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

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 et al. (2006) employed a repetitive picture viewing paradigm,

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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., Littell 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-min 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 m from the participant's eyes. From this distance, the stimuli subtended a visual angle of 21°. 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 Fig. 1). In all blocks, stimuli were presented for 2 s, followed by a variable (2–3 s) 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

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