-related effects. Men and women also did not differ in measures of smoking deprivation (desire to smoke, withdrawal, etc.) at the start and end of sessions, ruling out differential deprivation before the sessions or differential satiation during the sessions as reasons for these sex differences. Thus, our findings indicate that cigarette nicotine dose influences subjective and reinforcing effects of smoking to a lesser degree in women than in men. These findings are consistent with previous research indicating that, relative to men, women appear to find nicotine intake via novel means less reinforcing (Perkins et al. 1996, 1999).

Women showed a smaller difference in smoke-reinforced responding between doses than did men in the independent assessment condition, but this sex difference was not significant in the concurrent assessment condition. Independent assessment, where only one cigarette brand is available at a time, is thought to maximize the influence of conditioned reinforcing effects of smoking (Shahan et al. 1999). Therefore, less difference in reinforcement between cigarette doses in women than men under the independent assessment condition is consistent with other research suggesting that conditioned reinforcement is more influential of smoking behavior in women than in men (Perkins et al. 2001). Furthermore, little difference between cigarette doses among women under the independent assessment, particularly with subjects blind to brand, also supports the notion that a relative absence of environmental context (e.g. no brand information, no alternative brands for concurrent comparison) impedes women's ability to detect some nicotine effects (Perkins 1999).

A limitation of this study was the fact that the low nicotine cigarette used here was also lower in tar than subjects' preferred cigarette. Thus, it is conceivable that the sex differences observed in this study reflect differential subjective and reinforcing effects of cigarette tar intake and not nicotine. This would seem unlikely given the evidence indicating that nicotine in isolation, separate from smoking (and tar), is less reinforcing among women than men, as presented in the introduction. Nevertheless, sex differences in the influence of tar on smoking reinforcement would certainly be a novel and important finding. Development and wide dissemination of improved denicotinized cigarettes containing standard tar levels is needed to control for this confound of tar and nicotine between cigarettes (e.g. Robinson et al. 2000). Second, the low nicotine cigarette also was less familiar to the smokers than their preferred brand, but we know of no reason why women should be less responsive to a difference in familiarity between cigarettes. Their preferred brands were similar to those of men, and thus comparably different from the low nicotine cigarette. A third limitation was the higher smoking frequency (cigarettes per day) of men versus women, leaving the possibility that greater nicotine dependence among men may have produced the observed differences, rather than sex per se. However, reanalyses involving ANCOVAs, with cigarettes per day and FTND as covariates, and with ANOVAs that included only subjects smoking 10–20 cigarettes per day did not substantially change results. Moreover, recent research suggests that denicotinized cigarettes elicit pleasurable subjective effects more similar to the effects of one's preferred brand, as we found here with women, among more dependent rather than less dependent smokers (Brauer et al. 2001). This is contrary to what would be expected if the responses of women versus men were due to their daily smoking rate differences, rather than to sex per se.

Our finding of sex differences in the subjective and, under independent assessment, reinforcing effects of cigarette nicotine dose may have implications for understanding factors that promote smoking behavior in women. For example, because smokers tend to "try" a new brand "independently", without concurrently smoking another brand, women may be better able to switch to lower-yield brands without compensatory increases in

smoking topography or switching back to higher-yield brands (Grunberg et al. 1991). However, the possible regulation of cigarettes gradually to lower the maximum nicotine content allowed (Benowitz and Henningfield 1994) could have less impact in reducing smoking among women than men. Conversely, aspects other than nicotine dose may be more influential in women, as suggested by tobacco industry marketing efforts in women's magazines aimed at health benefits of low-nicotine brands, weight concerns, the "image" represented by certain brands, etc. (Pierce et al. 1994; USDHHS 2001).

Future research should examine whether this reduced influence of nicotine dose on subjective and reinforcing effects of smoking in women occurs across a wider range of cigarette doses and levels of tobacco dependence. This sex difference may be specific to the lower end of the cigarette nicotine dose range studied here (i.e. ultra-low versus moderate yields of subjects' preferred brands). At doses much higher than those of subjects' preferred brands, where the effects of nicotine may overwhelm conditioned reinforcing effects, smoking responses may be similarly influenced (i.e. decreased) between men and women, as suggested by clinical research with nicotine replacement (Hatsukami et al. 1995). Research should also attempt to match cigarettes on characteristics other than nicotine, to minimize the potential influence of tar and other non-nicotine factors on smoking reinforcement. These sex differences due to cigarette nicotine dose may be different for smokers who are older and more dependent than our relatively young sample. These differences may also vary as a function of women's menstrual cycle phase, which was not controlled in this study, although other research indicates little or no effect of cycle on acute responses to nicotine (Marks et al. 1999) and smoking behavior (Pomerleau et al. 1994). Finally, more research is needed to examine the influence of dose on the acute reinforcing effects of other drugs in women versus men (e.g. Evans et al. 1999; Zacny 2001). There is little reason to believe that the sex differences seen here are specific to the effects of nicotine and not other drugs.

Acknowledgements This research was supported by Grant DA12655 from the National Institute on Drug Abuse. The authors thank Cynthia Conklin, Carolyn Fonte, Jennifer Meeker, and Elizabeth Pelayo for their assistance.

References

American Psychiatric Association (1994) Diagnostic and statistical manual – IV. American Psychiatric Association, Washington D.C.

Arnold JM, Roberts DCS (1997) A critique of fixed and progressive ratio schedules used to examine the neural substrates of drug reinforcement. Pharmacol Biochem Behav 57:441–447

Battig K, Buzzi R, Nil R (1982) Smoke yield of cigarettes and puffing behavior in men and women. Psychopharmacology 76:139–148

Benowitz NL (2001) Compensatory smoking of low-yield cigarettes. In: Risks associated with smoking cigarettes with low machine-measured yields of tar and nicotine. National Cancer Institute monograph 13. US Government Printing Office, Washington D.C. pp 39–63

Benowitz NL, Henningfield JE (1994) Establishing a nicotine threshold for addiction. N Engl J Med 331:123–125

Brauer LH, Behm FM, Lane JD, Westman EC, Perkins C, Rose JE (2001) Individual differences in smoking reward from denicotinized cigarettes. Nicotine Tobacco Res 3:101–109

Comer SD, Collins ED, Fischman MW (1997) Choice between money and intranasal heroin in morphine-maintained humans. Behav Pharmacol 8:677–690

Eissenberg T, Adams C, Riggins ED, Likness M (1999) Smokers' sex and the effects of tobacco cigarettes: subject-rated and physiological measures. Nicotine Tobacco Res 1:317–324

Evans SM, Haney M, Fischman MW, Foltin RW (1999) Limited sex differences in response to "binge" smoked cocaine use in humans. Neuropsychopharmacology 21:445–454

Grunberg NE, Winders SE, Wewers ME (1991) Gender differences in tobacco use. Health Psychol 10:143–153

Hatsukami D, Skoog K, Allen S, Bliss R (1995) Gender and the effects of different doses of nicotine gum on tobacco withdrawal symptoms. Exp Clin Psychopharmacol 3:163–173

Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom K-O (1991) The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict 86:1119–1127

Hofer I, Nil R, Battig K (1991) Nicotine yield as determinant of smoke exposure indicators and puffing behavior. Pharmacol Biochem Behav 40:139–149

Hughes JR, Gust SW, Skoog K, Keenan RM, Fenwick JW (1991) Symptoms of tobacco withdrawal. Arch Gen Psychiatry 48:52–59

Huitema B (1980) Analysis of covariance and alternatives. Wiley, New York

Jacob P, Wilson M, Benowitz NL (1981) Improved gas chromatographic method for the determination of nicotine and cotinine in biologic fluids. J Chromatogr 222:61–70

Killen JD, Fortmann SP, Newman B, Varady A (1990) Evaluation of a treatment approach combining nicotine gum with self-guided behavioral treatments for smoking relapse prevention. J Consult Clin Psychol 58:85–92

Marks JL, Pomerleau CS, Pomerleau OF (1999) Effects of menstrual phase on reactivity to nicotine. Addict Behav 24:127–134

Norman WD, Jongerius JL (1985) Apple Picker: computer software for studying human responding on concurrent and multiple schedules. Behav Res Meth Instr Comp 17:222–225

Perkins KA (1999) Nicotine discrimination in men and women. Pharmacol Biochem Behav 64:295–299

Perkins KA, Sexton JE, Reynolds WA, Grobe JE, Fonte C, Stiller RL (1994) Comparison of acute subjective and heart rate effects of nicotine intake via tobacco smoking versus nasal spray. Pharmacol Biochem Behav 47:295–299

Perkins KA, Grobe JE, D'Amico D, Fonte C, Wilson A, Stiller RL (1996) Low-dose nicotine nasal spray use and effects during initial smoking cessation. Exp Clin Psychopharmacol 4:157–165

Perkins KA, Sanders M, D'Amico D, Wilson A (1997) Nicotine discrimination and self-administration as a function of smoking status. Psychopharmacology 131:361–370

Perkins KA, Donny E, Caggiula AR (1999) Sex differences in nicotine effects and self-administration: review of human and animal evidence. Nicotine Tobacco Res 1:301–315

Perkins KA, Gerlach D, Vender J, Grobe JE, Meeker J, Hutchison S (2001) Sex differences in the subjective and reinforcing effects of visual and olfactory cigarette smoke stimuli. Nicotine Tobacco Res 3:141–150

Pierce JP, Lee L, Gilpin EA (1994) Smoking initiation by adolescent girls 1944 through 1988: an association with targeted advertising. JAMA 271:608–611

Pomerleau CS, Cole PA, Lumley MA, Marks JL, Pomerleau OF (1994) Effects of menstrual phase on nicotine, alcohol, and caffeine intake in smokers. J Subst Abuse 6:227–234

Robinson ML, Houtsmuller EJ, Moolchan ET, Pickworth WB (2000) Placebo cigarettes in smoking research. Exp Clin Psychopharmacol 8:326–332

Shahan TA, Bickel WK, Madden GJ, Badger GJ (1999) Comparing the reinforcing efficacy of nicotine containing and de-nicotinized cigarettes: a behavioral economic analysis. Psychopharmacology 147:210–216

US Department of Health and Human Services (2001) Women and smoking: a report of the Surgeon General. US Government Printing Office, Washington D.C.

Weinhold LL, Stitzer ML, Yingling JE (1988) Carbon monoxide exposure from commercial brand cigarettes under controlled smoking conditions. Pharmacol Biochem Behav 31:93–96

Westman EC, Behm FM, Rose JE (1996) Dissociating the nicotine and airway sensory effects of smoking. Pharmacol Biochem Behav 53:309–315

Woodward M, Tunstall-Pedoe H (1993) Self-titration of nicotine: evidence from the Scottish Heart Health Study. Addiction 88:821–830

Zacny JP (2001) Morphine responses in humans: a retrospective analysis of sex differences. Drug Alcohol Depend 63: 23–28