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Cigarette cues capture attention of smokers and never-smokers, but for different reasons

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Abstract

Background—While the notion that smokers reliably show higher reactivity to cigarette-related versus neutral cues is both theoretically and empirically supported, it is unclear why never-smokers also show enhanced brain responses to cigarette-related cues.

Methods—Using a repetitive picture viewing paradigm, in which responses evoked by affective cues are more resistant to habituation, we assessed the effects of stimulus repetition on event-related potentials (ERPs) evoked by pleasant, unpleasant, cigarette-related, and neutral images in 34 smokers (SMO) and 34 never-smokers (NEV). We examined the early posterior negativity (EPN) and the late positive potential (LPP), two ERP components which are sensitive to a picture's motivational qualities.

Results—Before stimulus repetition, pleasant, unpleasant, and cigarette-related cues produced greater EPN and LPP amplitudes than neutral cues in all subjects. During stimulus repetition, both components were similarly modulated by emotional arousal, such that pleasant, unpleasant, and cigarette-related cues evoked greater EPN and LPP amplitude, relative to neutral. Smoking status did not modulate these effects. While there were no group differences in self-reported stimulus ratings of valence for pleasant, unpleasant, or neutral stimuli, NEV rated cigarette-related cues as unpleasant. We observed a moderate, negative correlation between LPP amplitude and self-reported valence ratings of cigarette-related cues among NEV.

Conclusions—These data suggest that cigarette-related cues capture attentional resources of both SMO and NEV, but for different reasons. For SMO, cigarette-related cues have acquired

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motivational significance through repeated associations with nicotine delivery, whereas for NEV, cigarette-related cues are perceived as unpleasant.

Keywords

Event-related potentials; repetition; addiction; smoking

1. Introduction

Neurobiological models of drug dependence propose that cues preceding drug delivery can acquire motivational properties through associative learning processes (Koob and Volkow, 2010; Robbins and Everitt, 1996; Robinson and Berridge, 1993). In fact, smokers report that the presence of cigarette-related cues (e.g., ashtrays, other people smoking) is sufficient to induce cravings and spur compulsive smoking (Shiffman et al., 2007; Stewart, 2008). Neurophysiological measures support the idea that for smokers, cigarette-related cues are motivationally relevant cues that attract attention. Cigarette-related cues increase the amplitude of both the early posterior negativity (EPN) and the late positive potential (LPP), two components of the event-related potential (ERP) reflecting both the engagement of attentional resources by emotional stimuli and the activation of cortico-limbic appetitive and defensive systems (Littel et al., 2012; Versace et al., 2011; Codispoti et al., 2016). However, recent studies have reported that never-smokers also show enhanced brain responses to cigarette-related cues relative to neutral (e.g., Deweese et al. 2016; Littel et al. 2012; McDonough and Warren 2001; Minnix et al. 2013; Robinson et al. 2015; Oliver et al. 2016). Since never-smokers have not experienced the effects of nicotine, researchers hypothesized that reactivity to cigarette-related cues for never-smokers might be driven by an overall more negative perception of smoking (i.e., a top-down driven process), rather than by the motivational relevance of the cigarette-related stimuli (Yiend, 2010; Robinson et al., 2015). In fact, both cognitive (top-down) and affective (bottom-up) processes can have similar effects on brain responses evoked by natural scenes and increase the amplitude of the late positive potential (LPP) over centro-parietal sensors (Ferrari et al., 2008). Codispoti and colleagues (2006) employed a repetitive picture viewing paradigm, in which a small set of images (e.g., 1 pleasant, 1 unpleasant, 1 neutral) is repeated many times, to disentangle the effects that cognitive and affective processes exert on ERPs. An advantage of this paradigm is that repeated presentation reduces stimulus novelty (Öhman,1992; Siddle and Spinks, 1992; Kahneman, 1973), which may allow for motivational effects to emerge more clearly. Several studies consistently showed that even after massive repetition, pleasant and unpleasant cues continue to elicit larger EPNs and LPPs compared to neutral ones, a result suggesting that, also when the images are no longer novel, affectively engaging pictures to continue to activate mental representations with strong associations to motivational circuits (Bradley et al., 2006; Codispoti et al., 2007; Ferrari et al., 2011; Ferrari et al., 2017; Mastria et al., 2017).

In the present study, we used this same paradigm to investigate the extent to which top-down and bottom-up processes influence reactivity to cigarette-related cues in smokers and never-smokers. We examined the effects of stimulus repetition on the amplitude of the EPN and LPP components, and whether smoking status modulated any observed differences among a

group of 34 smokers and 34 never-smokers. For never-smokers, in particular, this paradigm allows us to assess whether cigarette-related cues continue to elicit enhanced ERP amplitude (relative to neutral) similar to that of other motivationally salient cues (bottom-up), or whether these cues habituate as they lose novelty and salience as a function of stimulus repetition (top-down). Existing cue-reactivity studies assessing reactivity to cigarette-related cues among smokers and never-smokers were not designed to test whether enhanced responses to cigarette-related cues were due to the motivational significance of the stimulus or to stimulus novelty (e.g., Littel et al. 2012; Minnix et al. 2013; Deweese et al. 2016). Thus, the repetition paradigm will allow us to explore the cognitive processes underlying the amplitude and modulation of the EPN and LPP by emotional arousal during picture viewing (Codispoti et al., 2007).

We expected pleasant, unpleasant, and cigarette-related stimuli to produce larger EPNs and LPPs relative to neutral in both smokers and never-smokers when presented for the first time. Following stimulus repetition, we expected emotional pictures (pleasant, unpleasant) to produce larger EPNs and LPPs relative to neutral in both smokers and never-smokers. We hypothesized that only smokers would maintain enhanced brain responses to cigarette-related cues, relative to neutral. This finding would indicate that cigarette-related cues are motivationally salient stimuli only for smokers, as attenuation of ERP amplitude to cigarette-related cues across blocks in the repetition phase for never-smokers could reflect changes in resource allocation as the pictures become less novel with repetition. In the reinstated novel phase, we expected full recovery of all habituated responses, except for the EPN and LPP evoked by cigarette-related cues in never-smokers, as these cues should have limited motivational significance for this group.

2. Material and Methods

2.1 Participants

We recruited 86 participants from the Houston metropolitan area using radio and newspaper advertisements. Participants were eligible for the study if they were: between 18 and 65 years of age, were fluent in English, had access to a working telephone, were neither pregnant nor breastfeeding, were not currently enrolled in a formal smoking-cessation activity, did not report any history of psychiatric disorders, substance abuse disorder, history of seizures or seizure disorder, head injuries with a loss of consciousness, uncorrected visual or auditory impairments or use of any non-cigarette tobacco products (e.g., pipe tobacco, cigars, snuff, chewing tobacco, hookah), or be unwilling to change hairstyle (e.g., braids, pony tails, or dread locks) or remove a wig to accommodate application of the EEG net. Smoking participants had to report a baseline expired carbon monoxide (CO) at least six-parts per million (ppm) and reported smoking 5 or more cigarettes per day for the last six-months. To be eligible for the never-smoker group, participants must have smoked less than 100 cigarettes in their lifetime (Bondy et al., 2009) and produce a baseline expired CO less than 4 ppm. All participants received monetary compensation for their time and parking/travel, totaling $60.

2.2 Procedures

The procedures were approved by The University of Texas MD Anderson Cancer Center Institutional Review Board. All participants were initially screened in a 30-minute telephone interview to establish initial eligibility for the study. Eligible participants were then invited to attend an in-person visit, where a trained member of the staff explained the study procedures to the potential participants and collected written, informed consent. Biochemical verification of smoking status was assessed by measuring expired carbon monoxide levels, and participants completed questionnaires regarding demographics, medical, mood, and smoking history. After questionnaire completion, participants then completed the EEG recording session (see *Stimuli and experimental paradigm*).

2.3 Self-report Measures

For smokers, nicotine dependence was measured using the Fagerström Test for Nicotine Dependence (FTND), a 6-item questionnaire that assesses various components of smoking behavior such as daily intake and time to the first cigarette after waking (Heatherton et al., 1991). In all participants, affect was assessed using the Center for Epidemiologic Studies Depression Scale (CES-D), a 20-item self-report measure developed to assess depressive symptoms in community (non-clinical) populations (Ross and Mirowsky, 1984), as well as the Positive and Negative Affect Scale (PANAS; Watson et al., 1988), comprised of two 10-item mood scales, Positive Affect (PA) and Negative Affect (NA), rated on a scale of 1-5. One participant chose not to respond to self-report measures; thus, data from 33 smokers and 34 never-smokers were included in the final demographic and questionnaire analysis.

2.4 Stimuli and Experimental Paradigm

Stimuli were presented with a PC using E-Prime software (version 2.0.8.74; PST Inc., Pittsburgh, PA) on a 42-inch high-definition plasma screen approximately 2.25 meters from the participant's eyes. From this distance, the stimuli subtended a visual angle of 21 degrees. Picture stimuli consisted of 48 pleasant (PLE; 24 erotica and 24 romance), 48 cigarette-related (CIG; people smoking), 48 neutral (NEU; neutral people), and 48 unpleasant (UNP; 24 mutilation and 24 attack) images selected in part from the International Affective Picture System (Lang et al., 2005), the International Smoking Image Series (Gilbert and Rabinovich, 1999), the Emotional Picture Set (Wessa et al., 2010) and other images previously used in our laboratory (Deweese et al., 2016; Minnix et al., 2013; Robinson et al., 2015). Because the LPP varies with emotional arousal (Schupp et al., 2004b), only high-arousing PLE (e.g., erotica; ERO) and UNP (e.g., mutilations; MUT) images were used in the repetition phase.

The repetitive picture-viewing paradigm was modified from Codispoti et al., 2006, and consisted of three phases: an initial novel phase (block 1), a repetition phase (blocks 2, 3, 4) and a reinstated novel phase (block 5; see Figure 1). In all blocks, stimuli were presented for 2 seconds, followed by a variable (2-3 second) inter-trial interval during which a white fixation cross appeared on a black screen. In block 1, the initial novel phase, 96 unique images (24 PLE, 24 CIG, 24 NEU, and 24 UNP) were presented with no stimulus repetition. In blocks 2, 3, and 4, the repetition phase, the last image from each stimulus category presented in block 1 was repeated a total of 24 times, for a total of 96 trials per block. Thus,

the same 4 stimuli (1 ERO, 1 CIG, 1 NEU, and 1 MUT) were repeated 24 times each in blocks 2, 3, and 4. In block 5, the reinstated novel phase, a previously unseen set of 96 images (24 PLE, 24 CIG, 24 NEU, and 24 UNP) was presented with no stimulus repetition. Stimulus presentation was pseudo-randomized such that no more than two images of the same category were presented consecutively. Images repeated in the repetition phase were counterbalanced across participants.

Following the experimental session, participants were asked to rate a subset of the images presented during the experiment using a computerized version of the Self-Assessment Manikin (SAM; Lang, 1980) on the dimensions of affective valence and arousal. The total duration of the EEG session, including SAM ratings, was approximately 50 minutes.

2.5 ERP Recording

During the picture presentation, we recorded EEG using a high-input impedance (200 MΩ) 129-channel Geodesic Sensor System (Geodesic EEG System 200; Electrical Geodesics, Inc., Eugene, OR) and referenced to Cz. We used a sampling rate of 250 Hz, and data were filtered online by using 0.1 Hz high-pass and 100 Hz low-pass filters. Scalp impedances were kept below 70 KΩ, as suggested by the manufacturer.

2.6 ERP Scoring

Following the EEG recording session, a 60-Hz low-pass filter was applied off-line. Data were visually inspected, and channels contaminated by artifacts for more than 50% of the recording were interpolated with use of spherical splines. On average, approximately 3.4% of the channels met this criterion and were interpolated. Eye blinks were corrected using a spatial filtering method implemented in BESA version 5.1.8.10 (MEGIS Software GmbH, Gräfelfing, Germany), and the EEG data were then transformed to the average reference. The Brain Vision Analyzer (version 2.0.2; Brain Products GmbH, Munich, Germany) software program was used to extract single epochs from the continuous EEG signal. The data were segmented into 1100 ms segments, beginning 100 ms before the onset of the image, and baseline was defined as the 100 ms interval preceding picture onset. Using the segmented data, artifacts affecting sensors within specific trials were identified by the following criteria: EEG amplitude above 100 or below −100 μV; absolute voltage difference between any two data points within the segment larger than 100 μV; voltage difference between two contiguous data points above 25 μV and less than 0.5 μV variation for more than 100 ms. A segment was excluded from the subsequent averages if more than 10% of the sensors within the segment were contaminated by artifacts. The average number of trials for the EPN and LPP components by phase and condition are presented in Table 2. There were no significant differences among the number of trials retained per condition during the novel (EPN: p=.4; LPP: p=.3) or repetition (EPN: p=.1; LPP: p=.08) phases.

Due to poor recording quality, largely attributed to excessive movement, eighteen participants were excluded from further analysis. Laboratory data from 34 smoking (SMO) and 34 never-smoking (NEV) participants were included in the final EEG analyses.

2.7 Statistical Analysis

To identify time regions and sensors (within time regions) to include in our ERP analyses, we used a functional localizer approach, which accounts for between-subject differences in latency and scalp distribution (Luck and Gaspelin, 2017). First, we calculated the mean global field power (GFP, the sum of the squared potential differences of all 129 sensors (Lehmann and Skrandies, 1980), for each time point for each picture type for each participant, separately for each of the 5 blocks. Then, analyzed variance (ANOVA) to test for the main effect of Picture Type (four levels: pleasant, cigarette-related, neutral, and unpleasant) on each time point, separately by block. If the F value observed at a given time point was significant at the $p<.05$ level ($F[3, 201] = 2.65$) in each of the 5 blocks, that time point was included in a temporal region of interest (ROI; Figure 2A). Within each temporal ROI, separately by block, we computed the mean voltage at each electrode for the four picture conditions. We used these values to conduct an ANOVA to test for the main effect of Picture Type at each sensor, separately by block. If the F value observed for a given electrode was significant at the $p<.05$ level in each of the 5 blocks, that electrode was included in the spatial ROI (Figure 2B).

This approach identified two segments of time in which cortical activity was differentially modulated by picture type: a segment extending from 216 to 276 ms post-picture onset and another from 380 to 532 ms post-picture onset. The 216-276 ms time window, which we refer to as the early posterior negativity (EPN) component of the ERP, included 26 electrodes in three spatially distinct clusters: (left) 50, 51, 52, 57, 58, 59, 60, 64, (center), 70, 71, 72, 74, 75, 76, 77, 81, 82, 83, 84, 85 and (right) 91, 92, 95, 96, 97, 100, and 101 (Figure 2B). Left, right, and center EPN clusters did not differ statistically; thus, results are presented as an average of all sensors. The 380-532 ms time window, which we refer to as the late positive potential (LPP), included 11 centro-parietal electrodes: 6, 31, 54, 55, 79, 80, 87, 105, 106, 112, and 129 (Figure 2B).

As a first step, we sought to confirm that the presentation of emotionally arousing (including cigarette) cues produced larger EPN and LPP amplitudes, relative to neutral, in the initial novel block. Then, to test whether smoking status modulated ERPs to picture type as a function of stimulus repetition, we examined the significance of the interaction Group (NEV, SMO) by Picture Type (PLE, CIG, NEU, UNP) by Block (2, 3, 4). Finally, to determine whether smoking status affected recovery of habituated responses following stimulus repetition, we tested the significance of the interaction group (NEV, SMO), by Picture Type (ERO, CIG, NEU, UNP) by Block (4, 5). The above statistical tests were computed separately for the LPP and EPN components, and where appropriate, significant effects were further evaluated using Bonferroni error corrected pairwise comparisons (Luck and Gaspelin, 2017).

3. Results

3.1 Participant Characteristics

Participant characteristics for smokers and never-smokers are presented in Table 1. Smokers did not differ from never-smokers in racial composition ($p=.8$), but included significantly

more males (p<.0003) and were, on average, 6.6 years older (p<.04) than the never-smoking sample. After controlling for age and gender, smokers had significantly lower PANAS Positive Affect scores (p<.003) and significantly higher CES-D scores (p<.001), indicating that smokers were reporting less positive affect and more depressive symptoms, relative to never-smokers. There were no group differences in PANAS Negative Affect scores (p=.7).

3.2 EPN Component (216 – 276 ms)

3.2.1 Novel phase—When shown for the first time, PLE, UNP, and CIG stimuli evoked significantly greater negativity than NEU (all ps<.0001, η_p^2 > .38; Figure 3A). PLE was significantly more negative than both CIG and UNP cues (all ps<.0001, η_p^2 > .33; CIG and MUT did not differ (p>.3).

Repetition phase: For the EPN component, we found a significant interaction of Picture Type and Block (F[6, 396] = 4.45, p <.0001, η_p^2 = .33), where for each repetition block, ERO evoked significantly greater negativity than CIG (all ps<.001, η_p^2 > .16) and MUT (all ps<.006, η_p^2 > .11), and all emotional stimuli (including cigarettes) evoked significantly greater negativity than NEU (all ps<.003, η_p^2 > .12). MUT and CIG were not significantly different within any repetition blocks (all ps>.1); see Figure 3A). Although attention to ERO, MUT, and CIG cues decreased as a function of stimulus repetition (block 2 vs. block 4, F[1, 67] = 11.325, p <.001, η_p^2 = .29), these cues remained significantly more negative than NEU (all ps<.03).

3.2.2 Reinstated novel phase—When a novel set of images was presented following the repetition phase, PLE, UNP, and CIG evoked significantly greater negativity than NEU (all ps<.0001, η_p^2 > .44; Figure 3A). PLE was significantly more negative than both CIG and UNP cues (all ps<.0001, η_p^2 > .24); CIG and UNP did not differ (p>.8).

We did not observe any effects of Group on the EPN during either the novel or repetition phases, suggesting that the EPN was not modulated by smoking status. Grand averaged ERP waveforms are averaged across all blocks and participants and are plotted by the condition in Figure 3B.

3.3 LPP Component (380 – 532 ms)

3.3.1 Novel phase—Similar to the EPN, when presented for the first time, LPP amplitude evoked by PLE, UNP, and CIG was significantly greater than NEU (all ps<.0001, η_p^2 > .48; Figure 4A). PLE and UNP evoked significantly greater LPP amplitude relative to CIG (all ps<.0001, η_p^2 > .26). PLE and UNP did not differ (p>.3, η_p^2 > .02)

3.3.2 Repetition phase—We observed an interaction of Picture Type and Block for the LPP component, F(6, 396) = 5.88, p <.0001, η_p^2 = .46. Pairwise comparisons indicated that in

all blocks of the repetition phase, ERO, MUT, and CIG evoked greater LPP amplitude relative to NEU (all *ps*<.04, $\eta_p^2 > .09$; Figure 4A), and ERO and MUT images evoked significantly greater LPP amplitude than CIG (all *ps*<.0001, $\eta_p^2 > .002$). Follow-up tests indicated a significant decrease in LPP amplitude across the repetition phase (block 2 vs block 4, $F[1, 66] = 215.3$, $p < .0001$, $\eta_p^2 = .39$), replicating previous studies (Codispoti et al., 2006, 2007; Mastria et al., 2017). In other words, there was a significant decrease in observed LPP amplitude for all picture types (ERO, MUT, CIG, NEU), such that the amplitude for a given condition in block 3 was less than the amplitude observed in block 2 (all *ps* < .006), and the amplitude observed in block 4 was less than the amplitude observed in block 3 (all *ps* < .001). Further, the introduction of novel stimuli following the repetition phase elicited a significant reinstatement of cortical positivity (block 4 vs. block 5, $F[1,67] = 65.15$, $p < .0001$, $\eta_p^2 = .63$), suggesting that the observed decrease in amplitude was due to stimulus repetition rather than study fatigue.

3.3.3 Reinstated Novel Phase—When a novel set of images was presented following the repetition phase, LPP amplitude evoked by emotional stimuli (including cigarettes) was significantly greater than NEU (all *ps*<.0001, $\eta_p^2 > .36$; Figure 4A). PLE and UNP evoked significantly greater LPP amplitude relative to CIG images (all *ps*<.0001, $\eta_p^2 > .31$). PLE evoked significantly greater amplitude than UNP (*p*<.02, $\eta_p^2 > .08$).

We did not observe any effects of Group on the LPP during either the novel or repetition phases, suggesting that smoking status did not modulate the LPP Grand averaged ERP waveforms are averaged across all blocks and participants and are plotted by the condition in Figure 4B.

3.4 Potential Covariates of the ERP Response

To determine whether any of the baseline demographic variables functioned as a covariate of the ERP response, we ran a Group × Picture Type × Block analysis, separately for each ERP component, and included the following potential moderators as covariates in the model: gender, race, and age. We found no main effects for any of the baseline measures on either of the ERP components, indicating that none of the baseline measures covaried with ERP response during the EPN or LPP time window. Likewise, the presence of the covariates did not alter significant main effects or interactions within the EPN and LPP time windows.

3.5 SAM Ratings

A significant interaction between smoking status and picture type emerged when we analyzed ratings of emotional valence, $F(3, 198) = 6.88$, $p < .0001$, $\eta_p^2 > .09$. There were no group differences in self-reported valence ratings of pleasant and unpleasant cues, which were rated by all participants as more pleasant (*p*<.0001) and more unpleasant (*p*<.0001) than neutral cues. However, unlike smokers, never-smokers rated cigarette cues as significantly more unpleasant than neutral ($p < .0001$, $\eta_p^2 = .56$). Groups did not differ on

ratings of arousal (p=0.5); all subjects rated pleasant and unpleasant stimuli as significantly more arousing than neutral (all ps<.0001), and arousal ratings for cigarette cues did not differ from neutral (p=.2).

To determine whether never-smokers' rating of cigarette-related cues was related to attentional biases toward cigarette-related stimuli, we ran a correlation analysis with SAM ratings and grand-averaged ERP amplitude as variables. We ran these analyses across all blocks, separately for each group (smokers, never-smokers) and ERP component (EPN, LPP). There was a moderate, negative correlation between LPP amplitude and self-reported valence ratings of cigarette-related cues among never-smokers, $\rho(30) = -.32$, $p = .04$. In other words, a more unpleasant rating of cigarette-related cues was related to higher LPP amplitude. No other correlations reached statistical significance.

4. Discussion

In the present study, we used a repetitive picture viewing paradigm to assess the extent to which cognitive (top-down) and affective (bottom-up) processes influence neurophysiological responses to cigarette-related cues in smokers and never-smokers. Overall, our findings are in line with a large body of research demonstrating that emotional cues are processed in a mandatory fashion, and continue to engage cortico-limbic appetitive and defensive systems even after massive repetition, as suggested by the affective modulation of the LPP (Codispoti et al., 2006; Codispoti et al., 2016; Ferrari et al., 2017; Mastria et al., 2017). Contrary to our predictions, our results indicate that cigarette-related cues continue to evoke larger ERPs than neutral images in both smokers and never-smokers, even when the stimuli have been repeated 96 times and are no longer novel.

While a lack of group differences may be surprising, our findings are in line with those from other ERP (Bloom et al., 2013; Deweese et al., 2016; Engelmann et al., 2016; Littel et al., 2012; Robinson et al., 2015) and reaction time (Oliver and Drobes, 2012) studies showing a cognitive, attentional bias toward cigarette-related cues in both smokers and non-smokers.

We think that it is unlikely that a purely perceptual explanation would account for our findings. Using a second-order conditioning paradigm, we recently showed that both smokers and non-smokers respond to perceptually identical cues when they precede both pleasant and cigarette-related images (Deweese et al., 2016). However, because pleasant and unpleasant stimuli evoke comparable ERP responses (Bradley et al., 2012; Keil et al., 2002; Schupp et al., 2004a; Wiens and Syrjänen, 2013; Leite et al., 2012), we are unable to discriminate whether cigarette-related cues are being processed as pleasant or unpleasant cues. Our self-report ratings, however, support the notion that, unlike smokers, never-smokers find cigarette-related cues unpleasant (Engelmann et al., 2011; Robinson et al., 2016; Robinson et al., 2015). These findings are also supported by studies that measured peripheral physiology and showed that in never-smokers, cigarette-related cues elicited responses similar to those evoked by unpleasant stimuli (Dempsey et al., 2007; Gantiva et al., 2016; Geier et al., 2000). The moderate, negative correlation between LPP amplitude and self-reported valence ratings of cigarette-related cues further supports the conclusion that

never-smokers maintain enhanced ERP responses to cigarette-related cues because they perceive them as unpleasant.

Although we did not find evidence of a correlation between EPN amplitude and self-reported valence ratings of cigarette-related cues, these results were also not surprising. The EPN is largely associated with amplitude modulation of primarily pleasant stimuli (De Cesarei and Codispoti, 2006; Schupp et al., 2004a; Keil et al., 2002). Because smokers' valence ratings of cigarette-related cues did not differ from neutral, and never-smokers rated cigarette-related cues as more unpleasant than neutral, we would not anticipate a correlation among these measures.

Our findings may also be interpreted in the light of results from studies showing that the imminent possibility of smoking increases craving intensity (Carter and Tiffany, 2001; Wilson and Sayette, 2015) and brain responses (Wilson et al., 2005; Jasinska et al., 2014) evoked by cigarette-related cues. In fact, a recent study investigating the effects of nicotine exposure and dose expectancy on the EPN and LPP reported that the anticipated effects of nicotine improve attention similar to receiving nicotine (Robinson et al., 2016). In our study, however, smokers were aware that smoking was not possible during or immediately following the EEG recording session, which may have affected the salience of cigarette-related cues.

In a recent study designed to examine the impact of an explicit categorization task on the emotional processing of repeated pictures, Mastria and colleagues (2017) found that while affective modulation of the LPP was unaffected by the categorization task, stimulus-specific effects emerged as a function of task-relevance. Task-relevant images evoked LPPs on the level of non-target emotional cues, whereas the same images evoked LPP amplitude comparable to neutral ones when presented in the passive viewing condition. Through years of repeated use, smoking cues have acquired strong motivational properties powerful enough to capture attention, activate affective states, and guide behavior (Robinson and Berridge, 1993). However, even following massive repetition, we observed an increase in ERP amplitude to cigarette-related cues in never-smokers who have not experienced the associative learning processes associated with the effects of nicotine. Thus, future studies might capitalize on how cognitive mechanisms, such as task relevance (implicit and explicit), and external cues such as nicotine availability, might influence reactivity to cigarette-related cues in smokers and never-smokers.

Taken together, we believe these data make an important contribution to the literature by demonstrating that cigarette-related cues are relevant to smokers and never-smokers. Even following massive repetition, never-smokers produced higher EPNs and LPPs to cigarette-related cues relative to neutral, despite never having been exposed to nicotine. In combination with the self-report data, we conclude that smoking cues capture attentional resources of smokers and never-smokers, but for different reasons. While never-smokers perceive cigarette-related cues as unpleasant stimuli, smokers preferentially allocate attention to cigarette-related cues because these cues have been imbued with incentive salience through years of repeated associations with the delivery of nicotine.

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Highlights

- We measured event-related potentials in smokers and never-smokers.
- Stimuli were repeated up to 96 times.
- Emotional stimuli evoked greater EPN and LPP amplitude than neutral.
- These effects were not modulated by smoking status.
- Unlike smokers, never-smokers rated cigarette-related cues as unpleasant.

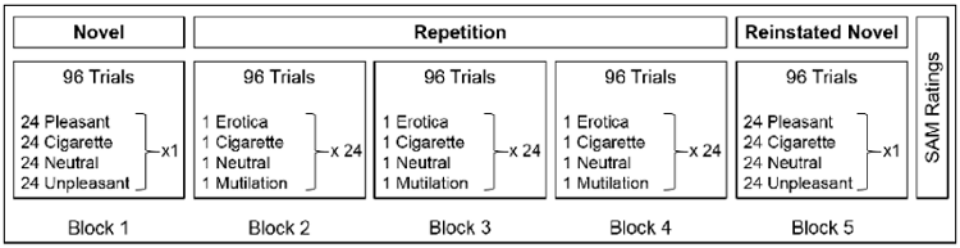

Figure 1.
Schematic diagram depicting the sequence of events in the study.

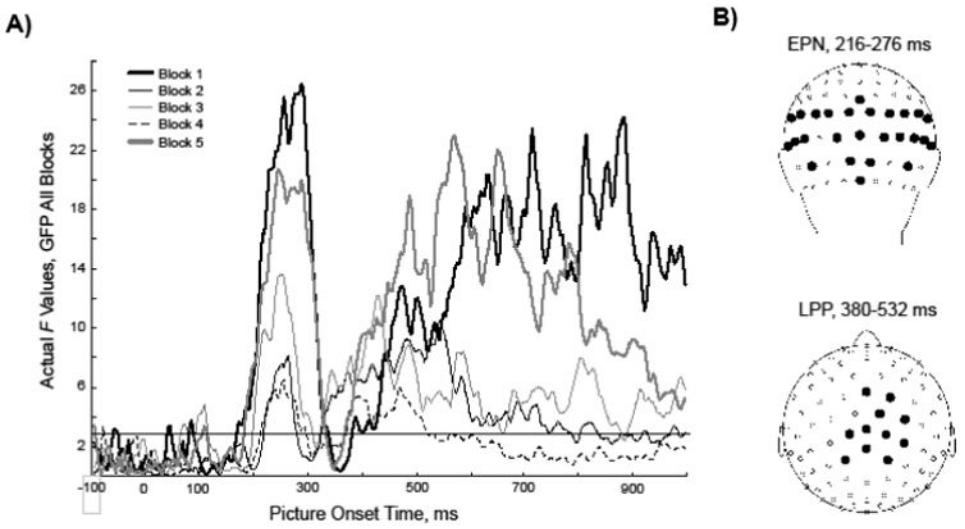

Figure 2.

A) F values for the main effect of Picture Type on the global field power at each time point, plotted separately for each block. The dotted line indicates the F value corresponding to p<. 05 (F=2.65). **B)** Filled circles indicate electrodes included in the EPN (top) and LPP (lower) spatial regions of interest.

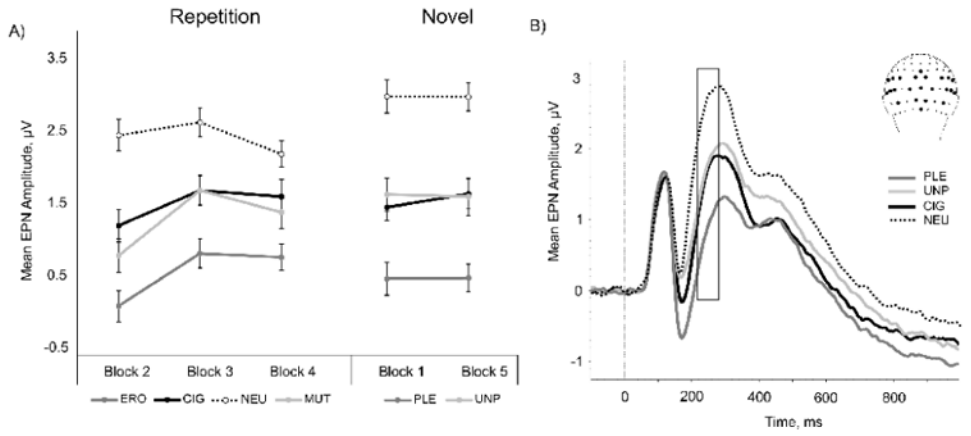

Figure 3.

A) Mean amplitude for the early posterior negativity (216-276 ms) component evoked by picture stimuli during the repetition and novel phases, averaged across all subjects. Bars denote standard error of the mean. Note: High-arousing erotica and mutilations were repeated in the repetition phase; high- and low-arousing pleasant (erotica and romance) and unpleasant (mutilations and attack) cues were presented in the novel phase. **B)** Event-related potential waveforms of mean channel regions of interest (inset) are averaged across all participants and blocks, and are plotted by condition. Box denotes time region of the EPN (216-276 ms). Note different scales.

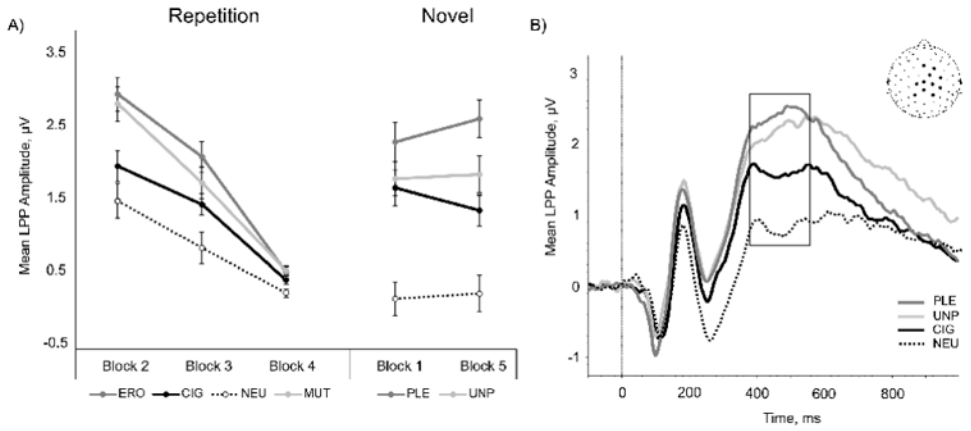

Figure 4.

A) Mean late positive potential (380-532 ms) amplitude evoked by picture stimuli during the repetition and novel phases, averaged across all subjects. Bars denote standard error of the mean. Note: High-arousing erotica and mutilations were repeated in the repetition phase; high- and low-arousing pleasant (erotica and romance) and unpleasant (mutilations and attack) cues were presented in the novel phase. **B)** Event-related potential waveforms of mean channel regions of interest (inset) are averaged across all participants and blocks, and are plotted by condition. Box denotes time region of the LPP (380-532 ms). Note different scales.

Table 1

Demographic and smoking characteristics.

	Never-smokers n=34	Smokers n=34
Gender	*%(N)*	*%(N)*
Male	47(16)	87(28) *
Race		
African American, non-Hispanic	32.4(11)	39.4(13)
White, non-hispanic	52.9(18)	48.5(16)
Other	14.7(5)	9.1(3)
	Mean (SE)	*Mean (SE)*
Age	40.44(2.22) *	47.03(2.29)
Cigarettes/day	--	19.13(12.35)
FTND[a]	--	4.66(2.15)
PANAS Positive Affect[b]	37.93(1.09)	32.75(1.12) *
PANAS Negative Affect[b]	14.94(0.83)	15.38(0.86)
CES-D[c]	5.5(0.66)	8.625 (0.68) *

* $p<.05$

[a] Fagerström test for nicotine dependence

[b] Positive and Negative Affect Scale

[c] Center for Epidemiologic Studies Depression Scale

Table 2

Number of trials per condition for the EPN and LPP components during the Novel and Repetition phases, for each picture type.

		Novel				Repetition			
		PLE	**CIG**	**NEU**	**UNP**	**PLE**	**CIG**	**NEU**	**UNP**
	Average	19.38	19.66	19.35	19.27	18.67	19.08	18.71	19.15
	Percent	80.80%	81.90%	80.60%	80.30%	77.80%	79.50%	78%	79.80%
EPN	*Maximum*	24	24	24	24	24	24	24	24
	Minimum	7	7	9	5	6	6	8	7
	SD	4.08	3.88	3.72	4.11	4.03	3.83	3.76	3.81
	Average	19.19	19.53	19.16	19.09	18.57	19.01	18.62	19.12
	Percent	80%	81.40%	79.80%	79.50%	77.40%	79.60%	77.60%	79.70%
LPP	*Maximum*	24	24	24	24	24	24	24	24
	Minimum	7	7	9	5	6	6	8	7
	SD	4.06	3.86	3.68	4.03	4.01	3.81	3.73	3.84

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