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P3 Event-Related Potential Reactivity to Smoking Cues: Relations With Craving, Tobacco Dependence, and Alcohol Sensitivity in Young Adult Smokers

Thomas M. Piasecki, Kimberly A. Fleming, Constantine J. Trela, and Bruce D. Bartholow
University of Missouri

The current study tested whether the amplitude of the P3 event-related potential (ERP) elicited by smoking cues is (a) associated with the degree of self-reported craving reactivity, and (b) moderated by degree of tobacco dependence. Because alcohol and cigarettes are frequently used together, and given recent evidence indicating that individual differences in alcohol sensitivity influence reactivity to alcohol cues, we also investigated whether alcohol sensitivity moderated neural responses to smoking cues. ERPs were recorded from young adult smokers ($N = 90$) while they participated in an evaluative categorization oddball task involving 3 types of targets: neutral images, smoking-related images, and images of drinking straws. Participants showing larger P3 amplitudes to smoking cues and to straw cues (relative to neutral targets) reported greater increases in craving after cue exposure. Neither smoking status (daily vs. occasional use) nor psychometric measures of tobacco dependence consistently or specifically moderated P3 reactivity to smoking cues. Lower alcohol sensitivity was associated with larger P3 to smoking cues but not comparison straw cues (relative to neutral targets). This effect was further moderated by tobacco dependence, with the combination of lower sensitivity and higher dependence associated with especially pronounced P3 reactivity to smoking cues. The findings suggest the smoking-cue elicited P3 ERP component indexes an approach-oriented incentive motivational state accompanied by a subjective sense of cigarette craving. Self-reported low sensitivity to the pharmacologic effects of alcohol may represent a marker of drug cue reactivity and therefore deserves attention as a potential moderator in smoking cue exposure studies.

Keywords: alcohol, cue reactivity, event-related potentials, smoking, tobacco dependence

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For drug users, including smokers, drug-related cues are motivationally salient and capable of capturing attention (Littel, Euser, Munafò, & Franken, 2012). This is congruent with major tenets of Incentive Sensitization Theory (T.E. Robinson & Berridge, 1993, 2000), which posits that drugs of abuse act to sensitize neural circuits governing the attribution of motivational significance to previously neutral cues. With repeated drug use, drug-related cues are hypothesized to be transformed from mere visual percepts into attention-grabbing, behavior-motivating spurs to action accompanied by a subjective sense of "wanting" or craving (Berridge & Robinson, 2003).

The P3 event-related potential (ERP) represents one promising index of the motivational salience of smoking cues (Warren & McDonough, 1999). ERPs are voltage fluctuations in the scalp-recorded electroencephalogram (EEG) that emerge when EEG data are time-locked to the presentation of critical stimuli and averaged across many trials. The parietally maximal P3 (i.e., P3b or P300) component is the third prominent positive-going voltage deflection in the stimulus-locked ERP, typically emerging between 300 and 600 ms after the presentation of a task-relevant stimulus. The P3 tends to be most pronounced when elicited in the context of an "oddball" task, in which subjects are presented with stimuli (auditory or visual) from two categories or classes, one of which appears more frequently (i.e., context) than the other (i.e., the oddball). In such tasks, P3 amplitude is much larger to the infrequent oddball stimuli than to the context stimuli (see Friedman, Cycowicz, & Gaeta, 2001). Notably, the amplitude of the P3 is highly sensitive to the motivational significance of the eliciting cue. Strong emotional stimuli, whether positive or negative in valence, elicit larger P3s than do neutral stimuli (Briggs & Martin, 2008, 2009; Schupp et al., 2000; Weinberg & Hajcak, 2010).

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Thomas M. Piasecki, Kimberly A. Fleming, Constantine J. Trela, and Bruce D. Bartholow, Department of Psychological Sciences, University of Missouri.

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Correspondence concerning this article should be addressed to Thomas M. Piasecki, Department of Psychological Sciences, University of Missouri, 210 McAlester Hall, Columbia, MO 65211. E-mail: piaseckit@missouri.edu

Several studies have tested the influence of smoking-related cues on P3 (or the related Late Positive Potential; LPP) using various picture viewing paradigms. These investigations have consistently demonstrated that current smokers show more pronounced P3/LPP responses to smoking cues than to neutral stimuli (Bloom, Potts, Evans, & Drobes, 2013; J. D. Robinson et al., 2015; Littel & Franken, 2007, 2011, 2011, 2012; McDonough & Warren, 2001; Versace et al., 2011; Warren & McDonough, 1999).

This corpus of research attests to the potential utility of cue-elicited P3 in smoking research, but important questions remain concerning the interpretation of this marker and its place in the nomological network surrounding tobacco addiction. One unresolved question is whether cue-elicited P3 is associated with the activation of acute cigarette cravings. The two processes might be expected to be associated because (a) smokers routinely report elevated craving in response to smoking cues (Carter & Tiffany, 1999), (b) theories such as the Incentive Sensitization account posit that drug-related cues should become potent triggers of neural systems subserving drug 'wanting' (T.E. Robinson & Berridge, 1993), and (c) ERPs and other indices of attentional bias to drug cues have been shown to correlate with cravings in users of alcohol and illicit drugs (Field, Munafò, & Franken, 2009). However, available evidence in smokers is mixed, with studies finding no association (Warren & McDonough, 1999), a positive correlation (Littel & Franken, 2007), and a negative correlation (Littel & Franken, 2011) between smoking cue-elicited P3 amplitude and assessments of craving reactivity.

A second unresolved question is whether P3 cue reactivity is related to the degree of tobacco dependence. Two studies have addressed this question directly (Bloom et al., 2013; Littel & Franken, 2011), with both reporting no correlation between P3 amplitude to smoking cues and scores on the Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991). These null findings are surprising from the standpoint of the Incentive Sensitization model, which identifies the attribution of exaggerated salience of drug-paired cues as the pivotal neuroadaptation in addiction (T.E. Robinson & Berridge, 1993, 2000). Conceivably, the lack of correlation between FTND and P3 in prior studies may be attributable to limited power associated with small samples of current smokers ($ns < 30$) or use of strict inclusion criteria (e.g., consumption of $\geq$10 cigarettes per day) that might have led to a restriction of range by excluding smokers from the low end of the dependence continuum.

The current study sought to investigate these issues more sensitively. We conducted an ERP cue reactivity study in which all participants were current smokers and therefore could contribute information about craving and tobacco dependence. We assessed acute craving before and after cue exposure to investigate whether P3 responses to smoking cues were related to change in craving. To ensure that the sample contained variation in degree of dependence, we recruited young adults representing two smoking groups: daily smokers and occasional smokers. Our prior research involving young adult smokers indicated that daily smokers achieve higher scores on measures of tobacco dependence compared with nondaily smokers, with large effect sizes (Piasecki, Piper, Baker, & Hunt-Carter, 2011; Piasecki, Richardson, & Smith, 2007).

A secondary goal was to investigate whether individual differences in sensitivity to alcohol's acute effects are associated with P3 reactivity to smoking cues in a sample of current smokers. Previous research has used the ERP method and a version of the evaluative categorization oddball task employed here to investigate risk for alcohol use disorder from the perspective of the Incentive Sensitization account (Bartholow, Henry, & Lust, 2007; Bartholow, Lust, & Tragesser, 2010). In these studies, participants were recruited to represent extreme groups with respect to their self-reported level of sensitivity to alcohol. A great deal of research indicates that, relative to individuals with higher sensitivity, individuals reporting a diminished sensitivity to the intoxicating effects of alcohol are at elevated risk for alcohol use disorder (Ray, Bujarski, & Roche, 2016; Trim, Schuckit, & Smith, 2009). Consistent with this idea and with the tenets of the Incentive Sensitization model, Bartholow et al. (2007, 2010) found that the P3 elicited by alcohol-related cues was enhanced in lower- relative to higher-sensitivity individuals, but that the groups did not differ with respect to their P3 responses to other appetitive stimuli, including nonalcoholic beverages, adventure-related scenes and mild erotica.

There are several reasons to think that alcohol sensitivity might also moderate P3 responses to smoking cues. First, alcohol and tobacco use disorders are frequently comorbid (Grant, Hasin, Chou, Stinson, & Dawson, 2004). Second, the two drugs are frequently used simultaneously, even in very light smokers, providing an opportunity for smoking cues to acquire motivational significance for drinkers (Piasecki, Jahng, et al., 2011; Shiffman & Paty, 2006). Third, cigarettes enhance subjective response to alcohol and therefore may be more highly prized by low sensitivity drinkers seeking to enhance alcohol response (Piasecki, Jahng, et al., 2011; Piasecki, Wood, Shiffman, Sher, & Heath, 2012). Finally, both alcohol and nicotine act on common reward/incentive neural circuits (Doyon, Thomas, Ostroumov, Dong, & Dani, 2013), providing an opportunity for experience with (or constitutional risk for) one drug to influence motivational responding to the other. To extend prior work and formally investigate this possibility, we included an assessment of alcohol sensitivity in the current study and tested whether lower sensitivity moderated P3 responses to tobacco cues, either alone or in concert with individual differences in tobacco dependence.

Method

Participants

Participants were 90 current smokers (42 female) recruited from psychology classes at the University of Missouri and from the surrounding community through advertisements posted online and on public bulletin boards. Because there is evidence of age-related effects on P3 amplitude (van Dinteren, Arns, Jongsma, & Kessels, 2014), we limited enrollment to individuals between the ages of 18 and 29 years. Exclusion criteria were (a) a history of neurological disease, (b) prior head injuries that resulted in a loss of consciousness for more than 3 min, (c) plates or other implants inside the skull, (d) a hairstyle preventing access to the scalp with EEG electrodes, and (e) bald scalp (potentially leading to electrical bridging between electrodes). Candidates were asked a series of screening questions by phone concerning smoking behavior. Participants were eligible for the Daily Smoker (DS; $n = 46$) group if they reported smoking on a daily basis and consuming 5 or more

cigarettes per day. Participants were considered eligible for the Occasional Smokers (OS; $n = 44$) group if they reported smoking at least one day per week in the past month but did not smoke on a daily basis. Participants recruited from classes received course credit; community-recruited participants were compensated at a rate of $12 per hour. The University of Missouri Campus Institutional Review Board approved the study protocol.

Self-Report Measures

Tobacco dependence. Participants completed the Fagerström Test for Nicotine Dependence (FNTD; Heatherton et al., 1991) and the Wisconsin Inventory of Smoking Dependence Motives (WISDM; Piper et al., 2004). The FTND ($\alpha = .66$) consists of 6 items tapping physical dependence on cigarettes. The WISDM contains 68 items organized into 13 subscales tapping distinct smoking motives. Each WISDM item consists of a statement about smoking (e.g., "I frequently light cigarettes without thinking about it"). Participants are asked to rate their agreement with each statement using a scale from 1 (*not at all true of me*) to 7 (*extremely true of me*). Scores for each of the 13 WISDM subscales were computed by taking the average scores for items belonging to each scale. A WISDM total score was calculated by summing scores on all 13 subscales ($\alpha = .97$ for 68 items, .93 for 13 scale scores).

Cigarette craving. Participants completed the Questionnaire of Smoking Urges—Brief (QSU-B; Cox, Tiffany, & Christen, 2001) before and after the picture viewing task. The QSU-B consists of 10 items rated on 7-point scales ranging from 0 (*strongly disagree*) to 6 (*strongly agree*). The items form two factors, tapping immediate desire to smoke for positive reinforcement and negative reinforcement. These two factor scores were highly correlated in the current sample (rs = .90 at pretest and .89 at posttest). To simplify presentation, the analyses used a global QSU score formed by summing all 10 items ($\alpha = .94$ at pretest and .95 at posttest).

Alcohol sensitivity. Individual differences in alcohol sensitivity were assessed using the Alcohol Sensitivity Questionnaire (ASQ; Fleming et al., 2016). The ASQ contains 9 items assessing effects of alcohol ostensibly associated with smaller alcohol doses and rising blood alcohol concentration (BAC; e.g., relaxation, feeling flirtatious) and 6 items associated with heavier alcohol doses and falling BAC (e.g., vomiting, blacking out). For each item, respondents indicate whether they have experienced the given effect from drinking alcohol; if so, they are asked to estimate the minimum number of drinks required to feel the effect (for rising BAC items) or the maximum number of drinks they can consume without experiencing the effect (for falling BAC items). A total alcohol sensitivity score was calculated for each participant using the average number of drinks across all items ($\alpha = .93$ in the current sample). Higher ASQ scores indicate lower alcohol sensitivity (i.e., more drinks are required to experience alcohol effects). Fleming et al. (2016) demonstrated that ASQ scores robustly predicted stimulation, sedation and subjective intoxication following a laboratory-based alcohol challenge. Prior research linking low alcohol sensitivity to enhanced P3 to visual alcohol cues was conducted using extreme groups selected on the basis of ASQ scores (Bartholow et al., 2007; Bartholow et al., 2010).

Problematic alcohol involvement. The 10-item Alcohol Use Disorder Identification Test (AUDIT; Babor, Higgins-Biddle, Saunders, & Monteiro, 2001) was used to assess typical alcohol use patterns and negative consequences of drinking ($\alpha = .83$).

Picture Viewing Task

Participants completed an evaluative categorization picture-viewing oddball task modeled on tasks used in studies examining neural correlates of affective/emotional stimuli (e.g., Cacioppo et al., 1993, 1996; Ito & Cacioppo, 2000; Ito, Larsen, Smith, & Cacioppo, 1998; Weinberg, Hilgard, Bartholow, & Hajcak, 2012) and alcohol cue-reactivity (Bartholow et al., 2007, 2010). The task included three types of color images.[1] Twenty affectively *Neutral* scenes selected from the International Affective Picture System (Lang, Bradley, & Cuthbert, 2001) on the basis of published valence ratings were used as context. Oddball stimuli were drawn from two categories. Ten *Smoking* images were selected from a set of 12 psychometrically evaluated images (Carter et al., 2006). The smoking images selected for the current study were those with the largest mean effect sizes for eliciting craving in nondeprived smokers in a previous cue reactivity study (see Table 3 in Carter et al., 2006). Finally, 10 images of drinking *Straws* selected from a stock photo vendor were included as comparison stimuli; straws and cigarettes are both cylindrical and used via sucking, but only cigarettes are associated with nicotine delivery. Thus, we expected images of drinking straws would serve as a suitable control that would permit comparison to the P3 response associated with oddball reactivity that is unrelated to drug use. Because images of people elicit larger ERPs than other stimuli (Weinberg & Hajcak, 2010), we matched the two oddball sets for the presence of people (5 images per set). Straw images were selected to avoid depictions of emotional facial expressions or alcohol imagery.[2]

Following prior work (e.g., Cacioppo et al., 1993, 1996; Ito et al., 1998; Weinberg et al., 2012) the images were presented on a computer screen against a black background one at a time in sequences of 5 (constituting a trial), at least 4 of which were context images drawn from the Neutral category (thus ensuring that smoking and straw images were infrequent oddballs within sequences).[3] Targets were defined as images appearing in the fourth or fifth position in each sequence and were equally likely to

[1] Neutral stimuli were the following IAPS images: 2840, 2850, 2880, 2890, 6150, 7002, 7004, 7020, 7034, 7050, 7090, 7160, 7161, 7179, 7185, 7187, 7233, 7235, 7950, and 9070. Smoking images were drawn from a published report by Carter et al. (2006): 401, 403, 404, 411, 412, 413, 414, 415, 416, and 417. Straw images were purchased from iStockphoto.com: photo numbers 2835350, 10446134, 11388618, 2705252, 4617899, 9356829, 18321532, 18397224, 627603, and 631358.

[2] The straw images were digitally transformed to reduce their resolution to 72 × 72 dpi, to more closely approximate the resolution of the smoking and neutral images.

[3] Tasks constructed in this way—with images or words presented in sequences of five or six in which participants evaluate each stimulus—are specifically designed for investigations of evaluative categorization. In traditional oddball paradigms, stimuli are presented in very long sequences, often involving 100 to 200 stimuli or more. As described by Cacioppo et al. (1993) and Ito et al. (1998), evaluative categorization of long sequences of complex, affectively laden visual stimuli is difficult for participants to perform. The shorter sequences used here (and in similar, previous research) have the benefit of reducing variability in the ERP by increasing participants' attention to and discrimination of the stimuli.

represent each of the three image categories (determined randomly across trials). Thus, there were 6 types of trials, differing with respect to stimulus type and target status in positions 4 and 5 (targets designated by italic typeface): *Neutral*/Neutral, Neutral/*Neutral*, *Smoking*/Neutral, Neutral/*Smoking*, *Straw*/Neutral, and Neutral/*Straw*. Each trial type was used 15 times, for a total 90 trials (450 images viewed), with each participant viewing each type of image in the target position 30 times. Only P3 amplitudes elicited by targets were used for analyses. Participants were instructed to categorize every image as either *neutral* or *pleasant* by using one of two buttons on a button box. Button-category associations were counterbalanced across participants. Unlike in traditional cognitive oddball tasks (see Courchesne, Hillyard, & Courchesne, 1977; Squires, Wickens, Squires, & Donchin, 1976), participants were instructed to respond in the same manner to all images. This ensures that "target" status is not confounded with decision requirements or behavioral task requirements, in that all stimuli (targets and context) require the same decision and behavioral response, thereby limiting sources of P3 amplitude variation irrelevant to the images' inherent motivational significance. Each image was presented for 1,000 ms, followed by an interstimulus interval (blank screen) that varied randomly from 900 to 1,200 ms. Trials were separated by 500 ms, during which the word "pause" appeared on the computer screen.

Electrophysiological Recording

EEG data were recorded from 36 standard scalp locations (American Encephalographic Society, 1991) using tin electrodes fixed in a stretch-lycra cap (Electro-cap International, Eaton, OH). EEG was sampled continuously at 1,000 Hz (amplifier gain was set to 500 for all channels) and filtered online at .05 to 40 Hz. Scalp electrodes were referenced online to the right mastoid; an average mastoid reference was derived offline. Eye movements were monitored using electrodes placed above and below the left eye and 2 cm lateral to the outer canthus of each eye. Impedance was kept below 8 KΩ. Ocular artifacts (blinks) were corrected from the EEG signal off-line using a regression-based procedure (Semlitsch, Anderer, Schuster, & Presslich, 1986). Epochs of −100 to 1,000 ms poststimulus activity were defined for each target image. All epochs were visually inspected for the presence of movement artifacts or other aberrant EEG activity; those containing voltage deflections of ±75 microvolts (μV) or linear drifts >50 μV were eliminated. Trials were then averaged according to electrode and stimulus (target type) conditions for each participant (25 trials per participant, on average).

Procedure

Candidates were screened by telephone, and eligible individuals were scheduled to participate in a single laboratory session. Participants were instructed to refrain from smoking for at least one hour prior to the visit to minimize possible acute nicotine effects on ERP amplitudes (Pritchard, Sokhadze, & Houlihan, 2004). Upon arrival at the laboratory, participants provided a breath sample to test for carbon monoxide (CO) concentration (Micro + Smokerlyzer, Bedfont Scientific, Ltd., Kent, U.K.). They were then fitted with electrodes and completed a computer-administered battery of questionnaires including the FTND, WISDM, ASQ, and QSU-B. Participants then performed the picture-viewing task while EEG data were recorded. Upon task completion, participants were administered the QSU-B a second time. Next, they were shown each of the target oddball stimuli used in the picture-viewing task and asked to rate them for valence and arousal using the 9-point Self-Assessment Manikin (Bradley & Lang, 1994).

Analytic Approach

Visual inspection of the target-locked ERPs indicated that the P3 peaked at roughly 530 ms poststimulus across participants. To account for interindividual variability in the timing of the P3, each participant's grand average waveforms were visually inspected to determine the appropriate 300-ms time window for quantifying their P3 amplitude. For most participants (n = 72, or 80% of the sample), P3 was measured as the average amplitude within a 300-ms time window within the range of 350 to 750 ms following picture onset (latency minimum and maximum were 275 and 840 ms, respectively, across participants). Figure 1 illustrates grand average waveforms recorded at electrode Pz as a function of smoker group and target stimulus.

Analyses of P3 amplitude data were carried out using multilevel linear regression modeling. Preliminary analyses examined the distribution of P3 amplitudes across a core set of 21 scalp locations using a 2 (Stimulus: oddball vs. context) × 7 (Coronal site: frontal, fronto-central, central, centro-parietal, parietal, parieto-occipital,

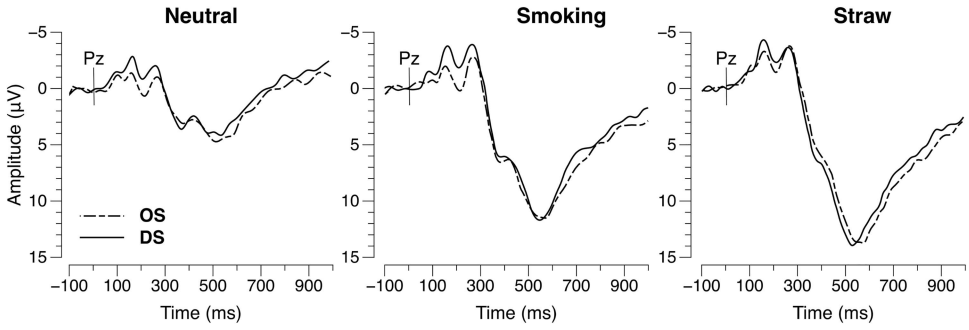

Figure 1. Grand average ERP waveforms measured at the Pz electrode site as a function of stimulus type and smoker group. OS = Occasional Smokers; DS = Daily Smokers. The vertical line on each set of waveforms indicates stimulus onset (0 ms).

occipital) × 3 (Lateral site: left, midline, right) linear mixed model with random intercepts for participant. This analysis revealed a main effect of Stimulus, $F(1, 5539) = 2064.46$, $p < .001$, indicating that, as expected, oddball stimuli elicited larger P3s ($M = 6.37$ μV) compared with context stimuli ($M = 1.26$ μV). There was a significant main effect for Coronal site, $F(6, 5539) = 896.20$, $p < .001$, indicating that, as is typical, P3 amplitude increased from anterior to posterior scalp locations (see Fabiani, Gratton, & Federmeier, 2007). A main effect for lateral site was also observed, $F(2, 5539) = 18.30$, $p < .001$. Pairwise comparisons of marginal means revealed that, consistent with previous reports using evaluative categorization tasks (e.g., Cacioppo, Crites, & Gardner, 1996), P3 amplitude was significantly larger ($p < .001$) over the right hemisphere ($M = 4.29$ μV) compared with the midline ($M = 3.50$ μV) and the left hemisphere ($M = 3.64$ μV), which did not differ from one another ($p = .31$). Finally, there was a significant Coronal x Stimulus interaction, $F(6, 5539) = 38.58$, $p < .001$, indicating that the "oddball effect" was larger at more posterior sites. On the basis of these findings, we focused primary analyses on data collected from the parietal, parietal-occipital, and occipital sites where the largest oddball effects were observed. Thus, subsequent analyses of P3 utilized 3-level linear mixed models including data from 9 electrodes (P3, Pz, P4, PO3, POz, PO4, O1, Oz, and O2), with random intercepts for participant and electrode site.

Results

Descriptive Findings

Table 1 provides descriptive statistics for the OS and DS participants. The groups were comparable with respect to age and sex composition. As expected, relative to OS, DS had higher exhaled breath carbon monoxide levels and scored higher on the FTND and the WISDM ($ps \leq .001$). The groups were comparable with respect to alcohol-related measures. On the AUDIT, both groups had mean scores indicative of hazardous alcohol use (i.e., scores ≥8; Babor et al., 2001). DS and OS did not differ significantly with respect to ASQ scores, but there was a trend toward lower sensitivity in OS participants.

As expected, the FTND and WISDM were interrelated, $r = .58$, $p < .001$. Alcohol sensitivity was not significantly correlated with either the FTND ($r = -.11$, $p = .30$) or the WISDM ($r = -.13$, $p = .21$).

In-Task Picture Categorizations

The mean proportions of "pleasant" categorizations for each stimulus type, as indicated by button-presses during the oddball task, are given for each group in Table 2. A 2 (Group; OS vs. DS) × 3 (Stimulus; Neutral, Smoking, and Straw) repeated measures ANOVA revealed a significant main effect for Stimulus, $F(2, 86) = 104.69$, $p < .001$, $\eta_p^2 = .53$, a nonsignificant main effect for Group, $F(1, 87) = 2.32$, $p = .13$, $\eta_p^2 = .03$, and a marginal Group × Stimulus interaction, $F(2, 86) = 2.62$, $p = .08$, $\eta_p^2 = .06$. The main effect for stimulus reflects increased categorization of oddballs as pleasant compared with context images. Compared with OS, the DS group categorized more Smoking stimuli as pleasant, but OS and DS did not differ in their responses to Neutral and Straw cues. DS categorized a significantly higher proportion of Smoking stimuli pleasant compared with Straw cues, $t(45) = 2.09$, $p = .04$. Categorization did not differ between Smoking and Straw cues among OS, $t(42) = 0.53$, $p = .60$.

Posttask Stimulus Ratings

Ratings of both Smoking and Straw images indicated that they were neutral to slightly negative in valence and moderately arousing (see Table 2). A 2 (Group: OS vs. DS) × 2 (Stimulus: Smoking vs. Straw) repeated measures ANOVA on the valence ratings revealed a main effect for Stimulus type $F(1, 88) = 4.20$, $p = .04$, $\eta_p^2 = .05$, but no main effect for Group, $F(1, 88) = 0.03$, $p = .87$, $\eta_p^2 = .00$ and no Group × Stimulus interaction, $F(1, 88) = 1.86$, $p = .18$, $\eta_p^2 = .02$. The main effect for stimulus type indicated that Straw images were rated as more pleasant than Smoking cues. Similarly, analysis of the arousal ratings revealed a main effect for Stimulus type $F(1, 88) = 8.62$, $p = .004$, $\eta_p^2 = .09$, indicating that Straw images were rated as more arousing than Smoking cues. For arousal, there was no main effect for Group, $F(1, 88) = 1.15$, $p = .29$, $\eta_p^2 = .01$, and no Group × Stimulus interaction, $F(1, 88) = 1.65$, $p = .20$, $\eta_p^2 = .02$.

Table 1
Participant Characteristics by Smoker Group

Measure	Occasional smokers ($n = 44$)	Daily smokers ($n = 46$)	Effect size	p
Age (years), *M* (*SD*)	19.14 (1.55)	19.76 (1.91)	$d = 0.36$	.093
Male, *N* (%)	23 (52.3)	25 (54.3)	*OR* = 1.09	.844
CO (ppm), *M* (SD)	3.11 (3.37)	5.58 (3.35)	$d = 0.55$	.001
Cigarettes per day,[a] *M* (*SD*)	1.63 (2.44)	8.93 (6.78)	$d = 1.42$	<.001
FTND, *M* (*SD*)	0.27 (.66)	2.07 (2.12)	$d = 1.15$	<.001
WISDM, *M* (*SD*)	33.10 (10.94)	48.38 (12.81)	$d = 1.28$	<.001
AUDIT, *M* (*SD*)	13.14 (5.85)	11.30 (7.56)	$d = -0.27$	.204
ASQ, *M* (*SD*)	6.02 (2.25)	5.18 (1.91)	$d = -0.40$	.061

Note. CO = carbon monoxide; ppm = parts per million; FTND = Fagerström Test for Nicotine Dependence; WISDM = Wisconsin Inventory of Smoking Dependence Motives; AUDIT = Alcohol Use Disorders Identification Test; ASQ = Alcohol Sensitivity Questionnaire; *OR* = odds ratio.
[a] Cigarettes per day determined by smoking history questionnaire. Daily smokers answered this question directly. Occasional smokers reported typical number of cigarettes per smoking day and number of smoking days per week. The product of the two responses was divided by 7 to derive an estimate of daily smoking rate.

Table 2
Stimulus Ratings and Craving Scores by Smoker Group

Measure	Occasional smokers *M* (*SD*)	Daily smokers *M* (*SD*)
Proportion categorized 'pleasant'		
Neutral	.23 (.22)	.22 (.17)
Straw	.64 (.33)	.67 (.31)
Smoking	.60 (.33)	.76 (.23)
Stimulus ratings		
Straw valence	4.12 (1.47)	4.35 (1.25)
Smoking valence	3.98 (1.71)	3.67 (1.84)
Straw arousal	5.08 (1.52)	5.05 (1.35)
Smoking arousal	4.74 (1.65)	4.17 (1.95)
Craving ratings		
Pretask QSU-B total	25.05 (12.53)	36.43 (14.80)
Posttask QSU-B total	29.50 (15.26)	41.48 (16.40)

Note. See text for results of statistical comparisons. Valence was rated on a scale from 1 (*very negative*) to 9 (*very positive*). Arousal was rated on a scale from 1 (*completely calm*) to 9 (*completely excited*).

Group and Smoking Cue Effects on P3 Amplitude

Group and stimulus effects on P3 amplitude were examined using a linear mixed model. Sex and age were included as covariates because they have been related to P3 amplitude in prior studies (van Dinteren, et al., 2014). In this model, the OS served as the reference category for group and Neutral images were the reference category for the 3-level stimulus variable. P3 amplitude was lower in men relative to women ($b = -2.62$, $p = .003$), as is typical (e.g., Hoffman & Polich, 1999), but was not related to participant age ($b = -0.3$, $p = .18$). Adjusted means are depicted in Figure 2A as a function of group and stimulus. There was an overall main effect for Stimulus, $F(2, 1616) = 568.34$, $p < .001$, with model coefficients indicating that the P3 was larger to each class of oddballs compared with context stimuli (Smoking vs. Neutral $b = 5.59$, $p < .001$; Straw vs. Neutral $b = 7.74$, $p < .001$). There was no main effect for Group, $F(1, 86) = .093$, $p = .76$, and the Stimulus × Group interaction was not significant, $F(2, 1616) = 2.60$, $p = .08$. We reestimated the model treating Straw stimuli as the reference category to directly compare P3 responses across the two oddball classes. This model revealed that P3 was significantly smaller when elicited by Smoking versus Straw images, $b = -2.15$, $p < .001$. The Group × Smoking stimulus interaction was not significant, $b = -0.62$, $p = .06$, though the trend suggested that this difference between stimuli tended to be slightly larger among DS.

It was expected that straw stimuli would be affectively neutral and would elicit P3 amplitudes intermediate between those of neutral cues and smoking images. Contrary to this expectation, the P3 was more pronounced to the Straw versus Smoking oddballs. Although this was not anticipated, it is consistent with the posttask stimulus ratings, which indicated that participants found the Straw images to be more pleasant and arousing than the smoking cues.

For each individual, an overall estimate of P3 response to Smoking and Straw cues was calculated by subtracting the participants' grand mean P3 response to Neutral targets from his or her mean response on Smoking and Straw trials, respectively. P3 reactivity to Smoking and Straw cues were substantially correlated with one another, $r = .68$, $p < .001$.

Pre- and Posttask Cigarette Craving

Table 2 summarizes mean global QSU-B scores before and after the picture-viewing task as a function of smoking group. A 2 (Group) × 2 (Time) repeated measures ANOVA revealed significant main effects for Group, $F(1, 87) = 14.81$, $p < .001$, $\eta_p^2 = .15$, and for Time, $F(1, 87) = 40.27$, $p < .001$, $\eta_p^2 = .32$. DS reported more craving than did OS, and craving increased from before to after the cue exposure. The Group × Time interaction term was not significant, $F(1, 87) = 0.33$, $p = .57$, $\eta_p^2 = .004$.

Craving Response and P3 Amplitude

A linear mixed model was used to evaluate whether individual differences in self-reported cue-induced craving were related to P3 amplitude. The dependent measure was P3 amplitude, and covariates were sex, age, and baseline craving. The focal predictors were ratings of posttask craving (conceptualized as change in craving from baseline, given that baseline craving is included in the model), stimulus type, and their interaction The critical test was the posttask Craving × Stimulus interaction evaluating whether change in craving was related to the P3 oddball effects. This interaction was significant, $F(2, 1598) = 6.58$, $p = .001$. Participants who showed higher craving at the end of the session relative to pretask ratings had differentially larger P3 to both Smoking and Straw cues (Smoking × Posttask QSU-B $b = 0.03$, $p = .001$; Straw × Posttask QSU-B $b = .03$, $p = .008$).

We also conducted correlation analyses relating participants' grand mean P3 to each oddball (relative to neutral targets) with change in craving. Mean responses to Smoking cues were correlated with change in craving, $r = .23$, $p = .03$. Mean responses to Straw cues were not significantly correlated with craving change, $r = .17$, $p = .12$.

Individual Differences in Tobacco Dependence and P3 Amplitude

A linear mixed model tested whether individual differences in tobacco dependence, indexed by the FTND total score, moderated P3 response. In this model, P3 amplitude was the dependent variable, age and sex were covaried, and Stimulus was entered as a 3-level factor with context as the reference category. The

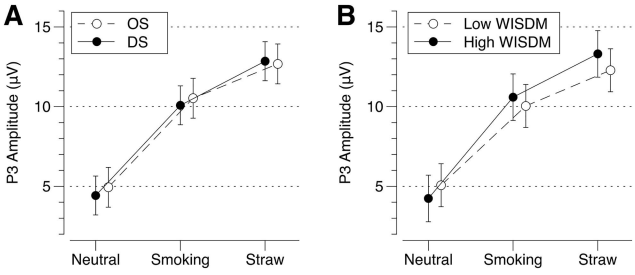

Figure 2. Model estimated P3 amplitude means (and associated 95% confidence intervals) as function of smoker group and stimulus type (A) and as a function of WISDM scores and stimulus type (B). OS = Occasional Smokers, DS = Daily Smokers. Adjusted means for Low and High WISDM were computed at the mean scores for the first and fourth quartiles, respectively.

FTND × Stimulus interaction was not significant, $F(2, 1616) = 1.64$, $p = .19$. In a parallel model using the WISDM total score, the WISDM × Stimulus interaction was significant, $F(2, 1616) = 10.60$, $p < .001$. Model coefficients indicated that individuals with higher WISDM dependence scores showed larger responses to both classes of oddballs versus context (Smoking × WISDM $b = 0.04$, $p < .001$; Straw × WISDM $b = 0.05$, $p < .001$). Model-estimated means illustrating this effect are shown in Figure 2B.

Alcohol Sensitivity and P3 Amplitude

A linear mixed model with age and sex as covariates tested whether individual differences in alcohol sensitivity moderated P3 response. This model revealed a significant ASQ x Stimulus interaction, $F(2, 1616) = 8.68$, $p < .001$. Model coefficients indicated that higher ASQ scores (indicating lower sensitivity) were associated with differentially larger P3 to Smoking cues (Smoking × ASQ $b = .29$, $p < .001$); ASQ scores did not moderate response to Straw cues, however (Straw × ASQ $b = .02$, $p = .76$). Figure 3 illustrates this interaction effect.

Additional models explored whether degree of tobacco dependence further moderated this alcohol sensitivity effect. In a model using the FTND, there was a significant 3-way Dependence × ASQ × Stimulus interaction, $F(2, 1576) = 4.51$, $p = .011$. The Smoking × ASQ × FTND coefficient was significant, $b = .12$, $p = .003$, whereas the Straw × ASQ × FTND effect was not, $b = .07$, $p = .08$. When the WISDM was substituted for the FTND, a significant 3-way interaction was again observed, F, $(2, 1576) = 19.00$, $p < .001$. Model coefficients indicated that the combination of low sensitivity and high dependence was associated with differentially larger responses to both Smoking cues and to Straw cues relative to neutral cues (see Figure 4).

Discussion

A major aim of this study was to investigate whether the amplitude of the P3 ERP elicited by smoking cues is associated with the intensity of cue-provoked craving in young adult smokers.[4] As expected, we found that participation in a picture-viewing task including smoking-related images acutely increased smokers' cigarette cravings. Those participants who displayed relatively larger differences in P3 amplitude to smoking oddballs compared with neutral context cues also tended to show larger increases in craving after cue exposure. Expressed as a simple correlation, the magnitude between P3 and change in craving was modest ($r = .23$) but similar to the effect size found in a meta-analysis of studies relating measures of attentional bias to drug cues and craving ($r = .19$; Field et al., 2009). Thus, the findings are broadly consistent with the hypothesis that the smoking-cue elicited P3 ERP component indexes an approach-oriented incentive motivational state accompanied by a sense of subjective drug 'wanting.'

An important caveat was that individuals showing greater craving reactivity also showed larger P3 responses to straw oddballs (vs. context). Additional studies would be needed to identify the reasons for this lack of specificity in P3-craving association. Practically, this may arise simply because individuals' P3s to smoking and straw cues were substantially correlated ($r = .68$). Substantively, it could be that neural reactivity to *any* infrequent "oddball"

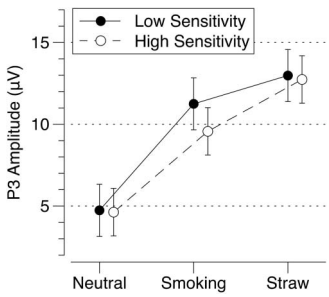

Figure 3. Model estimated means (and associated 95% confidence intervals) for the P3 amplitude as function of level of alcohol sensitivity and stimulus type. The Low and High estimates for alcohol sensitivity and tobacco dependence were computed at the mean scores for the fourth and first quartiles of the ASQ, respectively.

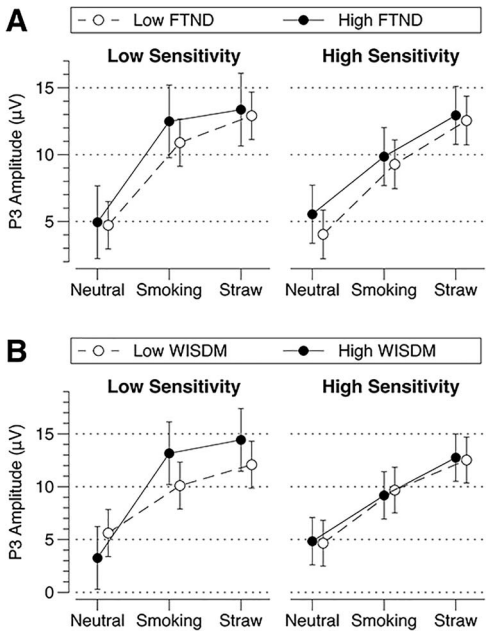

Figure 4. Model estimated P3 amplitude means (and associated 95% confidence intervals) as function of smoker group, stimulus type, and tobacco dependence when individual differences in dependence were measured using the FTND (A) and the WISDM (B). Adjusted means for Low and High dependence were computed at the mean scores for the first and fourth quartiles of the respective dependence instrument, The Low and High estimates for alcohol sensitivity were computed at the mean scores for the fourth and first quartiles of the ASQ, respectively.

[4] Some ERP studies of smoking cue reactivity have examined the amplitude of the late positive potential (LPP), a sustained positivity in the stimulus-locked waveform often visible after the peak of the P3 (Littel & Franken, 2007, 2011; J.D. Robinson et al., 2015; Versace et al., 2011). We repeated all analyses using average amplitudes measured 700–1000 ms following target onset in each condition. Findings for LPP generally paralleled effects seen in the main P3 analyses, with the exception that craving reactivity was not related to LPP amplitude and there was no evidence for a 2-way WISDM × Stimulus interaction in a model predicting LPP amplitude. These analyses are presented in greater detail in the online supplementary material.

stimulus may reflect activity in neural generators related to cued cigarette craving. This is unlikely because an extensive literature has demonstrated that *reduced* P3 amplitude to generic oddballs (geometric shapes; rotated heads) is associated with increased risk for externalizing psychopathology, including smoking and other drug abuse (e.g., Anokhin et al., 2000; Iacono & McGue, 2006).

A more likely explanation is that the comparison stimuli selected for the current study were themselves motivationally significant. As noted decades ago by Tomkins (1966), sucking (as with a straw) is a pleasurable behavior, evoking developmentally primitive, unlearned nursing responses that reduce distress and increase positive affect (cf. Johnson, Valle-Inclán, Geary, & Hackley, 2012). This fact could explain the unexpected finding that the straw images used here were rated as more pleasant and arousing, and elicited larger P3 amplitudes than the smoking cues. That P3 amplitude covaries with the arousal level of eliciting stimuli has been well documented (Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Delplanque, Silvert, Hot, Rigoulot, & Sequeira, 2006). Our prior alcohol study (Bartholow et al., 2010, which used a sample drawn from the same population used here) provides useful benchmarks for understanding the stimulus ratings. The arousal ratings of the straw images in the current sample ($M = 5.1$) are higher than those provided by the young adults recruited by Bartholow et al. (2010) for alcohol images ($M = 4.4$) and nonalcohol images ($M = 3.6$) but lower than arousal ratings for adventure scenes ($M = 6.9$) and erotic images ($M = 5.9$). Bartholow et al. (2010) found that the erotic and adventure targets elicited larger P3 compared with the less arousing alcohol cues and nonalcohol cues.

Although in hindsight the decision to use straws as comparison stimuli was unfortunate in that it complicated interpretation of the P3 response to smoking images, straws arguably provide a better comparison than do the control stimuli used in many prior smoking cue-reactivity studies. Specifically, straws are not only cylindrically shaped like cigarettes but also are used in consummatory behavior via sucking, as are cigarettes. The same cannot be said of the "everyday objects (such as staplers and lamps)" (Rubinstein et al., 2011, p. 8), images of people reading magazines (Goudriaan et al., 2010), or even people holding pens and pencils (Carpenter et al., 2014; Gilbert & Rabinovich, 1999) that prior researchers have used. In other words, drinking straws have appetitive connotations that other types of comparison stimuli do not. Some empirical evidence suggests that the magnitude of cue-induced cravings for food and cigarettes are correlated in smokers (Mahler & de Wit, 2010; Styn, Bovbjerg, Lipsky, & Erblich, 2013). In the current study, larger increases in cigarette craving were associated with and heightened P3 responding to both smoking and straw targets. This may reflect that a subset of smokers is generally reactive to reward cues (Mahler & de Wit, 2010). However, this could also reflect unique incentive properties of nicotine, which not only acts as a primary reinforcer, but can also enhance the reinforcing value of nonpharmacologic stimuli (Chaudhri, Caggiula, Donny, Palmatier, Liu, & Sved, 2006). Additional studies using a wider array of putatively neutral and appetitive stimulus classes are needed to investigate these possibilities.

A second major aim of the study was to investigate the relation between individual differences in tobacco dependence and smoking cue-elicited P3. Daily and occasional smoker groups differed in overall levels of tobacco dependence, but group membership did not moderate P3 reactivity to smoking cues. Congruent with results of two prior studies (Bloom et al., 2013; Littel & Franken, 2011), we found that FTND scores did not relate to P3 reactivity. WISDM scores did moderate reactivity to smoking cues, but this effect was not specific to the smoking cues. The FTND and WISDM were correlated but not redundant ($r = .58$). Prior research suggests the WISDM is a broader of the two measures and that it often accounts for incremental variance in dependence-related outcomes after FTND scores are covaried (Piasecki et al., 2010a; Piper, McCarthy, et al., 2008). Thus, it is plausible that the unique content in the WISDM indexes individual differences in reactivity to motivationally significant stimuli.[5] On balance, the findings indicate there is a potential for some features of tobacco dependence to be related to cued P3 responding, but this effect may be rather subtle and further research is needed to investigate its reproducibility and specificity.

The absence of robust, dependence-related moderation of neural reactivity to smoking cues challenges the Incentive Sensitization model, as this account posits that the attribution of exaggerated salience to drug-related cues is a hallmark of drug dependence acquisition (T.E. Robinson & Berridge, 1993, 2000). The current sample was arguably well suited to evaluating this question; participants were young, tended to be light smokers, many achieved very low scores on dependence scales, and the two smoker groups differed on measures of tobacco dependence with large effect sizes. It seems likely that a sample with these characteristics will contain a mix of individuals on either side of a hypothesized 'tipping point' into tobacco dependence. However, as the exact location (i.e., dependence scale cut score) of such a 'tipping point' is unknown, it may be necessary to include a broader range of participants to further test this theoretical assertion. It is also possible that behavioral or physiological measures other than cue-elicited P3 might more sensitively reflect dependence-related shifts in the salience of drug cues. Finally, nicotine may have unique incentive properties compared with other drugs of abuse, possibly making tobacco addiction a suboptimal 'model system' for probing central tenets of the Incentive Sensitization model (Yager & Robinson, 2015).

[5] The multidimensional structure of the WISDM permits exploration of the possible source of the interaction. The WISDM subscales can be combined to form two composites, labeled the Primary (PDM) and Secondary Dependence Motives (SDM). A number of investigations suggest the PDM scales tap more advanced or later-emerging features of dependence and are more strongly related to the FTND compared with the SDM (Piasecki, Piper, & Baker, 2010b). Using these composites in place of the full scale indicated there was not a Dependence x Stimulus interaction for PDM, $F(2, 1616) = 1.54$, $p = .22$, but this effect was significant for SDM, $F(2, 1616) = 17.34$, $p < .001$. Higher SDM scores were associated with larger P3 to both types of oddballs versus context (Smoking × SDM $b = 0.59$, $p < .001$; Straw × SDM $b = 0.89$, $p < .001$). Follow-up analyses substituted the individual SDM subscales in the model. Significant omnibus Subscale × Stimulus interactions were found in 8 of 9 analyses; Cognitive Enhancement did not moderate P3 response ($p = .13$). In most models, higher scores were associated with differentially larger P3 to both Smoking cues and Straw cues relative to Neutral images. The exceptions were in the models testing Weight Control and Taste subscales, for which higher scores were related to larger P3 to Straws versus context (Straw × Weight Control $b = .94$, $p < .001$; Straw × Taste $b = .38$, $p < .001$) but did not moderate responses to Smoking cues (Smoking × Weight Control $b = .15$, $p = .25$; Smoking × Taste $b = .07$, $p = .53$).

A final goal of this study was to examine whether P3 reactivity to smoking cues was related to low alcohol sensitivity, a trait associated with risk for alcohol use disorder (see Ray et al., 2016; Trim et al., 2009) and with exaggerated P3 to alcohol cues (Bartholow et al., 2007, 2010). We found that lower alcohol sensitivity was associated with differentially larger P3 to smoking cues. Interestingly, alcohol sensitivity was the only trait to be associated with a specific enhancement of P3 to smoking cues but not straw cues. Taken together with prior findings (Bartholow et al., 2010), low sensitivity seems to be related to enhanced motivational salience of *drug-related cues* that does not extend to other arousing or appetitive stimuli.

Why might low alcohol sensitivity be associated with enhanced P3 reactivity to smoking cues? One possibility is that a history of simultaneous use of alcohol and tobacco may forge learned associations between their respective cues, and the enhanced pleasurable and intoxicating effects associated with cues (Piasecki, Jahng, et al., 2011) might inflate their incentive value and contribute to cross-sensitization. This possibility could be explored in future studies by explicitly measuring individual differences in simultaneous use patterns and testing whether these account for low sensitivity drinkers' exaggerated response to smoking cues.

A second possibility is that the low alcohol sensitivity trait may reflect an innate vulnerability to the sensitization of neural incentive circuits by drugs of abuse (cf. T.E. Robinson, Yager, Cogan, & Saunders, 2014). We also observed three-way interactions indicating that P3 to smoking cues (relative to neutral context stimuli) was more pronounced in participants who reported both high tobacco dependence and low alcohol sensitivity, though this effect was only specific to smoking cues in the analysis using the FTND (see Figure 4). Notably, individual differences in alcohol sensitivity were not correlated with measures of tobacco dependence in our sample. This indicates low alcohol sensitivity is not necessary for displaying dependence features. Instead, low sensitivity individuals may represent a subgroup of smokers who more closely conform to the expectations of the Incentive Sensitization model.

A final possibility is that low sensitivity individuals' bias for alcohol cues generalizes to other drug-related cues as a result of higher-order conditioning resulting from culturally transmitted associations between smoking and drinking behaviors (Littel & Franken, 2012). Testing this idea would require measuring smoking cue reactivity responses among nonsmokers with varying degrees of alcohol sensitivity.

The current study has a number of limitations that should be acknowledged. As noted previously, the comparison straw stimuli were unexpectedly potent. Although it complicates interpretation of the current results, this finding also may suggest generative avenues for future research. Cue exposure studies that parametrically vary the contents of comparison stimuli may serve to place the magnitude of smoking cue reactivity in proper perspective and clarify the scope of the domain of incentive stimuli in smokers and other groups. It is possible our findings would not generalize to older smokers with more severe tobacco dependence and longer smoking histories. To maximize power for testing effects involving cigarette craving and levels of tobacco dependence, we did not include a nonsmoking control group in our design. Doing so would have offered more perspective on the normative psychological impact of the straw cues and the salience of the smoking images for current smokers. Including nonsmokers might also have helped to narrow interpretation of the alcohol sensitivity findings, indicating whether they depend on personal experiences with cigarettes. Craving was measured before and after a picture-viewing task in which neutral, smoking, and straw images were equally likely to be present in the target position. More specific findings might emerge using a design in which the smoking and straw targets were organized into discrete blocks, with craving measured before and after each one (e.g., Namkoong et al., 2004). Finally, we did not examine associations between cue-elicited P3 and important criteria such as smoking behavior or postcessation relapse.

These limitations notwithstanding, the current study advances the smoking cue reactivity literature by demonstrating that the amplitude of the P3 elicited by visual smoking cues is associated with acute changes in cigarette craving. The current study also extends prior work by demonstrating that smokers at risk for alcohol use disorder (due to a lower sensitivity to alcohol) showed more pronounced neural responses to smoking cues. This suggests that alcohol sensitivity may be a risk factor for smoking onset or progression and that the ERP methodology may be a useful tool for investigating the psychological mechanisms contributing to the comorbidity of tobacco dependence and alcohol use disorder. Self-reported low sensitivity to the pharmacologic effects of alcohol may represent a marker of drug cue reactivity and therefore deserves attention as a potential moderator in smoking cue exposure studies and as a predictor of cue-provoked smoking relapse.

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