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Conditioned cortical reactivity to cues predicting cigarette-related or pleasant images

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ABSTRACT

Through Pavlovian conditioning, reward-associated neutral stimuli can acquire incentive salience and motivate complex behaviors. In smokers, cigarette-associated cues may induce cravings and trigger smoking. Understanding the brain mechanisms underlying conditioned responses to cigarette-associated relative to other inherently pleasant stimuli might contribute to the development of more effective smoking cessation treatments that emphasize the rehabilitation of reward circuitry. Here we measured brain responses to geometric patterns (the conditioned stimuli, CSs) predicting cigarette-related, intrinsically pleasant and neutral images (the unconditioned stimuli, USs) using event-related potentials (ERPs) in 29 never-smokers, 20 nicotine-deprived smokers, and 19 non-deprived smokers. Results showed that during US presentation, cigarette-related and pleasant images prompted higher cortical positivity than neutral images over centro-parietal sensors between 400 and 800 ms post-US onset (late positive potential, LPP). The LPP evoked by pleasant images was significantly larger than the LPP evoked by cigarette images. During CS presentation, ERPs evoked by geometric patterns predicting pleasant and cigarette-related images had significantly larger amplitude than ERPs evoked by CSs predicting neutral images. These effects were maximal over right parietal sites between 220 and 240 ms post-CS onset and over occipital and frontal sites between 308 and 344 ms post-CS onset. Smoking status did not modulate these effects. Our results show that stimuli with no intrinsic reward value (e.g., geometric patterns) may acquire rewarding properties through repeated pairings with established reward cues (i.e., cigarette-related, intrinsically pleasant).

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1. Introduction

For smokers, cigarette-related cues are salient stimuli that can induce cravings and trigger smoking behavior (Shiffman et al., 2007; Stewart, 2008). Animal models of drug addiction have demonstrated that drug-related cues acquire incentive salience via Pavlovian conditioning (Flagel et al., 2008; Kruzich et al., 2001; Uslaner et al., 2006). Through Pavlovian conditioning, an organism learns the relationship existing between two events, for example a light being turned on (the conditioned stimulus, CS) and the subsequent delivery of a primary reward, such as food or a drug infusion (the unconditioned stimulus, US; Rescorla, 1988). Once an organism learns the CS–US relationship, CSs can become incentive stimuli and, with their presence, trigger motivational states and addictive behaviors (Meyer et al., 2012; Mucha et al., 1998; Robinson and Berridge, 2001; Winkler et al., 2011).

Human studies assessing peripheral and central nervous system responses to emotional and cigarette-related stimuli have shown that smokers process cigarette-related cues similarly to inherently pleasant stimuli: both categories of stimuli inhibit startle and corrugator electromyographic responses (Dempsey et al., 2007; Geier et al., 2000), increase activation in brain regions supporting attentional (e.g., the extended visual system) (Dunning et al., 2011; Littel et al., 2012; Minnix et al., 2013; Robinson et al., 2014) and reward processes (e.g., medial prefrontal cortex, striatum) (Engelmann et al., 2012; Sweitzer et al., 2014; Versace et al., 2011a; Wilson et al., 2014). These findings are consistent with the hypothesis that, by being repeatedly associated with nicotine delivery, cigarette-related stimuli acquire enough incentive salience to trigger cravings and may prompt smoking relapse among those trying to quit (e.g., Ferguson and Shiffman, 2009).

Recent studies, however, have reported that never-smokers also show enhanced brain responses to cigarette-related compared with neutral stimuli (Littel and Franken, 2012; McDonough and Warren, 2001; Minnix et al., 2013; Oliver and Drobes, 2012; Robinson et al., 2014). Such findings are puzzling because, unlike smokers, never-smokers should not have experienced the associative learning processes between nicotine and cigarette-related cues that turn them into motivationally relevant stimuli. Because never-smokers tend to respond to cigarette-related cues less than smokers, these authors speculated that for never-smokers, reactivity to cigarette cues is not due to their

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motivational relevance per se, but rather might be attributed to higher-order evaluative processes (Robinson et al., 2014), to specific perceptual characteristic of cigarette-related stimuli (Minnix et al., 2013; Robinson et al., 2014), to the familiarity that also never-smokers might have for cigarette-related stimuli (Oliver and Drobes, 2012), or to an overall more negative attitude toward smoking cues by never-smokers (Robinson et al., 2014).

Apart from directly recording electrocortical reactivity to cigarette-related cues, another approach to evaluate the level of motivational relevance attributed to cigarette-related cues is to use them in a second-order conditioning procedure. In second-order conditioning, a conditioned stimulus acquires associative strength and elicits a conditioned response by being paired not with a primary reward (e.g., nicotine), but with another conditioned stimulus (called a secondary reinforcer) that holds motivational relevance by having been previously associated with the primary reward (e.g., a cigarette-related cue). Animal models have shown that secondary reinforcers can be effective in maintaining complex behavioral chains even when primary rewards are not consistently delivered (Gewirtz and Davis, 2000; Grabus et al., 2005). These results suggest that cigarette-related stimuli should be effective secondary reinforcers in a second-order conditioning paradigm only to the extent to which they hold motivational relevance. Recently, Littel and Franken (2012) examined electrophysiological responses to geometric figures preceding either cigarette-related or neutral images in smokers and never-smokers. The authors reported that even though the geometric figures predicting cigarette cues were never directly paired with nicotine delivery, they elicited significantly larger positive ERPs than geometric figures predicting neutral cues. These effects were observed in both early (250–280 ms) and late (280–500 ms) time windows. Given that modulation of the ERP amplitude within these time windows is considered an index of enhanced motivated attention (Cuthbert et al., 2000; Hajcak et al., 2010; Lang et al., 1997; Lang and Bradley, 2010; Olofsson et al., 2008; Schupp et al., 2000), the findings by Littel and Franken (2012) support the idea that neutral stimuli can acquire relevance simply by being paired with cigarette-related cues.

A second-order conditioning paradigm might also contribute to clarifying the role that nicotine plays in influencing the level of incentive salience that smokers attribute to non-nicotine-related natural rewards (e.g., food, sex). Neurobiological models of drug addiction emphasize that drug use alters the brain mechanisms involved in the processing of rewards, and suggest that drug-induced amelioration of reward deficits might contribute to addictive disorders and substance abuse (Goldstein and Volkow, 2002; Koob and LeMoal, 2008; Koob and Volkow, 2010; Volkow et al., 2010). Mounting evidence shows that low hedonic capacity (i.e., diminished reactivity to pleasurable stimuli; (Huys et al., 2013) might contribute to both nicotine addiction vulnerability and smoking maintenance (Audrain-McGovern et al., 2012; Rubinstein et al., 2011; Versace et al., 2012). Individuals with low hedonic capacity might have more difficulty quitting smoking because they rely on nicotine to increase the salience of otherwise "bland" natural rewards (de Wit and Phan, 2010). This hypothesis is in line with the dual-reinforcement model of nicotine addiction: nicotine is not only a primary reinforcer, but also acts as a reinforcement enhancer, magnifying the incentive value of stimuli accompanying nicotine delivery (Caggiula et al., 2009). Accordingly, by amplifying the incentive value of natural rewards, nicotine might help individuals with low hedonic capacity normalize their hypo-responsive reward system. Hence, we hypothesized that nicotine deprivation should reduce the capacity of pleasant stimuli to act as secondary reinforcers.

In this study, we recruited never-smokers and smokers under nicotine deprived or sated conditions and measured event-related potentials (ERPs) to geometric patterns (i.e., the conditioned stimuli, CS) preceding the presentation of cigarette-related, intrinsically pleasant (i.e., erotic), or neutral stimuli (i.e., the secondary reinforcers, US). ERPs are a particularly useful measure to explore cognitive processes and attentional biases in addiction, as the amplitude of the ERP provides information regarding the extent of attentional and motivational engagement in the presence of visual stimuli. Both pleasant and unpleasant stimuli lead to higher activity in the primary and secondary visual cortical areas and this activation can be reliably detected over posterior regions of the scalp (Keil et al., 2002; Lang et al., 1997; Liu et al., 2012; Schupp et al., 2000).

Both animal and human studies have shown that the presence of conditioned stimuli increases electrophysiological activity in the visual sensory areas (Ihssen et al., 2007; Shuler and Bear, 2006). Hence, we expected to observe increased cortical reactivity over occipital and parietal regions of the scalp to CSs paired with cigarette-related images in smokers, relative to never-smokers. Further, we expected both smokers and never-smokers to show increased cortical reactivity to CSs paired with inherently pleasant (erotic) images, relative to neutral images. To the extent that nicotine acts as a reinforcement enhancer, we hypothesized higher responses to CSs paired with erotic images in nicotine sated smokers versus nicotine deprived smokers.

2. Methods

2.1. Participants

Participants were recruited from the Houston metropolitan area using flyers, magazine, and newspaper advertisements. The inclusion/exclusion criteria are listed in Table 1. Never-smoking participants were recruited using the same methods and were subject to the same inclusion and exclusion criteria as the smokers, except that they must have smoked less than 100 cigarettes in their lifetime and produce a baseline expired CO less than 4 parts per million (ppm). The "less than 100 lifetime cigarettes" threshold was chosen because it is the oldest (Bondy et al., 2009) and most frequently used criterion for distinguishing never-smokers from ever smokers (CDC, 2011; Gilpin et al., 2004). The number of cigarettes that never-smokers reported smoking ranged from 0 to 10 (mean: 0.9, SD: 2.09).

Fig. 1 explains the recruitment process for this study. Due to poor recording quality, largely attributed to excessive movement and eye blink artifacts, nineteen participants were excluded from further analysis. Laboratory data from 19 nicotine-satiated (SMO), 20 nicotine-deprived (DEP), and 29 never-smoking (NEV) participants were included in the final analyses, yielding a total of 68 participants. All participants received monetary compensation for their time and for parking/travel, totaling $60.

Table 1
Inclusion and exclusion criteria for smokers and non-smokers.

Inclusion criteria
Aged 18–50 years
Fluent in English
Have a working telephone
Smokers
Smoke ≥5 cigarettes per day
Baseline expired carbon monoxide (CO) level >6 parts per million (ppm)
Non-smokers
Smoked <100 cigarettes in their lifetime
Baseline expired CO level <4 ppm
Exclusion criteria
Current psychiatric disorder (within 6 months, as established by self-report)
Current substance abuse (with the exception of smoking)
Current participation in a formal smoking-cessation activity
Current use of non-cigarette tobacco products (e.g., pipe tobacco, cigars, snuff, chewing tobacco, and hookah)
Currently pregnant or breast-feeding
Use of psychotropic medication or illicit drug use (within 30 days)
History of seizures or a seizure disorder
A head injury with a loss of consciousness
Visual or auditory problems

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