Cognitive and neuropsychopharmacological processes in human drug craving
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Neurophysiological Evidence for Abnormal Cognitive Processing of Drug Cues in Heroin Dependence

Recent studies provide evidence for abnormal information processing in addictive disorders. The present study employs Event Related Potentials (ERPs) to investigate heroin related visual information processing. Neutral and heroin related pictures were presented to 19 male abstinent heroin dependent patients and 14 male healthy controls. Patients exhibited larger Slow Positive Wave (SPW) components of the ERP on heroin related pictures than on neutral pictures. Within healthy control subjects there was no difference on the SPW between neutral and heroin pictures. Within heroin dependent patients, mean SPW response to heroin pictures was correlated with post-experiment craving. This study provides neurophysiological evidence that information processing of drug-related information is abnormal in heroin dependent patients. The results provide further evidence for the cognitive and neurobiological accounts of substance dependence such as the Incentive-Sensitization theory.


Introduction

Recently, it has become clear that substance dependence is associated with a cognitive processing bias. Studies indicate that individuals with heroin, cocaine, nicotine, and/or alcohol dependence process substance related stimuli in an abnormal way. One of the cognitive processes that is changed is the excessive attentional focusing on drug-related cues: attentional bias. Attentional bias is regarded as a cognitive component of craving or may even be responsible for craving. Craving is one of the hallmarks of addiction and is partly responsible for relapse in drug use after a period of abstinence. In previous studies, attentional bias has been demonstrated using paradigms that employ behavioral measures (reaction time) as index of these cognitive biases. However, event-related potentials (ERPs) of the electroencephalogram (EEG) offer a more direct measure to study information processing and cognitive biases. Compared to behavioral measures, the advantages of ERPs measures are that they include information on the spatial resolution of the cognitive response, although this is rather limited compared to other measures as functional Magnetic Resonance Imaging (fMRI). For example, EEGs provide information on the lateralization of emotional information processing. More importantly, the ERP measures have an extended temporal range compared to behavioral measures. While typical reaction times are measured within a time-frame of a second, the cognitive processing of stimuli can be measured within 6 seconds or longer.

More traditionally, the waves of interest within emotionally elicited ERP are P3 and P3-alike waves. The P3 component reflects basic cognitive processes such as attention allocation and activation of immediate memory. The P3 is also influenced by fluctuations in the arousal state of subjects. This evidence has resulted in the use of the P3 amplitude as a tool for studying the cognitive and affective processing of emotional information. In general, emotional stimuli elicit a more positive wave in the P3 area than neutral stimuli. In addition, the P3 component has been investigated in the field of psychopathology. It has been found that aversive disorder-related information results in enhanced P3's in panic disorder patients and post-traumatic stress patients. In addition to enhanced P3's on aversive stimuli in avoidance-oriented disorders such as anxiety, positive related information in approach related disorders also elicit an enhanced P3.
leagues found that cue elicited P3 was enhanced in alcoholics, suggesting an enhanced attentional processing of alcohol cues. In smokers, a similar effect of smoking cues on a P3 related component of the ERP, the P412, has been found.

Although the study of P3 components in the ERP has advanced the knowledge on information processing in psychopathological disorders, the early ERP reactions do not capture the continuation of allocating attentional resources that result in behavior seen in real life. Little is known about the continuation of the processing of disorder-related information after 400 ms. In real life, when emotional or disorder-related cues are able to modify behavior they should elicit cognitive processes that last longer and should be measurable beyond 400 ms.

For example, it is demonstrated that drug-related cues can elicit a cognitive-motivational state that results in relapse within in drug addicted subjects. Slow positive waves of the ERP may reflect this continued processing. Recent studies demonstrate that slow positive waves (positivity after 400 ms) are adequate indicators of selective cognitive processing, reflecting an activation of a motivational system in the brain. These properties make Slow Waves useful for investigating the cognitive processing of drug cue elicited responses.

Although reaction time paradigms have demonstrated that processing biases are present in addiction, their relationship with drug craving is relative unclear. In previous research, we found a relation between craving and attentional bias in cocaine and heroin dependent patients. Furthermore, a relation was found between memory bias and alcohol craving.

As far as we know, no study addressed the neurophysiological evidence for abnormal cognitive processing in heroin dependent subjects. The main hypothesis of the present study is that heroin dependent patients have larger slow positive voltage change on heroin pictures compared to neutral pictures. According to the attentional bias theory, this effect should not be present in healthy control subjects. In addition to Slow Waves, the differences on earlier components of the ERP are investigated. In addition, the hemispheric distribution of this effect is investigated. If the heroin stimuli represent appetitive emotional value, left hemisphere should be more activated. In contrast, if heroin stimuli represent aversive emotional value, right hemisphere should be more activated. Furthermore, the correlation between the magnitude of the mean amplitude of the slow positive waves and the magnitude of subjective experience of heroin craving is examined.

**Methods And Materials**

**Participants**

Twenty-three eligible male heroin dependent subjects were recruited from a detoxification unit of a substance abuse program (Parnassia Mental Health Care). All participants had been abstaining from illicit drug use (including heroin and cocaine) for a minimum of 2 weeks. At the time of testing none of the subjects was taking prescribed or non-prescribed medications. Fifteen healthy control subjects who never used opiates were recruited from treatment staff. This group was chosen in order to control for familiarity effects on the ERP measure, as it is likely that treatment staff is frequently exposed to heroin related cues and heroin related problems. Data from one control subject and four heroin dependent subjects were excluded from the analyses because of excessive artifacts in the EEG signal, resulting in a final group of 19 heroin dependent subjects and 14 healthy control subjects. Candidates were excluded from the study if one of the following conditions was present: withdrawal symptoms, lifetime use of neuroleptic medication, schizophrenia, affective disorder, mental retardation, significant somatic disorders such as Parkinson disease (or symptoms). All subjects were male in order to rule out gender effects.

The heroin dependent group consisted of 10 subjects with lower education, 7 subjects with middle education and 2 subjects with higher education (according to the Dutch educational system). For the control
group these numbers were 3, 5, and 6, respectively. Chi-square analysis showed that the educational level was not different for both groups \( \chi^2 = 5.47, p = \text{ns} \). The mean age of the heroin dependent group was 33.5 years \((SD = 7.7)\) and of the control group 33.7 years \((SD = 9.0)\), \(t(31) = .08, p = \text{ns} \). Drug use characteristics of the heroin dependent group are summarized in table 1. Most heroin dependent subjects \((n=17)\) had a history of additional cocaine use and most subjects had ever been in a methadone maintenance program \((n=12)\). The study was approved by the Ethical Committee of the institution in which the work was performed.

**Stimulus materials**
From the 36 color pictures \((18\) neutral, 18 heroin\) that were relevant for the present study\(^b\), the neutral pictures were selected from the international affective picture system \((2190, 2200, 5500, 7000, 7010, 7020, 7050, 7080, 7090, 7100, 7130, 7150, 7160, 7170, 7180, 7500, 7550, 7700)\). In addition, 18 heroin related color pictures consisting of digital photographs of heroin use, and heroin paraphernalia were produced. All pictures appeared on an IBM-G54 monitor for 6000 ms in random order. The inter-stimulus interval was a random time between 2 and 6 seconds in 3 blocks of pictures. Before the pictures were shown, two neutral pictures \((7233, 7175)\) served as practice trials.

**Procedure**
Eligible subjects were asked to participate in a study concerning the processing of heroin pictures. They were informed that participation involved EEG measurements and viewing pictures of heroin use. Both the patients and control subjects received a remuneration of 20 euro. All subjects provided written informed consent. The experiment started with a short explanation of the procedure and informed consent was obtained. Personal data and history of drug use were recorded by the experimenter.

Then the subject completed the pre-exposure questionnaires. After completion the subject was seated in the EEG chair and electrodes were attached. Instructions were to sit relaxed and still, and to attend to all pictures without employing distracting fantasies. Then the task was started. After the picture viewing, electrodes were removed and the heroin dependent group completed a post-exposure craving questionnaire. In addition, both groups rated the pictures on their arousal and valence properties. After having completed the experiment, subjects received their financial compensation and there was a check by the experiment leader whether the craving levels in the heroin dependent group were not unacceptable high. If so, a cool-down-talk was provided until craving levels were decreased to an acceptable level.

**Self-report measures**
Demographic data were self-reported (age, education, and length of treatment). Instant craving was measured by the 14-item Desire for Drug Questionnaire (DDQ)\(^b\). This questionnaire was adapted from the Desires for Alcohol Questionnaire (DAQ)\(^b\) for use in heroin addicts. It measures instant (now) craving and consists of three subscales. The three subscales are: desire and intention to use drugs, negative reinforcement (the relief of negative states), and perceived control over drug-use. The three subscales have good reliability and concurrent validity\(^b\). Drug use severity was assessed by means of the Drug Use scale of the Addiction Severity Index (ASI)\(^b\). Questions in this scale refer to the different types of drugs used, the numbers of days used, and duration of use. Valence and arousal properties of the pictures were assessed by the 2-item Self Assessment Manikin (SAM; Bradley & Lang\(^b\)). The SAM was used in order to quickly assess reports of affective response on the alcohol pictures. The SAM is a non-verbal pictorial assessment technique that directly measures the valence and arousal associated with a person's affective reaction to emotional stimuli.

\(^b\) Other pictures were used, however not reported here.
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**Physiological measures**

EEG was measured with a digital Schwartz amplifier using Electrocap Ag/AgCl electrodes at the 21 scalp sites according to the International 10 / 20 System, right and left mastoid locations. Data were recorded using the Cz-channel as reference and off-line re-referenced to linked mastoid. The vertical electro-oculogram (VEOG) was recorded with an Ag/AgCl electrode located above the right eye, using the same reference. The horizontal electro-oculogram (HEOG) was recorded with two Ag/AgCl electrodes located at the outer canthus of each eye. A ground electrode was placed between Fz and Cz. All signals were digitized without filtering on a PC using Brainlab (OSG, Belgium) software with a sample rate of 500Hz and 16-bit A/D conversion. Off-line, the time constant was set at 6 seconds and high frequencies were cut-off at 30 Hz (both phase shift-free Butterworth filters; 24dB/octave slope). For all electrodes, impedance was kept under 10 KOhm. All physiological signals were analyzed using BrainVision software (Brain Products, Germany). ERTS software (Berisoft, Germany) run on an IBM PC was used for timing and stimulus presentation. Eleven scalp electrodes (Cz, Pz, Fz, O2, O1, F4, F3, C4, C3, P4, P3) were used in the present study.

**Data reduction and analysis**

EEG signal was measured from 200 ms before to 6000 ms after the onset of the visual stimulus. After ocular correction for blinks with the Gratton and Coles algorithm, all segments with an EEG activity above 150 µV or a gradient above 50 µV (more than 50 µV step / sampling point) were excluded from further analysis. After baseline correction all segments were averaged by category. Based on visual inspection of the overall grand average waveform (including neutral and heroin trials patient and control groups) three early peaks could be identified, the N1, P2 and P3. The N1 was defined as the local maximum negative peak amplitude in the 0-100 ms time range. The P2 was defined as the local maximum positive peak amplitude in the 150-200 ms time range. The P3 was defined as the local maximum positive peak amplitude in the 300-400 ms time range. For the early waves, for each peak a repeated measurement ANOVA with group as between-subjects factor and picture category and electrode site as within-subjects factor was used to test for between- and within-group differences and interactions, resulting in a 11 (Electrode site) x 2 (Cue type) x 2 (Group) repeated measurement ANOVA.

In contrast to the early waveforms, visual inspection of the ERP grand average waveform showed that slow wave peaks were not pronounced (figure 1) and area measurement, according to Cuthbert et al., seemed more appropriate. Since in the present study the same paradigm was used for stimulus presentation, for replication purposes we used the same time windows as Cuthbert and colleagues. A window from 400-700 captured the extended P3 (Ext. P3) area, a window from 700 to 1000 ms captured the slow positive wave (SPW), and the 1000 to 6000 window captured the sustained slow positive wave (SSPW). For the slow waves, repeated measurement ANOVA with group as between-subjects factor and picture category and electrode site and time-domain as within-subjects factor resulted in a 3 (Time-domain) x 11 (Electrode site) x 2 (Cue type) x 2 (Group) repeated measurement ANOVA which was used to test for between- and within-group differences and interactions. Contrast analysis was used in order to identify specific differences. In addition, four separate ANOVA's were conducted in order to investigate laterality effects on frontal, central, parietal, and occipital sites. For this ANOVA, the site factor was replaced by the laterality as within-subjects factor. For all ANOVA's reported, a Greenhouse-Geisser adjustment on the df's was conducted when appropriate. In addition, Spearman correlation coefficients were calculated between craving levels after the experiment and mean amplitude of ERP components of responses on neutral and heroin pictures. An alpha-level of 0.05 was used for all statistical tests.
Results

Main and interaction effects of early waves

For the N1 peak, no significant main or interaction effect could be observed \( [F's<3.49, \text{ns}] \). For the P2 peak, only a main electrode site effect was found \( [F(10,31)=12.69, \ p<.0001] \). Because this finding was not relevant for the hypothesis, no contrast analysis was conducted.

<table>
<thead>
<tr>
<th></th>
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<th>SD</th>
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<td>Age of first heroin use (&gt; 3 times a week) (n=19)</td>
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<tr>
<td>Age of first cocaine use (&gt; 3 times a week) (n=17)</td>
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<td>Age of first methadone use (&gt; 3 times a week) (n=12)</td>
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<tr>
<td>Total years of cocaine use (n=17)</td>
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<td>Number of days of methadone use in month before detoxification (n=12)</td>
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</table>

Table 1. Drug use characteristics of the heroin dependent group.

For the P3 peak, main effects were found for electrode site \( [F(10,31)=22.72, \ p<.0001] \) and Cue-type \( [F(1,31)=5.09, \ p=.031] \). Overall, heroin pictures elicited larger P3 peak amplitude compared to the other categories. Furthermore, a main effect was found for picture category \( [F(1,31)=7.10, \ p=.012] \). Compared to neutral pictures, wave amplitude was more pronounced on heroin pictures compared to neutral pictures. A main site effect revealed that amplitudes were not equally distributed among the sites. Contrast analysis showed that the largest positivity was found for P3, P4 and Pz sites \( [F(1,31)=25.74, 7.74, 36.89] \) respectively. In addition to the within-subjects effects, a main between-subjects effect was found \( [F(1,31)=10.42, \ p=.003] \). Overall, patients exhibited more positivity than control subjects.

Main effects of slow waves

All main effects in the ANOVA were significant. A main effect was found for time-domain \( [F(2,30)=20.07, \ p<.0001] \). Analysis of the means indicated that the Ext-P3 had the largest amplitude compared to the other categories. Furthermore, a main effect was found for picture category \( [F(1,31)=7.10, \ p=.012] \). Compared to neutral pictures, wave amplitude was more pronounced on heroin pictures compared to neutral pictures. A main site effect revealed that amplitudes were not equally distributed among the sites. Contrast analysis showed that the largest positivity was found for P3, P4 and Pz sites \( [F(1,31)=25.74, 7.74, 36.89] \) respectively. In addition to the within-subjects effects, a main between-subjects effect was found \( [F(1,31)=10.42, \ p=.003] \). Overall, patients exhibited more positivity than control subjects.

Figure 2. Average event related potentials at the vertex (Cz) site for control subjects (black line) and heroin dependent subjects (gray line) in response to neutral pictures (above) and heroin related pictures (below).
Interaction effects of slow waves

Concerning the main hypothesis of this study, a Cue type x Group interaction effect was found \( [F(1,30)=8.87, p=.006] \), indicating that overall positivity in the heroin group, but not in the control group, was more pronounced on heroin pictures than on the neutral pictures. The mean amplitudes of the three slow waves are displayed in Table 2. In addition two more significant interaction effects were found (time x site; time x site x cue). However, they are not further reported here because they are not relevant for the aim of the present study.

Laterality effects of slow waves

For frontal, occipital and parietal sites, no significant effect was found on laterality. For central sites (C4-C3), a time-domain x laterality x cue type effect was observed \( [F(2,30)=13.74, p<.0001] \). Contrast analysis indicated that within the SPW and the SSPW, heroin cues elicited larger positivity on the left hemisphere sites \( [F(1,30)=6.07, p=.019; F(1,30)=18.25, p<.0001] \) than right hemisphere. However, no significant group effect on these analyses could be observed.

Self-reported craving and slow waves

None of the Ext. P3, SPWs or SSPWs elicited by neutral cues were significantly correlated with self-reported craving \( [\text{all } p's > .11] \). However, a significant correlation was found between SPW amplitudes at the Fz site on heroin cues and the DDQ-control scale \( [r=-.48, p=.038] \). Furthermore, significant correlations were found between the SSPW amplitude at the C3 site and the DDQ scales desire \( [r=.47, p=.042] \) and negative reinforcement craving \( [r=.48, p=.039] \). At the C4 site a correlation was found between SSPW amplitude and negative reinforcement craving \( [r=.46, p=.045] \). Furthermore, a negative correlation was found for the SSPW amplitude at the Pz site and the DDQ control scale \( [r=-.50, p=.030] \). The strongest correlation was found between the DDQ desire scale and the SSPW amplitude at the Cz site \( [r=.60, p=.006; \text{figure 3}] \).

<table>
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<tr>
<th>Cue type</th>
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<th>Heroin dependent patients</th>
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<tr>
<td></td>
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<td>Heroin</td>
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<tr>
<td>SPW</td>
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<tr>
<td>Heroin</td>
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<td>6.4</td>
</tr>
<tr>
<td>SSPW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutral</td>
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<td>4.1</td>
</tr>
<tr>
<td>Heroin</td>
<td>-2.2</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Self-reported valence, arousal and slow waves

Self-reported valence and arousal using the SAM was not correlated with any of the ERP waves elicited by neutral cues. Valence was also not correlated with any of the ERP waves elicited by heroin cues. However, for the central sites (C4, C3 and Cz), Ext. P3 amplitude elicited by heroin cues \( [r=.51, p=.52, r=.49, \text{respectively; all } p<.035] \) and SPW amplitude elicited by heroin cues \( [r=.42, r=.48, r=.54, \text{respectively; all } p<.035] \) were significantly correlated with self-reported arousal. The SSPW amplitude elicited by heroin cues was also correlated with self-reported arousal at Cz site \( [r=.77, p<.0001] \).
Figure 3. Correlation between the amplitude of SSPW at Cz (in µV) and cue-elicited self-reported heroin craving.

Conclusions
The main finding of this study is that heroin dependent patients exhibited enhanced Slow Positive Wave amplitude elicited by heroin pictures compared to neutral pictures. This difference was specific for the group of abstinent heroin patients, and was not found within the healthy controls. The finding that the Slow Wave to heroin pictures is greatly enhanced in heroin dependent patients suggests that these heroin cues are selected by the brain for sustained attention processing. This is in accordance with the Incentive-Sensitization Theory of Robinson & Berridge, who claim that classically conditioned drug related stimuli have acquired attention-grabbing properties. The present study shows that this enhanced attentional processing sustains during at least a period of 6 seconds. Although the present study design does not allow for causality speculating, it is conceivable that this prolonged processing bias results in increased craving. Although the reactivity of the Slow Waves was in the hypothesized direction, we failed to find any Group x Cue interaction effects on the earlier (<400 ms) ERP components. Typically, studies using emotional information yield mainly effects in the post 400 ms time-frames in contrast to the earlier time-frames. However, there are previous studies using pictures as stimuli that did find differences on early ERP components such as the P3. However, in their study, Herrmann and colleagues did not statistically correct for multiple testing and their findings were also marginally significant.

Furthermore, the question can be raised whether early ERP components are adequate measures when it comes to measuring reactivity on pictorial stimuli. Probably, early components reflect rather basic stimulus properties such as contrast, complexity of the scene, and colors. It is conceivable that early components are more useful when using less complex stimuli such as words.

The finding that the amplitude of the slow waves of the cue elicited ERP are correlated with self-reported heroin craving and arousal, suggests that the slow wave in these kinds of paradigms represent motivational significance. This concurs with the view of Schupp and colleagues that the late positive potential is modulated by motivational relevance. However, this finding is in contrast with Warren & McDonough, who failed to find a relation between smoking urge and earlier ERP components (P412). Together, these findings indicate that slow waves may be more adequate indexes of motivational relevance than earlier components. Although it should be noted that the correlation testing comprises multiple significance testing, thereby inflating Type I errors, the correlations between the Slow Waves at Central sites and reported craving were very consistent and large in effect and can therefore be considered robust.

In concordance with earlier work by Cuthbert and colleagues, we did not find laterality effects. Although we did find an indication that the evoked potentials responses on the heroin pictures were more pronounced in the left hemisphere than the right hemisphere we failed to find any group differences. It was hypothesized that heroin stimuli elicited more pronounced activation in one hemisphere compared to control subjects for whom the heroin pictures can be regarded as neutrally valenced. The hypothesis concerning the appetiveness
or the aversiveness of heroin pictures could not be confirmed by looking at laterality effects in the present study. As physiological alternative for self-report, measurement of the modulation of the eye-blink startle response is probably a better way to evaluate the valence of the presented stimuli than ERPs, even though the results on the startle response in addiction are not always consistent.

Research is needed that addresses the causal role of cognitive biases and cue-elicited craving. Several studies now reveal that biased cognitive processing is related to heroin, cocaine and alcohol craving. Specifically designed studies should focus on the question whether cognitive biases results in an increased motivational state such as craving, or vice versa. The present study shows that cue-elicited event-related potentials, and particularly the later waves, can be a useful and direct measurement for cognitive processing of pictorial cues in this kind of research.

References


