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).

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, 15% 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 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.
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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 do-
paminergic (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 hav-
ing 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 ex-
plicitly 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 neutral 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
elicted 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 con-
text 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 accom-
modate that unexpected event (Donchin and Coles, 1998). For a stimu-
lus 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 compre-
hensive 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 individ-
uals with SUDs relative to controls without SUDs, indicating preferential
attention to drug-related stimuli in SUDs (Littel et al., 2012). Further-
more, 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 ciga-
rette smokers have not included a control group of non-smokers
(Versace et al., 2010, 2011), a particularly important issue as P3 ampli-
tude increases to smoking cues have also occurred in nonsmokers
(McDonough and Warren, 2001) and recent work indicates that atten-
tion is engaged by drug-related cues in both users and non-users
(Oliver and Drobes, 2013).

Given that the P3 is a relatively late ERP component, reflecting
attention allocation, which occurs after perceptual formation and moti-
vational 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 am-
plitude 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 fron-
tal 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 percep-
tual modality, and when responses are either overt (e.g. key press) or co-
vert (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 with-
holds predicted and unpredicted rewards has explicitly linked the P2a
to the DA reward system (Potts et al., 2006). Neurons in the ventral teg-
mental area (VTA) show enhanced firing when an unexpected reward is
delivered and suppress their firing when an expected reward is not de-
ivered (Schultz et al., 1997). Likewise, the P2a is most positive to
unpredicted rewards and least positive (acturally negative) when a pre-
dicted 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, ve-
hicle) and cigarette images, with one image category (e.g. “animal”) was
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
(paired) 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 consid-
ered an impulsive behavior since smokers choose the short-term re-
wards 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 personali-
ty 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) re-
ward system (Braver and Cohen, 2000; Carli et al., 1985; Matthysse,
1978; Servan-Schreiber et al., 1998; Smillie and Jackson, 2006; Williams
and Dayan, 2005). Therefore we investigated whether self-reported im-
 pulsivity 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 two
those cigarette stimuli, indexed by a larger P3.
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