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Transient Compensatory Smoking in Response to Placebo Cigarettes

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Abstract

Rationale—To address the public health problems caused by smoking, researchers have suggested a gradual reduction in the nicotine content of cigarettes. There remain concerns, however, about the potential for smokers to compensate for reductions in nicotine content by altering their smoking behavior. Such compensatory behaviors may negate any potential cessation and/or harm reduction benefits.

Objective—The purpose of this study was to quantify smoking behavior (e.g., puff number, volume, duration, inter-puff interval, and peak flow) in response to cigarettes varying only in nicotine content, administered repeatedly.

Methods—Sixty-seven dependent smokers participated in this two session, within-subject study. Moderate nicotine content and placebo cigarettes (Quest© brand) were administered in a double-blind and counterbalanced manner. Each session required 12-hours of tobacco abstinence, and included four ad lib smoking bouts of the condition-assigned cigarette with 40 minutes separating each bout.

Results—Placebo cigarettes produced increases in total puff volume and duration and decreases in total inter-puff interval relative to cigarettes with moderate nicotine content. Differences in total puff volume and duration generally dissipated across smoking bouts, with differences in total puff volume non-existent by the 3rd and 4th bouts.

Conclusions—Placebo cigarettes produce compensatory smoking during initial exposures; however, these effects appear to be short lived. These findings are consistent with previous work where smoking compensation has been observed in response to a single cigarette but not over several days of smoking.

Keywords

Smoking; topography; compensation; nicotine; extinction

As an instrument for nicotine delivery, the cigarette is ideal for producing dependence. Inhaled nicotine is absorbed rapidly into the bloodstream and delivered to the brain within 7–10 seconds, with blood levels peaking within a few minutes (Benowitz 1996; Benowitz and Henningfield 1994; Hoffmann et al. 1997). The speed of nicotine delivery appears critical to the reinforcement of nicotine administration, with slower methods of delivery such as buccal (gum) and transdermal (patch) generally recognized as less addictive than inhalation (i.e., smoking; Perkins 1999). Benowitz and Henningfield (1994) have proposed a threshold value of nicotine that a cigarette must contain to maintain dependent smoking.

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This threshold is based upon the estimated daily nicotine intake of minimally dependent smokers (4–6 mg daily) and the absolute bioavailability of the nicotine contained in cigarettes. In turn, it has been suggested that the reinforcing value of smoking behavior could be reduced or extinguished by limiting the nicotine delivered via cigarettes (Benowitz and Henningfield, 1994; Walker et al., 2009).

In contrast to the hypothesis that reductions in nicotine will reduce smoking behavior, there is considerable evidence demonstrating that smokers compensate for these reductions by altering their smoking behavior (Scherer, 1999). Smokers have been shown to take more frequent, larger, and/or longer puffs when they switch from higher (e.g., full-flavor) to lower (e.g., light and ultra-light) nicotine yield commercial cigarettes (Blank et al., 2009; Herning et al., 1981). Importantly, although full-flavor and light cigarettes yield different levels of nicotine as measured by machine-based smoking, light cigarettes do not actually contain less nicotine than full-flavor cigarettes. In fact, among typical brand cigarettes, the percentage of nicotine in tobacco has an inverse relationship with machine measured nicotine yield (Benowitz et al. 1983). Light cigarettes produce reduced nicotine yields by diluting smoke with air drawn in through ventilation holes on the filter. However, if smokers' block these ventilation holes and/or alter their puff topography, the nicotine dose delivered by these cigarettes may be increased. As such, the machine derived nicotine yield of consumer brand cigarettes does not predict blood levels of nicotine exposure biomarkers (Benowitz et al. 1983).

Moreover, reductions in nicotine yield achieved by smoke dilution are traditionally accompanied by reductions in other tobacco smoke constituents such as tar (see FTC, 2000), which may also result in compensatory smoking behavior (Sutton et al., 1982). It remains unclear whether compensatory smoking patterns occur in response to reductions in nicotine, tar, or a combination of the compounds present in tobacco smoke. To provide a more stringent test of the effects of nicotine on smoking behavior it is prudent to examine the effects of cigarettes which vary in nicotine content, but produce similar levels of tar and other tobacco smoke constituents (Robinson et al. 2000). Well-suited for this purpose, Quest cigarettes (Vector Tobacco, Inc., Research Triangle Park, NC) are manufactured from tobacco that has been genetically modified to vary in nicotine content but produce comparable levels of other smoke constituents (e.g., 10mg tar). Specifically, Quest cigarettes are available with nicotine contents of 8.9mg (Quest 1), 5.1mg (Quest 2), and 1.0mg (Quest 3) per cigarette; resulting in machine smoking based nicotine yields of 0.6mg, 0.3mg, and <0.05mg, respectively. Quest 3 cigarettes can be considered placebo cigarettes as their nicotine yield is negligible (Robinson et al. 2000).

Smokers have been administered all three of these nicotine doses in counterbalanced order (30 minute inter-bout-interval), 30 minutes after smoking their own brand of cigarette ad libitum (Strasser et al. 2007). Larger puff volumes were observed for the placebo dose (Quest 3) relative to a moderate dose (Quest 2), but not the highest dose (Quest 1), providing partial evidence for compensatory smoking between single cigarette trials of varying nicotine content (see also Pickworth et al., 1999). Smoking topography across nicotine dose has also been investigated during extended periods of repeated exposure. Smokers given an unlimited supply of either placebo (Quest 3) or nicotine containing (Quest 1) cigarettes over an 11 day period showed no changes in smoking topography (i.e., puff volume, puff duration, inter-puff interval, peak flow or average flow) between doses across three evaluation days (Donny et al., 2007). However, overall daily consumption decreased among those receiving placebo cigarettes, supporting the hypothesis that lower nicotine content cigarettes may reduce the reinforcement value of smoking (see also Buchhalter et al. 2005). A separate study found that individuals assigned to smoke only placebo cigarettes for a seven day period actually displayed reduced total puff volumes relative to those receiving

nicotine containing cigarettes (Donny and Jones, 2009). These findings appear to contradict earlier studies which have observed persistent compensatory smoking patterns when smokers switched from high-yield to lower-yield commercial cigarettes (as in Guyatt et al., 1989). Again, this discrepancy may be explained by differences in the amount of nicotine contained (as opposed to machine derived nicotine yield) in the cigarettes investigated.

As with many other substances of abuse, pre-clinical studies investigating the self-administration of nicotine have consistently observed inverted U-shaped dose response patterns; self-administration rates increase and then decrease with increasing dose concentrations (Meisch 2000; Rose and Corrigall 1997; Fowler and Kenny 2011; Corrigall and Coen 1989, Donny et al. 1995; Risner and Goldberg 1983; Sannerud et al. 1994). Along the descending end of the curve, a reduction in dose concentration can result in an increased self-administration rate. This is consistent with the prolonged compensatory smoking patterns observed when smokers are switched from high yield (full flavor) cigarettes to lower yield (light) cigarettes (Guyatt et al. 1989). In contrast, placebo doses should produce extinction of self-administration.

Indeed, extended use of placebo cigarettes has been shown to result in a gradual reduction in smoking behavior (Benowitz et al., 2007; Donny et al. 2007; Hatsukami et al. 2010a). A simulation study predicted that reduced nicotine content cigarettes could reduce national smoking rates to 5% and save 157 million quality-adjusted life years (Tengs et al. 2005). However, there is also evidence that individuals show acute compensatory smoking behaviors in response to these same cigarettes, potentially increasing harm from smoke exposure (Strasser et al. 2007). Given the limited number of studies using such cigarettes and the potential impact of this research for informing public policy (Hatsukami et al., 2010b) it is imperative to characterize the presence, magnitude, and duration of compensatory smoking in response to placebo cigarettes. Doing so will also help delineate the effects of total cigarette nicotine content on smoking behavior and reconcile human and animal investigations of nicotine self administration.

The present study investigated the effects of nicotine content on smoking topography measures using experimental cigarettes which vary only in nicotine content. Within each of two sessions, dependent smokers' puff topography was observed across four nicotine containing (8.9mg) or placebo (1.0mg) cigarettes. Previous work suggests that compensatory smoking behavior would be observed in response to the placebo cigarette, relative to the nicotine containing cigarette, and that the magnitude of compensatory smoking would diminish across cigarette trials.

Method

Participants

Eighty-three smokers were recruited from the Tampa Bay area for participation in a study investigating the effects of nicotine content on neural indices of attention (primary study data not reported here). Inclusion criteria were as follows: between the ages of 18–70 years, and use of 15 or more cigarettes a day for the past 2 years (current smoking was biochemically verified; carbon monoxide ≥ 10ppm, urinary cotinine level ≥100 ng/mL). Participants were excluded if they used nicotine products other than cigarettes within the past 3 months, tested positive for psychoactive drug use (i.e., benzodiazepines, barbiturates, opiates, amphetamines, cocaine, PCP), tricyclic antidepressants, or pregnancy, reported any past head injury or loss of consciousness, had a current serious medical condition (e.g., cardiopulmonary problems, cancer, other major life threatening illnesses), or were unable to read and understand consent forms and questionnaires. Participants were also administered a Structured Clinical Interview for DSM disorders (SCID; First et al. 1994) and were excluded

if they met criteria for a DSM-IV Axis I disorder (i.e., psychosis, major depressive episode, manic/hypomanic episode, panic disorder, current alcohol or substance dependence).

Sixteen participants were excluded from the present analysis because of procedural errors in the use of the smoking topography equipment that occurred during a two month period of time. Of the remaining sample of 67 participants (49 male), 54 identified themselves as white, 12 as black or African American, and 1 as an American Indian or Alaskan Native. Average age was 39.8 years old (range = 19–63; *SD* = 11.6), participants smoked 22.4 cigarettes per day (range = 15–40; *SD* = 6.7), and had a Fagerström Test of Nicotine Dependence (FTND; Heatherton et al., 1991) score of 5.74 (*SD*=1.85); indicative of moderate dependence on nicotine. The study was approved by the institutional review board of the University of South Florida and as such was conducted in accordance with the standards outlined in the 1964 Declaration of Helsinki.

Procedure

Following the completion of an assessment session (during which informed consent was obtained and eligibility was established), participants completed two separate 2.5 hour experimental sessions (scheduled three to fourteen days apart). Sessions were double-blind, counterbalanced and only differed by the nicotine content of the cigarettes administered: Quest 1 (8.9mg) or Quest 3 (1.0mg) cigarettes (Vector Tobacco Inc., Research Triangle Park, NC). To standardize pre-session tobacco and alcohol consumption, 12-hour abstinence from smoking (CO level <10 ppm or no greater than half of their CO level at initial assessment) and alcohol (blood alcohol level <.001%) was required. Participants who complied with these restrictions then smoked the first of four cigarettes at their own pace through a mouthpiece connected to a smoking topography device (they were told that cigarettes would contain varying doses of nicotine). Each subsequent cigarette was smoked 40 minutes following initiation of the previous cigarette, and all cigarettes were followed immediately by completion of a subjective questionnaire (described below). Participants were prepped with an electroencephalogram (EEG) cap between smoking bouts 1 and 2 and administered attention and working-memory tasks between smoking bouts 2 and 3 and bouts 3 and 4 (data to be reported elsewhere).

Measures

Smoking topography measures included total puff volume, total puff duration, total inter-puff-interval, total number of puffs, and average maximum peak air velocity per cigarette. These data were measured using the Clinical Research Support System (CReSS; Borgwaldt, K.C.), a computerized device shown to have negligible effects on smoking behavior and to be effective for quantifying smoke exposure (Blank et al. 2009; Lee et al. 2004).

The subjective questionnaire administered after each smoking bout was the Modified Cigarette Evaluation Questionnaire (mCEQ; Cappelleri et al. 2007). The mCEQ contains twelve items and assesses five domains: smoking satisfaction, psychological reward, aversion (e.g., dizziness and nausea), sensory feelings, and reduction in craving.

Data Analyses

To examine compensatory effects we assessed nicotine effects (nicotine vs. placebo) across the four cigarettes via mixed-model repeated measures analyses. The models included effects for nicotine content (nicotine vs. placebo), cigarette trial (1, 2, 3, and 4), and the interaction of these two factors as fixed effects, with cigarette trial as a random effect. Primary dependent variables included all topography values mentioned above. For each measure, values for the first puff which occurred directly after lighting were omitted. Subjective responses to smoking were also examined with mixed-model analyses. Planned

comparisons of nicotine content, across each smoking bout, were conducted when mixed-models revealed significant main effects that included nicotine content (i.e., nicotine content or nicotine content X cigarette trial interaction),

Results

Smoking Topography

Figure 1 shows the descriptives for topography measures for each cigarette smoked during the two sessions. For total puff volume and total puff duration (Figure 1-A and B), there were significant effects for nicotine content [$F(1, 74) = 5.8$ and $F(1, 76) = 20.2$, p's ≤ .02], as well as a significant nicotine content X cigarette trial interaction [$F(3, 140) = 2.9$ and $F(3, 143) = 3.4$, p's < .05]. This indicates that there were differential changes in puff volume and duration across cigarette trials, as a function of nicotine content. Specifically, participants produced significantly elevated puff volumes while smoking the placebo cigarettes during the first [$F(1, 77) = 4.4$, $p = .04$] and second [$F(1, 75) = 13.3$, $p < .001$] smoking bouts, but not during the remaining smoking bouts (p's > .33). A similar pattern was apparent for puff duration [first bout: $F(1, 79) = 14.5$, $p < .001$; second bout: $F(1, 75) = 29.5$, $p < .001$], except that the difference between the lowest and highest nicotine content during the final cigarette trial was also significant, $F(1, 68) = 5.2$, $p = .03$. Total inter-puff-interval (Figure 1C) was significantly reduced with placebo cigarettes, $F(1, 66) = 28.2$, $p < .001$; however, no effects were evident for cigarette trial or the interaction term (p's > .29). Thus, there were significantly longer intervals between puffs for nicotine containing cigarettes, across all four bouts (p's ≤ .03). Number of puffs taken and average peak air velocity (Figure 1-D and E), showed no significant effects for nicotine content (p's > .07), cigarette trial (p's > .50), or their interaction (p's > .12).

Subjective Effects

Figure 2 depicts the subjective ratings for each cigarette smoked during the two sessions. Smoking satisfaction and sensory feelings were greater in the nicotine condition [$F(1, 76) = 12.9$ and $F(1, 75) = 11.8$, p's = .001, respectively]. These subjective ratings also showed reduction across cigarette trial [$F(3, 271) = 5.0$ and $F(3, 263) = 7.7$, p's ≤ .002, respectively], but no interactions between nicotine and cigarette trial were observed (Figure 2-A and B; p's > .21). Thus, participants rated cigarettes with higher nicotine content as more satisfying and indicated that they enjoyed the sensory aspects to a higher to degree than when smoking cigarettes with lower nicotine content; and these effects diminished across smoking trials, regardless of nicotine content. The nicotine containing cigarettes were also found to reduce cigarette cravings in comparison to the placebo cigarettes [Figure 2C; $F(1, 89) = 10.3$, $p = .002$)]. In addition, a statistical trend for the interaction between cigarette trial and nicotine content indicated that craving reduction occurred following the first cigarette trial, but was attenuated thereafter, $F(3, 150) = 2.5$, $p = .07$. Differences between nicotine content were significant only during the first cigarette trial, $F(1, 74) = 4.0$, $p < .001$, and approached significance for the second bout, $F(1, 73) = 1.2$, $p = .05$. Finally, psychological reward and aversion ratings were significantly affected by nicotine content [$F(1, 65) = 9.1$ and $F(1, 85) = 27.3$, p's ≤ .004], cigarette trial [$F(3, 219) = 5.6$ and $F(3, 237) = 15.9$, p's ≤ .001], and their interaction [$F(3, 117) = 3.1$ and $F(3, 118) = 3.3$, p's < .05] (Figure 2-D and E). That is, smoking was generally more rewarding and aversive (i.e., caused a higher degree of dizziness and nausea) for higher dose cigarettes, but these differences attenuated across bouts.

Discussion

The aim of this study was to examine the time course of compensatory smoking behavior by comparing smoking topography responses to multiple nicotine containing (8.9 mg) and placebo (1.0 mg) cigarettes smoked during two separate sessions. This sample of dependent smokers demonstrated compensatory behavior while smoking placebo cigarettes, but these effects generally dissipated across cigarette trials. For total puff volume, differences between nicotine containing and placebo cigarettes were no longer detectable by the third cigarette smoked. For total puff duration and total IPI, some significant differences between conditions were still observable at the third and/or fourth smoking bouts, though they were markedly less pronounced than those observed at the first and second smoking bouts. For example, the absolute mean difference between nicotine and placebo for total puff duration was 2.5s (*SE* = 0.65), 3.1s (*SE* = 0.56), 1.2s (*SE* = 0.70), and 1.5s (*SE* = 0.66) for bouts 1 through 4, respectively. The differences in total puff duration at these later bouts were insufficient to produce significant elevations in total puff volume.

This pattern of results appears to differ from that of previous work where exclusive use of placebo cigarettes reduced smoking behavior relative to otherwise identical nicotine containing cigarettes (Donny et al., 2007; Hatsukami et al., 2010). Of course, that smoking behavior diminished in the absence of nicotine was not unexpected given that nicotine is considered the agent primarily responsible for maintaining smoking. However, increased self-administration responding is sometimes observed when dependent smokers are required to respond for placebo nicotine or have the effects of nicotine blocked by antagonist drugs (Rose and Corrigall 1997). Such compensatory responses are short lived and resemble extinction bursts of the sort observed in humans and animals when reinforcer delivery is suspended.

Extinction burst responding has typically not been observed in animal investigations of nicotine self-administration, though such an effect has been recently documented in rodents (Harris et al. 2007). Substitution of nicotine with saline after establishment of nicotine self-administration produced increases in rate of self-administration. However, these extinction bursts were very short lived (observable only during a period of an hour or two) and the magnitude and timing of extinction bursts was variable between subjects. This is consistent with our own data and suggests that the subtle and short-lived nature of these responses may make them difficult to detect with more distal measures of nicotine self-administration (e.g., cigarettes per day). Interestingly, in rodents, the production of an extinction burst was predicted by rate of self-administration during the first two hours of drug availability during maintenance, and burst responding subsequently predicted resistance to extinction. As a proximal measure of nicotine administration, acute compensatory responses to placebo cigarettes may have utility for predicting treatment responses in humans as well. Other topography measures have already been determined to predict cessation outcomes in adolescents (Franken et al., 2006) and adults (Strasser et al., 2004).

One might also consider the present findings in the context of the response cost of drug seeking behavior. When the nicotine yield of a cigarette is reduced via design features (i.e., ventilation), the user must smoke more intensively to deliver a nicotine dose comparable to that which could be obtained through less intensive smoking of a higher-yield cigarette. In both humans and animals, the self-administration of drugs can be maintained when response cost is increased. However, the persistence of self-administration in the context of increased response cost is dose-dependent; that is, persistent responding is maintained when response cost is increased at higher doses, but is not maintained at low doses (Meisch 2000). Thus, increased responding may be maintained when dependent smokers switch to commercial lower-yield cigarettes (which contain considerable nicotine), but not when switched to

reduced nicotine content cigarettes. Because content is limited, compensation strategies that are employed while smoking these cigarettes does not produce notable increases in nicotine delivery (Benowitz et al., 2006).

It is important to note, however, that most smokers do not completely cease smoking even when restricted to placebo cigarettes (Hatsukami et al., 2010a). Furthermore, smokers often consider placebo cigarettes as more aversive (e.g., increased ratings of “harsh”, decreased ratings of “taste good”) than their usual brand (Buchhalter et al., 2005; Donny et al., 2007), which may influence natural smoking behavior. In the current study, ratings for aversion were generally low for both types of Quest cigarettes. Although the nicotine containing cigarettes were rated as more aversive than the placebo dose initially, these differences also dissipated over the repeated smoking bouts. Taken together, current and previous work suggest the need for additional research to validate the idea that placebo cigarettes are unlikely to maintain self-administration behavior, and thus may be effective as a smoking cessation aide (see Hatsukami et al., 2010b; Walker et al., 2009). Future studies using multiple doses of nicotine will be necessary to determine if there is a indeed a threshold dose of nicotine content necessary to maintain regular smoking as proposed by Benowitz and Henningfield (1994). Fortunately, a new line of reduced nicotine cigarettes are currently being tested for research purposes through the National Institute of Drug Abuse. Several doses of nicotine will be offered, including doses that fall below those previously available with Quest (i.e., 0.02mg).

To confirm that the compensatory patterns described presently reflect extinction burst responding, it will be important for future studies to demonstrate that short-lived compensation emerges when dependent smokers are switched to placebo cigarettes after being maintained on otherwise identical nicotine containing cigarettes. Comparisons with conventional brand smoking should be avoided, as these traditional cigarettes also vary in ingredient and design features likely to affect smoking topography. The present study tested smokers after 12-hours of smoking abstinence. This was done to standardize pre-session nicotine exposure. Sessions began in the morning hours, and thus the present findings may be most relevant to the effects of nicotine content after overnight abstinence. Future research should determine whether these same effects are observed after shorter periods of abstinence. Additionally, larger sample sizes will be necessary to detect moderators of compensation. For example, genetic polymorphisms (e.g., Strasser et al. 2011) or assessments of dependence (e.g., Brauer et al. 2001) may predict those more or less likely to compensate and/or to extinguish smoking behavior with reduced nicotine cigarettes.

In summary, the present results are consistent with prior observations of smoking compensation in response to placebo (Quest 3) versus nicotine containing (Quest 2) cigarettes during a single smoking trial (Strasser et al., 2007). Furthermore, we provide evidence that compensatory smoking in response to placebo cigarettes partially extinguishes over the course of several cigarettes. These findings appear to be consistent with a lack of compensation when smokers are observed across multiple days of testing (Donny et al., 2007) and suggest that compensatory smoking may not pose a significant limitation to the use of low nicotine cigarettes for cessation and harm reduction efforts. However, these results should be replicated and extended before being applied to smoking cessation and harm reduction treatment protocols.

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References

Benowitz NL. Pharmacology of nicotine: addiction and therapeutics. Annu Rev Pharmacol Toxicol. 1996; 36:597–613. [PubMed: 8725403]

Benowitz NL, Hall SM, Stewart S, Wilson M, Dempsey D, Jacob P 3rd. Nicotine and carcinogen exposure with smoking of progressively reduced nicotine content cigarette. Cancer Epidemiol Biomarkers Prev. 2007; 16:2479–2485. [PubMed: 18006940]

Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction. The implications for tobacco regulation. N Engl J Med. 1994; 331:123–125. [PubMed: 7818638]

Benowitz NL, Jacob P 3rd, Herrera B. Nicotine intake and dose response when smoking reduced-nicotine content cigarettes. Clin Pharmacol Ther. 2006; 80:703–714. [PubMed: 17178270]

Benowitz NL, Porchet H, Sheiner L, Jacob P 3rd. Nicotine absorption and cardiovascular effects with smokeless tobacco use: comparison with cigarettes and nicotine gum. Clin Pharmacol Ther. 1988; 44:23–28. [PubMed: 3391001]

Blank MD, Disharoon S, Eissenberg T. Comparison of methods for measurement of smoking behavior: mouthpiece-based computerized devices versus direct observation. Nicotine Tob Res. 2009; 11:896–903. [PubMed: 19525207]

Brauer LH, Behm FM, Lane JD, Westman EC, Perkins C, Rose JE. Individual differences in smoking reward from de-nicotinized cigarettes. Nicotine Tob Res. 2001; 3:101–109. [PubMed: 11403723]

Buchhalter AR, Acosta MC, Evans SE, Breland AB, Eissenberg T. Tobacco abstinence symptom suppression: the role played by the smoking-related stimuli that are delivered by denicotinized cigarettes. Addiction. 2005; 100:550–559. [PubMed: 15784070]

Buchhalter AR, Schrinel L, Eissenberg T. Withdrawal-suppressing effects of a novel smoking system: comparison with own brand, not own brand, and de-nicotinized cigarettes. Nicotine Tob Res. 2001; 3:111–118. [PubMed: 11403724]

Cappelleri JC, Bushmakin AG, Baker CL, Merikle E, Olufade AO, Gilbert DG. Confirmatory factor analyses and reliability of the modified cigarette evaluation questionnaire. Addict Behav. 2007; 32:912–923. [PubMed: 16875787]

Cobb CO, Weaver MF, Eissenberg T. Evaluating the acute effects of oral, non-combustible potential reduced exposure products marketed to smokers. Tob Control. 2010; 19:367–373. [PubMed: 19346218]

Corrigall WA, Coen KM. Nicotine maintains robust self-administration in rats on a limited-access schedule. Psychopharmacology (Berl). 1989; 99:473–478. [PubMed: 2594913]

Donny E, Caggiula A, Knopf S, Brown C. Nicotine self-administration in rats. Psychopharmacology. 1995; 122:390–394. [PubMed: 8657839]

Donny EC, Houtsmuller E, Stitzer ML. Smoking in the absence of nicotine: behavioral, subjective and physiological effects over 11 days. Addiction. 2007; 102:324–334. [PubMed: 17222288]

Donny EC, Jones M. Prolonged exposure to denicotinized cigarettes with or without transdermal nicotine. Drug Alcohol Depend. 2009; 104:23–33. [PubMed: 19446968]

Comission, FT., editor. Federal Trade Comission. Tar, nicotine, and carbon monoxide of the smoke of 1294 varieties of domestic cigarettes for the year 1998. Washington, DC: 2000.

First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Biometrics Research. New York State Psychiatric Institute; 1994. Structured Clinical Interview for Axis I DSM-IV Disorders - Patient Edition (SCID-I/P, version 2.0).

Franken FH, Pickworth WB, Epstein DH, Moolchan ET. Smoking rates and topography predict adolescent smoking cessation following treatment with nicotine replacement therapy. Cancer Epidemiol Biomarkers Prev. 2006; 15:154–157. [PubMed: 16434603]

Fowler CD, Kenny PJ. Intravenous nicotine self-administration and cue-induced reinstatement in mice: effects of nicotine dose, rate of drug infusion and prior instrumental training. Neuropharmacology. 2011; 61:687–698. [PubMed: 21640128]

Guyatt AR, Kirkham AJ, Mariner DC, Baldry AG, Cumming G. Long-term effects of switching to cigarettes with lower tar and nicotine yields. Psychopharmacology (Berl). 1989; 99:80–86. [PubMed: 2506607]

Harris AC, Pentel PR, LeSage MG. Prevalence, magnitude, and correlates of an extinction burst in drug-seeking behavior in rats trained to self-administer nicotine during unlimited access (23 h/day) sessions. Psychopharmacology. 2007; 194:395–402. [PubMed: 17611741]

Hatsukami DK, Kotlyar M, Hertsgaard LA, Zhang Y, Carmella SG, Jensen JA, Allen SS, Shields PG, Murphy SE, Stepanov I, Hecht SS. Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation. Addiction. 2010a; 105:343–355. [PubMed: 20078491]

Hatsukami DK, Perkins KA, Lesage MG, Ashley DL, Henningfield JE, Benowitz NL, Backinger CL, Zeller M. Nicotine reduction revisited: science and future directions. Tob Control. 2010b; 19:e1–e10. [PubMed: 20876072]

Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict. 1991; 86:1119–1127. [PubMed: 1932883]

Herning RI, Jones RT, Bachman J, Mines AH. Puff volume increases when low-nicotine cigarettes are smoked. Br Med J (Clin Res Ed). 1981; 283:187–189.

Hoffmann D, Djordjevic MV, Hoffmann I. The changing cigarette. Prev Med. 1997; 26:427–434. [PubMed: 9245661]

Kleykamp, BA.; Jennings, JM.; Sams, C.; Shaffer, D.; Austin, J.; Gray, J.; Weaver, M.; Eissenberg, T. The Effects of Smoking-Related Stimuli on Cognitive Performance; Paper presented at the 13th annual meeting of the Society for Research on Nicotine and Tobacco; 2007 Feb.

Lee EM, Malson JL, Moolchan ET, Pickworth WB. Quantitative comparisons between a nicotine delivery device (Eclipse) and conventional cigarette smoking. Nicotine Tob Res. 2004; 6:95–102. [PubMed: 14982693]

Meisch RA. Relative persistence of behavior: a fundamental measure of relative reinforcing effects. Exp Clin Psychopharmacol. 2000; 8:333–349. [PubMed: 10975621]

Perkins KA. Nicotine self-administration. Nicotine Tob Res. 1999; 1(Suppl 2):S133–S137. discussion S139-40. [PubMed: 11768171]

Pickworth WB, Fant RV, Nelson RA, Rohrer MS, Henningfield JE. Pharmacodynamic effects of new de-nicotinized cigarettes. Nicotine Tob Res. 1999; 1:357–364. [PubMed: 11072433]

Risner ME, Goldberg SR. A comparison of nicotine and cocaine self-administration in the dog: fixed-ratio and progressive-ratio schedules of intravenous drug infusion. J Pharmacol Exp Ther. 1983; 224:319–326. [PubMed: 6822957]

Robinson ML, Houtsmuller EJ, Moolchan ET, Pickworth WB. Placebo cigarettes in smoking research. Exp Clin Psychopharmacol. 2000; 8:326–332. [PubMed: 10975620]

Rose JE, Corrigall WA. Nicotine self-administration in animals and humans: similarities and differences. Psychopharmacology (Berl). 1997; 130:28–40. [PubMed: 9089846]

Sannerud CA, Prada J, Goldberg DM, Goldberg SR. The effects of sertraline on nicotine self-administration and food-maintained responding in squirrel monkeys. Eur J Pharmacol. 1994; 271:461–469. [PubMed: 7705446]

Strasser AA, Benowitz NL, Pinto AG, Tang KZ, Hecht SS, Carmella SG, Tyndale RF, Lerman CE. Nicotine metabolite ratio predicts smoking topography and carcinogen biomarker level. Cancer Epidemiol Biomarkers Prev. 2011; 20:234–238. [PubMed: 21212060]

Strasser AA, Lerman C, Sanborn PM, Pickworth WB, Feldman EA. New lower nicotine cigarettes can produce compensatory smoking and increased carbon monoxide exposure. Drug and Alcohol Dependence. 2007; 86:294–300. [PubMed: 16930853]

Strasser AA, Pickworth WB, Patterson F, Lerman C. Smoking topography predicts abstinence following treatment with nicotine replacement therapy. Cancer Epidemiol Biomarkers Prev. 2004; 13:1800–1804. [PubMed: 15533910]

Sutton SR, Russell MA, Iyer R, Feyerabend C, Saloojee Y. Relationship between cigarette yields, puffing patterns, and smoke intake: evidence for tar compensation? Br Med J (Clin Res Ed). 1982; 285:600–603.

Tengs TO, Ahmad S, Savage JM, Moore R, Gage E. The AMA proposal to mandate nicotine reduction in cigarettes: a simulation of the population health impacts. Prev Med. 2005; 40:170–180. [PubMed: 15533526]

Walker N, Bullen C, McRobbie H. Reduced-nicotine content cigarettes: Is there potential to aid smoking cessation? Nicotine Tob Res. 2009; 11:1274–1279. [PubMed: 19793786]

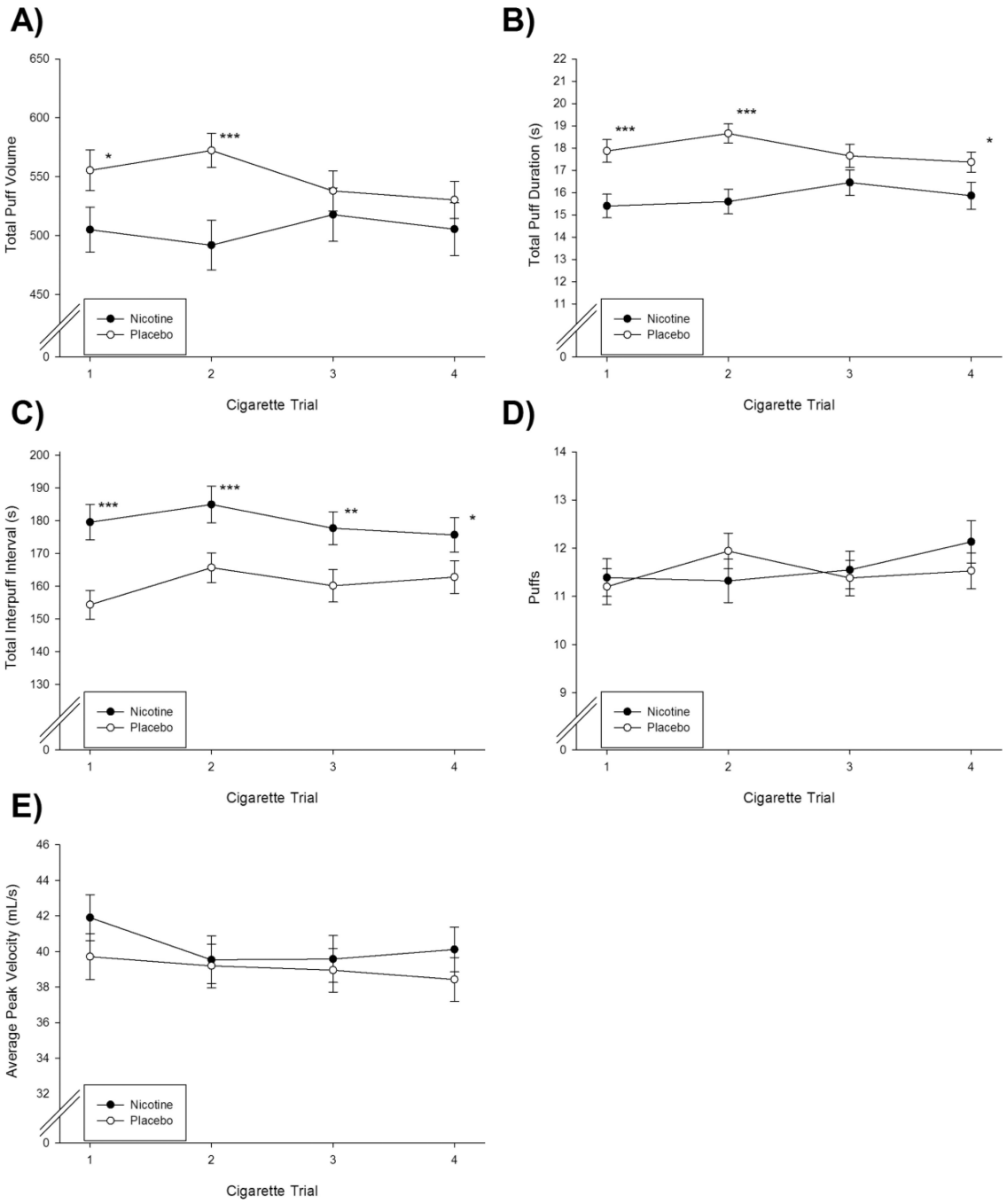

Figure 1.

Comparison of nicotine (solid circles) versus placebo (open circles) Quest cigarettes across sessions on: (A) Total Puff Volume; (B) Total Puff Duration; (C) total interpuff interval; (D) number of puffs; and (E) average maximum peak air velocity. Error bars indicate standard error. * $p < .05$; ** $p < .01$; *** $p < .001$.

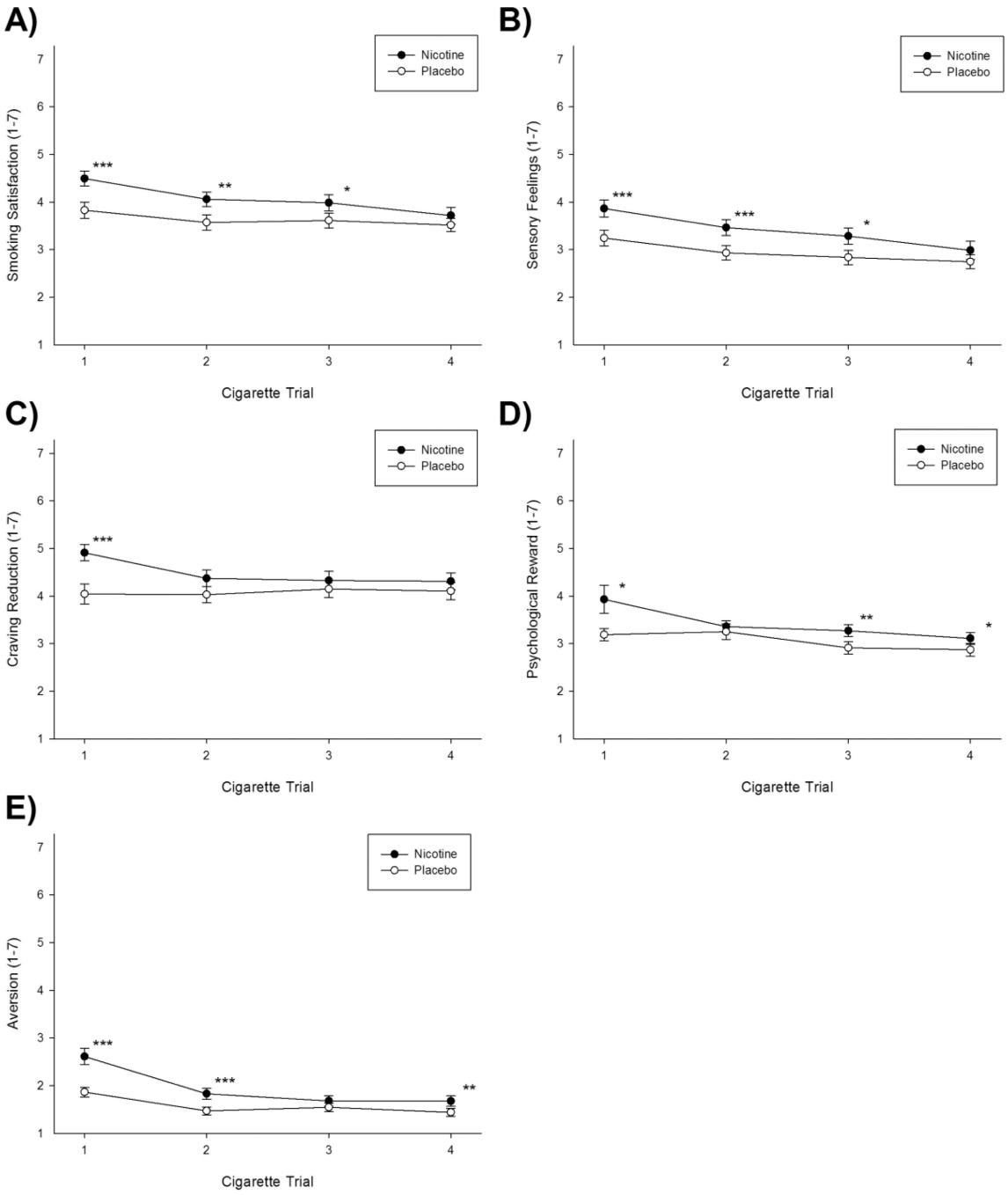

Figure 2.

Comparison of nicotine (solid circles) versus placebo (open circles) Quest cigarettes across sessions on mCEQ domains: (A) smoking satisfaction; (B) sensory feelings; (C) craving reduction; (D) psychological reward; and (E) aversion. Error bars indicate standard error. * $p < .05$; ** $p < .01$; *** $p < .001$