



Cue reactivity in smokers: An event-related potential study



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ABSTRACT

Drugs-of-abuse may increase the salience of drug cues by sensitizing the dopaminergic (DA) system (Robinson and Berridge, 1993), leading to differential attention to smoking stimuli. Event-related potentials (ERPs) have been used to assess attention to smoking cues but not using an ERP component associated with DA-mediated salience evaluation. In this study the DA-related P2a and the P3, were compared in smokers ($N = 21$) and non-smokers ($N = 21$) during an attention selection cue exposure task including both cigarette and neutral images. We predicted that both the P2a and P3 would be larger to targets than non-targets, but larger to non-target cigarette images than non-target neutral images only in the smokers, reflecting smokers' evaluation of smoking stimuli as relevant even when they were not targets. Results indicated that smokers showed behavioral cue reactivity, with more false alarms to cigarette images (responding to cigarette images when they were not targets) than non-smokers; however, both smokers and non-smokers had a larger P2a and P3 to cigarette images. Thus, while smokers showed behavioral evidence of differential salience evaluation of the cigarette images, this group difference was not reflected in differential brain activity. These findings may reflect characteristics of the ERPs (both ERP components were smaller in the smokers), the smoking sample (they were not more impulsive, i.e. reward sensitive, than the non-smokers, in contrast to prior studies) and the design (all participants were aware that the aim of the study was related to smoking).

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1. Introduction

Tobacco use remains the leading preventable cause of premature death and disability in the United States (CDC, 2008; Mokdad et al., 2004). As of 2010, 19% of US adults were cigarette smokers (CDC, 2011b). Most smokers express a desire to quit and engage in quit attempts (CDC, 2011a). However, nicotine dependence is notoriously difficult to treat, and 70–95% of quit attempts are unsuccessful (Fiore et al., 2008; Hughes et al., 2004). A better understanding of the cognitive, personality, and neural factors that maintain nicotine dependence could contribute to improved screening, intervention, and outcome assessment, including improved targeting of treatments that match individual smoker characteristics. The current study compared smokers and non-smokers on event-related potentials (ERPs) elicited during an attention selection task that included both smoking cues (i.e., images of cigarettes) and neutral cues (i.e., images of flowers, vehicles, and animals),

and examined the relationship between ERP amplitude markers of reward sensitivity and trait impulsivity.

1.1. Reactivity and attention to smoking cues

Exposing smokers to smoking-related cues (e.g., images of cigarettes) reliably induces self-reported craving or urge, as well as physiological responses, a phenomenon consistent with classical conditioning theory, and termed “cue reactivity” (Carter and Tiffany, 1999). The degree to which smokers react to smoking cues predicts their ability to remain abstinent in some studies (e.g., Niaura et al., 1989; Payne et al., 2006), indicating a possible link between cue reactivity and addictive processes. In addition to cue-elicited craving and physiological responses, smokers show preferential attention to stimuli related to tobacco use. For example, smokers respond faster to identifying targets that occur in a location preceded by a smoking-related image and slower when preceded by a smoking-related picture presented in a different location from the target (Bradley et al., 2003; Ehrman et al., 2002; Waters et al., 2003a). Smokers also exhibit increased reaction time in response to naming the color of smoking-related words relative to neutral words, thereby indicating greater attentional capture by the smoking-related words (Drobes

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et al., 2006; Gross et al., 1993; Waters et al., 2003a). This interference effect has also predicted relapse (Waters et al., 2003b), suggesting this effect is related to addiction. However, the neural basis of attentional capture by smoking cues is less well understood.

1.2. Neural model of cue reactivity

Robinson & Berridge's incentive salience system was proposed as part of a model of cue-related drug craving (Berridge and Robinson, 1995; Robinson and Berridge, 1993). This model proposes that the dopaminergic (DA) reward system functions to attach motivational value to perceptual representations. The incentive salience system has been hypothesized as an attention selection neural mechanism (Potts et al., 2006; Potts, 2004). It is hypothesized that drugs-of-abuse, through their impact on the DA system, sensitize incentive salience evaluation to drug cues, thereby resulting in drug-related items being tagged as having high motivational value compared to neutral representations. This sensitization accounts for the preferential attention allocated to drug cues in addicted individuals. Neural systems of cue reactivity have explicitly linked motivation-based selection to the DA reward system (Chase et al., 2011).

1.3. Using event-related potentials to assess cue reactivity

Event-related potentials (ERPs) provide a functional index of perceptual and attentional neural systems, and may provide a sensitive assessment of cue reactivity as measured by altered attention to addiction-relevant cues. The P300 (or P3) is a centro-parietal positivity elicited by relatively rare events in an attended stream of stimuli (Donchin et al., 1984; Johnson, 1984; Sutton and Ruchkin, 1984); thus the P3 provides an index of attention: attended stimuli elicit a larger P3 than ignored stimuli. The most prominent theory of the P3 is the context updating theory, which states that we maintain an internal model of our current environment, the context, and when an unexpected (i.e., rare) event occurs, we must update that internal model to accommodate that unexpected event (Donchin and Coles, 1998). For a stimulus to be rare in contrast to the other stimuli in the stream, it must be distinguishable from the other stimuli. As such, the P3 can serve as an index of stimulus distinctiveness or categorization. The P3 is also larger to emotional, compared to neutral, stimuli (Olofsson et al., 2008). Thus the P3 may index stimuli that have relevance due to their ability to elicit an emotional response.

The P3 component has frequently been used to assess cue reactivity among individuals with substance use disorders (SUDs) (for a comprehensive review, see Littel et al., 2012), including nicotine dependence (Jang et al., 2007; Littel and Franken, 2007, 2011a, 2011b, 2012; McDonough and Warren, 2001; Versace et al., 2010, 2011, 2012; Warren and McDonough, 1999). A recent meta-analysis indicated that the P3 is of significantly larger amplitude in response to drug-related stimuli vs. neutral stimuli, and that the difference in amplitude between drug-related and neutral stimuli is significantly larger among individuals with SUDs relative to controls without SUDs, indicating preferential attention to drug-related stimuli in SUDs (Littel et al., 2012). Furthermore, larger effects have been observed in heavier users of the drugs (Herrmann et al., 2001) or users in a withdrawal period (McDonough and Warren, 2001), implying a relationship between drug craving and attention to drug-related stimuli. However, some prior studies of cigarette smokers have not included a control group of non-smokers (Versace et al., 2010, 2011), a particularly important issue as P3 amplitude increases to smoking cues have also occurred in nonsmokers (McDonough and Warren, 2001) and recent work indicates that attention is engaged by drug-related cues in both users and non-users (Oliver and Drobos, 2013).

Given that the P3 is a relatively late ERP component, reflecting attention allocation, which occurs after perceptual formation and motivational evaluation, if cue reactivity is associated with incentive salience

then effects of drug-related stimuli should occur earlier in processing and be reflected earlier in the ERP. Therefore, in addition to revisiting P3 amplitude reactivity to smoking cues among smokers, in the current study we also examined an earlier ERP component. This component, variously called the anterior P2 (P2a), frontal polar component (FP), and the frontal selection positivity (FSP), responds exclusively to the task relevance of a stimulus, i.e. its motivational value, with an onset at about 150–200 ms after the stimulus appears and peaking at about 250–300 ms, and has been reliably associated with incentive salience (Guillem et al., 2001; Kenemans et al., 1993; Potts et al., 1996). The P2a has been elicited to visual and auditory stimuli, indicating that it is independent of perceptual modality, and when responses are either overt (e.g. key press) or covert (e.g. silent counting), indicating that a motor response is not required. The critical element in the elicitation of a P2a is that the presented stimulus has motivational relevance (incentive salience) to the individual (e.g., emotional stimuli, Kanske et al., 2011).

Recent work using an experimental design that delivers or withholds predicted and unpredicted rewards has explicitly linked the P2a to the DA reward system (Potts et al., 2006). Neurons in the ventral tegmental area (VTA) show enhanced firing when an unexpected reward is delivered and suppress their firing when an expected reward is not delivered (Schultz et al., 1997). Likewise, the P2a is most positive to unpredicted rewards and least positive (actually negative) when a predicted reward is not delivered, mirroring the firing pattern of the VTA neurons, supporting the P2a as an index of the DA reward system (Potts et al., 2006). The current study is the first study to examine P2a responses to drug-related stimuli.

1.4. The current study

The current study employed an attention selection cue exposure task using a stimulus set consisting of non-cigarette (animal, flower, vehicle) and cigarette images, with one image category (e.g. "animal") made explicitly task-relevant on each trial by designating that category as the target, requiring a response from the participant. This design combines aspects of attention selection designs (instructed targets, which have incentive salience) we have used in prior studies (e.g., Potts, 2004) with a cue reactivity assessment of incentive sensitization (presentation of cigarette-related images to smokers). We predicted that both smokers and non-smokers would have an enhanced P2a (and P3) to instructed targets, but that only the smokers would show an enhanced P2a to the cigarette images when they were not instructed targets, i.e. when they were not made explicitly relevant by the task, reflecting incentive salience of the smoking cues in nicotine addiction.

In addition, we examined how individual differences, specifically self-reported impulsivity, might modify these ERP effects. Impulsivity is described as the propensity to make decisions without thoughtful consideration of long-term consequences, and is characterized by rapid responding and a heightened immediate reward preference (Evenden, 1999; Whiteside and Lynam, 2001). Smoking may be considered an impulsive behavior since smokers choose the short-term rewards of smoking cigarettes despite the potential long-term negative consequences. Prior studies have shown that smokers rate themselves as more impulsive, compared to non-smokers, on self-report personality inventories (Dinn et al., 2004; Mitchell, 1999, 2004; Terracciano and Costa, 2004) and are behaviorally more likely to choose smaller, more immediate rewards over larger delayed rewards (Baker et al., 2003; Bickel et al., 1999; Reynolds et al., 2004). Like incentive salience and cue reactivity, impulsivity has been related to the dopamine (DA) reward system (Braver and Cohen, 2000; Carli et al., 1985; Matthisse, 1978; Servan-Schreiber et al., 1998; Smillie and Jackson, 2006; Williams and Dayan, 2005). Therefore we investigated whether self-reported impulsivity might be related to cue reactivity, i.e. whether impulsive smokers might be more susceptible to incentive sensitization, indexed by a larger P2a to cigarette stimuli, and direct more attention to those cigarette stimuli, indexed by a larger P3.

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