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ORIGINAL ARTICLE

Implicit processing of heroin and emotional cues in abstinent heroin users: early and late event-related potential effects

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Abstract

Background: The abnormal cognitive processing of drug cues is a core characteristic of drug dependence. Previous research has suggested that the late positive potential (LPP) of heroin users is increased by heroin-related stimuli because of the attention-grabbing nature of such stimuli. *Objectives*: The present research used a modified emotional Stroop (eStroop) task to examine whether there was an early posterior negativity (EPN) modulation to heroin cues compared with emotional or neutral stimuli in heroin dependent subjects. *Methods*: Fifteen former heroin users and 15 matched controls performed the eStroop task, which was composed of positive, negative, heroin-related, and neutral pictures with superimposed color squares. Participants responded to the color of the square and not to the picture while behavioral data and event-related potentials were recorded. *Results*: There were no significant differences of EPN amplitudes to emotional and neutral stimuli between heroin users and controls. However, heroin users displayed increased EPN modulation for heroin cues, whereas this modulation was absent in controls. *Conclusions*: Drug-related cues acquire motivational salience and automatically capture the attention of heroin users at early processing stages, even when engaged in a non-drug-related task. The EPN to heroin cues could represent a novel electrophysiological index with clinical implications for selecting abstinent drug users who are at increased risk of relapse or to evaluate treatment interventions.

Keywords

Attentional bias, early posterior negativity (EPN), event-related potentials (ERP), heroin dependence, late positive potential (LPP)

History

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Introduction

Drug abuse is a chronic disorder characterized by the compulsive urge to use the drug resulting in physical, psychological, and social harm to the user and by the continued use despite long-term negative consequences. Moreover, even after treatment and regardless of motivation to quit, relapse is common (1). Recurring drug dependence is commonly associated with increased cue reactivity and coupled with heightened attention for drug-related stimuli; this abnormal cue reactivity is an important mechanism in the development of addictive behaviors and promotes relapse in drug users (2–4). Drug cue reactivity consists of a physiological component (e.g. skin conductance), a psychological component (e.g. self-reported drug craving), and a cognitive component (5). Attentional bias, an important cognitive component in cue reactivity (3,6,7), is a consistent feature of addiction, which is defined as the drug user's tendency to direct attention unconsciously to stimuli previously associated with drug use (8).

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Over the past 21 years, studies have provided evidence for the attentional bias toward drug-related cues in drug dependence, and how drug-related stimuli acquire the ability to grab the user's attention (7,8). Attentional bias is generally considered to be the consequence of enhanced sensitivity to drug-related rewards and further increases the risk for developing cue-reactivity, which in turn elicits a subjective experience of drug craving that can ultimately lead to relapse (8). According to the theory of incentive-sensitization in addiction (9,10), the biological basis of this processing bias is associated with changes in brain function caused by repeated administration of the drug. Subsequently, this change will make the drug users become increasingly sensitive to drugs and drug-related stimuli and ultimately lead to pathological sensitivity to these stimuli. The abnormal process alters the way these stimuli are perceived; drug-related stimuli will be regarded as particularly salient and reinforcing, and attention will be preferentially allocated to these stimuli. This hypothesis has been verified in a study of heroin users (11). In recent years, studies focusing on neurobiological substrates found that attentional bias to drug cues may be associated with increased activity in the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), and other cortical areas such as the insula as well as subcortical structures such

as the nucleus accumbens and amygdala (2,12,13). The ACC and DLPFC play a key role in attention and flexibility (e.g. set formation and maintenance versus set-shifting and task switching), and activation of the ACC and DLPFC in drug users during a cue-reactivity paradigm indicates that these regions may be involved in the processing of attentional bias to drug-related stimuli (2,12).

Nevertheless, there remain controversial issues regarding the mechanisms of how the attentional bias influences drug-seeking behavior (14,15). More specifically, what kind of attention processing (explicit or implicit) and which stage of cognitive processing are involved in attentional bias? Event-related potentials (ERP) provide a direct measurement of the time course of neural activity and are therefore highly suitable for exploring attentional processing of drug-related stimuli in addiction (16). Numerous studies have shown the important relationship between two late positive ERP components (the P300 and the late positive potential [LPP]) and attentional bias in drug cue-reactivity paradigms (5). The P300 component refers to a large positive deflection of the ERP arising about 300 ms after stimulus onset, which is typically maximal at medial central and parietal electrode sites. The LPP is an ERP component that reaches a maximum over central-parietal regions occurring between 400 and 700 ms after stimulus onset. Traditionally, the P300 and LPP have both been strongly associated with the allocation of attentional resources to motivationally relevant stimuli (17). However, it is more accurate to say that the P300 is usually elicited by top-down, explicit attention to neutral stimuli, while the LPP is more likely to be elicited by bottom-up, motivated attention to emotional stimuli (18). In addiction studies, these enhancements of late positive ERP responses (P300 and LPP) to drug-related stimuli are typically interpreted as drug users' motivated attention toward drug-related cues (5). More recently, researchers have identified an earlier ERP component over the posterior scalp (early posterior negativity [EPN]) starting 180–300 ms after stimulus onset. This ERP component appears as a negative deflection over the posterior scalp and a corresponding polarity reversal over the anterior scalp (early anterior positivity, EAP). It is known that the EPN is critically involved in the differential processing of emotional cues and represents earlier stages of selective attentional processing (19). Unfortunately, only a few studies have investigated this short-latency ERP in response to drug cues. Two studies about cocaine users and tobacco smokers reported no EPN amplitude differences in response to drug cues between substance users and controls (16,20), while Versace et al. (2011) reported an enhanced EPN to cigarette-related and positive pictures compared to negative pictures during passive viewing in abstinent tobacco smokers (21). In addition, a significant EAP effect was reported in chronic cannabis users during an emotional Stroop (eStroop) task (22). These early components may be particularly useful for delineating specific attentional processing stages for drug-related stimuli that are abnormal in drug users (23).

With regard to heroin abuse, only two ERP studies have explored drug cue reactivity during passive viewing paradigms. In the first study, abstinent heroin users showed larger LPP to heroin-related pictures than to neutral pictures (24). In the second study, heroin users and non-user controls passively watched heroin-related, negative, positive, and neutral pictures. The P300 elicited by heroin-related pictures was significantly greater than that elicited by affective and neutral stimuli in heroin users but not in controls (23). However, these two heroin cue-reactivity studies used passive viewing paradigms in which attention was not manipulated; therefore, it is unclear whether the effect was caused by an implicit, involuntary attention capture or by an explicit, voluntary choice to focus attention on the drug-related stimuli (5). Lubman et al. (2007) used a visual oddball task consisting of heroin-related and neutral pictures to explore drug cue reactivity in heroin users (25). Their study showed that heroin pictures increased P300 amplitude in heroin users compared to controls; drug cues captured heroin users' attention even when they were distracted. This result confirms that drug-related cues still capture the attention of former heroin users in an implicit and involuntary way. However, it is important to note that these studies did not determine whether drug-related cues automatically captured the attention of heroin users during early processing stages (100–300 ms).

To address the limitations of these studies in heroin users and to further verify recent findings about electrocortical processing of drug cues during early processing stages, the present study used ERP in combination with the eStroop task to examine the early attentional bias to drug-related pictures in abstinent heroin users and a control group of non-users. In addition, we compared processing of drug-related cues with other emotional stimuli in the two groups. As previous studies have indicated, heroin users also show abnormal processing of emotional stimuli (23,26). According to previous research results and considering the purpose of this study, we primarily investigated two ERP components (EPN and LPP). We hypothesized that heroin users would show an attentional enhancement to drug-related cues. More specifically, compared to controls, heroin users would demonstrate longer behavioral reaction times (RT) and larger electrophysiological (LPP and EPN) responses to heroin-related versus neutral stimuli due to their abnormal cue reactivity.

Methods

Participants

The Northwest Normal University Research Ethics Board approved this study. Participants without heroin use history were recruited at the Faculty of Psychology of the Northwest Normal University through interviews and online advertisements. Former drug users were recruited from the Addiction Recovery Center of Gansu province in Lanzhou city. All participants provided a written acknowledgment of informed consent in advance. A total of 30 participants agreed to take part in the experiment (15 heroin users and 15 matched controls, 30–46 years old, all males, see Table 1). All participants reported normal color vision and normal or corrected-to-normal visual acuity. Exclusion criteria included current or past cognitive impairments, learning disabilities, medication for any neurological or psychiatric disorder, current use of psychotropic medication, or use of other recreational drugs. All abstinent heroin users in the present study met the criteria for heroin dependence according to the

Table 1. Demographic characteristics of heroin users and controls.

	Heroin users ($n = 15$)	Controls ($n = 15$)
Male/female	15/0	15/0
Education (years)	10.20 (1.90)	10.40 (3.68)
Age (years)	38.40 (8.81)	38.14 (7.06)
Beck Depression Inventory	19.07 (12.71)	17.33 (9.97)
Beck Anxiety Inventory	9.60 (9.42)	6.80 (4.63)
Nicotine dependence (%)	100.00	66.67
Age at onset of heroin use (years)	31.67 (8.20)	–
Average of heroin use (years)	9.4 (5.98)	–
Duration of current abstinence (years)	0.75 (0.33)	
Drug craving level	4.47 (3.94)	–
Heroin use per day before abstinent (gram)	1.29 (0.73)	–

Diagnostic and Statistical Manual of Mental Disorders (4th ed, DSM-IV, American Psychiatric Association, 1994), and abstinence was confirmed by the Addiction Recovery Center of Gansu province. Specific exclusion criteria for abstinent abusers included no recent heroin use (i.e. no use in the past two weeks) and no dependence on any other non-prescribed medication. For the sample of abstinent heroin users, the average duration of current abstinence was 0.75 (SD 0.33) years and the average age at the time of first heroin use was 31.67 (SD 8.20) years. They had been using heroin for an average of 9.4 (SD 5.98) years. Two abstinent users were enrolled in a methadone maintenance treatment program with a prescribed median equivalent methadone dose of 20–50 mg, and four were prescribed compound aminopyrine phenacetin tablets and crispin melanate. For all users, heroin was the primary drug of abuse but some had occasionally consumed other drugs and most had consumed methamphetamine and ketamine in addition to heroin.

After a brief description of the experiment, the participants were seated facing a computer monitor in a sound-attenuated room, and brain electrical activity was recorded while they performed the modified eStroop task. After completion of the task, the participants filled out two questionnaires, the Beck Depression Inventory (BDI-II) (27) and the Beck Anxiety Inventory (BAI) (28). There were additional questions for the heroin users, such as the age at onset of heroin use, amount of heroin use per day before becoming abstinent, and duration of abstinence. Moreover, a visual analog scale for craving was administered in order to measure the drug craving level (29). Participants rated craving intensity on a 9-point scale by selecting an appropriate position along a line ranging from 0 (not at all) to 9 (strong craving).

Emotional stroop task

The stimuli consisted of 20 neutral (e.g. household objects, tools, neutral facial expressions), 20 negative (e.g. animal attacks, scenes of violence and accidents, facial expressions of sadness and anger), and 20 positive (e.g. landscapes, sports, human babies, family scenes) affective valence images from the International Affective Picture System (IAPS) (30). Images were chosen according to their normative ratings of valence and arousal. We created a fourth category that included 20 heroin pictures collected from freely available online sources, which consisted of individuals preparing or using heroin (e.g. injecting, snorting, or smoking). Heroin pictures were matched for arousal with the positive and negative pictures using a computerized version of the Self-Assessment Manikin (31) (see Table 2), and were matched to the IAPS pictures in size and ratio of human to non-human content. All pictures were scaled to 12×8 cm with the central colored square target superimposed (1×1 cm; red, yellow, blue, or green). To complete all eStroop runs, each participant was required to finish 320 trials interrupted by short breaks (each picture was presented four times with a differently colored central square superimposed). Each trial began with the presentation of a fixation cross in the center of the screen for 500–1000 ms followed by a blank screen lasting 200–400 ms. Then, the stimuli were presented for 500 ms with their order randomized, followed by a blank screen lasting 1000 ms. During the experiment, the participants were instructed to identify the target color of the small square as quickly and accurately as possible and ignore the surrounding pictures. The buttons were color-coded with ''red,'' ''yellow,'' ''blue,'' or ''green'' to correspond to left-hand middle-finger, left-hand index-finger, right-hand index-finger, and right-hand middle-finger button presses, respectively.

Table 2. Ratings of International Affective Picture System (IAPS) pictures and heroin pictures.

Emotion type	Valence *M* (SD)	Arousal *M* (SD)
Heroin	4.29 (0.44)	5.70 (1.25)
Positive	7.22 (0.45)	5.76 (0.89)
Negative	2.84 (0.82)	5.75 (0.7)
Neutral	5.14 (0.55)	3.18 (0.75)

EEG recording and analysis

The electrical brain activity was recorded with a 256-channel EEG system (EGI, Eugene, USA) and filtered with an on-line bandpass filter from 0.1–100 Hz. The EEG signal was digitized at a 500 Hz sampling rate with a 22-bit A/D converter. Data were continuously recorded with the vertex sensor (Cz) as reference electrode. Electrode impedance was kept below 50 KΩ (32).

Offline processing was carried out using the Net Station acquisition software and Electrical Geodesics (EGI, Eugene, USA) that involved the following steps: first, EEG data were digitally filtered using a 0.01-Hz digital high-pass and a 30-Hz digital low-pass filter. Second, stimulus-synchronized epochs lasting from 200 ms before until 1000 ms after picture onset were extracted and baseline-corrected for pre-stimulus (200 ms) ERP activity. Potential artifacts were screened using automatic detection methods provided by Net Station. The artifact rejection was based on the exclusion of all epochs that were contaminated by eye blinks and movement artifacts or epochs that had 10 or more channels exceeding a voltage threshold of 200 μV or changing more than 100 μV. Flawed channel data were replaced using spherical spline interpolation of neighboring channel values (33).

Data analysis

For behavioral data, the mean accuracy ratings and mean reaction times (150 ms < RT < 1500 ms) were calculated for each picture type in each participant. Then, mixed-design repeated-measures analyses of variance (ANOVAs) were performed with group (heroin users, controls) as the between-subjects factor, and picture type (heroin, positive, negative, neutral) as the within-subjects factor. For the ERP data, we first formed two different clusters of scalp sites: centro-parietal (C1, Cz, C2, CP1, CPz, CP2) and occipito-temporal (TP7, P7, PO7, TP8, P8, PO8). Next, the mean amplitude value of each ERP component was calculated for each participant and picture type as the average of the selected time window. The mean activity in the occipito-temporal cluster was calculated between 200 ms and 300 ms for the EPN, the activity at the centro-parietal cluster was calculated between 450 ms and 600 ms for the LPP (34). For each time window, the averaged ERP amplitude was analyzed with a 4 (picture type: heroin, positive, negative, neutral) × 2 (group: heroin users, controls) × electrode site (for EPN: C1, Cz, C2, CP1, CPz, CP2; for LPP: TP7, P7, PO7, TP8, P8, PO8) mixed-design ANOVA. The main effect of electrode site and the interaction effect between electrode site and other factors were not reported because they were not our concern in this experiment.

Results

Group characteristics

For the demographic characteristics of the participants, we examined potentially confounding factors that could affect the experimental results (Table 1). The results showed that there were no significant group differences in age or education, $t(28) = 0.093$, $p > 0.05$. But there were significant group differences in education, $t(28) = 0.187$, $p < 0.05$. For the questionnaire scores, there were no significant differences between the two groups in the BDI-II scores, $t(28) = 0.42$, $p > 0.05$, and BAI scores, $t(28) = 1.03$, $p > 0.05$. However, there was a significant group difference in nicotine dependence, $\chi^2 = 6.00$, $p < 0.05$.

Behavioral results

For accuracy, the main effect of stimulus type approached significance, $F(3, 84) = 2.656$, $p = 0.057$, $\eta_p^2 = 0.087$, while the main effect of group and the interaction between picture type and group were not significant (for both, $p > 0.10$). Contrary to our prediction, for the RT data, the main effects of group and picture type and their interaction were all non-significant (for all, $p > 0.10$). Although the RTs for the four picture types tended to be longer in heroin users than in controls, these differences did not reach statistically significant levels (Table 3).

Table 3. Emotional Stroop reaction time (ms) in heroin users and controls.

Emotion type	Heroin users *M* (SD)	Controls *M* (SD)
Heroin	617.34 (58.95)	593.62 (65.85)
Positive	614.79 (60.84)	592.60 (68.16)
Negative	620.58 (60.52)	598.34 (59.31)
Neutral	620.17 (58.83)	605.14 (71.70)

ERP analysis

EPN effects

For the EPN amplitudes (Figure 1, top panels), there was a significant main effect of picture type, $F(3, 84) = 9.579$, $p < 0.001$, $\eta_p^2 = 0.255$. Positive and negative pictures elicited a more negative EPN than neutral or heroin pictures, while there was no significant difference between the two types of emotional pictures in the post-hoc test ($p > 0.05$). The main effect of group was not significant, $F(1, 28) = 2.102$, $p = 0.158$, $\eta_p^2 = 0.07$; however, the interaction between picture type and group was significant, $F(3, 84) = 4.396$, $p < 0.01$, $\eta_p^2 = 0.136$. This interaction was driven by more negative EPN amplitudes elicited by the heroin pictures in heroin users than in controls ($p < 0.05$), while for the other pictures, there were no such differences between the two groups (for all, $p > 0.05$), as illustrated in Figure 2. Then a 4 (picture type: heroin, positive, negative, neutral) × 6 (electrode site: C1, Cz, C2, CP1, CPz, CP2) repeated measures ANOVA with pairwise comparison by Bonferroni post hoc test was carried out respectively to examine whether the magnitude of these differences varied between groups. The results of this ANOVA showed that for heroin users, the heroin pictures and the two types of emotional pictures (negative and positive) elicited more negative EPN than the neutral pictures did (for all, $p < 0.05$). There were no significant differences between the heroin, negative, and positive pictures (for all, $p > 0.05$). In contrast, for the control group, only the positive pictures elicited more negative EPN than did the neutral pictures ($p < 0.01$); furthermore, positive and negative pictures elicited more negative EPN than heroin pictures ($p < 0.01$ and $p < 0.05$, respectively), but did not differ from each other ($p = 1.00$). There were no significant differences between heroin and neutral pictures either ($p > 0.05$). The scalp topographies of the grand-mean ERPs for the EPN component are shown in Figure 3.

LPP effects

The LPP amplitudes (Figure 1, bottom panels) were significantly affected by picture type, $F(3, 84) = 10.304$, $p < 0.001$, $\eta_p^2 = 0.269$, but not by group, $F(1, 28) = 0.595$, $p = 0.447$, $\eta_p^2 = 0.021$; the interaction between picture type and group was not significant either, $F(3, 84) = 1.901$, $p = 0.138$, $\eta_p^2 = 0.064$. The picture type's main effect was driven by the larger LPP for positive and negative pictures than for heroin and neutral pictures; the two emotional picture types did not differ from each other ($p > 0.05$). The scalp topographies of the grand-mean ERPs for the LPP component are shown in Figure 4.

Discussion

In the present study, behavioral and ERP measures were used to investigate the time-course of emotional processing and drug cue reactivity in abstinent heroin users and control group

during an eStroop task. With the high temporal resolution provided by ERP, the results demonstrate that drug-related cues capture attentional resources of heroin users at early stages of selective attention processing.

Behavioral effects

Contrary to our hypothesis, we did not observe any significant main or interaction effects in the behavioral results of the eStroop task. We propose that the absence of a significant group difference in the behavioral eStroop data may be attributable to our selection of experimental stimuli, as our pictures did not include high-arousal images (e.g. erotica or mutilation), which have been found to produce the greatest emotional response (35). Second, the small sample size in the present study reduces the external validity of our conclusions. In order to investigate such group differences of cognitive processing, future research will benefit from a larger sample of participants. In addition, the absence of eStroop interference may be associated with the relatively long inter-trial interval (ITI) in our experimental design. Research investigating the eStroop task showed that in long ITI conditions (e.g. 500 or 1000 ms), the interference effect completely disappeared at the behavioral level. It has been further suggested that long ITIs increase the risk of losing the behavioral eStroop effect in ERP and fMRI studies that require longer ITIs (36).

ERP effects

The key finding of our study was that heroin users showed an early modulation of the ERP response over the occipital-temporal scalp (EPN, 200–300 ms) in response to drug stimuli, although this modulation was not greater than the activity evoked by emotional stimuli. Thus, both emotional categories (positive and negative) and the heroin pictures induced an enhanced EPN compared with the neutral pictures in the group of abstinent heroin users. However, an enhanced EPN only appeared for the positive pictures in the control group. It is also worth noting that the heroin users showed an increased EPN response for heroin cues compared with controls, but such a difference between groups was absent for the emotional pictures. These results are partly consistent with a study that reported an enhanced EPN to cigarette-related and positive pictures relative to negative pictures in abstinent tobacco smokers (21). Our findings suggest that heroin users process heroin-related pictures as fast and automatically as emotional

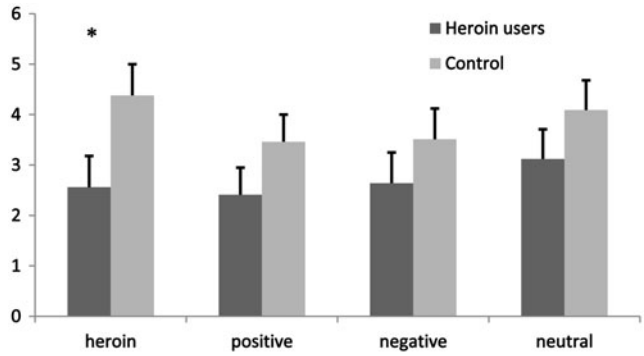

Figure 2. Mean amplitudes (± SEM) of early posterior negativity (EPN) for heroin, positive, negative, and neutral pictures during the eStroop task. *$p < 0.05$.

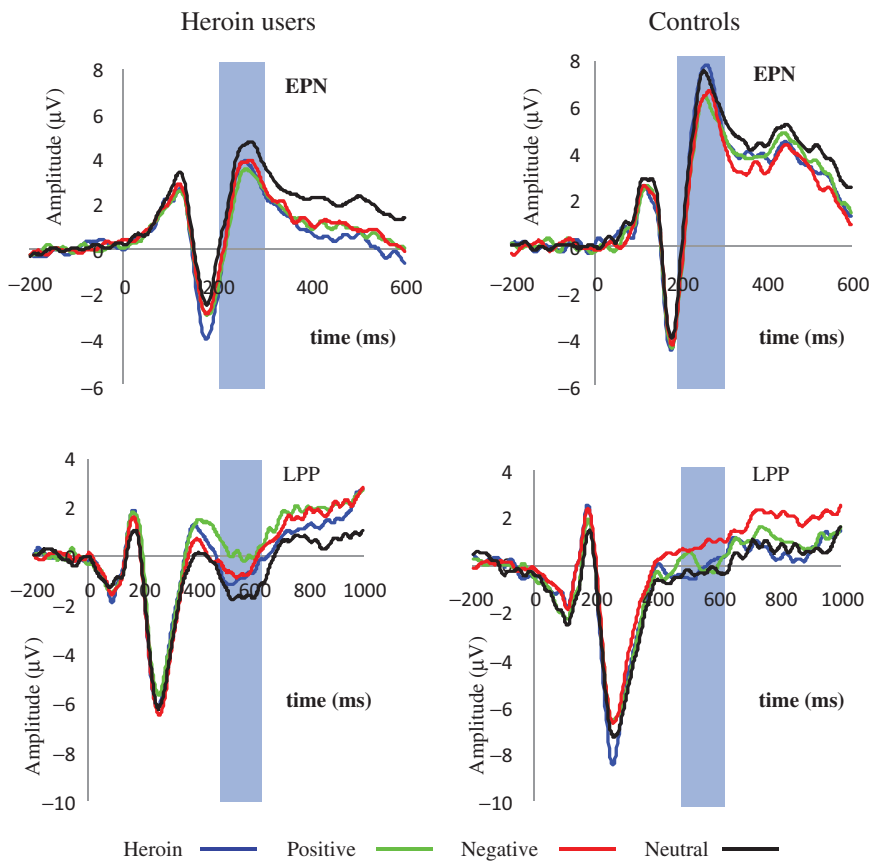

Figure 1. Mean event-related potentials (ERP) waves for heroin, positive, negative, and neutral pictures during the eStroop task across relevant electrodes for early posterior negativity (EPN) (top) and late positive potential (LPP) (bottom). (This Figure is reproduced in color in the online version of *The American Journal of Drug and Alcohol Abuse*.)

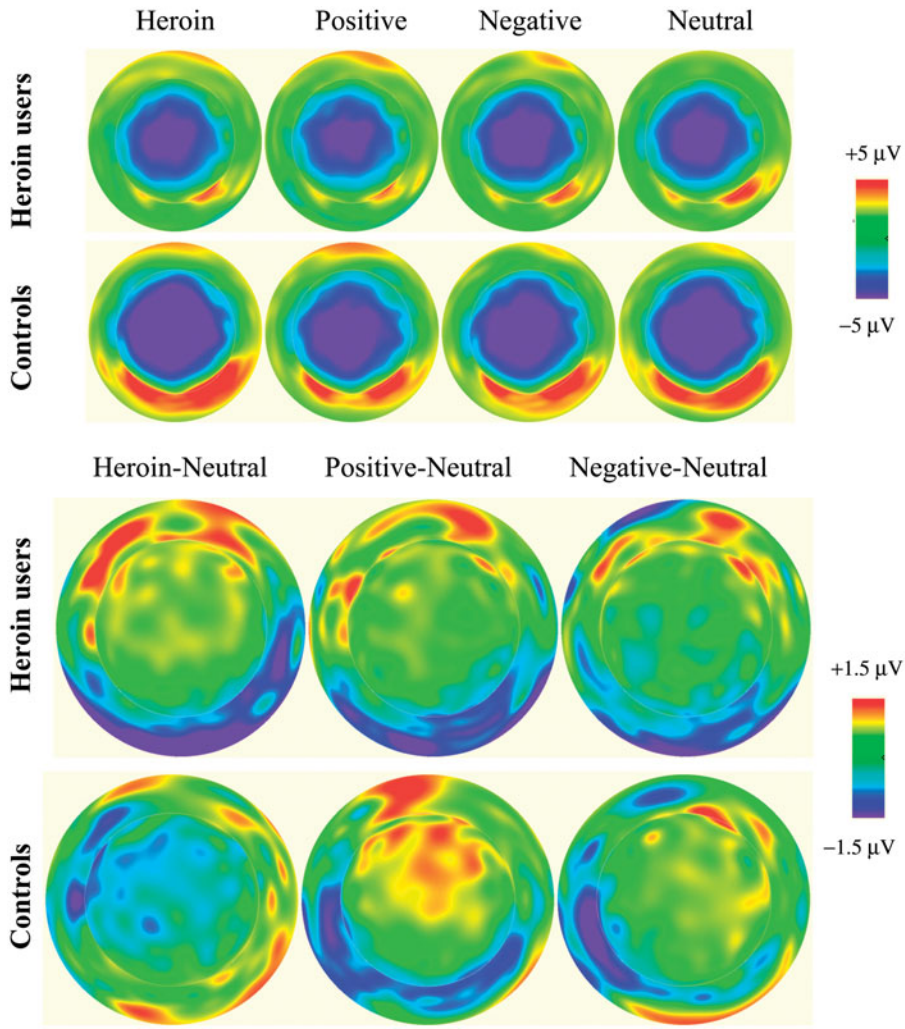

Figure 3. Top row: Grand-average topographic maps of the early posterior negativity (EPN) component (200–300 ms) during the eStroop task in heroin users and controls. Bottom row: Scalp topography of difference wave (heroin minus neutral, positive minus neutral, negative minus neutral). (This Figure is reproduced in color in the online version of *The American Journal of Drug and Alcohol Abuse*.)

pictures. Previous studies suggested that EPN modulation for emotional stimuli reflects early selective processing of emotional material (19,37,38). Therefore, the most plausible explanation for the enlarged EPN for heroin pictures in heroin users may stem from the fact that heroin users share a tendency to preferentially direct attention toward drug-related stimuli (similar for emotional stimuli) during early selective attention stages. This further confirms that cognitive processing for drug-related cues in heroin users is abnormal, and that the drug-related cues hold an intrinsic significance even in the early selective processing stages. Furthermore, we conclude that these effects arise because of an implicit, involuntary capture of attention, which occurs even when the subjects' attention is directed away from the surrounding pictures. However, it is worth noting that our results are inconsistent with studies in cocaine users and tobacco smokers, which reported no enhanced EPN to drug-related cues in drug users compared with controls (16,20). We speculate that this discrepancy results from differences in state of abstinence, severity of addiction, experimental task, sample size, and other factors, which emphasizes the need for further studies.

Our current findings demonstrate that abstinent heroin users remain sensitive to drug cues even during early, implicit processing stages. This development of incentive motivational properties to drug-related stimuli is mainly associated with the neurophysiological and pathological changes caused by repeated heroin self-administration that have been described in theories of incentive-sensitization (9,10). The automatically captured attention triggered by heroin-related cues in heroin users might play an important role in maintaining drug-seeking behavior and relapse, especially weakening the addict's ability to implement cognitive strategies for resisting drug craving and inhibiting the automatic behaviors related to drug addiction (21,39). In addition, an fMRI study related to emotional stimulus processing reported that when subjects passively viewed emotional and neutral pictures, cortical activity for emotional pictures increased in occipital, temporal, and parietal structures (40,41). This increased activation within the extended visual system might reflect facilitated processing of stimuli with greater motivational salience (41). These fMRI results are consistent with source analysis of the EPN component, which showed that this component was primarily localized in a widespread network of temporo-parieto-occipital areas (42). Therefore, we suggest that the increased EPN response for heroin-related cues in heroin users indicates the facilitated processing of drug cues at an early perceptual level associated with increased activations of the visual system.

However, contrary to our prediction, the LPP for heroin pictures in heroin users was neither greater for drug pictures

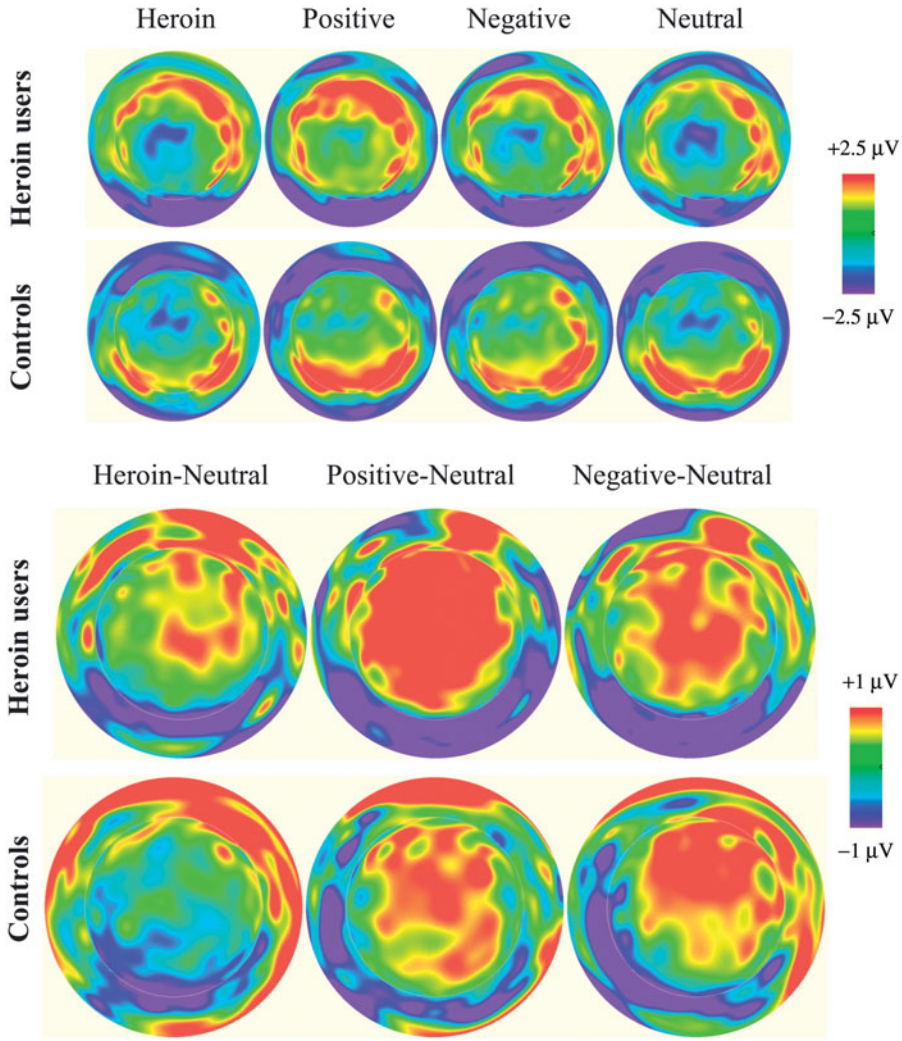

Figure 4. Top row: Grand-average topographic maps of the late positive potential (LPP) component (450–600 ms) during the eStroop task in heroin users and controls. Bottom row: Scalp topography of difference wave (heroin minus neutral, positive minus neutral, negative minus neutral). (This Figure is reproduced in color in the online version of *The American Journal of Drug and Alcohol Abuse*.)

than for emotional pictures, nor was it greater than in controls in the present study. This result is not consistent with previous findings that drug-abstinent groups showed an increase in LPP to drug pictures (16,24,43). More specifically, we only found a significant main effect of picture type, with positive and negative pictures eliciting larger LPP compared with heroin and neutral pictures in the two groups, which can be explained by the fact that the LPP often has been interpreted to reflect increased attention to motivationally relevant stimuli (37,44–47). We conclude that the reasons for this difference consist mainly of the following points: first, the different methods used to measure LPP may have an important influence on the results. ERP studies that reported enhanced LPP responses to drug-related stimuli usually used comparatively simple paradigms (i.e. viewing/rating a set of drug-related stimuli). In particular, Moser et al. (2006) reported that the LPP was reduced when participants were asked to suppress their responses to highly arousing unpleasant stimuli during a passive viewing paradigm (48). This suggests that the reinforcing LPP effect can be down-regulated intentionally; therefore, this effect may possibly disappear in an eStroop task, which requires subjects to focus their attention on the task-irrelevant stimuli (36). Moreover, we cannot completely exclude the possibility that the heroin users suppressed their emotional response to heroin pictures deliberately. In addition, the inconsistencies between our study and others are probably the result of the small sample size. Due to the small number of participants, there is insufficient statistical power, which weakens the ability to detect a difference. In addition, differences in type of used drug and clinical status of the subjects may have had a complex and subtle impact on the experimental results. Notably, our results are consistent with recent research that shows that chronic cannabis users' LPP amplitude is neither greater for drug pictures than for negative pictures, nor is it greater than in controls (22). Through extensive literature review, we found that other studies focusing on special groups such as obese people (49,50) or chocolate cravers (51) reported results that were similar to our study. These studies found that LPP amplitude to appetitive stimuli was not affected by obesity or trait-craving status and therefore interpreted the LPP modulation as reflecting a later, more controlled conscious stage of processing for culturally salient and study-relevant stimuli (50,51). In summary, the differences between results of these studies and their interpretation of the LPP emphasize the need for further research about the nature of the LPP modulation and the relationship between LPP and drug-related stimuli.

The present study has some limitations. The first is that the participants in the present study included only males. We

deliberately did not include female participants, considering that substance abuse rates tend to be higher in males and because of the need to limit other potentially confounding gender-sensitive factors (22). In addition, the participants in this study were all abstinent heroin users, and therefore we cannot make horizontal comparisons with current users of heroin. Valuable information might be provided by such a comparison. These limitations notwithstanding, the present study is the first to our knowledge to examine early processing of drug and emotional stimuli in heroin users. The results complement and extend existing findings of abnormal cognitive processing of drug cues in heroin dependence and reveal the early electrocortical processing of heroin and emotional cues in abstinent heroin users.

Conclusion

In conclusion, in one of the first studies examining ERP correlates of early attention bias to drug-related stimuli in abstinent heroin users, we found that heroin pictures captured motivated attention in abstinent heroin users during early processing stages but not in controls. This implies that the incentive motivational properties of drug-related cues in heroin addicts will last a long time due to the repeated heroin use, and that these abstinent heroin users may still be at risk for relapse. Further ERP studies are needed to examine whether current heroin users show a similar pattern of brain reactivity in early electrocortical processing of heroin cues that appeared in the abstinent heroin users in this study. In addition, we propose that the EPN elicited by heroin cues could be a novel electrophysiological index for predicting the attentional bias or severity of addiction in heroin dependence.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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