Motivated attention to cocaine and emotional cues in abstinent and current cocaine users – an ERP study

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Abstract

Event-related potentials (ERPs) are a direct measure of neural activity and are ideally suited to study the time-course of attentional engagement with emotional and drug-related stimuli in addiction. In particular, the late positive potential (LPP) appears to be enhanced following cocaine-related compared with neutral stimuli in human participants with cocaine use disorders (CUD). However, previous studies have not directly compared cocaine-related with emotional stimuli while examining potential differences between abstinent and current cocaine users. The present study examined ERPs in 55 CUD (27 abstinent and 28 current users) and 29 matched healthy controls while they passively viewed pleasant, unpleasant, neutral and cocaine-related pictures. To examine the time-course of attention to these stimuli, we analysed both an early and later window in the LPP as well as the early posterior negativity (EPN), established in assessing motivated attention. Cocaine pictures elicited increased electrocortical measures of motivated attention in ways similar to affectively pleasant and unpleasant pictures in all CUD, an effect that was no longer discernible during the late LPP window for the current users. This group also exhibited deficient processing of the other emotional stimuli (early LPP window – pleasant pictures; late LPP window – pleasant and unpleasant pictures). Results were unique to the LPP and not EPN. Taken together, results support a relatively early attention bias to cocaine stimuli in cocaine-addicted individuals, further suggesting that recent cocaine use decreases such attention bias during later stages of processing but at the expense of deficient processing of other emotional stimuli.

Introduction

Drug-related compared with neutral stimuli elicit increases in physiological reactivity in drug-addicted individuals (Carter & Tiffany, 1999). Similar research demonstrates unique reactions to emotional compared with neutral stimuli in healthy individuals (Lang *et al.*, 1997; Vuilleumier, 2005; Schupp *et al.*, 2007). Termed 'motivated attention', it is hypothesized that motivational systems automatically allocate attention to, and enhance the salience of, emotional stimuli (Lang *et al.*, 1997). Two event-related potentials (ERPs), the early posterior negativity (EPN) and the late positive potential (LPP), are larger for both pleasant and unpleasant compared with neutral visual stimuli, interpreted as reflecting increased attention to motivationally relevant stimuli (Cuthbert *et al.*, 2000; Schupp *et al.*, 2000, 2003a, 2004b; Hajcak *et al.*, 2007; Hajcak & Olvet, 2008; Foti *et al.*, 2009). These ERPs capture different stages within emotional processing; specifically, the EPN reflects early selective attentional processing, while the LPP reflects continued processing of motivationally significant stimuli. Also, evidence suggests that the LPP further comprises both early (reflecting initial attention capture; similar to the P300) and later parietal components (reflecting sustained processing and encoding; Foti *et al.*, 2009).

Several studies have reported that larger LPPs are elicited by drug-related compared with neutral pictures in alcohol- (Namkoong *et al.*, 2004), heroin- (Franken *et al.*, 2003) and cocaine-addicted individuals (Franken *et al.*, 2004; van de Laar *et al.*, 2004); studies have not similarly examined the EPN. The extant LPP data have been interpreted as increased allocation of neural resources to addiction-related stimuli among addicts. However, more nuanced interpretations have been complicated given the inconsistent use of control groups, comparison stimuli, and variability in recency of drug use in the addicted participants. Specifically, only a few ERP studies have directly compared drug-related with other emotional stimuli in both drug-addicted and control individuals (Lubman *et al.*, 2008, 2009). This is a crucial comparison given that emotion-related abnormalities have been implicated among substance-dependent individuals (Aguilar de Arcos *et al.*, 2005; Verdejo-Garcia *et al.*, 2006). In addition, recency of drug use may relate to aberrant neural reactivity to drug cues among addicted individuals (Wilson *et al.*, 2004). Therefore, the current sample of individuals with cocaine use disorders (CUD) included those who tested positive (CUD+) vs. negative (CUD−) for recent cocaine use.

Specifically, we examined the EPN and LPP in 55 CUD (28 CUD+ and 27 CUD−) and 29 matched healthy controls while subjects passively viewed pleasant, unpleasant, neutral and cocaine-related pictures. We hypothesized that in both CUD groups, LPPs elicited by cocaine pictures would be larger than neutral LPPs and similar to other emotional picture LPPs in the early time window, suggesting enhanced attention to drug-related cues. We further hypothesized cocaine-related LPPs to be most pronounced in CUD+, consistent with suggestions for enhanced drug cue cortical reactivity with perceived drug use opportunity (Wilson *et al.*, 2004) and enhanced cortical glucose metabolism among cocaine users during earlier compared with later abstinence (see Goldstein & Volkow, 2002). Analyses of the EPN were more exploratory.

Materials and methods

Participants

Fifty-five individuals with CUD and 29 healthy control subjects participated in the current study. All subjects were medically healthy right-handed native English-speakers (exclusion criteria are described in Supporting Information). Based on an extensive psychiatric interview (see Supporting Information), all CUD met DSM-IV criteria for current cocaine dependence. A positive urine screen indicated cocaine use within 72 h (maximal resolution of the urine test) of study day in 28 participants (CUD+), while 27 participants tested negative (CUD−). The three groups (CUD+, CUD−, Controls) did not differ in distributions of sex and race, or in mean age, socio-economic status, years of education and non-verbal intellectual functioning (Table 1; also see Supporting Information for treatment seeking status and analyses). However, CUD scored higher on depression and reported greater history of cigarette smoking than the controls (Table 1), and the possible confounding effects of these variables were examined as described in Analyses and Results. Additionally, compared with CUD−, CUD+ had increased frequency of cocaine use over the past 30 days, shorter duration of current abstinence, and higher craving but less self-reported severity of cocaine dependence (these variables did not correlate with LPPs). Subjects were fully informed of all study procedures and provided written consent for their involvement in this study in accordance with the local Institutional Review Board.

Stimuli

Ninety pictures were selected from the International Affective Picture System (IAPS; Lang *et al.*, 2005) based on normative ratings of valence and arousal, such that pleasant and unpleasant pictures would be more arousing than neutral pictures, and that each category of pictures would differ in their respective valence scores (see Supporting Information for analyses). Of these 90 pictures, there were 30 pleasant (e.g. smiling faces, nudes), 30 unpleasant (e.g. sad faces, violent images) and 30 neutral scenes (e.g. neutral faces, household objects).

We created a fourth category that included 30 pictures of cocaine and individuals preparing or using cocaine (e.g. snorting or smoking), collected from freely available online sources and adapted (as still images) from a cocaine video used previously in our laboratory (Volkow *et al.*, 2006). Cocaine pictures were matched to the IAPS pictures on size of presentation and ratio of human to non-human content.

One of 10 sequences of completely randomized pictures (across all four picture categories) was randomly assigned to each subject. Within each sequence, four blocks of 30 randomized pictures were presented during the task. All 120 pictures were presented for 2000 ms, with a 2500-ms inter-trial interval; each picture was viewed only once.

Procedure

After a brief description of the experiment, electroencephalograph (EEG) sensors were attached and participants were given more detailed task instructions. Participants were told that they would be viewing pictures depicting a wide range of scenes; some pleasant, unpleasant, neutral, or drug-related. Participants were asked to focus on the screen and simply watch all of the pictures as they were displayed. Following the EEG task, subjects then rated each picture on valence ('rate how pleasant or unpleasant you felt about this picture'), arousal ('rate how strong of an emotional response you had to this

TABLE 1. Demographic characteristics and drug use by study subjects

	CUD+ ($n = 28$)	CUD− ($n = 27$)	Controls ($n = 29$)
Male/female	27/1	26/1	25/4
Ethnicity (African–American/Caucasian/Hispanic)	20/5/3	19/5/3	20/8/1
History of cigarette smoking (current or past/never or tried)*	21/7[c]	21/6[c]	6/23[a,b]
Education (years)	13.09 (1.76)	12.69 (1.82)	13.81 (2.02)
Age (years)	45.55 (4.81)	42.47 (8.82)	41.17 (7.32)
Socio-economic status (A.B. Hollingshead, 1975, unpublished paper)	32.32 (11.03)	33.06 (11.63)	32.90 (13.56)
Non-verbal intellectual functioning: Wechsler Abbreviated Scale of Intelligence – matrix reasoning scaled score (Wechsler, 1999)	9.43 (3.72)	9.92 (3.06)	11.03 (2.72)
Self-reported state depression (Beck *et al.*, 1996)[†]	7.57 (7.56)[c]	7.63 (6.38)[c]	1.48 (2.87)[a,b]
Age at onset of cocaine use (years)	26.68 (5.23)	25.04 (6.47)	–
Duration of use (years)	16.56 (7.09)	14.46 (8.80)	–
Frequency of use (days/week) last 30 days[‡]	4.23 (2.40)[b]	1.53 (2.29)[a]	–
Current use in dollars per use (min – max, median) last 30 days	62.36 (2–200, 50)	109.23 (0–300, 80)	–
Duration of current abstinence (days) (min – max, median)[§]	2.25 (0–14, 2)[b]	214.85 (2–2555, 25)[a]	–
Length of longest abstinence (days) (min – max, median)	869.89 (19–3650, 365)	818.63 (25–2555, 560)	–
Total score on the Cocaine Selective Severity Assessment Scale (measure of withdrawal symptoms; 0–126)	19.11 (10.84)	15.74 (10.36)	–
Severity of Dependence Scale (0–15)[¶]	6.61 (3.40)[b]	8.44 (3.15)[a]	–
Cocaine Craving Questionnaire (0-45)**	22.18 (10.66)[b]	10.96 (9.58)[a]	–

Values in parentheses are standard deviations unless otherwise indicated. *χ^2(2)=23.79, $P < 0.001$ (Kruskal–Wallis). [†]χ^2(2)=25.07, $P < 0.001$ (Kruskal–Wallis). [‡]$Z=-4.00$, $P < 0.001$ (Mann–Whitney). [§]$Z=-5.71$, $P < 0.001$ (Mann–Whitney). [¶]$t_{53} = -2.08$, $P < 0.05$. **$t_{53} = 4.10$, $P < 0.001$. Superscript letters designate group differences ([a]significantly different from CUD+; [b]significantly different from CUD−; [c]significantly different from control group).

picture'), like cocaine ('rate how much you like (or do not like) cocaine in response to this picture') and want cocaine ('rate how much you want (or do not want) cocaine in response to this picture'). Subjects responded using a computerized version of the Self-Assessment Manikin (SAM; Bradley & Lang, 1994). The SAM depicted five characters that ranged on valence (happy to unhappy) or arousal (strong visceral response to no response); these same SAM scales were used to assess liking and wanting of cocaine. Subjects chose the numbers '1' to '9' ('1' corresponded to happy/liking/wanting/high visceral response, '9' to unhappy/not liking/not wanting/no response) that appeared below the SAM characters. Thus, low numerical ratings correspond to higher levels of pleasantness, arousal, and liking and wanting of cocaine. Consistent with previous work, we hypothesized that, of these four ratings, the arousal ratings would most parallel the LPP results (Cuthbert *et al.*, 2000; Olofsson *et al.*, 2008), at least in healthy control subjects (note self-report/awareness difficulties in CUD as we previously reported; Moeller *et al.*, 2010). Analyses and results pertaining to these ratings are reported in the Supporting Information Table S1.

Psychophysiological recording and data reduction

Continuous recordings of the EEG (Neuroscan Inc., Sterling, VA, USA) and electro-oculogram were obtained throughout passive picture viewing using a 64 silver/silver chloride electrode cap positioned according to the International 10/20 System (Klem *et al.*, 1999). All recordings were performed using a fronto-central electrode as ground, and electronically linked mastoid electrodes as reference. Electrodes were placed above and below the left eye to record vertical eye movements, and placed on the outer canthi of both eyes to record horizontal eye movements. The EEG was digitized at a rate of 500 Hz and amplified with a gain of 250, and band-pass filtered from 0 to 70 Hz. Amplifiers were calibrated prior to each recording. Electrode impedances were at or below 10 kΩ for all electrodes used in the analysis.

Analyses

All bioelectric signals were analysed off-line using Brain Vision Analyzer (Brain Products, Munich, Germany). Offline, all data were re-referenced to the numeric mean of the mastoids and band-pass filtered between 0.1 and 30 Hz; the EEG was corrected for blinks and eye movements using a previously developed method (Gratton *et al.*, 1983). In addition, a semi-automated procedure was used to identify and reject physiological artifacts according to the following criteria – a voltage step of more than 50.0 μV between sample points, a voltage difference of more than 300.0 μV within a trial, and a maximum voltage difference of less than 0.50 μV within 100-ms intervals; additional artifacts were identified and rejected through visual inspection following the semi-automated procedure.

The ERPs were constructed by separately averaging trials based on picture type – pleasant, unpleasant, neutral and cocaine-related pictures. For each ERP-averaged waveform, the average activity in the 200-ms window prior to picture onset served as the baseline. Previous research indicates that the EPN is maximal at temporo-occipital electrode sites during a 200–300-ms window after stimulus onset (Schupp *et al.*, 2003a,b, 2004b); therefore, we defined the EPN as the average activity at the Oz, POz, O1 and O2 electrode sites in a 200–300-ms time window after picture onset. For the LPP, previous research among both non-addicted (Cuthbert *et al.*, 2000; Hajcak *et al.*, 2007; Hajcak & Olvet, 2008; Foti *et al.*, 2009) and addicted (see Franken *et al.*, 2003, 2004, 2008; van de Laar *et al.*, 2004)

samples has assessed multiple time windows. In fact, a recent study utilizing principal components analysis (PCA) to investigate emotional picture processing (Foti *et al.*, 2009) provided insight on how to best conceptualize the LPP. Results indicated that an initial parietal positivity in the LPP, which occurred in the range of 300–600 ms, was highly consistent with the P3, probably indicative of initial attention capture. A later sustained portion of the LPP appeared distinct from the earlier P3-like component and was probably indicative of additional and sustained processes relevant for emotional processing (Foti *et al.*, 2009). Therefore, in the present study, we defined the LPP as the average activity in an early (400–1000 ms) and late (1000–2000 ms) time windows after picture onset. Previous investigations also indicate that drug-specific LPP modulation is maximal at fronto-central recording sites (Littel & Franken, 2007; Franken *et al.*, 2008); scalp topographies in the present study corroborated this effect (Fig. 1). Therefore, the LPP was scored as the average activity at the Cz, FCz, FC1, FC2 and Fz electrodes.

For each time window, the averaged LPP was analysed with a 4 (Picture Type – pleasant, unpleasant, neutral, cocaine-related) × 3 (Group – CUD+, CUD−, controls) mixed-model ANOVA. The EPN was similarly analysed. If significant interaction effects were present in the normally distributed EPN and LPP data, paired samples *t*-tests were used to assess within-group differences. Interaction effects were further explored through ERP difference scores, computed by subtracting neutral from all other picture types (pleasant, unpleasant, cocaine); these difference scores were then used to examine between-group differences via independent *t*-tests. This approach controls for general differences in ERPs across participants, examining the degree of emotional modulation of the EPN and LPP across groups. All averaged ERP amplitudes are presented in Table 2.

Correlations

Correlations were conducted between ERPs and selected drug use variables (in CUD only – whole sample and both subgroups separately; see Table 3). As drug use variables were distributed non-normally, non-parametric Spearman correlations were used. All correlations were corrected for a family-wise error rate ($P < 0.01$).

All analyses and effects of possible covariates

SPSS (Version 16.0) was used for all analyses. For ANOVAs, the General Linear Model was used and Greenhouse–Geisser correction was applied for violations of sphericity. In all analyses, $P < 0.05$ was considered statistically significant. To control for the effects of possible covariates, we conducted correlations between dependent variables (ERPs) with depression (drug use variables that differed between CUD subgroups were similarly treated). For history of cigarette smoking, differences in the dependent variables were inspected with *t*-tests. If significantly associated with the dependent variables across all study subjects ($P < 0.05$), these variables were entered as covariates in the relevant ANOVA (Stevens, 1992).

Results

EPN

The EPN varied as a function of Picture Type ($F_{3,243} = 14.80$, $P < 0.001$), but not group ($F_{2,81} = 0.41$, $P > 0.65$); the interaction between Picture Type and Group was also not significant ($F_{6,243} = 0.86$, $P > 0.50$). The main effect was driven by more negative EPNs for pleasant, unpleasant and cocaine pictures than neutral pictures (all significant $t > |3.60|$, $P < 0.001$); the emotional pictures did not differ from each other (all $t < |1.76|$, $P > 0.05$).
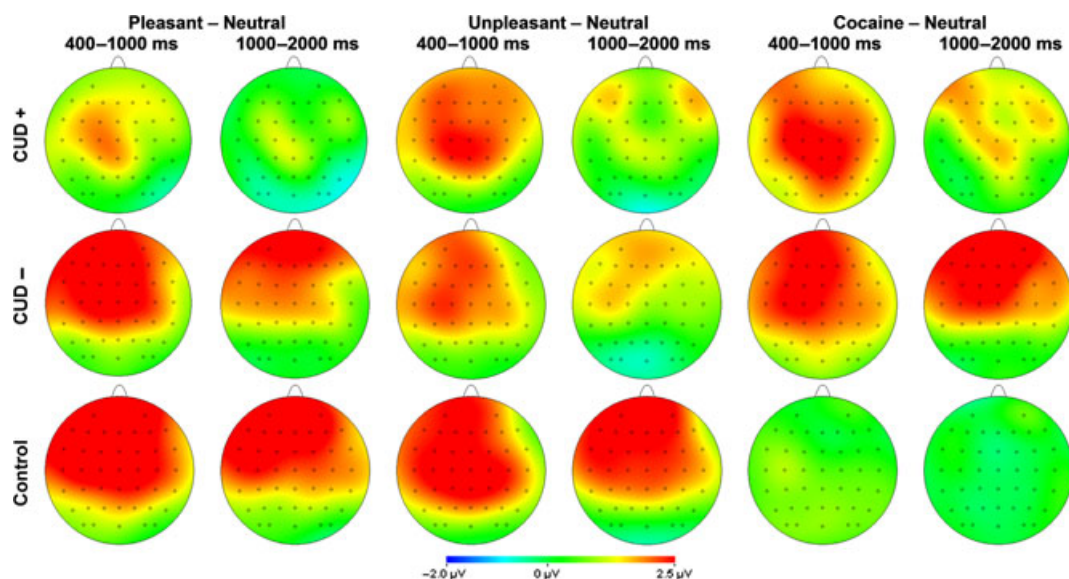
FIG. 1. Scalp topography of pleasant minus neutral (left columns), unpleasant minus neutral (middle columns) and cocaine minus neutral (right columns) differences in both the early (400–1000 ms) and late (1000–2000 ms) windows during passive viewing in CUD+ (top row), CUD− (middle row) and controls (bottom row).

TABLE 2. ERP (EPN and LPP) amplitudes (μV) to each picture type in CUD+, CUD− and controls

	EPN (200–300 ms)			LPP (400–1000 ms)			LPP (1000–2000 ms)		
	CUD+	CUD−	Controls	CUD+	CUD−	Controls	CUD+	CUD−	Controls
Pleasant	3.50 (2.16)	4.16 (3.15)	3.68 (3.01)	−1.70 (2.31)	−0.81 (3.04)	−0.85 (3.30)	−2.17 (1.97)	−1.30 (2.34)	−0.96 (2.57)
Unpleasant	3.07 (2.27)	4.05 (2.76)	3.53 (3.15)	−1.34 (3.24)	−1.86 (2.83)	−1.38 (3.91)	−2.06 (2.64)	−2.02 (2.27)	−0.95 (3.52
Neutral	4.17 (2.19)	4.54 (2.76)	4.47 (3.60)	−3.23 (2.92)	−3.63 (3.27)	−3.78 (3.32)	−2.64 (2.79)	−3.30 (2.97)	−3.40 (3.08)
Cocaine	3.11 (2.47)	3.72 (2.73)	3.72 (3.20)	−1.10 (4.18)	−1.16 (3.87)	−3.43 (3.63)	−1.55 (3.04)	−0.63 (3.14)	−3.64 (3.51)

Values are shown as mean (SD).

TABLE 3. Correlations between cocaine-related LPPs and drug use variables

	CUD+ ($n = 28$)		CUD− ($n = 27$)		CUD combined ($n = 55$)	
	Early LPP	Late LPP	Early LPP	Late LPP	Early LPP	Late LPP
Age at onset of cocaine use (years)	−0.21	−0.06	0.14	0.03	−0.04	−0.10
Duration of use (years)	0.32	−0.08	0.18	0.29	0.28*	0.17
Frequency of use (days/week) last 30 days	0.23	0.10	−0.10	−0.15	0.09	−0.02
Current use in dollars per use, last 30 days	0.16	0.68**	0.09	−0.05	0.11	0.30
Duration of current abstinence (days)	−0.17	−0.09	0.02	0.15	−0.05	0.14
Length of longest abstinence (days)	0.13	0.15	0.19	0.30	0.18	0.24
Total score on the cocaine selective severity assessment scale	−0.23	0.03	−0.45*	−0.42*	−0.32*	−0.22
Severity of dependence scale	−0.24	−0.12	0.27	0.15	0.04	0.09
Cocaine craving questionnaire	0.14	0.23	−0.25	−0.19	−0.05	−0.05

Asterisks indicate significance at: *$P < 0.05$, **$P < 0.01$. All values are Spearman correlation coefficients, reflecting the relationships between cocaine-related early and late LPP amplitudes and the respective cocaine use variables.

Hence, affective (including cocaine) compared with neutral pictures elicited increased EPNs across *all* study groups.

Early LPP (400–1000 ms)

The LPP varied as a function of Picture Type ($F_{3,243} = 26.57$, $P < 0.001$) and was qualified by a significant interaction between Picture Type and Group ($F_{6,243} = 4.84$, $P < 0.001$). Groups did not differ overall ($F_{2,81} = 0.28$, $P > 0.70$). The interaction was driven by significantly larger cocaine-related compared with neutral LPPs in both CUD subgroups (CUD+: $t_{27} = −3.25$, $P < 0.005$; CUD−: $t_{26} = −5.05$, $P < 0.001$) but not control subjects ($t_{28} = −0.79$, $P > 0.40$) (Figs 1 and 2). Also, only in the CUD, cocaine LPPs did not differ from either pleasant (CUD+: $t_{27} = −0.86$, $P > 0.35$; CUD−: $t_{26} = 0.58$, $P > 0.55$) or unpleasant (CUD+: $t_{27} = −0.38$, $P > 0.70$; CUD−: $t_{26} = −1.27$, $P > 0.20$) LPPs, while in controls cocaine LPPs

were significantly smaller than both pleasant ($t_{28} = 6.23$, $P < 0.001$) and unpleasant ($t_{28} = 4.62$, $P < 0.001$) LPPs. Furthermore, pleasant and unpleasant pictures elicited larger LPPs than neutral pictures ($t_{28} = 6.17$, $P < 0.001$ and $t_{28} = 5.80$, $P < 0.001$, respectively), but did not differ from each other ($t_{28} = 1.22$, $P > 0.20$) in the healthy subjects (Fig. 1, bottom; Fig. 2, bottom). The same pattern was observed in the CUD+ (pleasant and unpleasant > neutral: $t_{27} = 3.86$,

$P < 0.001$ and $t_{27} = 4.12$, $P < 0.001$, respectively; pleasant=unpleasant: $t_{27} = -0.69$, $P > 0.45$). In CUD−, pleasant and unpleasant LPPs were similarly larger than neutral LPPs ($t_{26} = 6.15$, $P < 0.001$ and $t_{26} = 3.99$, $P < 0.001$, respectively), also showing enhanced pleasant compared with unpleasant LPPs ($t_{26} = 2.26$, $P < 0.05$) (Fig. 1, middle; Fig. 2, middle).

In examining LPP difference scores, between-group analyses for each picture category revealed that both CUD groups had larger cocaine LPPs than controls (all significant $t > |2.24|$, $P < 0.05$), CUD− and controls had larger pleasant LPPs than CUD+ (all significant $t > |2.25|$, $P < 0.05$), and there were no group differences for the unpleasant LPPs (all $t < |1.04|$, $P > 0.30$).

Thus, for all CUD, the magnitude of LPPs elicited by cocaine, pleasant and unpleasant pictures was larger than the LPP elicited by neutral pictures; furthermore, the cocaine and other emotional picture LPPs did not differ from each other. In controls, by contrast, LPPs elicited by cocaine and neutral pictures were comparable in magnitude but both were significantly smaller than LPPs elicited by the pleasant and unpleasant pictures. Direct group comparisons showed that compared with controls, both CUD groups exhibited increased response to cocaine pictures. Interestingly, the CUD+ group also displayed reduced processing of pleasant pictures in the early LPP window.

Late LPP (1000–2000 ms)

In the late window, the LPP again varied as a function of Picture Type ($F_{3,243} = 10.40$, $P < 0.001$) and was qualified by a significant interaction between Picture Type and Group ($F_{6,243} = 32.49$, $P < 0.001$); a main effect of group was not significant ($F_{2,81} = 0.26$, $P > 0.75$). The interaction was driven by a similar pattern of results as for the early LPP in controls (all significant $t > |4.15|$, $P < 0.001$; Fig. 1, bottom; Fig. 2, bottom) and largely in the CUD− (all significant $t > |2.55|$, $P < 0.05$; the only change included a significant difference between cocaine-related and unpleasant LPPs, $t_{26} = -2.52$, $P < 0.05$; Fig. 1, middle; Fig. 2, middle) but not in CUD+ where no statistically significant differences emerged between any of the LPPs (all $t < |1.83|$, $P > 0.05$; Fig. 1, top; Fig. 2, top).

In comparing difference scores across groups, results were similar to the earlier window, except that in this later window, enhanced processing of the cocaine pictures was only discernible in the CUD− group (CUD− > Controls, $t_{54} = 3.16$, $P < 0.005$; CUD+ = Controls, $t_{55} = 1.42$, $P > 0.15$; CUD− = CUD+, $t_{53} = -1.91$, $P > 0.05$). Furthermore, CUD+ displayed decreased processing of both pleasant (CUD+ < Controls, $t_{55} = -2.7$, $P < 0.01$) and unpleasant (CUD+ < Controls, $t_{55} = -2.60$, $P < 0.05$) pictures.

Thus, in the late LPP window, CUD− maintained enhanced processing of cocaine pictures; both CUD− and controls continued to show an increased LPP in response to both pleasant and unpleasant compared with neutral pictures. Of note, the CUD+ group demonstrated an attenuated late LPP to pleasant, unpleasant and cocaine stimuli (the former two in between-subject analyses and as compared with controls, the latter in within-subject analyses and as compared with neutral pictures).

Correlations

The more money spent per each cocaine use in the last 30 days, the larger (more positive) the cocaine-related LPPs in the late window (r_s=0.676, $P < 0.001$) for CUD+ (Supporting Information Fig. S1). However, this was the only correlation reaching family-wise correction level (see Table 3 for all correlations between LPPs and drug use
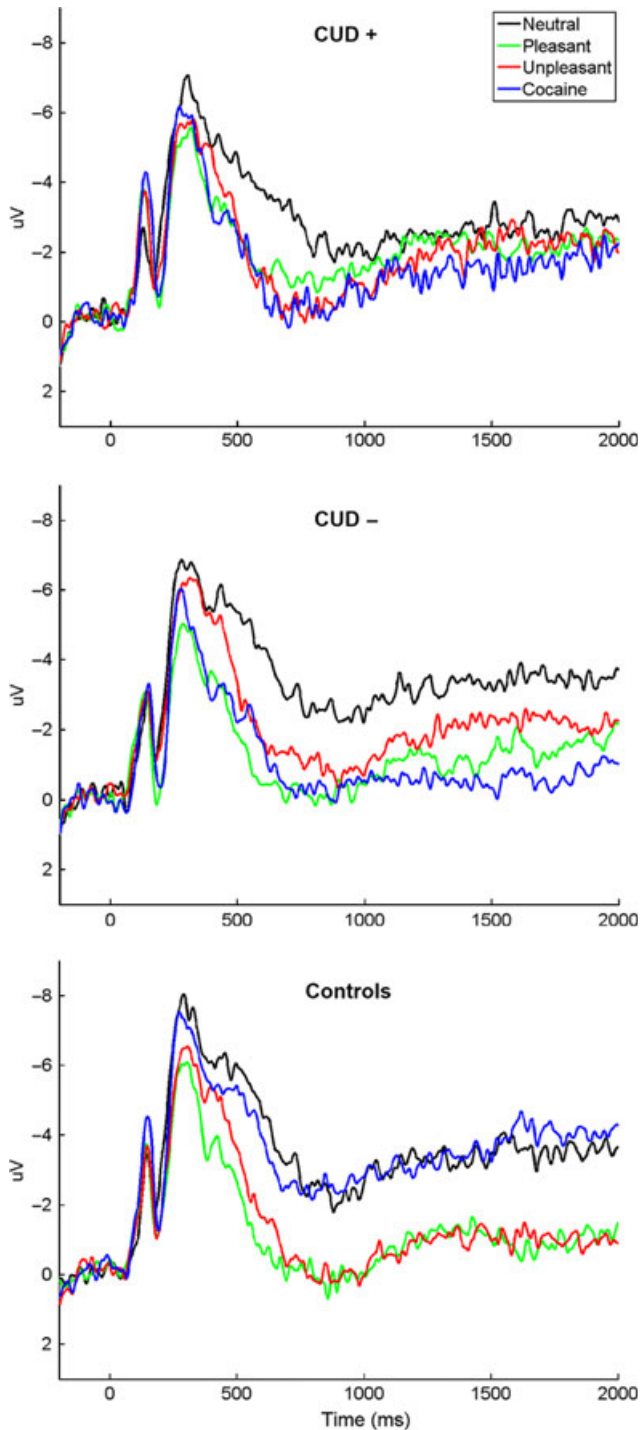

FIG. 2. Grand averaged late positive potentials (the average of sites Cz, FCz, FC1, FC2 and Fz) elicited by neutral, pleasant, unpleasant and cocaine-related pictures for CUD+ (top), CUD− (middle) and control subjects (bottom). Stimulus onset occurred at 0 ms.

variables); hence, because this correlation could be spurious, we reserve its interpretation until replicated in an independent study.

Control for depression and cigarette smoking as possible covariates

There were no significant correlations between the LPPs and depression scores (all $r_s < |0.26|$, $P > 0.15$) in either time window. Hence, it is unlikely that between-group differences in depression could have accounted for the differential LPP patterns reported in the current study. With regard to smoking history, non-smokers elicited larger pleasant, neutral and cocaine LPPs than smokers (all significant $t > |2.16|$, $P < 0.05$). In the 400–1000-ms window, smoking history interacted with study group and could not be entered as a covariate; therefore, we examined LPPs as a function of smoking history (as an independent variable) across all study subjects. Results revealed no main effect of smoking history ($F_{1,82} < 1$) nor an interaction between Picture Type and smoking history ($F_{3,246} < 1$). In the 1000–2000-ms window, we were able to enter smoking history as a covariate in the ANOVA for LPPs; both our main effect of Picture Type ($F_{3,240} = 5.80$, $P < 0.001$) and interaction between Picture Type and Group ($F_{6,240} = 5.75$, $P < 0.001$) remained highly significant.

Discussion

In the present study, we examined the EPN and early and late windows of the LPP, neurophysiological measures of increased attention to motivationally relevant stimuli, to study processing of drug-related vs. other emotional stimuli in drug-addicted individuals. This study includes several important novel elements: (i) it is the first to comprehensively include cocaine and emotional pictures in both cocaine addicted individuals and a matched control group; (ii) processing of cocaine and emotional cues are examined as a function of recent cocaine use, and hence the unique inclusion of both CUD+ and CUD− groups; and (iii) we have examined the EPN (which has not been investigated in previous cocaine-related studies) in addition to multiple windows of the LPP in an effort to elaborate on the time-course of emotional and drug cue processing among all experimental groups.

Given their excellent temporal resolution, ERPs are ideally suited to investigate the time-course of emotional processing and drug cue reactivity. Importantly, neural generators of the LPP invoke cortical regions that play an integral part in the cycle of drug addiction, which is characterized by Impairments in Response Inhibition and Salience Attribution (I-RISA), such that drug and drug-related reinforcers overwhelm all other non-drug related reinforcers and with a concomitant decrease in the ability to control behavior (Goldstein & Volkow, 2002). For example, stimulation of the dorsolateral prefrontal cortex, which is hyperactive in a drug-related context but hypoactive when performing neutral cognitive tasks in drug-addicted individuals, modulates the LPP (Hajcak *et al.*, 2010).

The current EPN results suggest that very early attentional allocation to emotional stimuli, including cocaine images, was similar across all groups. In addition, and in line with previous reports, all subjects displayed increased motivated attention to pleasant and unpleasant compared with neutral pictures in the early LPP time window (Cuthbert *et al.*, 2000; Schupp *et al.*, 2000, 2003b, 2004a; Hajcak *et al.*, 2007; Hajcak & Olvet, 2008; Foti *et al.*, 2009). However, for both CUD groups compared with controls in the early LPP window, cocaine pictures elicited electrocortical activity on a par with highly appetitive and aversive images and greater than neutral picture activity. These results support our first a priori hypothesis and

extend results by others (Franken *et al.*, 2004, 2008; van de Laar *et al.*, 2004), and suggest that cocaine stimuli are similar to other emotional stimuli in increasing motivated attention in CUD – this effect is first evident in the time window of the early LPP. In line with previous research in healthy controls (Schupp *et al.*, 2003a, 2004b), this suggests that early processing of emotional stimuli also remains intact in CUD.

Even during the early LPP response to emotional stimuli, however, CUD subgroups began to differ from one another – compared with CUD− (and controls), CUD+ showed attenuated responses to pleasant pictures. Abnormalities in the LPP were even more pronounced among CUD+ in the later window, which typically reflects sustained attentional engagement and elaborative processing and encoding of motivationally significant stimuli. Here, CUD+ did not differentiate any emotional pictures (including cocaine) from neutral pictures, and compared with controls, the CUD+ displayed significant impairments when processing both the pleasant and the unpleasant pictures. These results are broadly consistent with previous work in addicted populations. Specifically, Lubman *et al.* (2009) demonstrated lack of the typical startle-elicited P300 attenuation during pleasant vs. neutral (or drug) pictures in opiate-dependent individuals compared with controls. Also, the bilateral dorsolateral prefrontal cortex was activated to pleasant pictures in 18 healthy controls but not in 16 in-patient (abstinent for 1–24 weeks) male heroin-addicted individuals (Zijlstra *et al.*, 2009). This emotional processing impairment, which was most evident during the late LPP window in the CUD+, cannot be attributed to a cognitive deficit, which we showed to be less pronounced in the CUD+ than CUD− subgroups (Woicik *et al.*, 2009). Results instead suggest a difficulty in sustaining motivated attention to emotional stimuli that may predispose CUD to compulsive drug use as a compensatory mechanism. Indeed, habituated, or blunted, response to emotional stimuli has also been reported in other psychopathologies impacting affective processing, such as major depressive disorder (Rottenberg *et al.*, 2009; Foti *et al.*, 2010). Future replications could determine whether this impairment reliably generalizes to other motivational stimuli (e.g. monetary reward).

In contrast to CUD+, a processing bias to cocaine images remained significant for CUD−: the LPP was larger for cocaine than neutral (and unpleasant) images even during the late window. Thus, results did not support our second hypothesis that LPPs to cocaine stimuli would be most pronounced in CUD+. Nevertheless, we caution against drawing firm conclusions about the strength of the electrophysiological signature of attention bias to drug-related cues in CUD+ vs. CUD− because differences between these subgroups, for the cocaine related LPPs, were not significant in a direct group comparison. In general, these unexpected results remain to be studied in larger and more heterogeneous samples of CUD, including subjects with longer abstinence/remission periods. For example, consistent with results where glucose metabolism was higher in the orbitofrontal cortex in cocaine users within 1 week of last use than in healthy controls, while during more protracted withdrawal (1–6 weeks since last use) brain metabolism was lower in the cocaine users than controls (summarized in Goldstein & Volkow, 2002), we would predict eventual attenuation of LPPs to the cocaine-related stimuli in the CUD−.

Limitations of the study include the following: (i) Our choice of dividing the CUD into two subgroups based on cocaine in urine could be questioned. We therefore report in the Supporting Information results where the CUD are treated as a single group, further exploring correlations with time since last cocaine use; results were largely unchanged from those reported here. (ii) Results pertain mainly to males and remain to be further substantiated in women. Results in males only (excluding females) are reported in the Supporting

Information, again revealing no major change to the current conclusions. For the purposes of generalizability, we included females in the current report. (iii) Depression and history of cigarette smoking differed between the groups. However, depression did not correlate with LPPs, and all original effects remained significant after controlling for cigarette smoking. (iv) Correlations between the LPPs with drug use were mostly not significant, which we attribute to the high nominal statistical threshold we used to protect against Type I error. In this vein, of note is a recent meta-analysis that demonstrated a modest overall correlation ($r = 0.19$) between various measures of attentional bias and drug craving across several addiction types. Inspection of similar raw correlations was consistent with the meta-analysis results ($r = |0.14–0.25|$, Table 3). (v) The motivational relevance of the LPP among CUD needs further examination in future studies. For example, preliminary results suggest that LPPs predict actual choice behavior (as measured with a newly designed drug choice task; Moeller *et al.*, 2009, 2010) and longer-term abstinence in CUD (results to be reported separately).

In conclusion, we found that cocaine pictures capture motivated attention in ways similar to affectively pleasant and unpleasant pictures in abstinent and current users of cocaine but not in matched healthy controls. Furthermore, deficient electrophysiological response to pleasant and unpleasant images was most evident during later processing and in current users of cocaine. This deficit may be indicative of impairments in sustaining non-drug-related goal-oriented motivation, predisposing addicted individuals to drug use as a mechanism compensating for the reduced response to other reinforcement (including reward).

Supporting Information

Additional supporting information can be found in the online version of this article:

Fig. S1. Scatterplot of the correlation between cocaine-related LPPs (late window) and money spent per each cocaine use in the past 30 days (US dollars) in CUD+ ($n = 22$) and CUD− ($n = 13$) groups. Spearman correlation coefficients are presented.

Table S1. Averaged self-reported ratings of all picture types.

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Abbreviations

CUD, cocaine use disorder; CUD+, individuals with cocaine use disorders that tested positive for recent cocaine use; CUD−, individuals with cocaine use disorders that tested negative for recent cocaine use; EEG, electroencephalograph; EPN, early posterior negativity; ERP, event-related potential; IAPS, international affective picture system; LPP, late positive potential; SAM, self-assessment Manikin.

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