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Attentional bias to smoking and other motivationally relevant cues is affected by nicotine exposure and dose expectancy

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Abstract

We investigated the effects of acute nicotine dose and expected dose on attentional bias (AB) to smoking and affective cues in overnight nicotine-deprived smokers (n=51; 24 women) using a balanced placebo design, which counterbalanced given nicotine dose (Given-NIC vs. Given-DENIC) with instructed nicotine dose expectancy (Told-NIC vs. Told-DENIC). Before and after smoking a study cigarette, smokers completed a vigilance task where they pressed buttons to every third consecutive even or odd digit, while ignoring intermittent smoking, pleasant, unpleasant, and neutral picture distracters. We examined the early posterior negativity (EPN) and late positive potential (LPP) components of the event-related potentials (ERPs) to the distracters, reaction time (RT) to the target digits, and ratings of the study cigarettes. The EPN was sensitive to both given and instructed nicotine dose, while the instructed dose moderated the impact of given dose for the LPP. The RT metrics were sensitive to given but not to instructed dose. The effects of given dose on ratings following cigarette smoking (e.g., enjoyment) were moderated by the instructed dose. The ERP findings suggest that the anticipated effects of nicotine improve attention much like receiving actual nicotine.

Keywords

Smoking; expectancy; attentional bias; vigilance; ERP; reaction time; RVIP

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Conflict of Interest Statement

The authors declare that there is no conflict of interest.

Introduction

Exposure to drug-related cues has been found to elicit alterations in physiology, self-reported mood and craving, and drug-seeking behavior, collectively called cue reactivity (Carter and Tiffany, 1999; Oliver et al., 2013). A key supposition of cue reactivity is that a chronic drug-user's attention is drawn to stimuli previously associated with drug use, making the drug cues more salient than other stimuli, in a phenomenon called attentional bias (AB). Many theories have postulated that increased AB to drug cues is a key feature of drug dependence, whereby users assign too much salience to drugs, drug cues, and the act of drug taking (Franken, 2003).

Among smokers, this postulated AB to smoking cues has largely been supported by studies using cognitive tasks such as the modified dot-probe task (MDP; Bradley et al., 2003) and the modified Stroop color-word naming task (Drobes et al., 2006; Munafò et al., 2003; Waters et al., 2009; Waters et al., 2014). A review of the literature on smoking and AB found that smokers demonstrate significant bias towards smoking cues compared to nonsmokers (Waters and Sayette, 2006). Similar relationships between AB and drug cues have been found for alcohol abusers (Duka and Townshend, 2004; Fadardi and Cox, 2006; Jones and Bruce, 2006; Waters and Green, 2003), cocaine users (Hester et al., 2006), the heroin dependent (Franken et al., 2000; Lubman et al., 2000), and social alcohol and marijuana users (Jones et al., 2003), compared with respective drug nonusers. Thus, chronic, and in some cases social, users of drugs of abuse exhibit AB to drug cues that are not shown by nonusers.

An important question is the extent to which AB to smoking cues varies with acute smoking deprivation and nicotine satiation. According to Franken's model (2003), AB to drug cues exists in a reciprocal relationship with drug craving, meaning that an increase in craving due to drug deprivation should result in increased AB to drug cues. In general, AB has been found to correlate with cigarette craving in smokers (Mogg et al., 2003; Mogg and Bradley, 2002; Waters et al., 2003a; Zack et al., 2001), though a meta-analysis of multiple drugs of abuse, including smoking, suggests that this relationship is weak (Field et al., 2009).

Additionally, the relationships between acute drug deprivation, drug satiation, and AB to drug cues among drug users is equivocal. While several modified Stroop studies (Canamar and London, 2012; Field et al., 2013; Gross et al., 1993; Waters and Feyerabend, 2000; Zack et al., 2001) and a meta-analysis (Cox et al., 2006) found that acute abstinence increased the latency to color-name drug-related words, others did not (Hendricks et al., 2006; Mogg and Bradley, 2002; Munafò et al., 2003; Rusted et al., 2000). Further, the extant MDP studies found little evidence of increased AB to smoking cues during drug deprivation compared to nondeprivation (Field et al., 2004; Mogg and Bradley, 2002).

Franken's model (2003) is unclear whether a decrease in craving (i.e., due to drug satiation) would lead to a decrease in AB to drug-related cues. Evidence for whether nicotine use following acute smoking deprivation reduces AB to smoking cues is largely unresponsive, though the number of studies are relatively few. One study found that smoking a cigarette reduced AB to smoking words on the modified Stroop task (Zack et al., 2001), while other studies did not (Canamar and London, 2012; Colby et al., 2010). Acutely abstinent smokers

who received a nicotine patch relative to a placebo patch did not show reduced AB to smoking words on the modified Stroop task (Rzetelny et al., 2008; Waters et al., 2003b).

The relationship between drug use, craving, and AB to drug cues may also be influenced by non-pharmacological factors that result from classical conditioning, namely drug administration sensory effects and drug stimulus expectancy effects. Drug administration sensory effects are typically evaluated by having participants use substances that are pharmacologically inert or below reinforcement threshold, such as very low nicotine content (VLNC; or “denicotinized”) cigarettes. Smoking blindly administered VLNC cigarettes has been shown to reduce craving as much as smoking regular cigarettes in many (e.g., Baldinger et al., 1995b; Barrett, 2010; Darredeau et al., 2013; Domino et al., 2013; Rose et al., 2010) but not all studies (Baldinger et al., 1995a; Lindsey et al., 2013).

Drug stimulus expectancy, or the belief that one has received a pharmacologically active substance, has been shown to elicit responses similar to those elicited by receiving the actual substance (Vogel-Sprott and Fillmore, 1999). The gold standard for examining expectancy effects is the balanced placebo design (BPD), which counterbalances given dose with instructed dose, allowing for both placebo and anti-placebo conditions to be evaluated (George et al., 2012). While BPD designs have been used extensively in the alcohol field (Hull and Bond, 1986), adoption in the smoking field was hampered until VLNC cigarettes with tar levels matched to regular cigarettes became available. By our count, seven BPD studies using VLNC and regular cigarettes matched on tar have been published, five between-subjects (Juliano et al., 2011; Juliano and Brandon, 2002; Kelemen and Kaighobadi, 2007; Perkins et al., 2004; Perkins et al., 2008), one mixed between-within design (Darredeau et al., 2013), and one full within-subjects (Gu et al., 2015). Most of these smoking BPD studies investigated the effects of received dose and instructed dose on craving, and one examined the impact of these factors on attentional vigilance (Juliano et al., 2011). However, no published study, using a BPD or otherwise, has investigated the effects of drug administration sensory effects and drug stimulus expectancy effects on AB to smoking cues.

The equivocal findings found in the smoking and AB literature may be due to the unreliability of the cognitive tasks used to assess it, potentially due to the measurement error associated with RT (Ataya et al., 2012; Schmukle, 2005). A more reliable measure of AB may be event-related potentials (ERPs). While few studies have compared RT and ERPs measured during cognitive tasks, two studies found that ERPs revealed evidence of AB to drug cues where RT did not (Fehr et al., 2006; Fehr et al., 2007). An ERP component that has been found to be sensitive to AB is the late positive potential (LPP), also known as the P300, P3b, or slow positive component. The LPP typically peaks within 400–700 ms of the onset of a visual stimulus and has been found to increase with the motivational salience of the stimulus during passive picture viewing (Keil et al., 2002; Schupp et al., 2000). We (Minnix et al., 2013; Robinson et al., 2015) and others (Littel and Franken, 2007; Warren and McDonough, 1999) have found that smokers produce larger LPPs to smoking pictures than nonsmokers. However, there is no consistent evidence that LPPs to drug stimuli, or any other ERP component, is sensitive to drug deprivation or satiation. One study compared acute smoking deprivation and nondeprivation on LPP response to smoking and neutral cues

and found no differences by deprivation status (McDonough and Warren, 2001). Another study investigating acute smoking deprivation found no differences by 24-hr abstinence status on startle probe P3, which has been found to be suppressed to smoking cues relative to neutral cues among non-deprived smokers (Versace et al., 2010), but did find startle probe P3 suppression specific to smoking cues among abstainers who experienced the greatest amount of craving (Engelmann et al., 2011).

In the current study, we sought to determine whether the anticipated effects of nicotine improve attention similar to receiving actual nicotine. To do so, we examined the effects of acute nicotine administration and nicotine stimulus expectancy on AB to smoking and affective cues among 12-hr deprived smokers using a BPD design and a vigilance task, the rapid visual information processing task with central emotional distracters (CED-RVIP). The CED-RVIP task, developed by Gilbert and colleagues (Gilbert et al., 2007), is an index of attentional distraction that presents digits and intermittent distracters at a rapid pace, with smokers asked to identify any third consecutive odd or even digit sequences using RT buttons while ignoring occasional smoking-related (CIG), pleasant (PLE), unpleasant (UNP), and neutral (NEU) distracters. ERPs to the distracters and RT to the target digits were used to determine the attentional distraction caused by the preceding smoking and affective distracters. We hypothesized that smoking a nicotine-containing cigarette would reduce AB to CIG distracters on both measures compared to smoking a VLNC cigarette, and that instructed dose would moderate this relationship, such that believing that one smoked a nicotine-containing cigarette would further reduce AB to CIG distracters than believing one smoked a VLNC cigarette. We hypothesized similar findings for AB to UNP distracters, based on Gilbert and colleagues' findings that nicotine administration decreased distraction by UNP pictures (Gilbert et al., 2005; Gilbert et al., 2007). Additionally, we examined the potentially moderating effects of gender and menthol smoking status in our models because of the outstanding questions in the literature regarding these factors in relation to smoking reinforcement motivation (Ahijevych and Garrett, 2010; Perkins, 2009), nicotine metabolism (Benowitz and Jacob, 1984; Benowitz et al., 2004) and cessation outcome (Hoffman and Miceli, 2011; Torchalla et al., 2011).

Methods and Materials

Participants

Participants were 51 adult smokers ($n=22$ women) from the Houston metropolitan area who were between the ages of 18 and 65, smoked 10 or more cigarettes per day, produced an expired carbon monoxide (CO) greater than 8 ppm at screening, demonstrated fluency in spoken and written English, agreed to not use marijuana or other illicit drugs during the course of the study, were non-treatment-seeking or involved in current smoking cessation activity, were not taking psychotropic or narcotic medication, did not meet criteria for a current psychiatric disorder, reported no uncorrected visual acuity loss, had a working telephone, had not used marijuana or other illicit drugs within a week before orientation, and reported not being pregnant or breast-feeding (women only). Participants were paid a maximum of \$200 for attending the orientation and all four laboratory sessions (\$35 per completed laboratory session and \$5 for showing up on time to each session; participants

received no performance-based compensation). The University of Texas MD Anderson Cancer Center's Institutional Review Board approved the protocol. Further information about the inclusion/exclusion criteria and participant recruitment can be found in our previous manuscript (Robinson et al., 2014). Fifty-five participants were randomized, but four of them only completed the initial laboratory session and were removed from further analysis, leaving 51 participants who were included in the current study.

Procedures

Design Overview—Eligible participants completed a phone screen and five in-person sessions. Initial eligibility, interest, and demographic information were collected at the phone screen. At the in-person orientation session, participants had their smoking status verified using expired CO, completed questionnaires, practiced the vigilance task with feedback about their performance, and rated the distracter stimuli used with the vigilance task. At the remaining four in-person laboratory sessions, each participant (1) provided an expired CO sample to verify deprivation status, (2) completed questionnaires of withdrawal and mood, (3) received expectancy instructions about the type of study cigarette to be given after the first CED-RVIP task block, (4) completed the first CED-RVIP block, (5) smoked a study cigarette, either regular nicotine-containing or VLNC, (6) rated the cigarette, and (7) completed the second vigilance task block. The four laboratory sessions were part of a within-subjects BPD in which the randomized double-blind conditions of given dose (Given-NIC vs. Given-DENIC cigarettes) were counterbalanced against instructed dose (Told-NIC vs. Told-DENIC cigarettes). Participants were required to refrain from smoking for 12 hr prior to the four laboratory sessions. We measured AB to affective, smoking, and neutral distracters during the vigilance task using ERPs to the distracter pictures and RT to the target digits.

Biochemical verification of smoking status and deprivation—Participants provided an expired CO sample (Bedfont EC50 Micro III Smokerlyzer; Bedfont Scientific, Medford, NJ) at each session. The Orientation Session CO sample was used to verify eligibility, while the laboratory session CO samples were used to verify the required 12-hr abstinence. Participants were required to produce CO levels below 10 ppm or 37.5% of their Orientation session CO value, based on possible CO half-life of 2 to 8 hours, depending on activity level (Benowitz et al., 2002). Fifteen participants who failed biochemical verification of abstinence had that session rescheduled and did not receive reimbursement for that session until it was successfully completed.

Picture ratings and questionnaires—At the orientation session, participants completed measures of baseline smoking, nicotine dependence, and depressive symptoms (see below). Participants also rated half of the distracters they would be viewing at the subsequent laboratory sessions using valence (i.e., pleasure) and arousal ratings based on the self-assessment manikin (SAM; Lang, 1980), and a craving to smoke rating. The baseline questionnaire means and the SAM ratings, by distracter type, are detailed in a previous publication (Robinson et al., 2014).

Nicotine dose expectancy instructions—At each laboratory session, following questionnaire completion, we fitted a 128-channel EEG sensor net (Geodesic Sensor Net; Electrical Geodesics Inc., Eugene, OR, USA) to the participants, taking approximately 20 minutes. The participants then received instructions designed to manipulate nicotine dose expectancy, depending on the session, stating that they would be smoking either (1) a “regular cigarette containing nicotine” (Told-NIC) or (2) a “placebo cigarette containing no nicotine” (Told-DENIC). Participants were informed that they would be smoking the cigarette following the “first half of the Numbers Task” designed to assess their “ability to pay attention.”

Vigilance (RVIP-CED) task—The participants completed the first block of the RVIP-CED after receiving the dose expectancy manipulation instructions, and the results of this availability manipulation are detailed elsewhere (Robinson et al., 2014). After this first block, participants smoked either a nicotine or VLNC cigarette, completed the cigarette ratings described below, and then completed the second block of the RVIP-CED task. During the task, a PC using E-prime software (v1.4; Psychology Tools Inc., Pittsburgh, PA) presented a series of 10 cm × 10 cm images of digits (1 to 9) and distracters on an LCD monitor approximately 1 m from the participant’s eyes, with each stimulus shown consecutively for 800 ms. The participants were instructed to simultaneously push two buttons, using both index fingers, at the appearance of any third consecutive even or odd digits and to ignore the distracters. RT was defined as the first button pressed on a serial response box (model C-PKG-RSP-1000-01; Electrical Geodesics Inc., Eugene, OR, USA). Each block was comprised of 1752 numeric digits (1–9), interspersed with 288 distracters, containing 192 target sequences (i.e., 3 consecutive even or odd digits), of which 144 (75%) presented a distracter between the second and third digit, while 48 (25%) contained no distracters. No more than two target sequences occurred consecutively due to pseudo-randomization constraints. Participants briefly rested during a 30-s break at the midpoint of each block. The results of the first block, which pertain to the question of smoking availability on AB, are detailed elsewhere (Robinson et al., 2014). Here, we report the results of the second block in order to focus on the BPD manipulation and its impact on AB during the RVIP-CED task, as measured by ERPs to the distracter pictures and RT to the target digits.

Materials

Picture Distracter Stimuli—The four categories of distracters consisted of 144 CIG, PLE, UNP, and NEU pictures, divided into four picture sets of 36 per category. Within each block, each of the 36 distracters per category were shown twice, once during a target sequence and once during a non-target sequence. We selected the PLE, UNP, and NEU distracters from the International Affective Picture System (IAPS; Center for the Study of Emotion and Attention, 1999). We selected the CIG distracters from a set previously developed in our lab (Carter et al., 2006) and from the International Smoking Image Series (ISIS; Gilbert and Rabinovich, 1999). The CIG distracters consisted of images of burning cigarettes and people smoking in a social context. We matched the PLE and UNP distracters used in the four picture sets on IAPS arousal ratings. The four picture sets were randomly assigned to a laboratory session for each participants, and the within-block orders were

pseudo-randomly selected such that no more than two consecutive distracters of the same category were shown.

Study cigarettes—The study cigarettes were commercially available Quest-brand cigarettes (Vector Group, Ltd., Miami, FL). The “regular” cigarette was the Quest 1 brand (0.6 mg nicotine/cigarette) and the VLNC cigarette was the Quest 3 brand (0.05 mg nicotine/cigarette; also referred to as “denicotinized” or DENIC). Both types of cigarettes were identical in tar (10 mg) and size (85 mm). The cigarettes were administered using a double-blind: All cigarettes had their identifying markings covered and were stored in coded containers. The manufacturer had stopped production of menthol cigarettes before the study started, so we were unable to offer them to menthol smokers.

Measures and data analysis

Ratings of study cigarettes—The participants evaluated their perceptions of the study cigarettes using two questionnaires administered immediately after smoking one between the first and second blocks of the attentional task. The mCEQ (Cappelleri et al., 2007) evaluated satisfaction, psychological reward, physical sensations, craving reduction, and strength of the study cigarette (1=Not at all, 7=Extremely). Additionally, we created a brief 3-item questionnaire for this study, which we called the Cigarette Qualities Scale (CQS). Two items were incorporated that asked participants about the perceived nicotine (1=no nicotine, 7=very large amount of nicotine) and harshness (1=extremely harsh, 7=very smooth) of the study cigarette just smoked, adapted from Kelemen and Kaighobadi (2007). However, unlike those researchers, we did not ask participants whether they believed they received a regular or VLNC cigarette, to avoid alerting participants to our use of deception as part of the within-subjects design. Instead, we asked participants to rate “How similar was this cigarette to your usual brand” (1=Not at all like my cigarette brand, 7=Identical to my cigarette brand).

Reaction Time—We considered correct button presses occurring within a 150–1000 ms interval after target digit presentation as hits within the RVIP-CED. In addition to RT latency, hit rate, false positive rate, and accuracy, we calculated the signal detection metrics of sensitivity and response bias. As described in our previous publication (Robinson et al., 2014), we used parametric measures of sensitivity (d') and response bias (c) because the distributions of both indices suggested that they were normally distributed. Following Macmillan (2004), we calculated d' as $z(H) - z(FP)$, and c as $-0.5 (z[H] + z[FP])$, where z = z -score distribution, H = hit rate (number of hits/number of target digits), and FP = false positive rate (number of false positives/number of non-target digits and distracters). Larger d' sensitivity index values indicate a greater hit rate and correct rejection rate than smaller values, while larger, more positive values on the c response bias index indicate a more conservative response bias (i.e., less hits and false positives) than smaller, more negative values. We removed twelve sessions from further statistical analyses because of the participants' low accuracy and/or high false positives, which we defined as being in the lowest 5th percentile of the distribution on both the sensitivity (d') and response bias (c) indices. We removed one participant's initial session because there were no hits on trials following distracters, which suggested a misunderstanding of the task instructions.

ERP recording and scoring—During the RVIP-CED task, we recorded electroencephalograms (EEGs) using a 129-channel Geodesic Sensor Net using an AC-coupled high input impedance (200 M Ω) amplifier (Geodesic EEG System 200; Electrical Geodesics Inc., Eugene, OR). The voltages were referenced to Cz, collected using a 250 Hz sampling rate, and filtered online using 0.1 Hz high-pass and 100 Hz low-pass filters. Scalp impedances were kept below 70 k Ω , much less than the 1% maximum electrode impedance relative to input impedance (200 M Ω) recommended by established ERP guidelines (Picton et al., 2000).

After data collection, the following steps were taken. First, we applied a 30-Hz low-pass filter to optimize visual depictions of the ERP waveforms (Luck, 2005). Second, we visually inspected the data, and channels contaminated by artifacts for more than 50% of the recording were interpolated with the use of spherical splines (on average, 7.1% of the segmented channels were interpolated). Third, we corrected eye blinks using a spatial filtering method based on artifact topographies (Ille et al., 2002), as implemented in BESA (v5.3; BESA GmbH, Gräfelting, Germany). Fourth, we transformed the EEG data to the average reference. Fifth, we used Brain Vision Analyzer (v2.0.4; Brain Products GmbH, Munich, Germany) to segment the EEG into 900-ms segments, starting 100 ms before onset of the distracters, with baseline defined as the 100-ms interval preceding the picture. Sixth, using the segmented data, we identified artifacts affecting sensors within specific trials, and excluded a segment from the subsequent averages if more than 10% of the sensors were contaminated by artifacts. Three of the 55 participants were excluded from further analysis, primarily due to excessive movement and eyeblink artifacts. Finally, we exported the averaged segmented and filtered data for random permutation analysis.

We used random permutation analysis to identify the ERP temporal and spatial regions of interest (ROIs) to include in our Given Dose X Instructed Dose X Distracter Type analyses of means. Random permutation tests are distribution-free tests that, in the case of within-subjects designs, involve randomly swapping (i.e., permuting) values between conditions within subjects, running a statistical analysis on the permuted dataset, storing its result, and repeating these steps a large number of times (Edgington and Onghena, 2007). The distribution of the stored values obtained from the permuted data sets represents the distribution of the results that can be obtained by chance. The value obtained in the original dataset is evaluated against the distribution of the permuted datasets. If the result of the test conducted on the original data set is observed in the random distribution with a lower frequency than the significance threshold, it is possible to reject the null hypothesis with that level of confidence. Random permutation tests can be used with any test statistic, do not require normality or independence among observations, minimize the likelihood of Type I errors, and do not require random sampling from a population (Ludbrook, 1994; Maris, 2004). We have used random permutation tests to identify ERP ROIs in previous manuscripts (Robinson et al., 2015; Versace et al., 2010; Versace et al., 2011), as has been recommended by published guidelines for the analysis of ERP data (Keil et al., 2014).

We adapted SAS/IML permutation code (Vickery, 2015) to identify temporal and spatial ROIs by conducting random permutation tests in two steps. The initial step aimed at identifying temporal ROIs where there were likely differences by distracter. First, for each

subject we reduced the 129 channels to a single dimension by calculating mean global field power (GFP), the sum of the squared potential differences of all 129 channels (Lehmann and Skrandies, 1980), for each Distracter Type X Time Point cell. Next, we built a within-subjects permutation distribution by randomizing GFP voltage values between distracter types within each time point for each participant. Then, we conducted a within-subjects ANOVA on each time point, using Distracter Type as a main effect, storing the highest F value for each permutation, and repeating 10,000 times. The 99.99th percentile of the stored F values from the permutation testing was defined as the permutation F value, and any F values from the distracter type ANOVA performed on the actual data that exceeded the permutation F were considered to be significant at the 0.0001 level. We then averaged significant time points of at least 10 contiguous samples that exceeded the permutation F threshold and considered them as a single temporal ROI.

The second step involved identifying spatial ROIs by building separate permutation distributions for each temporal ROI identified in the previous step. For this step, we built permutation distributions by randomizing mean voltage values of the time ROIs between distracter types within each channel for each participant. The procedures used to identify the permutation F value for the spatial ROIs were similar to that used to identify the temporal ROIs. For each temporal ROI, we identified channels showing significant differences across picture distracters by comparing the actual channel F values to the 99.99th percentile permutation F. Channels exceeding the permutation F thresholds were identified as being part of the spatial ROIs. For the final step, we created mean voltages of the channels comprising each temporal ROI for each distracter type for each participant.

Statistical analyses

We checked the distributions of all variables for skewness, outliers, and normality prior to analysis. All analyses that examined the effects of given dose, instructed dose, distracter type, and their interactions, were conducted using repeated measures mixed models analyses using SAS PROC MIXED (version 9.3; SAS Institute Inc., Cary, NC), with subject modeled as a random effect. For significant interactions, we conducted post hoc pairwise tests of simple effects (Winer, 1971) on least-square means (LSM) to identify the sources of significant differences. The post hoc comparisons were adjusted using the Holm-Bonferroni correction to control type I error rate (Seaman et al., 1991).

Results

Baseline Participant Characteristics

As we previously reported (Robinson et al., 2014), the participants in this study were primarily African-American (55%), male (57%), who were 43 years old on average and who smoked 18 cigarettes per day. Additionally, 57% (n=29) were menthol smokers, and African-Americans were significantly more likely to be menthol smokers (82%) than European-American smokers (21%; $\chi^2 [47] = 17.28, p < .0001$). Menthol smokers were younger ($M = 40.48$ years, $SD = 10.41$) than non-menthol smokers ($M = 45.91$, $SD = 8.01$), $t(49) = 2.03, p = .0478$, but they did not differ on any other baseline measure.

Cigarette Ratings

To evaluate whether participants could detect differences among our study cigarettes, and whether expectancy influenced these ratings, the mCEQ and CQS items were separately analyzed using Given Dose X Instructed Dose linear mixed models, with subject as a random effect. Main effects and interactions involving gender and menthol status were also examined. There were main effects for given dose on all five scales of the mCEQ (see Table 1). Smokers Given-NIC rated the study cigarettes higher on the Satisfaction, Psychological Reward, Aversion, Enjoyment of Upper Respiratory Tract Sensations, and Craving Reduction scales than when they were Given-DENIC. There were only two significant main effects for Instructed Dose, such that Smokers Told-NIC only rated the cigarettes higher on the Satisfaction and Craving Reduction scales than when they were Told-DENIC. With the CQS, smokers Given-NIC rated the study cigarette as having more nicotine, being less harsh, and being more similar to their usual brand than when they were Given-DENIC. Smokers Told-NIC rated the study cigarettes as has having more nicotine and being more similar to their usual brand than when they were Told-DENIC, but did not differ on the harshness rating. There were no significant Given Dose X Instructed Dose interactions for any of the mCEQ scales or CQS items. In terms of gender, there were no significant main effects or interactions involving gender on any of the ratings. Because the CQS was not previously validated, and because we assumed that the 3 items measure aspects of the construct “cigarette liking,” we calculated a Cronbach’s alpha reliability coefficient, which resulted in a coefficient alpha of 0.68.

Menthol smokers did not significantly differ from non-menthol smokers on the mCEQ. With the CQS items, the only difference was to the similarity item, with menthol smokers ($M = 1.85$, $SE = 0.20$) rating the study cigarettes as less similar to their usual brand than non-menthol smokers ($M = 3.10$, $SE = 0.26$), $F(1,48) = 14.87$, $p < .0003$. Menthol status did not interact with either given or instructed dose for any of the mCEQ or CQS items.

Reaction Time

To assess RT performance on the RVIP-CED task, we examined the effects of given dose, instructed dose, distracter, and their interactions separately on RT latency, sensitivity, response bias, hit rate, false positive rate, accuracy, and specificity to the target digits that followed distracters using linear mixed models, with subject as a random effect. There was a main effect of Distracter Type on RT latency, such that PLE ($M = 448.53$, $SE = 11.95$) and UNP ($M = 446.91$, $SE = 11.95$) produced slower RTs to subsequent targets than CIG ($M = 441.39$, $SE = 11.95$) or NEU ($M = 437.92$, $SE = 11.95$), $F(3,150) = 5.75$, $p = .0009$. Smokers Given-NIC produced significantly faster RT, greater sensitivity, less conservative response bias, higher hit rates, higher false positive rates, and greater accuracy than when Given-DENIC (see Table 2). There were no Instructed Dose main effects or Given Dose X Instructed Dose interactions for any of the RT metrics. There were no main effects or interactions involving Distracter Type, except for the main effect on RT latency described previously. In terms of gender effects, women ($M = 0.49$, $SE = 0.06$) produced a more conservative response bias than men ($M = 0.28$, $SE = 0.05$), $F(1,49) = 7.78$, $p < .0008$, but no other gender main effects or interactions were found to be significant. There were no significant main effects or interactions involving menthol status on any of the RT metrics.

Event-Related Potentials

Identification of Time and Channel ROIs—The permutation analysis of the GFP at each individual time point for the distracter type main effect identified a permutation F of 7.01. As depicted in Figure 1, when we graphed the actual GFP F values for the distracter main effect, separately for each time point, two contiguous sets of time points exceeding the permutation F , 204–268 ms and 472–636 ms, corresponding to the early posterior negativity (EPN) and late positive potential (LPP) components, respectively. We next conducted separate permutation analyses of the individual channel voltages using the mean EPN and LPP time ROIs, resulting in permutation F s of 7.17 and 7.11, respectively. The channels exceeding these thresholds are depicted in Figure 2, along with the mean ERP waveforms, by distracter type, for the channels comprising the EPN and LPP components.

Analyses of ROI Means—We analyzed the ERPs using separate 2 (Given Dose) X 2 (Instructed Dose) X 4 (Distracter) mixed models analyses, with subject modeled as a random effect, separately for the EPN and LPP components. To evaluate our hypotheses that Given-NIC would reduce AB to CIG and UNP distracters, compared to Given-DENIC, we examined the Given Dose X Distracter interactions. To evaluate our hypothesis that instructed dose would moderate the relationship between given dose and distracter, we examined the 3-way Given Dose X Instructed Dose X Distracter interactions. Finally, we examined the potentially moderating effects of gender and menthol status in our models by including this factor as an interaction term in the above models.

For the EPN, there were no interactions involving given dose, instructed dose, or distracter. We found a significant Distracter main effect, $F(3,153) = 1021.19$, $p < .0001$, with pairwise comparisons indicating that PLE produced greater negativity (i.e., less positive mean voltages) than CIG, which in turn showed greater negativity compared to UNP, with all pairwise comparisons between distracter types $p < .0001$ (see Figure 3). There was a significant main effect of Given Dose, $F(1,47) = 39.38$, $p < .0001$, with Given-NIC ($LSM = 1.75$, $SE = 0.28$) producing greater negativity than Given-DENIC ($LSM = 1.82$, $SE = 0.28$). Likewise, we found a significant main effect of Told Dose, $F(1,47) = 114.99$, $p < .0001$, with Told-NIC ($LSM = 1.72$, $SE = 0.28$) producing greater negativity than Told-DENIC ($LSM = 1.85$, $SE = 0.28$). There were no interactions or main effect involving Gender or menthol status for the EPN component.

In terms of the LPP, we found a significant Given Dose X Distracter Type interaction, $F(3,111) = 10.86$, $p < .0001$, with post hoc pairwise comparisons indicating that Given-NIC produced less positive LPP than Given-DENIC for the NEU ($F(1,141) = 17.18$, $p < .0001$), PLE ($F(1,141) = 53.94$, $p < .0001$), and UNP ($F(1,141) = 72.68$, $p < .0001$) distracters (see Figure 4). However, the pairwise comparison for CIG distracters was nonsignificant, even before Holm-Bonferroni correction ($p = .084$). Additionally, we found a significant Given Dose X Told Dose X Distracter Type 3-way interaction, $F(3,111) = 10.86$, $p < .0001$. To parse this interaction, we examined the pairwise comparisons between Told-NIC and Told-DENIC separately for each distracter type and for each given dose (see Figure 5). When participants were Given-DENIC, post hoc pairwise comparisons indicated that Told-NIC evoked less positive LPP to the CIG ($F(1,111) = 31.51$, $p < .0001$), PLE ($F(1,111) = 10.48$, p

= .0016), and UNP ($F[1,111] = 22.64, p < .0001$) distracter types than Told-DENIC. When participants were Given-NIC, post hoc pairwise comparisons indicated that Told-NIC evoked less positive LPP to the PLE ($F[1,111] = 57.37, p < .0001$) and UNP ($F[1,111] = 26.91, p < .0001$) distracter types than Told-DENIC. For gender, we found a significant Gender X Distracter Type interaction for LPP, $F(3,150) = 196.07, p < .0001$, with pairwise comparisons indicating that men ($M = 1.42, SE = 0.14$) produced greater LPP to the PLE distracters than women ($M = 0.56, SE = 0.16$), $F(1,150) = 16.84, p < .0001$. We found no other interactions involving gender for the LPP component. There were no main effects or interactions involving menthol status for the LPP component.

Instructed dose manipulation check—To determine whether belief in the cigarette dose instructions impacted our results, we identified seventeen (30%) smokers who either rated the placebo condition (Given-DENIC/Told-NIC) as having less or equal nicotine content on the CQS than the “true placebo” condition (Given-DENIC/Told-PLA; $n=4$), rated the anti-placebo condition (Given-NIC/Told-DENIC) as having greater or equal nicotine content than the “true drug” condition (Given-NIC/Told-NIC; $n=5$), or met both criteria ($n=8$). We reran the above analyses, excluding these 17 participants, and the pattern and statistical significance of the RT and ERP results were unchanged.

Discussion

Our goal was to determine whether the anticipated effects of nicotine improve attention similar to receiving actual nicotine. We used a within-subjects balanced-placebo design to disentangle the effects of smoking stimulus expectancies from acute nicotine administration on attentional bias to smoking and affective cues among overnight-deprived smokers. Our LPP findings indicated that both receiving and believing that one received nicotine, following acute nicotine deprivation, reduces the distractibility of competing stimuli, particularly of intrinsically motivating pleasant and unpleasant stimuli. Instructed nicotine dose reduced the distractibility of cigarette-related stimuli only when participants had smoked the denicotinized experimental cigarette. In terms of RT metrics, only main effects for given dose were found, suggesting that RT metrics are not as sensitive as ERPs in detecting effects of expected dose on attentional bias. Overall, these findings suggest that simply believing that one has received nicotine can improve the attentional filtering of distracting stimuli as much as receiving the drug, although smoking-related cues' effects on attention were only reduced by expectancy during conditions of nicotine abstinence (i.e., following denicotinized cigarettes).

Our hypotheses that smoking a nicotine-containing cigarette would reduce attentional bias to smoking-related and unpleasant distracters were only partially confirmed by the Given Dose X Distracter Type interaction for LPP. The finding that smoking nicotinized cigarettes reduced LPP to unpleasant distracters compared to smoking denicotinized cigarettes confirmed our hypothesis and suggests that unpleasant distracters attracted less attentional resources following nicotine use among nicotine-deprived smokers. Unexpectedly, we found that smoking nicotinized cigarettes also reduced LPP to pleasant and neutral distracters compared to smoking denicotinized cigarettes, but failed to reduce LPP to smoking-related

distracters. The EPN and RT findings did differ by distracter type, but we did not find interactions with given or instructed dose.

Our LPP unpleasant distracter findings are consistent with the ERP results of Gilbert and colleagues, who found that nicotine, administered as nicotine patches to nicotine-deprived smokers, reduced attentional bias to unpleasant distracters during the RVIP-CED (Gilbert et al., 2007), the modified Stroop (Rzetelny et al., 2008), and a variant of the modified dot-probe task (Gilbert et al., 2004). However, our finding that smoking a nicotine cigarette reduced LPP to pleasant distracters compared to smoking a denicotinized cigarette was not found by Gilbert and colleagues in their studies that included pleasant stimuli (Gilbert et al., 2004; Gilbert et al., 2007). This discrepancy is not likely due to differences in ERP measurement, as the temporal and spatial ROIs we used largely overlapped those used in these two studies. This discrepancy for the pleasant distracters is possibly due to the fact that the pleasant pictures used in the studies by Gilbert and colleagues were not matched on arousal with the unpleasant pictures, a limitation conceded by the authors (Gilbert et al., 2004; Gilbert et al., 2007). However, our finding that smoking nicotine cigarettes also reduced LPP amplitude to neutral distracters compared to smoking denicotinized cigarettes suggests that acute nicotine use following acute (i.e., 12 hours) nicotine deprivation causes a nonspecific reduction in distractibility, not just to arousing distracters, consistent with nicotine's general effects on selective attention (Kassel, 1997).

Unlike Gilbert and colleagues (2007), we failed to find that acute nicotine administration reduced the distractibility of smoking-related pictures during the RVIP-CED. One possible explanation is that attentional bias to smoking cues might not be sensitive to acute nicotine deprivation and administration. Several studies involving smoking-related distracters failed to find evidence that acute nicotine administration following acute abstinence decreases attentional bias specifically to smoking cues (Canamar and London, 2012; Colby et al., 2010; Rzetelny et al., 2008; Waters et al., 2003b). Additionally, acute nicotine administration, following overnight deprivation, might not reduce the distraction by smoking-related pictures because the distraction evokes cue-induced craving, and there is evidence that acute nicotine administration following overnight deprivation fails to reduce cue-induced craving in nicotine patch (Havermans et al., 2003; Tiffany et al., 2000; Waters et al., 2004), lozenge (Schlagintweit et al., 2014), or gum (Niaura et al., 2005) studies. However, it should be noted that while cue-induced craving does not appear to be sensitive to acute nicotine deprivation and administration, abstinence-induced general craving is responsive, as shown by our mCEQ Craving Reduction ratings, and by the findings of others (Breland et al., 2002; Buchhalter et al., 2001; Butschky et al., 1995; Domino et al., 2013; Pickworth et al., 1999).

Another potential reason for the lack of acute nicotine effects on the LPP to smoking-related distracters is not that acute nicotine administration might reduce the distraction by arousing pictures after overnight deprivation, but that smoking-related pictures might not be arousing. This is important considering that the more highly arousing a picture is rated, the more attention it tends to capture (Cuthbert et al., 1996). Our RT latency data suggest that smoking-related pictures were not as arousing as pleasant or unpleasant, given that latencies to targets following smoking-related distracters were faster than those following pleasant or

unpleasant distracter types. However, we have other data that challenges this argument. First, there is some evidence that smoking-related distracters are arousing, at least on self-report picture ratings. For the previously published SAM ratings, we found that smoking-related distracters were rated just as highly arousing as pleasant distracters, and significantly higher than neutral and unpleasant distracters (Robinson et al., 2014). Second, we found that smoking a nicotine cigarette, compared to a denicotinized cigarette, significantly reduced LPP to neutral distracters, suggesting that the effects of nicotine on reducing distractibility were not specific to high arousing stimuli.

Our hypothesis that instructed dose would moderate the effects of given dose on attentional bias was confirmed by our LPP 3-way interaction results. Post hoc pairwise comparison indicated that believing one smoked a nicotine cigarette, compared to a denicotinized cigarette, reduced LPP to unpleasant and pleasant distracters regardless of cigarette dose, and reduced LPP to smoking-related distracters after smoking a denicotinized cigarette. The unpleasant and pleasant results suggest that distractibility by high arousing stimuli can be reduced by dose expectancy, regardless of whether nicotine was consumed, following overnight abstinence. The LPP smoking-related distracter findings, following smoking a denicotinized cigarette, suggest that the distractibility of smoking-related stimuli can be reduced, among nicotine-deprived smokers, simply by believing that one had smoked a nicotine-containing cigarette. However, the LPP smoking-related distracter findings following smoking a nicotine cigarette within this 3-way interaction suggest that nicotine expectancy's effect on attentional bias may be overshadowed by the pharmacological effects of nicotine.

While the EPN and LPP findings similarly suggest that affective cues attract more attention than neutral cues, the EPN results differed from those of the LPP in several ways. The EPN findings suggest that smoking-related distracters attracted more attention than unpleasant distracters, contrary to our LPP findings but consistent with our previous findings obtained from former, never, and current smokers (Robinson et al., 2015). Also contrary to our LPP findings, we found that smoking or believing that one smoked a nicotine-containing cigarette both increased the attentional bias to the distracters, regardless of distracter type. However, the EPN and LPP findings are not necessarily contradictory because the components are thought to reflect different stages of early attention. The EPN, which negatively peaks between 200–350 ms at temporal and occipital regions to visual stimuli, is thought to reflect the early discrimination of motivationally relevant stimuli (Schupp et al., 2003; Schupp et al., 2007). The LPP, which typically peaks between 350–750 ms over central and parietal sites, is thought to reflect selective processing of motivationally relevant stimuli (Cuthbert et al., 2000; Schupp et al., 2000). While there is some question about the extent to which the EPN and LPP overlap when viewing motivationally relevant stimuli, recent work using temporal principal components analysis (PCA) suggests that these components are distinct (Foti et al., 2009; Versace et al., 2011). Our EPN findings suggest smoking a nicotine-containing cigarette, or believing that one has done so, facilitates the recognition of motivationally significant stimuli, while the LPP findings suggest that receiving or believing that one received nicotine reduces the distractibility of such stimuli once they have been initially processed.

The RT to target digit findings involving given dose and instructed dose failed to confirm our hypotheses and were not consistent with our ERP results. The RT metrics were much less sensitive to our manipulations than ERPs. There were no main effects or interactions involving distracter type, except for a main effect on RT latency, which found that pleasant and unpleasant produced slower RTs than smoking-related or neutral distracters. All of the RT metrics were improved after smoking a nicotine cigarette compared to a denicotinized cigarette; none varied by instructed dose. Had we relied upon RT as our sole measure of attentional bias, we would have concluded that receiving nicotine following overnight abstinence improved RT performance, and that dose expectancy produced no measurable moderation of this effect. Thus, our findings suggest that RT is a much less sensitive measure for teasing apart the effects of nicotine dose and dose expectancy on attentional bias than ERP.

In terms of the mCEQ and CQS cigarette ratings, cigarettes containing nicotine were rated more positively than cigarettes without nicotine. Smokers rated the nicotine cigarettes as having more nicotine, producing greater craving reduction, being more enjoyable, and being more similar to their usual brand than the denicotinized cigarettes. However, the relationship between nicotine content and the unpleasant qualities was less clear, as the nicotine cigarettes were rated higher on the mCEQ Aversion scale, but as being smoother on the CQS, than the denicotinized cigarettes. Instructed dose also had a significant impact on the ratings of the study cigarettes, though on less of the measures than given dose. Smokers believing they smoked nicotine cigarettes rated them higher on the mCEQ Satisfaction, mCEQ Craving Reduction scales, and as having more nicotine and being more similar to their usual brand (both CQS items) than when believing they were denicotinized cigarettes. In summary, both smoking a study cigarette containing nicotine, and being told the study cigarette contained nicotine resulted in similar positive evaluations of the study cigarette. Unfortunately, the lack of a Given Dose X Told Dose interaction makes it difficult to determine whether the cigarette ratings reflect expectancy effects or simply experimenter demand effects.

Our cigarette ratings findings are consistent with previous studies that found that study cigarettes containing nicotine were rated as more satisfying (Darredeau et al., 2013) and craving reducing than tar-matched VLNC cigarettes (Benowitz et al., 2006; Hatsukami et al., 2013). These ratings differences are also consistent with many studies that compared VLNC with a usual brand nicotine-containing cigarette in terms of satisfaction (Benowitz et al., 2006; Brauer et al., 2001; Butschky et al., 1995; Gross et al., 1997; Lane et al., 1995) and immediate craving reduction ratings (Baldinger et al., 1995a; Lane et al., 1995). While less relative to the regular study cigarettes, the VLNC study cigarette did produce a moderate amount of enjoyment and reduction in craving on the mCEQ, consistent with other studies (Walker et al., 2012).

We found no evidence that gender moderates the impact of acute nicotine administration, or the expectancy of such administration, on attentional bias to smoking or other cues. There was a gender interaction with distracter type for the LPP, but it was specific to pleasant pictures and suggests that men found those images to be more distracting than women. In terms of RT, women had a more conservative response bias than men, suggesting that they

were either more careful or cautious to make a response. We found no gender differences on the mCEQ items, which is somewhat surprising, given that work by others suggests that men experience greater reductions in withdrawal symptoms to regular compared to VLNC cigarettes than women (Barrett, 2010; Perkins et al., 2002; Perkins et al., 2006; Perkins and Karelitz, 2015).

A limitation of this study was our relative imprecision in controlling for nicotine exposure. Given that the half-life of CO has been found to range from 2–8 hours, depending on activity (Benowitz et al., 2002), it is difficult to precisely determine the degree of overnight abstinence in our study. Thus, some of our participants who produced expired CO values within our cutoff could have smoked, or taken a few puffs, within the proceeding 12 hours. One solution would have been to assess salivary cotinine, which has a half-life of 16 hours (Benowitz et al., 1991; Benowitz et al., 2002), along with expired CO. The other issue with controlling nicotine exposure was the fact that the nicotineized experimental cigarette only contained nicotine amounts (0.6 mg nicotine/cigarette) that were less than FTC standard nicotine yields found in many commercially available “regular” cigarettes, typically 0.8–1.1 mg nicotine/cigarette (Kozlowski et al., 1998). Thus, the nicotineized cigarette condition may not have fully attenuated any nicotine deprivation-induced effects on functioning.

A potential limitation of our study is that we had menthol smokers smoke regular cigarettes in the lab, because of the unavailability of Quest menthol cigarettes by the time of our study start. However, we found no evidence that menthol smokers experienced the nonmenthol study cigarettes to be less enjoyable and reinforcing than nonmenthol smokers, or that they had differential attentional bias to the study stimuli. Unlike a previous study by Hatsukami and colleagues (2013; study 1), we did not find differences between menthol and nonmenthol smokers of regular and VLNC cigarettes on the mCEQ. This is all the more interesting because, unlike those researchers, we had menthol smokers smoke regular cigarettes. One possibility for our lack of differences may be that menthol smokers compared the regular study cigarettes not with their usual-brand menthol cigarettes, but with other regular cigarettes they had smoked in the past. The menthol smokers in the Hatsukami study, who were given menthol study cigarettes to smoke in the lab, may have compared them to their usual brand menthol cigarette and found them to be inferior. Another possibility is that while smokers in the Hatsukami study were nondeprived, our smokers were 12-hr nicotine deprived, meaning that even smoking regular cigarettes was a pleasant experience for the menthol smokers in our study.

A potential issue of concern in any study involving counterbalanced presentation of motivationally relevant (i.e., smoking) and irrelevant stimuli is that of carry-over effects. Indeed, our study was predicated on the presence of carry-over effects in terms of distracter types differentially influencing response to the target digits. The broader issues are whether presentation of smoking stimuli interferes with the processing of subsequent non-smoking stimuli, and whether this relationship is moderated by other factors, such as level of nicotine deprivation (Sayette et al., 2010). Additionally, participants were exposed to a powerful smoking cue prior to each block, in the form of smoking an experimental cigarette, which could have had carry-over effects on the processing of subsequent stimuli that were independent of actual or told nicotine dose. Unfortunately, our study was not designed to

address these issues. However, we believe that several aspects of our study suggest that carry-over effects, while likely present, were adequately controlled for and did not differentially bias our findings. First, we used a randomized presentation of distracters, which should average out short-term carry-over effects. Second, our RT latency, EPN, and LPP findings all suggest that the high arousing pleasant and unpleasant distracters captured the most attention, as we expected. Third, the LPPs to distracters were sensitive to nicotine and told dose, suggesting that any long-term carry-over cue effects of smoking an experimental cigarette were secondary to these dose factors.

Another potential shortcoming of this study was that our use of a within-subjects balanced-placebo design may have made the detection of deception easier for the participants. However, our results were unchanged whether we excluded or not those participants whose cigarette content ratings were possibly incongruent with belief in the cigarette dose instructions, results which were similar to other balanced-placebo design studies that evaluated the inclusion of these participants (Juliano et al., 2011; Juliano and Brandon, 2002; Perkins et al., 2004). Our rates of belief in the instructional sets (70%) are consistent with rates found in other cigarette balanced-placebo designs (Juliano and Brandon, 2002; Perkins et al., 2004; Perkins et al., 2008) though lower than the concordance rates in other studies (Juliano et al., 2011; Kelemen and Kaighobadi, 2007).

These findings have several implications. First, smokers' expectancies about the effects of nicotine should be measured and controlled for in laboratory studies of the effects of nicotine, particularly if blinded administration of nicotine is involved. Additionally, mode of nicotine administration may have effects beyond the amount and pharmacokinetics of nicotine delivery, as non-cigarette delivery of nicotine likely involves different expectancies. Second, these results suggest that both nicotine and the act of smoking reinforce drug use, and not simply nicotine alone. This is consistent with "behavioral withdrawal," the notion that the interruption of over-learned instrumental responses during drug cessation heightens withdrawal (Baker et al., 2006). Third, these findings have treatment implications and suggest that smoking and nicotine outcome expectancies need to be explicitly addressed among smokers preparing to quit. Smokers need to become aware of their own beliefs about the effects of smoking and nicotine and to challenge them as part of becoming a non-smoker, and to become aware of the importance of non-nicotine factors (e.g., the smoking ritual) in maintaining dependence.

In conclusion, these findings suggest that simply believing that one has received nicotine can improve the attentional filtering of distracting stimuli as much as receiving the drug, but also that the presence of smoking-related cues might be more difficult to ignore than other motivationally relevant stimuli. Our use of a balanced-placebo design with a vigilance task containing motivationally relevant distracters allowed us to isolate the impact of nicotine, nicotine deprivation, and nicotine expectancy on attentional bias to smoking and affective cues in smokers. The use of ERP methodology revealed that believing one has smoked a nicotine-containing cigarette reduces the salience of motivationally relevant distracters, similar to the pharmacological effects of nicotine. Had we simply relied upon RT metrics, we would not have uncovered the influence of the anticipated effects of nicotine on

attention. These findings have implications for the study of nicotine in the laboratory, for theoretical models of addiction, and for the treatment of smoking.

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Figure 1. Graph of the actual GFP F values for the distracter main effect, separately at each time point. The dashed line indicates the permutation F of 7.01. The two contiguous sets of time points exceeding the permutation F, 204–268 ms and 472–636 ms, were selected as time ROIs.

Figure 2. Mean ERP waveforms, by distracter, for the channels comprising the (A) EPN and (B) LPP components. The dotted-line boxes indicate the temporal ROIs and the shaded portions of the topographic insets identify the channel ROIs used to calculate the mean ERP waveforms.

Figure 3.
The significant main effect of distracter type on the mean ERP voltages for the EPN component. All pairwise comparisons were significant, $p < .0001$.

Figure 4.

The significant Given Dose X Distracter Type 2-way interaction on mean ERP voltages for the LPP component (472–636 ms). * = significant pairwise comparison, after Holm-Bonferroni correction.

Figure 5.

The significant Given Dose X Instructed Dose X Distracter Type 3-way interaction on mean ERP voltages for the LPP component (472–636 ms). * = significant pairwise comparison, after Holm-Bonferroni correction.

Table 1

Main effects for given dose and instructed dose on mCEQ scale and CQS item scores (Mean [SE]). The CQS Harshness item is reverse coded.

Performance Measure	Dose Exposure			Anticipated Dose		
	Given-DENIC	Given-NIC	<i>F</i> (1,46)	p value	Told-DENIC	Told-NIC
mCEQ						
Satisfaction	3.12 (0.21)	4.03 (0.20)	32.63	.0001 *	3.31 (0.20)	3.85 (0.21)
Psychological Reward	2.83 (0.17)	3.31 (0.16)	13.62	.0006 *	2.98 (0.16)	3.16 (0.16)
Aversion	1.69 (0.15)	2.23 (0.15)	16.71	.0002 *	2.03 (0.14)	1.89 (0.15)
Respiratory Tract Sensations	3.12 (0.22)	3.77 (0.22)	11.63	.0014 *	3.24 (0.22)	3.64 (0.22)
Craving Reduction	3.49 (0.20)	4.32 (0.19)	14.18	.0005 *	3.55 (0.19)	4.27 (0.20)
CQS						
Nicotine Amount	2.84 (0.16)	3.68 (0.16)	18.08	.0001 *	2.51 (0.16)	4.01 (0.16)
Harshness	3.59 (0.25)	4.25 (0.25)	8.93	.0045 *	3.78 (0.25)	4.06 (0.25)
Similarity to Usual Brand	2.03 (0.20)	2.62 (0.19)	12.34	.001 *	2.07 (0.19)	2.58 (0.20)

Note:

* significant after Holm-Bonferroni correction (adjusted $p < .05$).

Told-DENIC=participant expected a “placebo” cigarette, Told-NIC=participant expected a “regular” cigarette.

Table 2

Main effects for given dose and instructed dose on RVIP-CED RT performance measures (Mean [SE]).

Performance Measure	Dose Exposure			Anticipated Dose		
	Given-DENIC	Given-NIC	<i>F</i> (1,50)	Told-DENIC	Told-NIC	<i>F</i> (1,50)
Reaction time, ms	449.75 (11.86)	437.63 (11.86)	34.16	442.87 (11.86)	444.50 (11.86)	0.62
Sensitivity <i>d'</i>	1.64 (0.10)	1.82 (0.10)	83.40	1.73 (0.10)	1.73 (0.10)	0.10
Response Bias <i>c</i>	0.44 (0.04)	0.30 (0.04)	194.65	0.38 (0.04)	0.36 (0.04)	3.49
Hit Rate	0.64 (0.03)	0.72 (0.03)	190.88	0.67 (.03)	0.68 (0.03)	2.38
False Positive Rate	0.06 (.01)	0.07 (.01)	28.04	0.06 (.01)	0.07 (.01)	5.16
Accuracy	0.79 (0.02)	0.82 (0.02)	100.92	0.81 (0.02)	0.81 (0.02)	0.41

Note:

* significant after Holm-Bonferroni correction (adjusted $p < .05$).

Told-DENIC=participant expected a “placebo” cigarette, Told-NIC=participant expected a “regular” cigarette.