Original Investigation

Substance use, trait measures, and subjective response to nicotine in never-smokers stratified on parental smoking history and sex

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Abstract

Introduction: Male and female never-smokers stratified on parental history of smoking were tested for possible differences in susceptibility to the hedonic effects of nicotine.

Methods: We recruited nicotine-exposed never-smokers with two never-smoking biological parents (PH−) or two ever-smoking biological parents (PH+). After completing a baseline assessment battery focusing on conditions or behaviors associated with smoking, participants were tested for subjective and hedonic effects in response to administration of three different nicotine doses (0.0, 0.5, and 1.0 mg) via nasal spray. Physiological and biochemical reactivity also was monitored.

Results: PH+ were significantly more likely to report having experienced a “buzz” upon early smoking experimentation and to have histories of alcohol abuse and alcoholism; they also scored higher on disordered eating. In response to nicotine dosing, PH+ reported an increase in depressed mood, compared with a minimal response in PH−, in keeping with our expectation that nicotine would have more pronounced effects in PH+. Regardless of parental history, women reported experiencing greater anxiety in response to the highest nicotine dose, compared with men.

Discussion: Further exploration in larger samples, using more stringent selection criteria, a wider range of measures, and a less aversive dosing method, may provide a full test of the possible utility of the parental history model for illuminating biobehavioral mechanisms underlying response to nicotine. Also important would be broadening the scope of inquiry to include comparisons with ever-smokers to determine what protected PH+ from be-

coming smokers, despite the presence of factors that might be expected to decrease resilience and increase susceptibility.

Introduction

An understanding of individual differences in susceptibility to the effects of nicotine is crucial to explaining initiation and maintenance of smoking behavior (O. F. Pomerleau, Collins, Shiffman, & Pomerleau, 1993). To date, such investigations have been conducted predominantly by comparing light with heavy smokers or ever-smokers with never-smokers. Interpretation of the results of these studies, however, is complicated by the possible short- and long-term persistence of the effects of nicotine and nicotine withdrawal.

Relatively little work has been done on individual differences in the response to nicotine among never-smokers. An important exception is a study by Perkins, Gerlach, Broge, Grobe, and Wilson (2000), in which scores for sensation seeking were associated with significantly greater sensitivity to nicotine via nasal spray. Like novelty seeking, sensation seeking is robustly associated with greater likelihood of drug taking for many substances of abuse (Bickel, Odum, & Madden, 1999; Cloninger, Svrakic, & Przybeck, 1993; Heath, Madden, Slutske, & Martin, 1995; Hutchison, Wood, & Swift, 1999; Mitchell, 1999). This association was particularly pronounced for pleasurable/favorable responses such as vigor, arousal, and “head rush”—effects shown to be predictive of nicotine self-administration in smokers (Perkins, Grobe, & Caggiula, 1997; Perkins, Grobe, Weiss, Fonte, & Caggiula, 1996).

An alternative approach, involving the study of the response to nicotine in never-smokers with positive versus negative parental smoking histories, has proved to be extremely productive

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in a related field—namely, the response to alcohol in children of alcoholics. These studies typically involve the administration of small amounts of alcohol to test the reactivity of normal-drinking sons and daughters of people with and without alcohol problems. Individuals with a positive parental history for alcohol abuse (who are at higher risk for problem drinking) have been shown to be more sensitive to certain effects of alcohol (McCaul, Turkkan, Svikis, & Bigelow, 1991b; Vogel-Sprott & Chipperfield, 1987). Of particular significance is that these individuals exhibit more extended intoxication after ethanol administration (McCaul, Turkkan, Svikis, & Bigelow, 1991a).

Support for adapting this approach to individuals differing on familial smoking history is provided by studies of never-smoking twin pairs showing that familial smoking history accounts for 51% of the variability in feelings of dizziness, 52% of the variability in feelings of nausea, and 83% of the variability in overall mood rating in response to nicotine challenge (Lessov et al., 2001). Factor analysis of all subjective measures resulted in three separate factors that distinguished among measures related to sedation, stimulation, and physical sensation. Animal models also provide consistent support for the role of genetic factors in determining response to nicotine. In particular, in nicotine first-dose experiments in pure-bred mice, mouse strains that were the most sensitive to nicotine initially were the ones that developed the greatest tolerance following chronic exposure (Collins, Burch, de Fiebre, & Marks, 1988; Cools & Gingras, 1998). Of critical importance for the present approach, these strains took in the most nicotine when it was made available in a drinking solution (Collins & Marks, 1991).

Comparing never-smokers with positive versus negative parental smoking histories also may lead to a better understanding of the over-representation among smokers of a number of psychological or behavioral patterns, including alcohol and other drug use (Bobo, 1989; Breslau, Kilbey, & Andreski, 1991; Istvan & Matarazzo, 1984); disordered eating, dieting concerns, and body dissatisfaction (Anzengruber et al., 2006; Bulik et al., 1992; Killen et al., 1986; Krahn, Kurth, Demitrack, & Drewnowski, 1992; C. S. Pomerleau & Krahn, 1993; C. S. Pomerleau & Saules, 2007; Saules et al., 2004; Weiss & Ebert, 1983); personality dimensions including novelty seeking (Etter, Pélissolo, Pomerleau, & De Saint-Hilaire, 2003); and psychopathological conditions such as depression (Glassman, 1993), anxiety (Breslau et al., 1991), and attention-deficit/hyperactivity disorder (ADHD; Barkley, Fischer, Edelbrock, & Smallish, 1990; Borland & Heckman, 1976; Hartsough & Lambert, 1987; O. F. Pomerleau, Downey, Stelson, & Pomerleau, 1995). Studying these conditions in never-smokers may help to resolve questions relating to whether smoking constitutes “self-medication” or makes nicotine more rewarding for such individuals or whether, on the other hand, smoking causes or exacerbates these conditions. (For a review of these issues, see U.S. Department of Health and Human Services, 2001.) It also may shed light on the extent to which these cofactor smoking associations are genetically based.

In the present study, we first administered a baseline assessment battery, focusing on conditions or behaviors known to be associated with smoking, to male and female never-smokers stratified on parental history of smoking (two never-smoking vs. two ever-smoking biological parents). Participants were then tested for subjective and hedonic effects in response to three different doses of nicotine administered via nasal spray; physiological and biochemical reactivity also was monitored. We hypothesized that, compared with individuals with a negative parental history of

smoking, those with a positive parental history would more closely resemble smokers on measures of alcohol use and misuse; disordered eating, dieting concerns, and body dissatisfaction; personality; and measures of affect and attention. We also expected nicotine to have more pronounced effects on individuals with a positive parental history of smoking than on those with a negative parental history. Because of evidence that men and women may differ in sensitivity to nicotine (see Perkins, Donny, & Caggiula, 1999), we also included sex as a grouping variable in our analyses.

Methods

Participants

Participants were 132 never-smokers recruited from the local community via newspaper, radio, and television advertisements. To be eligible to participate, participants had to be in good health, be between the ages of 21 and 55 years, and have smoked 1–100 cigarettes in their lifetime. Participants had to be either parental history positive (PH+; $n = 56$; 50% female) or parental history negative (PH–; $n = 76$; 55% female) for smoking. To be considered PH+, both biological parents were required to have been regular daily smokers for at least 3 years at some time in their lives; for PH–, both biological parents had to have been never-smokers (<100 lifetime cigarettes) and never regular users of other tobacco products. All participants endorsed either “fairly certain” or “very certain” as their level of confidence about parental smoking status.

To ensure the integrity of our testing procedures, candidates were excluded if they had a current *DSM-IV* diagnosis of depression or alcohol dependence, or a current diagnosis or history of psychosis, as determined using a computerized version of the Composite International Diagnostic Interview (CIDI; a structured interview developed by the World Health Organization [WHO], the National Institute on Mental Health, the National Institute on Alcohol Abuse and Alcoholism, and the National Institute on Drug Abuse [WHO, 1997] to provide a comprehensive, fully standardized assessment of mental disorders consistent with definitions and criteria of the International Statistical Classification of Diseases and Related Mental Health Problems, 10th Revision (ICD-10) [WHO, 1992] and the *DSM-IV* [American Psychiatric Association, 1994]). Participants also were excluded if they were currently taking psychotropic medication, were night shift workers, or had a body mass index (BMI) of less than 18.5 or greater than 39.9.

To avoid the possibility of fetal exposure to nicotine, women had to be using a reliable form of birth control and could not be pregnant. Women also were scheduled to participate in the laboratory sessions in such a way as to avoid their perimenstrual phase (last 7 days before expected onset of bleeding through offset of bleeding).

Procedure

The study protocol and all consent forms were approved by the University of Michigan Medical School Institutional Review Board.

Screening and enrollment. Candidates who appeared to be eligible on the basis of a preliminary telephone screen were invited to a screening interview, at which time the study was explained and informed consent was obtained. Candidates were asked to fill out a health history questionnaire developed in the Nicotine Research Laboratory, and a research nurse conducted a brief physical

examination to confirm that the candidate was in good general health and to rule out cardiovascular, pulmonary, or other conditions that would preclude administration of nicotine. Blood pressure and pulse were taken, and height and weight were measured to determine BMI. Participants practiced dose administration using the intranasal saline spray until the spray could be administered efficiently without loss via dripping, swallowing, or sneezing.

Biochemical measures. To verify nonsmoker status, exhaled carbon monoxide levels were determined using a Vitalograph BreathCO monitor, and a urine sample was tested for nicotine metabolites using Quickscreen Cotinine Test (Craig Medical Distribution Inc., Vista, CA). In female participants, the Abbott TestPack Plus hCG-COMBO, a highly sensitive and specific immunoassay designed for the qualitative determination of hCG in urine, was used to screen out early pregnancy. Hematocrit levels were determined with a finger-prick blood sample using a Hemata-STAT-II (Separation Technology, Inc., Altamonte Springs, FL).

During each laboratory session, blood samples for nicotine, cotinine, and caffeine were drawn into lithium heparin (green top) Vacutainer tubes, and samples for cortisol were drawn into ethylenediaminetetraacetic acid (purple top) Vacutainer tubes, which were immediately stored in crushed ice. After a session, samples were centrifuged at 4 °C and stored in aliquot containers at -80 °C. Session concentrations of nicotine, cotinine, and caffeine in plasma, withdrawn prior to and 5 min following nicotine administration, were assayed by the University of California, San Francisco, Clinical Pharmacology Chemistry Laboratory using gas chromatography. Plasma cortisol concentrations withdrawn prior to and 40 min following nicotine administration were assayed in the laboratory of David Schteingart at the University of Michigan using radioimmunoassay; because the laboratory was unable to continue providing these assays through the completion of the study, cortisol data are available for only a subset of participants ($n = 23$).

Baseline assessment battery. Demographic data were collected via a general history developed in the Nicotine Research Laboratory.

Three instruments were used to assess history of tobacco use and exposure: (a) A smoking history developed in the Nicotine Research Laboratory was used to document lifetime nonsmoking status. (b) Early Smoking Experiences (O. F. Pomerleau, Pomerleau, & Namenek, 1998; Pomerleau, Pomerleau, Namenek, & Marks, 1999), developed in the Nicotine Research Laboratory and validated (for "buzz") in deprived smokers (O. F. Pomerleau, Pomerleau, Mehringer, Snedecor, & Cameron, 2005) and (for "buzzed" and "dizzy," though not for other items) in never-smokers (Perkins, Lerman, Coddington, & Karelitz, 2008), was used to assess the context of initial experimentation with cigarettes and sensations experienced. (c) The nonsmokers survey (NSS; C. S. Pomerleau, Pomerleau, Snedecor, & Mehringer, 2004) is an instrument developed to assess family history of smoking, passive exposure to smoking during childhood and adolescence, and multiple motivational and emotional reasons for having experimented with smoking. The NSS also includes assessment of prenatal exposure to nicotine (i.e., maternal smoking during pregnancy, as reported by participant).

Alcohol use was assessed with three tools: (a) A substance intake history asked about use of both alcohol and caffeine. It included the CAGE (Mayfield, McLeod, & Hall, 1974), a four-question screening test for alcohol dependence (dichotomized

as 0–1 vs. 2–4). (b) The Michigan Alcohol Screening Test (MAST; Moore, 1972) is a widely used 24-item questionnaire for detecting alcoholism. (c) Lifetime alcohol abuse also was evaluated via Section L of the CIDI (WHO, 1997).

Disordered eating, dieting concerns, and body dissatisfaction were assessed with three measures: (a) The Dieting and Bingeing Severity Scale (DBSS; Krahn et al., 1992; Kurth, Krahn, Nairn, & Drewnowski, 1993) is a self-report assessment of the severity of dieting and bingeing behavior adapted from an instrument developed by Krahn et al. (1992). (b) The Three-Factor Eating Questionnaire (TFEQ; Stunkard & Messick, 1985) is a self-report assessment of eating behavior with restrained eating, disinhibited eating, and hunger subscales. (c) The Body Image Questionnaire (Fallon & Rozin, 1985) asks respondents to identify which of 10 silhouettes of increasingly larger bodies (male bodies for men, female bodies for women) best represents how they look (perceived body shape) and how they wish they looked (preferred body shape). Body image dissatisfaction was computed by subtracting preferred body shape from perceived body shape.

Personality was assessed using the Tridimensional Personality Questionnaire (TPQ-brief; Cloninger, 1986; Cloninger, Przybeck, & Svrakic, 1991). This instrument generates scores on three dimensions of personality: novelty seeking, harm avoidance, and reward dependence. Trait measures of affect and attention were assessed using three instruments: (a) The Center for Epidemiological Studies Depression Scale (Weissman, Sholomakis, Pottenger, Prushoff, & Locke, 1977) is a population-based screening instrument for assessing depression/dysphoria, with high internal consistency, good test–retest reliability, and good correlation with clinical ratings of severity of depression (Radloff, 1977). (b) The State-Trait Anxiety Inventory (trait version; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983) is a widely used scale for measuring trait anxiety. (c) The Attention/Hyperactivity Assessment (AHA; Mehringer, Downey, Schuh, Pomerleau, Snedecor, & Schubiner, 2002), a measure of ADHD, was developed and validated in the Nicotine Research Laboratory.

Laboratory sessions. Three sessions in the University of Michigan Nicotine Research Laboratory were scheduled between noon and 2 p.m., at least 1 day apart. Participants were instructed to refrain from drinking alcohol for 24 hr prior to the session and to drink no more than one cup of their usual caffeinated beverage during the morning. They also were instructed to eat a typical lunch before the session.

Participants sat in a recliner throughout all testing sessions. Upon arrival, an indwelling 18-gauge catheter leading to a heparinized 1-m infusion–exfusion tubing was inserted in a forearm vein, and a 60-min interval was allowed to elapse prior to testing to allow cortisol levels to normalize. A one-way mirror was used to provide participant isolation, with a channel in the wall permitting unobtrusive collection of blood samples and physiological data from the adjacent room. Except in an emergency and during administration of the nasal spray, there were no participant–experimenter interactions once a session had started.

Heart rate was monitored continuously using an ECG100B amplifier (BioPac Systems, Inc., Goleta, CA). Blood pressure was obtained prior to and 10 min after nicotine administration, using an IBS Automated Blood Pressure and Pulse Rate Monitor (model SD 700A).

Following collection of baseline physiological measures, subjective ratings were obtained via Visual Analog Scales assessing relaxed, tense, irritable, restless, anxious, alert, depressed, hungry, dizzy, and nauseous, presented on a video touch screen. The labels and oral instructions (provided by a wave file) asked the participant to indicate the degree (intensity) of the sensation he or she was experiencing “right now” by touching the screen in the appropriate place on the thermometer-like 11-point Likert scale (with only the endpoints labeled).

Study drug was administered immediately following the collection of baseline physiological and subjective ratings. The active drug used in the study was Nicotrol Nasal Spray (10 mg/ml), manufactured and supplied by Pharmacia, Inc. The original placebo was Nicotrol Placebo Spray, an aqueous pepper solution that mimics some sensations of nicotine, manufactured and supplied by Pharmacia, Inc. After 30% of participants had completed the protocol, Nicotrol Placebo Spray could no longer be obtained. Sinus Buster Nasal Spray, a commercially available pepper-based spray (Dynova Laboratories, Parsippany, NJ) was substituted for the remaining 70% of participants. A research assistant administered the study drug to each participant in two sprays (one per nostril). The high-dose condition (1.0 mg nicotine) consisted of two nicotine sprays, the medium-dose condition (0.5 mg nicotine) consisted of one nicotine spray and one placebo spray, and the zero-dose condition (0.0 mg nicotine) consisted of two placebo sprays. Participants were assigned to one of three possible sequences, counterbalanced to rule out or control for order effects. To maintain the blind for the participants, bottles were kept behind a shield and replaced between each spray.

Immediately after nicotine administration, number and duration of “pleasurable sensations” and “displeasurable sensations” (hedonic effects of nicotine) were assessed for 10 min via depression of two foot pedals, one of which was labeled with a smiling face to signify euphoric sensations, the other with a frowning face to signify dysphoria. The following recorded instructions were provided (C. S. Pomerleau & Pomerleau, 1992):

People sometimes report experiencing pleasurable sensations from nicotine that might be described as a head rush, a buzz, or a high. If you happen to experience any of these pleasurable sensations after the nicotine administration, depress the right foot pedal and hold it down for the duration of the sensation. If you experience any unpleasant sensations, depress the left foot pedal and hold it down for the duration of the sensation.

At the end of each session, willingness to self-administer the same dose of nicotine was assessed by asking participants to select an amount of money (from -\$5 to +\$5) below which nicotine spray is preferred and above which money is preferred (adapted from Jones, Garrett, & Griffiths, 1999). The resulting “crossover point” defines the reinforcement value of the particular nicotine dosage.

Upon completion of the study protocol, participants were paid US\$265.

Data analyses

Group differences at baseline were analyzed using SAS PROC GLM and chi-square tests, as appropriate. Preliminary analyses revealed no significant differences based on either parental history

or sex in the proportion who received the Nicotrol placebo versus Sinus Buster. Nevertheless, to rule out the possibility of unwanted differences in reactivity to the two placebo sprays, we conducted independent *t* tests on placebo session data to compare responses of those who received the Nicotrol placebo with responses of those who received Sinus Buster. No significant differences were found for any variable, so session data were collapsed across the two placebo products in all subsequent analyses.

Session data were analyzed using mixed linear model techniques of SAS PROC MIXED (version 9.1) with fixed effects of parental history and sex and response variables at three nicotine dose levels as repeated measures, plus the interaction of the main factors with dose. In all cases, the autoregressive covariance structure was the best fit for response variables. Some models included age, BMI, or both, which differed significantly for parental history, as covariates, based on their relevance to specific variables (e.g., age in our analyses of novelty seeking, ADHD, and all physiological variables; BMI in measures of disordered eating, dieting concerns, and body image). Of particular interest in analyses of session data were interactions of parental history and sex effects with the dose effect. Pairwise contrasts were conducted to follow up on significant interaction effects.

Results

Participant characteristics

Demographic characteristics are shown in Table 1. Significantly higher proportions of PH+ participants and female participants were White. Significant parental history differences also were detected for age and BMI (PH+ > PH- for both variables). (A more extended treatment of the observed BMI differences, in a sample including qualified noncompleters as well as completers, can be found in C. S. Pomerleau, Snedecor, & Pomerleau, 2009).

Among PH+ participants, 32% reported prenatal exposure to nicotine via maternal smoking and 34% reported no prenatal exposure to nicotine; 34% indicating that they did not know.

Compared with the 53 enrollees who were dropped from the study (for reasons such as failure to return questionnaire packets, repeated no-show for scheduled appointments, or unable to contact after repeated attempts), the 132 participants who completed the protocol were significantly more likely to be male ($\chi^2 = 4.27$, $p < .05$) and White ($\chi^2 = 4.78$, $p < .05$). No differences emerged based on age or parental history.

Baseline tests

Group comparisons of scores on the baseline assessment battery are shown in Table 2. PH+ participants were significantly more likely to report experiencing a buzz upon early experimentation with smoking. They scored significantly higher on the CAGE and were more likely to have a history of alcohol abuse. Women had significantly higher plasma caffeine levels than men, despite no differences in self-reported caffeine intake. Men scored significantly higher on the MAST and were significantly more likely to be diagnosed with a history of alcohol abuse. PH+ participants scored significantly higher on the DBSS. Women scored higher than men on the TPQ reward dependence subscale, on the TFEQ

Table 1. Participant characteristics for entire sample and for groups based on family history and sex

Characteristics	Entire sample	Parental history negative	Parental history positive	Parental history significance (<i>p</i> value)	Men	Women	Sex significance (<i>p</i> value)
Age, years; <i>M</i> ± <i>SEM</i>	33.5 ± 0.92	31.6 ± 1.1	36.1 ± 1.5	$F(1, 130) = 6.29, p < .05$	34.2 ± 1.3	33.5 ± 1.3	<i>ns</i>
Race, % White	83%	76%	93%	$\chi^2(1) = 6.35, p < .05$	77%	90%	$\chi^2(1) = 4.11, p < .05$
Gender, % male	53%	55%	50%	<i>ns</i>	—	—	—
Body mass index, kg/m ² ; <i>M</i> ± <i>SEM</i>	25.2 ± 0.40	24.4 ± 0.52	26.3 ± 0.63	$F(1, 129) = 6.06, p < .05$	26.0 ± 0.54	24.7 ± 0.57	<i>ns</i>
Education, years; <i>M</i> ± <i>SEM</i>	15.9 ± 0.15	16.1 ± 0.20	15.7 ± 0.22	<i>ns</i>	16.0 ± 0.20	15.8 ± 0.21	<i>ns</i>

Note. The parental history × sex interaction was not significant for any variable and was removed from the model.

restrained eating subscale, and on body image dissatisfaction. No other main or interaction effects were observed.

Plasma nicotine increment following nicotine administration

Postdosing nicotine levels and physiological and biochemical changes (post minus pre) for the three sessions are shown in Figure 1. Significant dose effects emerged, $F(2, 259) = 229.75, p < .001$, with no dose × parental history interaction effect. A significant sex effect, $F(1, 129) = 11.13, p < .001$, also was observed (men > women for both active doses). A significant dose × sex interaction effect emerged, $F(2, 259) = 4.36, p < .05$, due to both genders having the same zero nicotine value during the placebo section, but the effect disappeared when only the two active doses were included in the analyses.

Subjective and hedonic responses to nicotine administration

Visual Analog Scale measures (postdosing minus predosing levels) are shown in Figure 2. Duration of pleasurable and displeasurable buzz sensations and willingness to readminister the same dose of nicotine following administration of the three different doses of nicotine are shown in Figure 3. Significant dose effects were observed for several variables (relaxed, tense, irritable, restless, anxious, depressed mood, dizzy, nausea, and concentration). In addition, an interaction of dose with parental history was detected for depressed mood, $F(2, 243) = 4.44, p < .05$, such that PH+ participants, unlike PH− participants, reported a small but significant increase in depressed mood in response to nicotine dosing. A sex effect emerged for depressed mood, $F(1, 129) = 5.29, p < .05$, and ability to concentrate, $F(1, 129) = 6.87, p < .01$ (men > women for both variables). Dose × sex interactions were observed for anxiety, $F(2, 240) = 6.22, p < .01$, such that women were more responsive than men to the high dose.

Physiological and biochemical responses to nicotine administration

As shown in Figure 4, significant dose-related increases emerged for heart rate, $F(2, 258) = 21.31, p < .001$; systolic blood pressure, $F(2, 244) = 17.70, p < .001$; and diastolic blood pressure, $F(2, 244) = 22.38, p < .001$. No other significant main or interaction effects emerged.

Discussion

Participants with a positive parental history for smoking were significantly more likely to report experiencing a buzz upon early experimentation with smoking. Previous research on early smoking experiences (Chen et al., 2003; DiFranza et al., 2004; Hahn et al., 1990; O. F. Pomerleau et al., 1998; C. S. Pomerleau et al., 1999) suggests that such experiences are associated with subsequent progression to smoking and provides a plausible explanation for how the rewarding effects of nicotine might be entrained in new smokers.

As hypothesized, participants with a positive parental history also were more likely to have histories of alcohol abuse, as measured by the CIDI, and alcoholism, as measured by the CAGE. Similarly, never-smokers with a positive parental history for smoking scored higher on a measure of disordered eating. One possibility raised by these findings is that the link between smoking and alcohol use disorders—and disordered eating, which also can be conceptualized as a form of substance abuse—is based on receptor commonalities (e.g., Collins et al., 1988; de Fiebre et al., 1991; Lopez, White, & Randall, 2001; C. S. Pomerleau et al., 1999; Radel & Goldman, 2001). By contrast, little evidence emerged for an association between positive parental smoking history and other forms of psychopathology (the rates of which were low in this never-smoking sample). However, exclusion of candidates meeting criteria for current depression or alcohol dependence, or for current or lifetime psychosis, may have muted possible differences in psychopathology.

With respect to sex differences, women posted higher caffeine levels but scored lower on the MAST and showed less likelihood of being diagnosed with alcohol abuse. They scored higher on measures of reward dependence, restrained eating, and body image dissatisfaction. These results are consistent with generally expected male–female differences independent of smoking status.

Our dosing procedure produced graded plasma nicotine increments. Physiological and biochemical variables tended to corroborate success in parametric dosing, with dose-related effects that were significant or, if, nonsignificant, in the expected direction. The same dose of nicotine produced significantly lower blood nicotine concentrations in women than in men, possibly due to faster nicotine metabolism in women (Benowitz, Lessov-Schlaggar, Swan, & Jacob, 2006). Physiological data,

Table 2. Differences in baseline measures for entire sample and for groups based on parental history and sex

Measure	Entire sample	Parental history negative	Parental history positive	Parental history significance (p value)	Men	Women	Sex significance (p value)
Lifetime number of cigarettes	14.8 ± 2.0	14.9 ± 2.7	14.6 ± 3.2	ns	15.6 ± 2.8	13.9 ± 3.0	ns
Percent who smoked							
1 cigarette/lifetime	16.7%	14.5%	19.6%	ns	18.6%	14.5%	ns
2–20 cigarettes/lifetime	29.6%	27.6%	32.1%		31.4%	27.4%	
21–100 cigarettes/lifetime (from the nonsmokers survey; mean ± SEM)	53.8%	57.9%	48.2%		50.5%	58.1%	
Age at first experimentation 01 (from the ESE; M ± SEM)	15.8 ± 0.4	16.4 ± 0.5	15.7 ± 0.6	ns	16.2 ± 0.5	15.9 ± 0.5	ns
Experienced upon early experimentation							
Global pleasurable	1.4 ± 0.1	1.3 ± 0.1	1.4 ± 0.1	ns	1.5 ± 0.1	1.3 ± 0.1	ns
Global displeasurable	2.8 ± 0.1	2.8 ± 0.1	2.8 ± 0.2	ns	2.7 ± 0.1	2.9 ± 0.2	ns
Pleasurable buzz	1.4 ± 0.1	1.3 ± 0.1	1.6 ± 0.1	F(1, 111) = 5.2, p < .05	1.5 ± 0.1	1.3 ± 0.1	ns
Dizziness	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	ns	1.6 ± 0.1	1.7 ± 0.1	ns
Nausea	1.6 ± 0.1	1.7 ± 0.1	1.5 ± 0.1	ns	1.7 ± 0.1	1.5 ± 0.1	ns
Relaxation	1.3 ± 0.1	1.3 ± 0.1	1.3 ± 0.1	ns	1.3 ± 0.1	1.3 ± 0.1	ns
Coughing	2.7 ± 0.1	2.7 ± 0.1	2.7 ± 0.2	ns	2.6 ± 0.1	2.8 ± 0.1	ns
Difficulty inhaling (from the ESE; M ± SEM)	2.7 ± 0.1	2.6 ± 0.1	2.7 ± 0.2	ns	2.6 ± 0.1	2.8 ± 0.1	ns
Self-reported caffeine use (mg/day; M ± SEM)	142.0 ± 12.1	146.0 ± 16.1	137.5 ± 18.7	ns	135.6 ± 16.9	148.0 ± 17.8	ns
Plasma caffeine levels (placebo session; ng/ml; M ± SEM)	1,329.2 ± 147.4	1,391.3 ± 193.1	1,297.2 ± 224.6	ns	1,024.4 ± 205.0	1,664.1 ± 213.8	F(1, 119) = 4.66, p = .05
Self-reported alcohol use (drinks per week; M ± SEM)	2.8 ± 0.4	2.2 ± 0.5	3.5 ± 0.6	ns	3.3 ± 0.5	2.3 ± 0.6	ns
MAST	2.9 ± 0.4	2.2 ± 0.5	3.7 ± 0.6	ns	3.81 ± 0.6	2.11 ± 0.6	F(1, 112) = 4.47, p < .05
CAGE positive (% scoring 2–4)	12%	5%	18%	$\chi^2(1) = 5.27, p < .05$	13%	8%	ns
Alcohol abuse (substance history, CIDI section 1.)	13%	8%	20%	$\chi^2(1) = 4.076, p < .05$	19%	7%	$\chi^2(1) = 4.29, p < .05$
Disordered eating/dieting							
DBSS	2.6 ± 0.1	2.4 ± 0.1	2.8 ± 0.1	F(1, 120) = 4.20, p < .05	2.5 ± 0.1	2.7 ± 0.1	ns
TFEQ cognitive restraint	6.7 ± 0.4	6.9 ± 0.5	6.7 ± 0.6	ns	5.9 ± 0.5	7.7 ± 0.6	F(1, 129) = 5.43, p < .05
TFEQ disinhibition	5.0 ± 0.3	4.6 ± 0.4	5.5 ± 0.5	ns	5.2 ± 0.5	5.0 ± 0.5	ns
TFEQ hunger	4.3 ± 0.3	3.8 ± 0.4	4.8 ± 0.5	ns	4.9 ± 0.4	3.7 ± 0.5	ns
Body image dissatisfaction (M ± SEM)	0.9 ± 0.1	0.8 ± 0.1	1.1 ± 0.1	ns	0.7 ± 0.1	1.3 ± 0.1	F(1, 119) = 10.35, p < .01
Personality dimensions							
Novelty seeking	8.1 ± 0.3	8.0 ± 0.4	8.2 ± 0.4	ns	8.2 ± 0.4	8.0 ± 0.4	ns
Harm avoidance	5.0 ± 0.4	5.1 ± 0.6	4.8 ± 0.6	ns	4.3 ± 0.5	5.6 ± 0.6	ns
Reward dependence (TPQ; M ± SEM)	11.8 ± 0.3	12.2 ± 0.4	11.5 ± 0.4	ns	10.9 ± 0.4	12.8 ± 0.4	F(1, 125) = 11.2, p < .01
Depression (CES-D; M ± SEM)	3.0 ± 0.4	2.7 ± 0.5	3.4 ± 0.6	ns	3.2 ± 0.5	2.9 ± 0.5	ns
Trait anxiety (STAI; M ± SEM)	10.7 ± 0.2	10.9 ± 0.3	10.5 ± 0.4	ns	10.9 ± 0.3	10.5 ± 0.4	ns
Attention-deficit/hyperactivity disorder (AHA; % yes)	3%	4%	2%	ns	4%	2%	ns

Note. The parental history × sex interaction was not significant for any variable and was removed from the model. AHA, Attention/Hyperactivity Assessment; CES-D, Center for Epidemiological Studies Depression Scale; CIDI, Composite International Diagnostic Interview; DBSS, Dieting and Bingeing Severity Scale; ESE, Early Smoking Experiences; MAST, Michigan Alcohol Screening Test; STAI, State-Trait Anxiety Inventory; TFEQ, Three-Factor Eating Questionnaire; and TPQ, Tridimensional Personality Questionnaire.

Figure 1. Nicotine levels achieved 5 min after nicotine administration for each of the three sessions. hx- = negative history; hx+ = positive history. Significant effects: * $p < .05$; ** $p < .01$; *** $p < .001$.

however, showed no evidence of differential dosing effects suggestive of less effective dosing in women.

Participants with a positive parental history reported an increase in depressed mood in response to nicotine dosing, compared with a minimal response in those with a negative parental history, in keeping with our expectation that nicotine would have more pronounced effects in individuals with a positive parental smoking history (i.e., that they would be more sensitive to the effects of nicotine). The direction of the observed response is consistent with the general pattern of adverse subjective effects of rapidly absorbed nicotine in nonsmokers (see review by Kalman, 2002). No other significant differences in subjective or hedonic effects in response to parametric doses of nicotine were observed based on parental history.

Overall, blood concentrations of nicotine were low. Higher doses of nicotine, or possibly nicotine delivered via a less aversive vehicle, might be needed to mimic fully the effects of smoking (e.g., significant differences based on parental history in retrospective

Figure 2. Mood change (Visual Analog Scale; post minus pre) in response to 0.0, 0.5, and 1.0 mg nicotine doses ($M \pm SEM$). Significant effects: * $p < .05$; ** $p < .01$; *** $p < .001$.

Figure 3. Duration of pleasurable and displeasurable sensations and willingness to readminister the same dose of nicotine in response to 0.0, 0.5, and 1.0 mg nicotine doses ($M \pm SEM$). Significant effects: * $p < .05$; ** $p < .01$; *** $p < .001$.

reports of buzz in response to experimentation with smoking were not reflected in differential responses to nasal spray, even though these variables have been shown to be correlated in never-smokers; Perkins et al., 2008). On the other hand, militating against the inference that dosing was inadequate, dose-related sex effects were seen for a number of variables, with women reporting greater irritability, anxiety, and restlessness in response to the highest dose of nicotine, compared with men. These findings may be related to reports of lower sensitivity to the rewarding effects of nicotine in women smokers (e.g., Perkins, Jacobs, Sanders, & Caggiula, 2002)—although, again, comparisons with response to self-administration of nicotine by nicotine-dependent smokers must be made with caution.

Additional caveats should be considered. Using more stringent criteria to define family history of smoking (e.g., smoking in additional first-degree relatives; minimum smoking requirements for parents) might have allowed for clearer differentiation between groups. The possibility of critical differences in response to nicotine based on family history warrants further investigation. Of the subset of participants with a positive parental smoking history who indicated knowledge of whether they were prenatally exposed to nicotine via maternal smoking, around half reported prenatal exposure to nicotine and half reported no exposure. Since prenatal nicotine expo-

sure has been shown to affect subsequent behavior of offspring in both animals and humans (see Winzer-Serhan, 2008), the possible impact of prenatal exposure on dependent variables in our study merits further research in its own right.

Also, we cannot be sure of the accuracy of retrospectively self-reported amounts of lifetime smoking. Given the conditions of furtiveness under which early smoking often occurs, independent confirmation seems unlikely to be more reliable than self-report. Our cutpoint of 100 lifetime cigarettes, the Centers for Disease Control and Prevention (CDC) definition of a lifetime never-smoker, also merits some comment. In a study designed to validate or refine this definition, we surveyed individuals who reported having smoked 1–200 lifetime cigarettes (C. S. Pomerleau et al., 2004). We found minimal withdrawal but a graded pattern of craving, tolerance, and subjective effects. Thus, although we stayed with the “official” CDC cutpoint to facilitate recruitment, a pack would be a more conservative cutpoint and a single cigarette even more stringent. Note, however, that means and distribution of lifetime cigarettes smoked were similar for the two groups; thus, the significant differences in likelihood of experiencing a buzz are unlikely to be attributable to group differences in amount of lifetime smoking.

As far as we know, this is the first study comparing baseline variables and response to nicotine administration in never-smokers

Figure 4. Physiological effects (change in heart rate, systolic, and diastolic blood pressure, and for a subset of 23 participants, cortisol) in response to 0.0, 0.5, and 1.0 mg nicotine doses ($M \pm SEM$). Significant effects: * $p < .05$; ** $p < .01$; *** $p < .001$.

prospectively recruited on the basis of parental smoking history. Although the differences observed were modest, further exploration in larger samples and using more stringent selection criteria, a wider range of measures of pleasurable response (including “liking” and “good drug effects”), and a less aversive dosing method will be needed to provide a full test of the possible utility of the parental history model for illuminating biobehavioral mechanisms underlying response to nicotine. Also important would be broadening the scope of inquiry to include environmental (epigenetic) factors and comparisons with ever-smokers to determine what protected individuals with a positive family history from becoming smokers in the presence of factors that might be expected to decrease resilience and increase susceptibility, in comparison with those with a negative family history. Including measured genetic data—for example, variants in nicotinic cholinergic receptor genes (Ehringer et al., 2007; Sherva et al., 2008; Zeiger et al., 2007) and/or dopamine receptor genes (Perkins et al., 2008), which may modulate differences between smokers and never-smokers in hedonic response to nicotine—should help in characterizing heritable diatheses for smoking and sensitivity to nicotine.

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Declaration of Interests

None declared.

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