Psychopharmacology (2004) 177: 121–129
DOI 10.1007/s00213-004-1928-1

ORIGINAL INVESTIGATION

Maria C. van de Laar · Robert Licht · Ingmar H. A. Franken · Vincent M. Hendriks

Event-related potentials indicate motivational relevance of cocaine cues in abstinent cocaine addicts

Received: 26 November 2003 / Accepted: 28 April 2004 / Published online: 25 June 2004

Abstract *Rationale:* Motivational drive and its underlying affect-related states are the core mechanisms that precede the seeking and taking of drugs in substance dependence. *Objective:* The present study aimed to investigate the motivational relevance of cocaine cues and whether or not an appetitive emotional system is involved employing event-related potential (ERP) measurements. *Methods:* Cocaine-addicted subjects and healthy controls were exposed to neutral and cocaine-related pictures whilst ERPs were recorded simultaneously over frontal, parietal and midline sites. *Results:* Patients exhibited ERP amplitude discrepancies between neutral and cocaine-related pictures for N300, late slow positive wave (LSPW) and sustained slow positive wave (SSPW), whilst this effect was absent in control subjects. Differences in neutral and cocaine cue-evoked ERP waves were also found at left frontal sites for LSPW and SSPW in the patient group only. No group-specific cue-evoked ERP amplitudes were observed at parietal and midline sites. *Conclusion:* The findings confirm the assumption that cocaine cues induce motivational relevance in cocaine-dependent individuals. It is possible that exposure to cocaine cues triggers an appetitive emotional system since left frontal sites are assumed to be involved in processing positive emotional-laden stimuli. The present study provides evidence that the sensitivity of ERP correlates for cocaine cues may be an indicator of motivational and emotional processes in drug-dependent individuals.

M. C. van de Laar (✉) · V. M. Hendriks (✉)
Parnassia Addiction Research Centre,
Jan Hein Donnerstraat 75,
2553 Den Haag, The Netherlands
e-mail: hendrv@parnassia.nl
Tel.: +31-70-3916140
Fax: +31-70-3917773

R. Licht
Department of Neuropsychology, Vrije Universiteit,
Amsterdam, The Netherlands

I. H. A. Franken
Institute of Psychology, Erasmus Universiteit,
Rotterdam, The Netherlands

Keywords ERP · Emotion · Motivation · Cocaine · Addiction · Laterality · Frontal · Drugs

Introduction

Craving describes a state of extreme desire (Kozlowski and Wilkinson 1987) and the pathological motivational drive that precede the seeking and taking of drugs (Van Ree et al. 1999). For various researchers, this prominent characteristic has created the impetus to investigate craving and the involvement of different brain areas in addictive individuals. It has also stressed the importance of understanding this motivational state in relation to other cognitive processes (i.e. memory, attention) and emotional conditions. Comparing the underlying brain mechanisms of craving and more general emotional processes may well provide us with more knowledge towards the comprehension of the interaction between craving, affect-related states and motivational processes.

A number of brain-imaging studies have stressed the importance of mesolimbic and mesocortical systems in the control and regulation of addictive behaviours (Garavan et al. 2000; Goldstein and Volkow 2002). These systems imply that dopaminergic projections of the ventral tegmental area to the nucleus accumbens, amygdala, hippocampus, anterior cingulate cortex and prefrontal cortex play a major role in the motivational and rewarding effects of addictive drugs (Wise 1996; Verheul et al. 1999). According to Goldstein and Volkow (2002), the mesolimbic system is involved in the reinforcing effects of drugs and conditioned responses during craving, whilst this system is also responsible for emotional and motivational changes during withdrawal. However, the mesocortical system is involved in the conscious experience of the intake of a drug and the attribution of incentive salience to environmental stimuli (drug cues) associated with drug use (for a review see Robinson and Berridge 1993, 2000, 2001). After being exposed to such incentives, craving experiences occur that may lead to

compulsive drug administration and relapse (McKay 1999).

With the knowledge of the involvement of the mesolimbic and mesocortical system in craving and relapse, further research is needed into the motivational drive of drug-seeking subjects and as to whether or not connections to an emotional system can be made. Relevant theories are provided in studies carried out by Watson et al. (1988) and Lang et al. (1993, 1998), where it was concluded that affect-related states are the core mechanisms of motivational drive that characterise approach and avoidance tendencies. From this point of view, it is highly likely that heightened approach tendencies could be preceded by appetitive responses whilst heightened withdrawal tendencies could be preceded by aversive responses. However, it is not yet clear whether drug-related stimuli have an appetitive or aversive value in drug-dependent individuals, since inconsistent findings are presented. A study by Geier et al. (2000) on motivational effects of drug cues in smokers provided evidence for appetitive values of cues related to smoking, whereas a study by Franken et al. (2004) found motivational relevance of cocaine cues in cocaine-dependent individuals. However, the latter study failed to differentiate between appetitive and aversive responses.

Recently, neuro-imaging techniques, such as positron emission tomography (PET) and fluorescence magnetic resonance imaging (fMRI), have been employed to assess craving experiences of drug-dependent subjects and their relationship with motivational and emotional processes. Several studies (Breiter et al. 1997; Maas et al. 1998; Weinstein et al. 1998; Childress et al. 1999; Volkow et al. 1999; London et al. 2000; Garavan et al. 2000; Wexler et al. 2001; Goldstein and Volkow 2002) suggest participation of the prefrontal cortex when subjects were exposed to drug-related stimuli due to dopaminergic projections from the anterior cingulate cortex. Moreover, London et al. (2000) together with Maas et al. (1998) found activation of left dorsolateral prefrontal sites to be significantly correlated with subjective measures of craving. The contribution of left frontal sites could be related to appetitive sensation of drug cues since left frontal brain areas are involved when subjects are experiencing increased approach tendencies and right frontal brain areas when experiencing increased avoidance tendencies (Watson and Tellegen 1985; Davidson et al. 1990; Fox 1991; Fox et al. 1995; Davidson 2000).

Another technique, which is useful to study the relationship between brain activity and the motivational relevance of drug cues in addicts, is a specific application of electroencephalogram (EEG), known as event-related potentials (ERPs). In particular, cue-evoked P300 and slow positive waves (SPWs) are thought to reflect allocation of attention and effort during a variety of cognitive processing tasks (Kok 1997). Both waves have also been shown to be sensitive to processing requirements in emotional tasks and, thus, could indicate motivational significance of affect-related processes (Cuthbert et al. 2000; Schupp et al. 2000). However, research on P300 and SPW responsiveness in addicted individuals is scarce. Herrmann et al. (2000, 2001) found enhanced P300 amplitudes in alcoholics whilst exposed to alcohol cues. Furthermore, similar outcomes were found in smokers whilst exposed to smoking cues (Warren and McDonough 1999). Franken et al. (2003) examined ERPs in heroin-dependent patients and control subjects whilst exposed to neutral and heroin-related pictures. No enhanced P300 amplitudes on heroin cues were found. However, they did find larger SPWs on heroin cues than on neutral cues in heroin addicts, indicating motivational relevance of heroin-related stimuli.

Various imaging studies have been conducted with the aim to find indications of the involvement of prefrontal brain areas in craving experiences and its relationship to motivational and emotional processes. ERP responses appear to offer a useful technique to assess motivational relevance and the emotional value of drug-related stimuli and may provide further understanding of craving and motivational drive to seek drugs in substance dependency. The present study aimed to investigate motivational relevance of cocaine cues in abstinent cocaine-addicted individuals. For that purpose, abstinent cocaine-addicted subjects and healthy controls were presented with neutral and cocaine-related pictures, whilst ERPs were recorded simultaneously over the left and right frontal and parietal sites, and over midline sites. The present study focussed on frontal and parietal electrode sites since those areas have been found to be activated during craving (London et al. 2000) and are involved in experiencing emotional states (Davidson 1992). In addition, midline electrodes were examined since most pronounced SPWs elicited by emotional cues have been reported at midline sites (Cuthbert et al. 2000; Franken et al. 2003). It was expected that cocaine pictures would evoke enhanced potentials at frontal, parietal and midline sites relative to neutral pictures in cocaine-dependent individuals, whereas this effect would be absent in healthy control subjects. More precisely, it was expected that the most pronounced effects would be observed at late positive potentials, since these have been found to be enhanced during exposure of motivational relevant cues (Schupp et al. 2000). Furthermore, previous components were assumed to differentiate between emotional stimuli (Kayser et al. 1997); thus, effects were expected in those potentials as well. It was further assumed that left frontal sites would be more responsive to cocaine pictures if these pictures had an appetitive value, whilst right frontal sites would be more responsive when cocaine pictures are perceived as aversive. Finally, positive correlations between cocaine cue-elicited ERP waves and subjective experience of cocaine craving were expected.

Method

Subjects

Twenty-six male cocaine-dependent patients (mean age 35.4 years, SD=7.6 years) and 20 healthy male control subjects (mean age 40.6 years, SD=9.9 years) voluntarily participated in the present study. The age difference between the groups was not significant (t_{44}=2.02, P>0.05). Patients were recruited from an inpatient treatment centre for substance dependency (Parnassia Psycho-Medical Center, the Hague, the Netherlands) and were abstinent of all psychoactive drugs (including methadone) for a minimum of 1 month (mean abstinence duration 7.6 months, SD=3.4 months). History of drug use and treatment are summarised in Table 1. All of the patients were free of withdrawal symptoms and none of them received any prescribed or non-prescribed medication prior to or throughout the experimental procedure. Since it is likely that treatment staff are frequently exposed to cocaine cues, 18 control subjects were recruited from the treatment staff to control for familiarity effects. None of the control group members experienced any addiction to substances. Level of education was determined in accordance with the Dutch educational system. The control group consisted of 15 subjects with higher education, one subject with middle education and four subjects with lower education. In the patient group, two subjects had higher education, one subject had middle education and 23 subjects had lower education. Chi-square analysis for educational levels showed a significant difference between groups (χ^2=22.2, P<0.001). All participants were right-handed and none experienced any neurological, psychopathological or ophthalmic problems. Approval from the Ethics Committee at the institution was obtained, and subjects provided a written informed consent.

Experimental design

Thirty-seven neutral photographs and 37 cocaine-related photographs were used in the present study. The neutral stimuli consisted of coloured pictures selected from the International Affective Picture System[1] (Lang et al. 1999). The cocaine-related stimuli were real-life digital photographs of cocaine use and cocaine paraphernalia that were edited identical to size and quality of the IAPS pictures. The pictures were presented in random order at the centre of a black screen using ERTS software (Berisoft, Germany) on an IBM-G54 monitor with a stimulus duration of 4000 ms. Prior to stimulus presentation, an empty screen appeared for 500 ms followed by a warning signal (three white exclamation marks) for 1000 ms. Then, again, an empty screen was presented for 250 ms followed by a white fixation cross for 500 ms at the centre of the screen. During stimulus presentation, subjects had to fixate their eyes on the fixation cross. After stimulus presentation, an empty screen appeared for 500 ms followed by a white response screen for 1500 ms, prompting the subject to respond. Four neutral photographs served as practice trials prior to the actual start of the experiment. The experiment started with two neutral pictures that were excluded from further analysis.

Table 1 History of drug use and treatment. *n* Number of subjects

	Mean	SD
Age at first cocaine use (>3 days a week) (*n*=26)	22.4	7.1
Age at first heroin use (>3 days a week) (*n*=15)	21.6	7.7
Total years of cocaine use (*n*=26)	9	5.1
Total years of heroin use (*n*=15)	5.5	6.6
Number of previous detoxifications	1.3	1.7
Number of previous addiction treatments (inpatient and outpatient)	1.2	1.3

[1] IAPS photograph numbers were: 2190, 2200, 2210, 2214, 2280, 2312, 2372, 2383, 2440, 2480, 2518, 2575, 2580, 5120, 5390, 5510, 5535, 5731, 6150, 7000, 7002, 7009, 7010, 7020, 7025, 7030, 7031, 7040, 7050, 7060, 7080, 7090, 7130, 7150, 7160, 7170, 7175, 7184, 7187, 7217, 7233, 7491 and 7705. Other photographs were used, although not reported.

Procedure

Before participation, personal data were recorded and information was provided concerning EEG measurements and exposure to cocaine-related stimuli. For the patient group, self-reported craving questionnaires [Desire for Drug Questionnaire (DDQ) and Obsessive Compulsive Drug Use Scale (OCDUS)] were completed prior to the preparation of physiological recordings. The subject was seated in a comfortable chair in front of the computer screen. The subject was told that he would see a sequence of photographs and instructed to delay their response until the response screen appeared. The response buttons were four keys in a row of the keyboard situated in front of the subject. The instruction was to push with their index fingers of both hands on the inner buttons when they found the picture positive whilst pushing their middle fingers on the outer buttons when they found the picture negative. The subjects had to press the buttons with both hands simultaneously in order to prevent lateralised ERP motor-activity. No response errors could be made since the response reflected the judgment of the subject regarding the valence of the presented picture. The subject was instructed to watch the photographs during the entire experiment in order to prevent distraction by surrounding stimuli. After the experiment, the self-reported craving questionnaire (DDQ) was completed again. All subjects were requested to return at least 1 week after the experiment to rate the presented pictures on their valence and arousal properties.

Behavioural measures

Demographic data were recorded for the control and patient groups (age, education, hand preference, physical and mental health). For the patient group, previous substance abuse was assessed using the Drug Use scale of the Addiction Severity Index (Hendriks et al. 1989).

Craving levels were assessed by means of two questionnaires: DDQ and OCDUS for use in heroin addicts (Franken et al. 2002). For the present study, the word “heroin” was replaced by the word “cocaine”. The DDQ measures instant craving and consists of three subscales: (a) desire and intention to use cocaine, (b) negative reinforcement and (c) perceived control over cocaine use. For the measurement of general craving (craving experiences over the previous week), the OCDUS was used. This questionnaire contains three subscales: (a) thoughts concerning cocaine, (b) control and desire to use cocaine and (c) resistance to thoughts and intentions to use cocaine. It was decided not to use the third scale for further analysis due to its low reliability (Franken et al. 2002). The subscales of the DDQ range from 1 (low score) to 7 (high score) and the subscales of the OCDUS range from 1 (low score) to 5 (high score).

The two-item Self-Assessment Manikin (Bradley and Lang 1994) was used to obtain subjective reports concerning valence and arousal properties of the cocaine-related pictures presented during ERP recordings in controls and patients. The SAM is a 9-point non-verbal affective rating scale that immediately measures valence and arousal levels of stimuli. Valence scores range from 1 (very negative) to 9 (very positive). Arousal is rated from experiencing low (≥1) to high (≤9) levels of arousal.

Electroencephalographic procedure

Continuous EEG and electro-oculogram (EOG) signals were recorded using digital Schwartzer amplifiers (Brainlab, OSG, Belgium) with a 16-bit A/D conversion and a sample rate of 500 Hz. The signals were analysed using BrainVision software (Brain Products, Germany). The EEG was recorded employing Electro-Cap Ag/AgCl electrodes at 21 scalp sites.[2] The recorded EEG data were referenced to Cz and off-line re-referenced to linked mastoids. A ground electrode was placed at a mid-frontal location. The vertical and horizontal EOGs (VEOG and HEOG, respectively) were bipolarly recorded with Ag/AgCl electrodes, located above and beneath the left eye for VEOG and at the outer cantus of each eye for HEOG. Electrode impedance was kept below 5 kΩ.

Data reduction and analysis

Continuous EEG and EOG were off-line filtered with a low-pass set at 35 Hz, both with 24 dB/Oct roll off. A notch filter of 50 Hz was employed to remove electrical line interference. EEG and EOG records were segmented in 4100-ms epochs including a pre-stimulus baseline of 100 ms. After segmenting, EEG was corrected for vertical and horizontal eye blinks employing Gratton and Coles algorithm (Gratton et al. 1983). In addition, EEG activity above −/+100 μV and a gradient above 50 μV (more than 50 μV step/sampling point) were excluded from further analysis. Pre-stimulus baseline correction was applied separately for each picture category (neutral and cocaine-related photographs) and epochs were averaged across trials. Overall grand averages were obtained for each picture category in both the patient and control groups. Visual inspection of the grand averages revealed that the ERP waveform was characterised by a sequence of positive and negative peaks at anterior sites (200–700 ms) and an early positive going wave at posterior sites (300–700 ms). At anterior and posterior sites, a positive slow wave can be observed (700–4000 ms). Since considerable variance in amplitudes and latencies was observed, it was decided to apply area measurements. See Fig. 1 for the time intervals at anterior sites. At anterior sites, mean amplitudes were calculated in the time range 200–400 ms (N300) and 400–700 ms (N600). The SPW was divided into three segments: a window from 700 ms to 1200 ms captured the early SPW (ESPW), a window from 1200 ms to 2000 ms captured the late SPW (LSPW) and a window from 2000 ms to 4000 ms captured the sustained SPW (SSPW). At posterior sites, average amplitudes were calculated in three time intervals: P600 with an interval from 400 ms to 700 ms, the SPW with an interval from 700 ms to 1500 ms and the SSPW from 1500 ms to 4000 ms. For replication purposes, the same time window was applied as by Franken et al. (2003) for midline sites. Mean amplitudes were calculated in four time windows: 300–400 ms (P300), 400–700 ms (the extended P300, Ext. P300), 700–1000 ms (the SPW) and 1000–4000 ms (the SSPW).

Statistical analysis

For each time interval, statistical significance of ERP effects was assessed by performing repeated-measures analysis of variance (ANOVA). Since frontal, parietal and midline sites were of importance, it was decided on the basis of previous studies (Davidson 1992; Schupp et al. 2000; Cuthbert et al. 2000; Franken et al. 2003) to limit the analysis to nine electrode sites (F8, F7, F4, F3, P4, P3, Fz, Cz, and Pz). In the ANOVAs on frontal ERP components, group (control versus patients) served as the between-subjects factor, and cue type (neutral and cocaine) and laterality (left, F3 and F7, versus right, F4 and F8) as within-subjects factors. Separate analysis was performed for F3 and F4, and F7 and F8. A similar design was employed for parietal amplitudes with two electrode sites (P3 and P4) as the laterality factor. For midline sites, the laterality factor was replaced by site (Fz, Cz and Pz) as within-subjects factor. Statistical analysis was performed with and without correcting for multiple tests by applying Bonferoni correction. To control for unequal error covariances, Huynh–Feldt or Greenhouse-Geisser correction on the df values were applied for analyses of midline sites and will be reported when relevant. To assess relationships between cue-evoked ERP amplitudes and craving levels (OCDUS and post-exposure questionnaire DDQ), Spearman correlation coefficients were calculated. Interpretations of correlations were as follows: negative correlations found between self-reported craving and ERP amplitudes indicate that when craving levels increase amplitudes decrease, whilst positive correlations signify that increasing craving experiences coincide with increasing amplitudes. It was decided to only calculate correlations between cocaine-cue-evoked ERP amplitudes found in significant group interaction effects and self-reported craving levels.

[2] Channels used: Fp1, Fp2, F7, F8, F3, F4, T3, T4, C3, C4, T5, T6, P3, P4, O1, O2, Fz, Cz, and Pz.

Results

Frontal sites

See Fig. 1 for grand averages of ERP waveforms at F3 and F4, and F7 and F8 for neutral and cocaine-related pictures of patients and controls. For N300, the overall analysis showed a significant main effect for cue type at F3 and F4 ($F_{1,44}$=23.20, P<0.0001), indicating that neutral pictures elicited larger negative amplitudes than cocaine pictures. A significant group×cue type interaction effect was found at F7 and F8 ($F_{1,44}$=5.87, P=0.02). Further analysis revealed a significant effect of cue type ($F_{1,25}$=14.62, P=0.001) in the patient group only, showing that neutral pictures evoked larger negative amplitudes than cocaine pictures. After Bonferoni correction for multiple tests, only cue type at F3 and F4 ($F_{1,44}$=23.20, P<0.0006) showed a significant effect.

For N600, main effects were found for cue type at F3 and F4 ($F_{1,44}$=4.58, P=0.038), and at F7 and F8 ($F_{1,44}$=5.27, P=0.027). Neutral pictures evoked larger negative amplitudes than cocaine pictures at F3 and F4, whilst this effect was reversed at F7 and F8. No significant effects were found after Bonferoni correction.

For ESPW, a cue type×laterality interaction effect was observed at electrode sites F3 and F4 ($F_{1,44}$=4.31, P=0.044). Compared with neutral pictures, cocaine pictures elicited more pronounced positive amplitudes at F4, whilst no differences were observed at F3. No group differences were found. No significant effects were found after Bonferoni correction.

Overall analysis of LSPW showed no significant effects at F3 and F4. However, at F7 and F8, a significant group×cue type×laterality interaction effect was found ($F_{1,44}$=7.55, P=0.009). Further analysis revealed no significant effects in the control group. In the patient group, a cue type×laterality interaction effect was found ($F_{1,25}$=4.65, P=0.041). In addition, it appeared that cocaine pictures evoked larger positive amplitudes than neutral pictures at F7 ($F_{1,25}$=6.78, P=0.015). No significant difference was found between neutral and cocaine pictures at F8. After Bonferoni correction, a significant group×cue type×laterality interaction effect was found

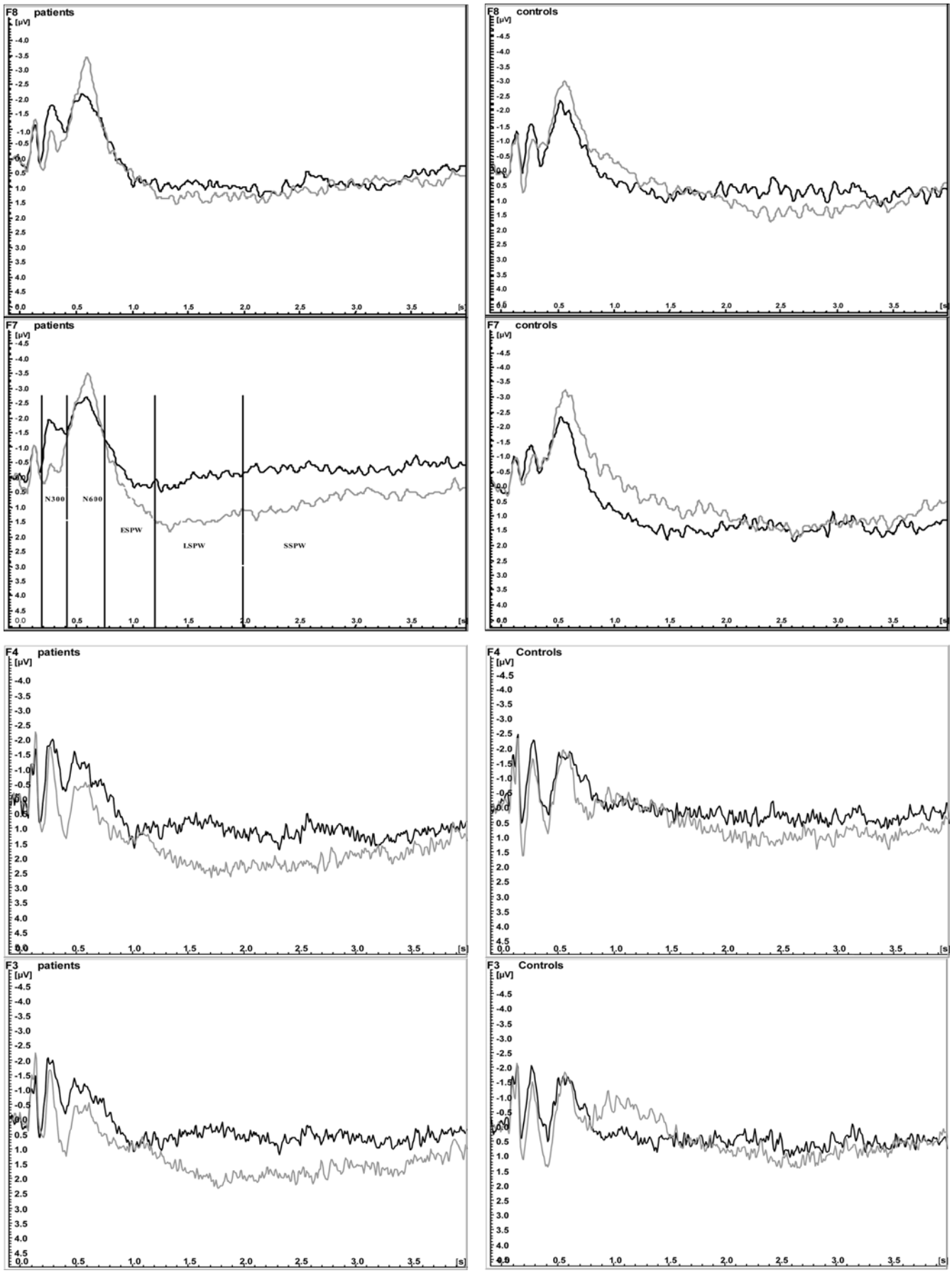

Fig. 1 Event-related potential averages for neutral (*black*) and cocaine (*grey*) cues at F3 and F4, and F7 and F8 of patients and controls. N300, N600, ESPW, LSPW, and SSPW refer to mean amplitudes in a specific time-interval

($F_{1,44}$=7.55, P=0.05) at F7 and F8. Further analysis revealed no significant effects.

For SSPW, a main cue-type effect was found at F3 and F4 ($F_{1,44}$=5.27, P=0.027), indicating larger positive amplitudes for cocaine pictures than neutral pictures. Furthermore, a significant group×cue type×laterality interaction effect was found at F7 and F8 ($F_{1,44}$=8.49, P=0.006). Further analysis showed a cue type×laterality interaction effect in the control group ($F_{1,19}$=4.38, P=0.05). However, contrast analysis revealed no significant effects. Further analysis of the patient group revealed a significant cue type×laterality interaction ($F_{1,25}$=4.97, P=0.035). This interaction revealed that cocaine pictures elicited larger positivity than neutral pictures at F7 ($F_{1,25}$=3.93, P=0.059), whereas no differences were found between neutral and cocaine pictures at F8. After Bonferoni correction, a significant group×cue type×laterality interaction effect was found at F7 and F8 ($F_{1,44}$=8.49, P=0.036). Further analysis revealed no significant effects. The mean amplitudes of N300, LSPW and SSPW are displayed in Table 2.

Parietal sites

For P600 and SPW, significant cue-type effects were found (all $F_{1,44}$ values>29.99, all P values<0.0001), indicating larger positive amplitudes for cocaine pictures than for neutral pictures. No significant group or laterality effects were observed at P3 and P4. After correction for multiple tests, significant cue-type effects were found for P600 and SPW (all $F_{1,44}$ values>29.99, all P values<0.0006).

Midline sites

A significant cue type×site interaction effect was found for P300 ($F_{2,88}$=11.10, P<0.0001), Ext. P300 ($F_{2,88}$=46.59, P<0.0001) and SPW ($F_{2,88}$=18.57, P<0.0001), showing that cocaine pictures elicited larger positivity than neutral pictures at Cz (all $F_{1,45}$ values>40.88, all P values<0.0001) and Pz (all $F_{1,45}$ values>74.73, all P values<0.0001). For SSPW, a significant cue-type effect was found ($F_{1,44}$=9.17, P=0.004), indicating larger positive amplitudes for cocaine pictures than for neutral pictures. ANOVAs revealed no significant group effects at Fz, Cz and Pz. All significant effects mentioned above were found after correction for multiple tests ($F_{2,88}$=11.10, P<0.0006; $F_{2,88}$=18.57, P<0.0006; all $F_{1,45}$ values>40.88, all P values<0.0006; all $F_{1,45}$ values>74.73, all P values<0.0006; $F_{1,44}$=9.17, P=0.024; respectively).

Table 2 Mean amplitudes (in μV) of N300, late slow positive wave (*LSPW*) and sustained slow positive wave (*SSPW*) on neutral and cocaine cues at frontal sites (F7 and F8) for both groups

	Electrode	Cue type	Controls		Patients	
			Mean	SD	*Mean*	SD
N300	F7/8	Neutral	−0.90	0.51	−1.48	0.45
		Cocaine	−0.71	0.54	−0.35	0.47
LSPW	F7	Neutral	1.47	0.57	0.05	0.50
		Cocaine	0.69	0.61	1.45	0.53
	F8	Neutral	0.76	0.51	0.91	0.45
		Cocaine	0.64	0.57	1.30	0.50
SSPW	F7	Neutral	1.37	0.59	−0.33	0.51
		Cocaine	1.17	0.61	0.71	0.54
	F8	Neutral	0.73	0.51	0.76	0.45
		Cocaine	1.17	0.50	0.93	0.44

Table 3 Self-reported craving data of the patient group. Pre-exposure and post-exposure Desire for Drug Questionnaire (DDQ): desire and intention to use cocaine (*des*), negative reinforcement (*neg*) and perceived control over cocaine use (*con*). Obsessive Compulsive Drug Use Scale (OCDUS): thoughts concerning cocaine (*ob*) and control and desire to use cocaine (*cd*)

	DDQdes		DDQneg		DDQcon			
	Pre	Post	Pre	Post	Pre	Post	OCDUSob	OCDUScd
Mean	1.33	1.45	2.31	2.63	1.87	2.08	1.59	1.38
SD	0.61	0.71	1.81	2.06	1.72	2.07	0.79	0.49

Self-reported craving and ERP waves

The scores on the post-exposure DDQ were slightly enhanced compared with those of the pre-exposure DDQ. The DDQ and OCDUS scores are presented in Table 3. None of the amplitudes of neutral cue-elicited ERP waves was significantly correlated with self-reported craving. However, cocaine-evoked N300 amplitudes at F7 and F8 showed a significant correlation with DDQ-desire and intention to use cocaine (r=0.41, P=0.038). No significant effects were found after correction for multiple tests.

SAM ratings concerning valence and arousal properties of cocaine-related pictures

Valence and arousal scores on cocaine-related pictures showed minimal variance between subjects in both groups and, furthermore, no significant differences in ratings were observed between the patient and control group. Valence and arousal ratings on the cocaine-related pictures in the present study are presented in Table 4.

Table 4 Valence and arousal ratings of cocaine-related pictures in the control and patient groups

Group	Valence		Arousal	
	Mean	SD	*Mean*	SD
Controls	3.2	1.6	3.1	1.7
Patients	3.0	1.7	4.3	2.3

Discussion

The present study investigated the motivational relevance of cocaine cues in cocaine-dependent individuals employing ERP measurements. Several hypotheses were formulated concerning group differences in neutral and cocaine cue-evoked ERP waves and self-reported craving. It was expected that cocaine cue-evoked potentials would be enhanced relative to neutral cue-evoked potentials at frontal, parietal and midline sites in cocaine-addicted subjects, whereas this effect was expected to be absent in healthy control subjects. Furthermore, left frontal sites would be more responsive when subjects were experiencing cocaine-related pictures as appetitive, whilst right frontal sites would be more responsive when subjects were experiencing cocaine-related pictures as aversive. In view of the described hypotheses, only interactions, which at least involved group as a factor, will be discussed.

The main results of the present study showed ERP amplitude discrepancies between neutral and cocaine-related pictures for N300, LSPW and SSPW at frontal sites. This prominent finding was only present in the patient group and not in the control group, confirming the assumption of motivational relevance of cocaine cues in cocaine-addicted individuals. Drug-related stimuli are assumed to grab the attention of the drug addict (Franken et al. 2000a,b) and, therefore, could have high motivational properties for substance-dependent patients (Franken 2003). The findings also support the incentive-sensitisation theory of Robinson and Berridge (1993, 2000, 2001), implying that the attribution of incentive salience to stimuli—related to drug use—triggers the addict's attention and motivation when exposed to those incentives. Although the cocaine-dependent individuals classified the cocaine-related pictures on their valence and arousal levels similar to controls, cocaine cue-evoked ERP responses seemed to reveal the contrary.

The present study found cue-evoked ERP amplitude discrepancies for an earlier negativity (N300). This component is associated with the initial semantic processing of pictorial stimuli (Barrett and Rugg 1990; McPherson and Holcomb 1999; Kounios 2002; West and Holcomb 2002) and direction of attention towards relevant cues (West and Ross-Munroe 2002). Since drug cues require additional attention in drug addicts due to their motivational significance (Franken 2003), it can be assumed that the motivational relevance of cocaine-related stimuli in addictive individuals is already detected at earlier stages of processing. This finding is partially in agreement with previous studies (Herrmann et al. 2000, 2001) which found enhanced P300 amplitudes in alcohol-dependent subjects whilst exposed to alcohol cues. However, no N300 differences in amplitudes were reported. Even though N300 and P300 probably represent different processes (due to their different topographical distribution), both seem to be sensitive to motivational processes.

Neutral and cocaine-related pictures also elicited variations in amplitudes for LSPW and SSPW. It appeared that cocaine cue-evoked amplitudes were larger than neutral cue-evoked amplitudes and that this effect was most pronounced at left frontal sites. Again, this latter effect was not found in healthy control subjects. It should be noted that the differentiation of the control and patient groups at left frontal sites seems to be due to differences in response to neutral cues; in particular, the control group seems to have a positive shift over the left hemisphere that overlaps with N600 and leads to a SSPW. However, closer inspection of the left neutral and cocaine-evoked ERP waves shows that the patients are characterised by larger peak–peak responses to cocaine cues than to neutral cues. This observed difference in neutral and cocaine cue-evoked ERP waves at left frontal sites could indicate the possible involvement of an emotional system, since frontal brain areas are differentially involved in processing emotional laden stimuli (Silberman and Weingartner 1986; Davidson 1992) and appear to play a fundamental role in approach and avoidance motivational tendencies (Watson and Tellegen 1985; Davidson et al. 1990; Davidson 2000). The results of the present study are in concordance with previous fMRI studies (Maas et al. 1998; Garavan et al. 2000), which demonstrated left frontal activation when cocaine addicts experience desirable sensation for cocaine when exposed to cocaine cues. The involvement of the frontal lobes in cocaine addiction has been consistently observed (Breiter et al. 1997; London et al. 2000; Goldstein and Volkow 2002). This frontal engagement has been interpreted in terms of cognitive behavioural and emotional changes during exposure to cocaine cues that could be related to the appetitive experience of cocaine-related pictures and could lead to approach tendencies towards drugs. Concerning inflating type-1 errors due to multiple significance testing, the overall analysis of LSPW and SSPW are still, after being corrected, significant in effect and therefore regarded robust.

Previous PET and fMRI studies reported the involvement of the prefrontal cortex in craving experiences in drug-dependent individuals (Maas et al. 1998; Weinstein et al. 1998; Volkow et al. 1999; London et al. 2000). The present study found a significant correlation between cocaine cue-elicited N300 wave at frontal sites and cocaine-induced craving experiences. It is enticing to conclude that ERPs may be an adequate index for measuring craving experiences in abstinent cocaine addicts. However, the correlation was not consistent and thus, in this perspective, should be interpreted with care. Cocaine-related pictures alone may not elicit strong craving experiences in this specific population of abstinent (7 months) cocaine addicts and the subjective experience of craving is more enduring than EEG correlates of craving (Bauer and Kranzler 1994); hence, it could not be related to cocaine cue-evoked ERP amplitudes. However, the results of an ERP study by Franken et al. (2003) revealed robust significant positive correlations between heroin cue-evoked ERP amplitudes and self-reported craving for heroin. A possible explanation for this divergence in outcomes could be that subjects in the

study by Franken et al. (2003) were recruited from a detoxification unit whereas subjects in the present study were recruited from a treatment centre and were therefore highly expected to respond in a socially desirable manner (Sjostrom and Holst 2002). Another explanation could be that the mean abstinence period for all addictive drugs in the current study was approximately 7 months, whilst being less than 1 month in the study by Franken et al. (2003). Therefore, it is assumable that craving levels of subjects in their study were considerably higher than in subjects in the present study.

The present study hypothesised that cocaine-addicted subjects would process cocaine cues differently than neutral cues and that this effect would be manifested in changes in late positive waves at midline sites. Late positive potentials reflect the involvement of a motivational system as a consequence of exposure to emotional laden stimuli (Cuthbert et al. 2000; Schupp et al. 2000; Franken et al. 2003). In the present study, cocaine-related pictures evoked larger late positive waves than neutral pictures for cocaine-addicted individuals as well as for healthy controls. A possible explanation could be that neutral cues can be very easily discriminated from cocaine cues possibly leading to the classification of stimuli.

Since group-specific ERP amplitude differences were observed at frontal sites, it is possible that emotional processing is more frontally distributed and that posterior sites are primarily involved in the process of classifying stimuli that are designated as significant (e.g. cocaine cues) by both groups (Daffner et al. 2003). Future studies are required into the consequences of processing emotional laden stimuli for cue-evoked ERP waves at posterior and anterior sites.

In summary, the present study illustrates that exposure to cocaine-related pictures could induce motivational relevance of cocaine cues and may trigger an appetitive emotional system in cocaine-dependent individuals. The absence of group-specific cue-evoked ERP responses at parietal and midline sites could indicate the unique function of the lateral frontal lobes in processing emotional and motivational relevant cues (drug-related pictures) in substance-dependent individuals. It should be noted that there were contradictory findings of similar valence and arousal reports on cocaine-related pictures by cocaine-addicted subjects and healthy controls and the observed patient group-specific cocaine cue-evoked ERP amplitudes. The participants in the present study consisted of abstinent cocaine addicts and, even after an abstinence period of approximately 7 months, the motivational properties of cocaine cues as manifested by brain activity are still present and may induce relapse.

Acknowledgements This study was supported by grant 985-10-005 of the Dutch Organization for Scientific Research (NWO). We would like to thank the clients and control members for their participation in the present study and Andre den Breejen for his technical assistance.

References

Barrett SE, Rugg MD (1990) Event-related potentials and the semantic matching of pictures. Brain Cogn 14:201–212

Bauer LO, Kranzler HR (1994) Electroencephalographic activity and mood in cocaine-dependent outpatients: effects of cocaine cue exposure. Biol Psychiatry 36:189–197

Bradley MM, Lang PJ (1994) Measuring emotion: the Self-Assessment Manikin and the Semantic Differential. J Behav Ther Exp Psychiatry 25:49–59

Breiter HC, Gollub RL, Weisskoff RM, Kennedy DN, Makris N, Berke JD, Goodman JM, Kantor HL, Gastfriend DR, Riorden JP, Mathew RT, Rosen BR, Hyman SE (1997) Acute effects of cocaine on human brain activity and emotion. Neuron 19:591–611

Childress AR, Mozley PD, McElgin W, Fitzgerald J, Reivich M, O'Brien CP (1999) Limbic activation during cue-induced cocaine craving. Am J Psychiatry 156:11–18

Cuthbert BN, Schupp HT, Bradley MM, Birbaumer N, Lang PJ (2000) Brain potentials in affective picture processing: covariation with autonomic arousal and affective report. Biol Psychol 52:95–111

Daffner KR, Scinto LF, Weitzman AM, Faust R, Rentz DM, Budson AE, Holcomb PJ (2003) Frontal and parietal components of a cerebral network mediating voluntary attention to novel events. J Cogn Neurosci 15:294–313

Davidson RJ (1992) Anterior cerebral asymmetry and the nature of emotion. Brain Cogn 20:125–251

Davidson RJ (2000) Cognitive neuroscience needs affective neuroscience (and vice versa). Brain Cogn 42:89–92

Davidson RJ, Ekman P, Saron CD, Senulis JA, Friesen WV (1990) Approach-withdrawal and cerebral asymmetry: emotional expression and brain physiology. I. J Pers Soc Psychol 58:330–341

Fox NA (1991) If it's not left, it's right. Electroencephalograph asymmetry and the development of emotion. Am Psychol 46:863–872

Fox NA, Rubin KH, Calkins SD, Marshall TR, Coplan RJ, Porges SW, Long JM, Stewart S (1995) Frontal activation asymmetry and social competence at four years of age. Child Dev 66:1770–1784

Franken IH (2003) Drug craving and addiction: integrating psychological and neuropsychopharmacological approaches. J Neuropsychopharmacol Biol Psychiatry 27:563–579

Franken IHA, Kroon LY, Hendriks VM (2000a) Influence of individual differences in craving and obsessive cocaine thoughts on attentional processes in cocaine abuse patients. Addict Behav 25:99–102

Franken IHA, Kroon LY, Wiers RW, Jansen A (2000b) Selective cognitive processing of drug cues in heroin dependence. J Psychopharmacol 14:395–400

Franken IH, Hendriks VM, Van den Brink W (2002) Initial validation of two opiate craving questionnaires the obsessive compulsive drug use scale and the desires for drug questionnaire. Addict Behav 27:675–685

Franken IH, Stam CJ, Hendriks VM, Van Den Brink W (2003) Neurophysiological evidence for abnormal cognitive processing of drug cues in heroin dependence. Psychopharmacology 170:205–212

Franken IHA, Hulstein KP, Stam CJ, Hendriks VM, Van den Brink W (2004) Two new physiological indices of cocaine craving: evoked brain potentials and cue modulated startle reflex. J Psychopharmacol (in press)

Garavan H, Pankiewicz J, Bloom A, Cho J-K, Sperry L, Ross TJ, Salmeron BJ, Risinger R, Kelley D, Stein E (2000) Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. Am J Psychiatry 157:1789–1798

Geier A, Mucha RF, Pauli P (2000) Appetitive nature of drug cues confirmed with physiological measures in a model using pictures of smoking. Psychopharmacology 150:283–291

Goldstein RZ, Volkow ND (2002) Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. Am J Psychiatry 159:1642–1652

Gratton G, Coles MGH, Donchin E (1983) A new method for off-line removal of ocular artifact. Electroencephalogr Clin Neurophysiol 55:468–484

Hendriks VM, Kaplan CD, Van Limbeek J, Geerlings P (1989) The addiction severity index: reliability and validity in a Dutch addict population. J Subst Abuse Treat 6:133–141

Herrmann MJ, Weijers HG, Wiesbeck GA, Aranda D, Böning J, Fallgatter AJ (2000) Event-related potentials and cue-reactivity in alcoholism. Alcohol Clin Exp Res 24:1724–1729

Herrmann MJ, Weijers HG, Wiesbeck GA, Boning J, Fallgatter AJ (2001) Alcohol cue-reactivity in heavy and light social drinkers as revealed by event-related potentials. Alcohol Alcohol 36:588–593

Kayser J, Tenke C, Nordby H, Hammerborg D, Hugdahl K, Erdmann G (1997) Event-related potential (ERP) asymmetries to emotional stimuli in a visual half-field paradigm. Psychophysiology 34:414–426

Kok A (1997) Event related-potential (ERP) reflections of mental resources: a review and synthesis. Biol Psychol 45:19–56

Kounios J (2002) A neural mechanism for non-verbal discourse comprehension. Trends Cogn Sci 6:272–275

Kozlowski LT, Wilkinson DA (1987) Use and misuse of the concept of craving by alcohol, tobacco, and drug researchers. Br J Addict 82:31–45

Lang PJ, Greenwald MK, Bradley MM, Hamm AO (1993) Looking at pictures: affective, facial, visceral, and behavioral reactions. Psychophysiology 30:261–273

Lang PJ, Bradley MM, Cuthbert BN (1998) Emotion and motivation: measuring affective perception. J Clin Neurophysiol 15:397–408

Lang PJ, Bradley MM, Cuthbert BN (1999) International affective picture system (IAPS): instruction manual and affective ratings. Center for Research in Psychophysiology, University of Florida, Gainsville

London ED, Ernst M, Grant S, Bonson K, Weinstein A (2000) Orbitofrontal cortex and human drug abuse: functional imaging. Cereb Cortex 10:334–342

Maas LC, Lukas SE, Kaufman MJ, Weiss RD, Daniels SL, Rogers VW, Kukes TJ, Renshaw PF (1998) Functional magnetic resonance imaging of human brain activation during cue-induced cocaine craving. Am J Psychiatry 155:124–126

McKay JR (1999) Studies of factors in relapse to alcohol, drug and nicotine use: a critical review of methodologies and findings. J Stud Alcohol 60:566–576

McPherson WB, Holcomb PJ (1999) An electrophysiological investigation of semantic priming with pictures of real objects. Psychophysiology 36:53–65

Robinson TE, Berridge KC (1993) The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Rev 18:247–291

Robinson TE, Berridge KC (2000) The psychology and neurobiology of addiction: an incentive-sensitization view. Addiction 95: S91–S117

Robinson TE, Berridge KC (2001) Incentive-sensitization and addiction. Addiction 96:103–114

Schupp HT, Cuthbert BN, Bradley MM, Cacioppo JT, Ito T, Lang PJ (2000) Affective picture processing: the late positive potential is modulated by motivational relevance. Psychophysiology 37:257–261

Silberman EK, Weingartner H (1986) Hemispheric lateralization of functions related to emotion. Brain Cogn 5:322–353

Sjostrom O, Holst D (2002) Validity of a questionnaire survey: response patterns in different subgroups and the effect of social desirability. Acta Odontol Scand 60:136–140

VanRee JM, Gerrits MAFM, Van der Schuren LJMJ (1999) Opioids, reward and addiction: an encounter of biology, psychology, and medicine. Pharmacol Rev 51:341–396

Verheul R, Van den Brink W, Geerlings P (1999) A three-pathway psychobiological model of craving for alcohol. Alcohol Alcohol 34:197–222

Volkow ND, Wang G-J, Fowler JS, Hitzemann R, Angrist B, Gatley SJ, Logan J, Ding Y-S, Pappas N (1999) Association of methylphenidate-induced craving with changes in right striato-orbitofrontal metabolism in cocaine abusers: implications in addiction. Am J Psychiatry 156:19–26

Warren CA, McDonough BE (1999) Event-related brain potentials as indicators of smoking cue-reactivity. Clin Neurophysiol 110:1570–1584

Watson D, Tellegen A (1985) Toward a consensual structure of mood. Psychol Bull 98:219–235

Watson D, Clark LA, Tellegen A (1988) Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 54:1063–1070

Weinstein A, Feldtkeller B, Malizia A, Wilson S, Bailey J, Nutt DJ (1998) Integrating the cognitive and physiological aspects of craving. J Psychopharmacol 12:31–38

West WC, Holcomb PJ (2002) Event-related potentials during discourse-level semantic integration of complex pictures. Brain Res Cogn Brain Res 13:363–375

West R, Ross-Munroe K (2002) Neural correlates of the formation and realization of delayed intentions. Cogn Affect Behav Neurosci 2:162–173

Wexler BE, Gottschalk CH, Fulbright RK, Prohivnik I, Lacadie CM, Rounsaville BJ, Gore JC (2001) Functional magnetic resonance imaging of cocaine craving. Am J Psychiatry 158:86–95

Wise RA (1996) Neurobiology of addiction. Curr Opin Neurobiol 6:243–251