Cognitive and neuropsychopharmacological processes in human drug craving
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Chapters 9

Two New Physiological Indices of Cocaine Craving: Evoked Brain Potentials and Cue Modulated Startle Reflex

Craving for cocaine is one of the hallmarks of cocaine dependence. One of the problems with craving is its measurement. Traditional psychophysiological indices such as skin conductance and heart rate yielded contradictory results. These measures of craving were found to correlate only moderately with self-reported craving. In the present study, event-related brain potentials (ERP's) and the cue modulated startle response (CMSR) are evaluated as indexes for cocaine craving. Twenty-one abstinent cocaine dependent subjects were divided in a high and low cravers group based on the median split of self-reported craving scores. ERP's and CMSR were measured while subjects watched neutral, pleasant, unpleasant and cocaine related pictures. Overall, it was found that the cocaine dependent subjects showed augmented slow-positive waves (SPWs) of the ERP on the cocaine pictures, compared to neutral pictures. Furthermore, it was found this cue-elicited SPWs were positively correlated with self-reported cocaine craving. Specifically, on the cocaine cues the high craving group showed more positivity on the late positive wave reactivity than low cravers. In contrast to the ERP measures, CMSR did not differentiate between cocaine pictures and neutral pictures. In addition, no differences between the low- and high cravers on the CMSR measure were found. The present results show that the evoked-potentials paradigm provides promising results to index cue-elicited craving. The use of startle modulation deserves further investigation in this respect.


Introduction

Craving, the intense desire to take a drug, is considered to be a central aspect of dependence and a contributing factor in relapse. Drug addicts frequently report the experience of craving prior to relapse. From a conditioning point of view, drug-associated cues are seen as a trigger of craving. These drug cues have been shown to elicit several behavioral and physiological effects (cue reactivity). Increases in anxiety, tension, and urge to drink have been demonstrated in alcoholics exposed to drug-cues. Therefore, reactivity to drug cues has been investigated as a possible indication of vulnerability to relapse.

One of the problems with craving is its measurement. For research and clinical purposes self-reported craving should be accompanied by more objective, physiological measures. With respect to the physiological assessment of craving, research to date used traditional indexes such as, heart rate, skin conductance, and skin temperature. These traditional physiological measures have produced rather low correlations with craving. There is a clear need to employ new concepts and new indices of craving. More recently two relative new techniques have been suggested, the cue modulated startle response (CMSR), and the slow positive wave of the event-related potentials (slow positive wave, SPW).

New physiological approaches to assess the involvement of motivational systems can globally be divided in techniques that measure whether an emotional system is involved (ERP's) and techniques that measure which emotional system is involved (appetitive or aversive; CMSR). Although it has been demonstrated that ERP's can measure the involvement of motivational and attentional systems of the
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... brain6-7,36, ERP’s do not differentiate between motivation for approach and for avoidance. Craving is generally seen as a conditioned desire for the pleasurable effects of a drug. In this vain, it may be that, over the course of several drug administrations, drug related stimuli come to predict the rewarding sensation of drugs. Thus, confronted with a conditioned drug related stimulus, the addicted subject will seek to obtain and ingest drugs followed by rewarding effects of that drug. This explanation is coined the ‘conditioned reward’ hypothesis39. A different view describes craving as a conditioned withdrawal-like state, which results in the desire for drugs to alleviate this negative affective state. Simply stated, cues become conditioned indicators of unpleasant withdrawal. This explanation is coined the ‘conditioned withdrawal’ hypothesis40. (For a review on craving theories (see6). To date, it is not exactly clear which of these theories is supported by empirical data. Do drug related cues evoke aversive or appetitive responses? In two studies on the motivational effects (appetitive and aversive) of drug cues in smokers and alcoholics6-10, the authors found that drug cues trigger an appetitive response on an aversive motivational response. These data lend support to the “conditioned reward” hypothesis of craving. However, a study by Drobos et al. (2001) found evidence that that in food deprived subjects, food cues trigger an aversive response. This suggests that these cues trigger the aversive motivational system of the brain. The motivational effects of cocaine related cues in humans have not been studied yet. It is interesting in this context that cocaine addicts occasionally report very strong cravings for cocaine (but no physical withdrawal symptoms as in alcohol and heroin dependence. Carter & Tiffany27 conducted a meta-analyses of cue-reactivity and craving, among cocaine, nicotine, heroin, and alcohol dependent individuals. They showed, using the following indexes: heart rate, skin temperature, and sweat gland activity, that cocaine addicts exhibit a trend towards the highest scores in the indexes heart rate and skin temperature. Sweat gland activity was highest in the nicotine group, followed by cocaine, heroin, and alcohol. It is expected that the positive motivational properties of cocaine cues are equal or greater than nicotine and alcohol cues. Below the two measures used in the present study are described in more detail.

Event Related Potentials (ERP)
The electroencephalogram (EEG) is used to measure event related potentials (ERP). Approximately 300 milliseconds after stimulus presentation (e.g. watching pictures) and onward, a slow positive wave (SPW) develops. This SPW is thought to reflect a cortical response to emotional cues6. It is known that emotional cues elicit larger slow positives (e.g., more positivity in the EEG), presumably because more attentional resources are allocated to emotionally arousing stimuli, reflecting the involvement of motivational systems in the brain6. In addiction research, ERPs have been used to assess cue reactivity in substance abuse17-19,20,28, showing increased reactivity for substance abusers. Schupp18 and colleagues found that the SPW component of the ERP is modulated by motivational relevance. In their study, pictures of emotional content evoked larger SPWs than neutral pictures. Highly arousing pictures generated larger slow positive potentials than pictures of low arousal value. This may suggest that, among cocaine addicts, high cravers should exhibit a larger SPW than low cravers, as cocaine pictures are assumed to have larger motivational relevance for high cravers than for low cravers.

Cue Modulated Startle Response (CMSR)
The cue modulated startle response (CMSR) paradigm can be employed in order to modulate the dominant motivational system6. In the CMSR paradigm, a subject is exposed to a noxious stimulus (loud noise), which will elicit a dominant defensive startle response as measured by eye-blink electromyogram (EMG) activity. In the concurrent presence of an unpleasant foreground stimulus (e.g., unpleasant picture), this de-
fensive startle response will be potentiated. In the presence of a pleasant foreground stimulus (e.g., pleasant picture), however, the startle response will be attenuated. To date, the CMSR technique has not been used for measuring craving among cocaine addicts. One of the aims of the present study was to assess the usefulness of this paradigm in predicting subjective craving report, and measuring the motivational valence of drug related cues in cocaine addicts.

The overall aim of the present study is to study whether two new techniques, CMSR and SPW, can differentiate between neutral cues and cocaine related cues in cocaine dependent subjects. Additionally, an attempt was made to differentiate between low and high cocaine cravers using these techniques. Specific hypothesis were:

1. Cocaine cues elicit larger SPW in cocaine users than neutral cues, indicating the involvement of a motivational system (within-subjects SPW effect).
2. High cocaine cravers exhibit larger SPW on cocaine cues than low cravers, indicating that this motivational activation is related to craving (between-subjects SPW effect).
3. The presence of cocaine cues will attenuate the startle response in cocaine cues as much as pleasant cues, in contrast to neutral and unpleasant cues (within-subjects CMSR effect).
4. This decrease in startle response will be larger among high cocaine cravers compared to low cravers (between-subjects CMSR effect), indicating that high cravers evaluate the cocaine cues as more pleasant than low cravers.

Methods and Materials

Participants

Twenty-one eligible cocaine dependent subjects were recruited among the participants of an inpatient substance abuse program (Parnassia Mental Health Care). The Ethical Committee of the institution in which the work was performed had approved the study. Participants were recruited from different drug-treatment facilities, all had been abstaining from drug use (mean=9.4 weeks; sd=6.7). The study population consisted of 16 men and 5 women. Subjects where divided into a high- and a low-craving group based on their post-exposure craving scores (DDQ, Desire Scale) by means of a median split.

Stimulus materials

Twenty-four color pictures (8 neutral, 8 appetitive, and 8 aversive slides) were selected from the international affective picture system (appetitive 4180, 4232, 4660, 5480, 8030, 8080, 8370, 8380; aversive 3000, 3010, 3102, 3150, 3170, 3530, 6230, 9410; neutral 2840, 5534, 6150, 7000, 7002, 7050, 7090, 7190). In addition, 16 cocaine related color pictures consisting of digital photographs of cocaine use, and cocaine paraphernalia were produced. All pictures appeared on an IBM-G54 monitor for 7000 ms in random order. The inter-stimulus interval was a random time between 5 and 10 seconds. The acoustic startle stimulus was a 95 dB (A) burst of white noise with a duration of 50 ms and a rise/fall time < 1 ms generated by a Creative Labs SoundBlaster 16. Sennheiser HD 420 SL headphones were used for binaural presentation of the startle stimulus. Delay from picture onset to onset of the startle stimulus was 3000, 5000, or 6500 ms. A startle stimulus was presented in 75% of the pictures. Before the start of the experiment two pictures were presented for practice purposes (neutral pictures 7175 and 7233).
Table 1. Characteristics of the high and low cravers group. Values represent means and standard deviation (in parenthesis). Significance was tested with unpaired t-test (alpha =0.05).

<table>
<thead>
<tr>
<th></th>
<th>Low cravers (n=11)</th>
<th>High Cravers (n=10)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>27.2 (7.21)</td>
<td>31.6 (10.65)</td>
<td>NS</td>
</tr>
<tr>
<td>Years of education</td>
<td>11.7 (3.0)</td>
<td>10.7 (2.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Years of cocaine abuse</td>
<td>7.6 (5.3)</td>
<td>8.6 (5.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Age of onset cocaine use</td>
<td>17.6 (1.5)</td>
<td>21.3 (1.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Using cocaine days/month</td>
<td>13.5 (14.1)</td>
<td>17.7 (14.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Weeks of current cocaine abstinence</td>
<td>7.5 (5.7)</td>
<td>10.9 (3.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Number of previous detoxifications</td>
<td>1.5 (1.7)</td>
<td>1.9 (1.7)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Procedure

Eligible subjects where asked to participate in a study concerning cocaine craving. They where informed that participation involved EEG/EMG measurements and viewing pictures of drug use. Compensation for participation was 5 euro. The experiment started with a short explanation of the procedure and informed consent was obtained. Personal data and history of drug use where recorded by the experimenter. Then the subject completed the pre-exposure questionnaires. After completion the subject was seated in the EEG chair and electrodes where attached. Headphones where placed on the head. A comment was made that the subject could ignore occasional noise that would be heard from the headphones during the experiment. Instructions where 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 where removed and a post-exposure craving questionnaire was completed. Upon dismissal, subjects received their financial compensation and there was a check by the experiment-leader whether the craving levels were not unacceptable high. If so, a cool-down-talk was provided until craving levels were decreased to an acceptable level.

Physiological measures

EEG was measured with a digital Schwartzter amplifier using four Ag/AgCl electrodes at the Cz, Pz, Fz, right and left mastoid locations (last two served as reference channel and ground respectively) according to the international 10-20 system. The vertical electro-oculogram (VEOG) was recorded with an Ag/AgCl electrode located above the right eye, using the same reference channel. All signals were unfiltered digitized on a PC with Brainlab (OSG, Belgium) software with a sample rate of 1000Hz and 16-bit A/D conversion. Off-line, the time constant was set at 2 seconds and high frequencies were cut-off at 35 Hz (both phase shift-free Butterworth filters; 24dB/octave slope). For all electrodes, impedance was kept under 10 Kohm. Startle eyeblink EMG responses were recorded bipolarily from the right orbicularis oculi muscle using two miniature Ag/AgCl electrodes with a distance of approximately 20 mm. The same amplifier was used as the EEG recordings for registering an unfiltered EMG signal with a sample-rate of 1000 Hz. Off-line EMG data records were high pass filtered by means of a phase shift-free Butterworth filter (24dB/octave slope) with a -3 dB cutoff frequency of 28 Hz. The low-pass cutoff was set on 500 Hz (24dB/octave slope). 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.

Self-report measures

Demographic data were self-reported (age, ethnicity, medication, and length of treatment).

Instant craving was measured by the Desire for Drug Questionnaire (DDQ)'. This questionnaire was originally adapted from the Desires for Alcohol Questionnaire (DAQ) for use in heroin addicts. In this study the same questionnaire was used for cocaine addicts by substituting the word "heroin" for the word "cocaine". It measures instant (now) craving and consists of three sub-
scales. 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.

For the measurement of general craving the Obsessive Compulsive Drug Use Scale (OCDUS) was used. This questionnaire was adapted from the Obsessive Compulsive Drinking Scale (OCDS) for use in heroin addicts. In this study the word "heroin" in the items of the OCDUS was substituted for the word "cocaine" to create an OCDUS version applicable for cocaine addicts. The OCDUS measures craving over the previous week and consists of three scales: thoughts about cocaine and experienced interference thereof; desire and control concerning the use of cocaine; and resistance to thoughts and intentions to use cocaine. For the heroin version, all three scales have good reliability and concurrent validity.

For the measurement of addiction severity, the Addiction Severity Index (ASI) was employed. Only the drug use severity subscale (ASI-DRUG) was used. Questions contained in the ASI refer to which different drugs were used, amount used, and duration of use.

**Data reduction and analysis**

EEG signal was measured from 200 ms before to 2000 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. Visual inspection of the ERP grand average waveform showed that peaks were not pronounced (fig. 2) 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 300-400 captured the P3 area, 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 2000 window captured the sustained slow positive wave (SSPW). Earlier time frames were not analyzed, because previous research showed that the slow positive voltage change occurred from 300 ms after picture onset (and onward). ERP reactivity was defined as ERP amplitudes of cocaine stimuli minus neutral stimuli in the different time domains. Repeated measure ANOVAs with craving group as between-subjects factor and picture category and electrode site as within-subjects factor (2x4x3 mixed design) were used to test for differences on the four ERP areas. Main electrode effects were present in all analyses (all p<.001), however not reported because overall differences between Fz, Pz and Cz were not of interest. In contrast, electrode x cue interaction effects are reported.

After filtering, the EMG signal was rectified. Eyeblink responses were defined as the peak amplitude in the EMG signal (in μV) between 40-80 ms following after the startle-probe onset. In two subjects, no detectable blink was observed. These subjects were excluded from startle-blink analyses. To reduce the effects of large inter-individual differences, EMG blink magnitudes are expressed in the standardized t-scores (mean=50, SD=10). For statistical testing of overall between group differences, raw scores were employed (see /). Within subject and interaction effects were analyzed using repeated measure ANOVAs with craving group as between-subjects factor and stimulus category as within-subjects factor (2x2 mixed design) for differences on the standardized t-score of the startle eyeblink. Between subject effects (group differences using raw score) were analyzed using the same ANOVA design. In addition to the startle peak amplitudes, the latencies of the peak amplitude were analyzed using the same ANOVA design.

For all ANOVA's reported in this study, a Greenhouse-Geisser adjustment on the df's was conducted when appropriate.
Figure 2. Grand mean ERP waveform for all cocaine dependent subjects on four types of pictorial cues (neutral, pleasant, unpleasant and cocaine-related content). Lines indicate the time-windows of interest (300-400, 400-700, 700-1000, 1000-2000 ms).
An alpha-level of 0.05 was used for all statistical tests.

Results

Self-report measures

The baseline OCDUS-cocaine scales revealed no differences between the two Low and High craving group on the subscales "thoughts about cocaine and experienced interference" (mean=9.9 vs. 13.4; t(19)=−1.4; p=.17), and "desire and control concerning the use of cocaine" (mean = 5.6 vs. 6.3; t(18)=−.69; p=.50).

Reactivity and baseline effects of the DDQ scales were analyzed with a 2 (time) x 2 (group) repeated measure ANOVA. No group, time or interaction effects were found on "Negative reinforcement" and "Control" scale (all p>0.05). Obviously, the DDQ desire showed significant differences between the two groups [(F(1,18)=9.24; p=.007]. Furthermore, a time effect was found [(F(1,18)=5.94; p=.025], indicating there was an overall increase in craving after the picture cues. A significant group x time effect [(F(1,18)=12.60; p=.002] indicated that the increase in craving was larger in the high craving group than in the low craving group.

Startle Data

A 4 (picture category) x 2 (group) repeated measure ANOVA was conducted on the standardized blink scores. A main effect for picture category was observed [F(3,51)=5.69; p=.002]. Contrasts showed that the only significant effect was a potentiation of the startle response of the total group on the unpleasant pictures compared to neutral pictures [F(1,17)= 14.29; p=.001]. No significant attenuating effect of the startle response on pleasant [F(1,17)=.31; ns] and cocaine cues [F(1,17)=1.15; ns] was found. No interaction effect was found between picture category and group was observed [F(3,51)=.47; ns]. The mean values of both groups on the four picture categories are displayed in figure 1. A between subjects ANOVA on the raw scores in order to test for group effects revealed no significant overall differences between the two groups [F(1,17)=.34; ns].

A 4 (picture category) x 2 (group) repeated measure ANOVA conducted on the blink latencies showed did not reveal significant differences [F(3,51)=2.71; ns].

Figure 1. Mean (with standard error) standardized startle blink values of low cravers and high cravers during the watching of neutral, pleasant, unpleasant and cocaine cues.

ERP Data

P3 (300-400 ms)

A main effect was found for picture category [F(3,57)=4.78; p<.0005]. Contrasts revealed that P3 was more positive for unpleasant pictures [F(1,19)=9.04; p=.08] and cocaine pictures [F(1,19)=18.52; p<.0005] compared to pleasant cues. Furthermore, no picture category x group interaction effect was found [F(3,57)=2.39; ns].

Extended P3 (400-700 ms)

A main effect was found for picture category [F(3,57)=7.98; p<.0005]. Contrast revealed that compared to neutral pictures, the extended P3 region was more pronounced on unpleasant cues [F(1,19)=7.96; p=.01] and cocaine cues [F(1,19)=12.93; p=.002]. No picture category x group interaction effect was found [F(2,57)=2.20; ns].
Figure 3. Grand mean ERP waveform for Fz, Cz, and PZ sites for high and low craving cocaine dependent subjects in response to neutral and cocaine-related pictures.
**Slow Positive Wave (700-1000 ms)**

A main effect was found for picture category \([F(3,57)=4.90; p=.004]\). Contrast revealed that compared to neutral pictures, the SPW was more pronounced on unpleasant cues \([F(1,19)=10.36; p=.005]\) and cocaine cues \([F(1,19)=14.20; p=.001]\). Although no picture category \(x\) group interaction effect was found \([F(2,57)=1.68; ns]\), a planned contrast analysis showed that the SPW in the high cravers group, but not in the low cravers group, was more pronounced on the cocaine pictures than on the neutral pictures \([F(1,19)=4.69; p=.043]\). For the pleasant and unpleasant pictures no significant differences between the two groups were found.

**Sustained Slow Positive Wave (1000-2000 ms)**

Again, as the other time frames, a main effect was found for picture category \([F(3,57)=4.22; p=.009]\). Just as the SPW, compared to neutral pictures, the SSPW was more pronounced on unpleasant pictures \([F(1,19)=7.04; p=.016]\) and cocaine pictures \([F(1,19)=7.03; p=.016]\). In addition, a picture category \(x\) group interaction effect was found \([F(2,57)=2.90; p=.043]\). A contrast analysis showed that the SSPW in the high cravers group, but not in the low cravers group, was more pronounced on the pleasant \([F(1,19)=8.02; p=.011]\), unpleasant \([F(1,19)=6.17; p=.023]\), and cocaine pictures \([F(1,19)=5.14; p=.035]\) than on the neutral pictures.

**Conclusion**

In this study we set out to test four hypotheses on the physiological measuring of drug craving. Two new psychophysiological measures (CMSR and SPW's) were used. Positive evidence for the first hypothesis, that cocaine cues elicit larger SPW's in cocaine users than neutral cues, was found. Both high and low cravers showed significant greater positivity in the EEG (P3, EXT P3, SPW, and SSPW) on cocaine cues than on neutral cues. This finding indicates that a motivational system is involved in cocaine dependent subjects when watching cocaine related pictures. This finding is compatible with theories claiming that the SPW (and SSPW) is an index of attentional functioning. Lang's theory on emotion and attention states that stimuli that have a high emotional impact automatically consume large parts of the attentional resources. The finding that cocaine cues have high motivational properties and grab the attention of the cocaine user is in agreement with previous studies. On both these studies a correlation was found between craving levels and attentional focusing on drug related (heroin and cocaine) stimuli. Furthermore, it is in concordance with the theory of Robinson and Berridge who claim that drug-related stimuli become especially salient, and grab the attention (incentive sensitization).

The second hypothesis, that high cocaine cravers exhibit larger SPW on cocaine cues than low cravers, could also be corroborated. This finding indicates that the slow wave ERP reactivity is a good discriminator of low and high cravers. This finding is in concordance with the first hypothesis and adds further evidence to the findings of Cuthbert and Schupp that the SPW of the ERP is an adequate index of motivational interest. The augmented motivational interest for cocaine pictures in high cravers as found in this study may possibly be explained by an enhanced sensitization of the dopamine system of high cravers. Several human studies indicate that selective attention is affected by dopaminergic abnormalities. Because attentional functioning may be one of the important factors in addictive behaviors, the biological underpinnings of attentional functioning in cocaine abuse should be high on the research agenda.

In contrast to ERP findings, no evidence was found for the third hypothesis that the valence of cocaine cues would be appetitive, as indicated by reduced startle responses when compared to neutral cues. The present results indicate that the valence related response (the CMSR) on cocaine related pictures does not differ from neutral pictures. These results do not confirm the findings of Mucha and Geier who found...
that drug related stimuli elicit appetitive motivation. A possible explanation is that cocaine cues do not trigger the modulation of the startle response in this population of abstinent cocaine dependent subjects, in contrast to smokers and alcoholics. It may be that the involvement of motivational systems is not the same for all drugs of abuse. A second explanation for this divergence is that the pictures were not salient enough to result in the modulation of the startle reflex. However, this appears to be in contrast with the ERP findings. A third, and more plausible explanation, is that the inter-individual differences of the present cocaine group was too large to achieve significant results. This conclusion is supported by the non-significant finding that the CMSR in the low-cravers group was more potentiated than the CMSR in the high cravers group. Possibly other factors that were not studied in the present design contribute to the modulation of the startle response during the watching of cocaine related pictures. For example, the heterogeneity of the cocaine pictures. Namely, after the experiment, cocaine dependent subjects frequently reported that pictures showing drugs exclusively activated aversive feelings, whereas pictures showing the actual use of drugs elicited appetitive feelings. Unfortunately, in the current study we were not able to discriminate between those two picture categories. Another factor that may contribute to the inter-individual differences is personality. Previous studies show that sensitivity for reward is associated with increased alcohol craving\(^1\). It is reasonable to assume that the sensitivity for reward is associated with CMSRs, which reflects approach motivation.

As with the cocaine pictures, watching appetitive cues did not result in an inhibition of the CMSR. This finding suggest that the appetitive cues did not elicit activation of the appetitive motivational system in these post-cessation cocaine users. Although this was not an explicit goal of the study, this finding is consistent with the anhedonia hypothesis of cocaine withdrawal. The current sample was recruited among recently abstaining cocaine users. It is known that, besides craving, anhedonia (the diminished capacity to experience pleasure) is one of the major symptoms of the cocaine abstinence syndrome\(^2\). In previous studies it has been found that reduced activity of the dopamine system is associated with this post-cessation anhedonia\(^3\). It is conceivable that this anhedonia is associated with failures in inhibiting CMSR since depressive symptoms are found to be related to failures to inhibit CMSR\(^4\). This way, the present study adds further neurophysiological evidence to the hypothesis that cocaine-cessation is related to anhedonia. Further investigation on the relation between the inhibition of the CMSR during cocaine abstinence and the experience of psychiatric pathology such as anhedonia and depression is clearly needed.

Consistent with previous findings in normal populations, both cocaine dependent groups displayed a potentiation of the CMSR when viewing aversive pictures\(^5\). This indicates that the aversive/avoidance motivational system of cocaine dependent subjects does not diverge from normal functioning. The fourth hypothesis was that high cocaine cravers should show a larger decrease in the startle response, to cocaine than to neutral pictures compared to low cravers. The present data does not support this hypothesis.

Of the two studied physiological indices of cocaine craving, the ERP (sustained) slow positive wave (SPW) turned out to provide the most unambiguous measure for cocaine craving. Since the SPW results did show an enhanced positivity of the wave on cocaine cues, it can be concluded that drug related stimuli do not only facilitate craving, but also have attention grabbing properties. This finding is supportive for theories describing addiction in general, and craving in particular, as connected with an alteration in attention\(^6\). More research using CMSR methodology for studying the involvement of motivational systems should be undertaken to investigate whether, and for which subtypes of cocaine abusers, cocaine re-
lated cues have appetitive motivational properties.

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