Responsiveness to Drug Cues and Natural Rewards in Opiate Addiction

Associations With Later Heroin Use

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Context: Although drug cues reliably activate the brain’s reward system, studies rarely examine how the processing of drug stimuli compares with natural reinforcers or relates to clinical outcomes.

Objectives: To determine hedonic responses to natural and drug reinforcers in long-term heroin users and to examine the utility of these responses in predicting future heroin use.

Design: Prospective design examining experiential, expressive, reflex modulation, and cortical/attentional responses to opiate-related and affective stimuli. The opiate-dependent group was reassessed a median of 6 months after testing to determine their level of heroin use during the intervening period.

Setting: Community drug and alcohol services and a clinical research facility.

Participants: Thirty-three opiate-dependent individuals (mean age, 31.6 years) with stabilized opiate-substitution pharmacotherapy and 19 sex- and age-matched healthy non–drug users (mean age, 30 years).

Main Outcome Measures: Self-ratings, facial electromyography, startle-elicited postauricular reflex, and event-related potentials combined with measures of heroin use at baseline and follow-up.

Results: Relative to the control group, the opiate-dependent group rated pleasant pictures as less arousing and showed increased corrugator activity, less postauricular potentiation, and decreased startle-elicited P300 attenuation while viewing pleasant pictures. The opiate-dependent group rated the drug-related pictures as more pleasant and arousing, and demonstrated greater startle-elicited P300 attenuation while viewing them. Although a startle-elicited P300 amplitude response to pleasant (relative to drug-related) pictures significantly predicted regular (at least weekly) heroin use at follow-up, subjective valence ratings of pleasant pictures remained the superior predictor of use after controlling for baseline craving and heroin use.

Conclusions: Heroin users demonstrated reduced responsiveness to natural reinforcers across a range of psychophysiological measures. Subjective rating of pleasant pictures robustly predicted future heroin use. Our findings highlight the importance of targeting anhedonic symptoms within clinical treatment settings.

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users develop increased reward thresholds to natural reinforcers following long-term drug exposure and may find it difficult to replace drug-taking behaviors with other, less-harmful rewarding activities.

An alternate model proposes that, with repeated drug use, cues associated with drug-taking acquire incentive value through sensitization of the brain’s reward system; as the number of paired stimuli–drug presentations increase, the incentive value of these stimuli intensifies, making them increasingly “wanted.” With ongoing use, drug cues acquire excessive incentive salience, “wanting” transforms into drug craving, and drug cues become potent perpetuators of further drug-taking despite awareness of associated adverse consequences. In support of this model, drug cues can selectively capture attentional resources as well as reliably activate key regions within the brain’s reward system. Recent studies have demonstrated that attentional bias to drug cues also predicts relapse after clinical treatment. However, such research predominantly focuses on responses to drug-related stimuli alone and rarely examines how these findings compare with the processing of natural reinforcers, despite evidence for associated anhedonia.

Recently, Lubman et al demonstrated that event-related potential responses to drug-related stimuli were greater than those elicited by affective and neutral stimuli in long-term heroin addicts. While these results support the notion of an appetitive bias toward drug cues, the heroin users also lacked the typical enhancement of event-related potential responses to nondrug affective stimuli, consistent with inhibited responding to natural rewards (ie, anhedonia). Few other studies examining affective processing in addiction have been conducted, with most research focused on the brain’s responses to drug stimuli (ie, incentive salience) rather than their relationship with natural reinforcers (ie, hedonic allostatics). Research investigating both phenomena is particularly important in determining whether these responses represent autonomous or interdependent processes and in determining their relevance to clinical outcomes.

We used an affective picture-viewing paradigm to comprehensively examine hedonic responses to natural and drug-related reinforcers in a sample of heroin users whose addiction was stabilized with methadone or buprenorphine. However, even with stabilization on opiate pharmacotherapy, prospective studies reveal that many heroin users continue to use illicit heroin while undergoing treatment, though typically at substantially lower levels. Although some of the factors that predict ongoing use of illicit opiates during substitution therapy have been identified (eg, treatment length, higher doses of pharmacotherapy), the role of hedonic processes has not been examined. Thus, we followed up our sample to explore the role of hedonic responses in predicting future heroin use.

In this study, negatively valent (unpleasant) pictures were also presented to determine the specificity of responses across affective stimuli. Psychophysiological responses that were examined included electromyographic (EMG) measurements of expressive facial responses (in the corrugator supercili and zygomaticus major), the startle-elicited postauricular reflex (an appetitive reflex that is potentiated during pleasant stimuli and inhibited during aversive stimuli), and the startle-elicited event-related potential (a measure of the attentional resources allocated to processing stimuli, indexed by the degree to which cortical processing of the startle stimulus is inhibited). When combined, these measures provide a comprehensive, multimethod description of experiential (self-report), expressive (facial EMG), reflex modulation (postauricular reflex), and cortical/attentional (startle-elicited event-related potential) responses to rewarding stimuli.

We hypothesized that (1) opiate-dependent individuals would demonstrate reduced reward responsiveness to natural reinforcers and increased reward responsiveness to drug cues compared with nondrug rewards; and (2) owing to difficulties in replacing drug use with other rewarding activities, addicted individuals who demonstrated reduced reward responsiveness to natural reinforcers, as well as increased reward responsiveness to drug cues (compared with nondrug rewards), would be at the greatest risk of ongoing heroin use (weekly or more frequent use) during the medium-term.

**METHODS**

**SUBJECTS**

Participants included 33 opiate-dependent individuals (recruited from local drug and alcohol services and pharmacies [via advertisement posters and flyers]) and 19 healthy volunteers (recruited through community advertising). Opiate-dependent subjects were required to (1) have a current IQ higher than 70; (2) be stable on their methadone/buprenorphine dosage for at least 2 months; and (3) have no current comorbid mental health disorder. None of the subjects had a history of significant head injury, neurological disease, electroconvulsive therapy, impaired thyroid function, or steroid use. Healthy controls had no history of psychiatric illness or substance misuse. Opiate-dependent subjects were required to abstain from using illicit heroin for at least 24 hours before testing. All subjects gave written informed consent to participate in the study, which was approved by local research and ethics committees.

**CLINICAL ASSESSMENT**

All subjects were screened using the patient edition of the Structured Clinical Interview for DSM-IV Axis 1 Disorders to ensure that they did not have a current anxiety, mood, or psychotic disorder. Diagnoses of DSM-IV opiate dependence were also established by structured interview. While opiates were the primary drug of abuse (current and lifetime) for all clinical participants, other substances were also commonly used, including tobacco (75.8% with daily use), alcohol (21.3% with at least weekly use), cannabis (30.3% with at least weekly use), and benzodiazepines (18.2% with at least weekly use). Thirty percent reported that they also used illicit heroin on at least a weekly basis. Depressive symptoms were assessed using the Beck Depression Inventory, while current mood state was assessed using the Positive and Negative Affect Schedule.

The opiate users reported minimal levels of opiate withdrawal (as indexed by the Short Opiate Withdrawal Scale) at the time of testing (Table 1) and reported experiencing a moderate degree of problems with psychological dependence (as indexed by the Severity of Dependence Scale). There were no significant differences between opiate-dependent subjects and healthy volunteers with respect to sex or age. The opiate users
did report a significantly higher level of depressive symptoms ($t_{33} = 4.61, P < .001$), though current mood ratings (ie, positive and negative affect) between the groups did not differ significantly. The opiate-dependent group reported a significant increase in craving scores from pre-to post–picture viewing (Wilcoxon signed rank, $t_{33} = 4.002; P < .001$, 2-tailed).

The opiate group was reassessed a median of 6 months after initial assessment (range, 3.9-8 months) to determine their level of heroin use during the intervening period. Participants were grouped by frequency of weekly heroin use, as this has been previously used as a key outcome variable in studies of opiate pharmacotherapy. Of the 33 opiate-dependent participants assessed at baseline, 12 reported using heroin at least once a week (36.4%) (ie, regular use) throughout the follow-up period, while 19 were using heroin less than once a week or not at all at follow-up (57.6%). Participants’ use of other drugs did not change during the follow-up period, though increased alcohol use was reported (33.4% with at least weekly use). Two participants (6.1%) could not be contacted at follow-up to determine frequency of heroin use and were therefore only included in baseline analyses.

### STIMULI

**Materials**

Affective slides included 30 opiate-related pictures (eg, drug paraphernalia, heroin preparation, and injection), 30 unpleasant pictures (eg, distressed individuals, snakes, mutilation; mean [standard deviation (SD)], valence score: 2.9 [1.6]; arousal score: 5.6 [2.2]; range, 1-9.32) 30 pleasant pictures (eg, erotic nudes [changed depending on the participant’s sex], food, action sports; valence, male: 7.3 [1.5]; valence, female: 7.1 [1.7]; arousal, male: 6.2 [2.1]; arousal, female: 5.7 [2.2]32), and 30 neutral pictures (eg, household and inanimate objects; valence: 5.0 [1.2]; arousal: 2.0 [1.2]32). The pleasant, neutral, and unpleasant pictures were selected from the International Affective Picture System, whereas the opiate-related pictures were taken from media libraries and were matched for social content. Three examples of the 4 slide categories were randomly allocated to 10 experimental blocks. Picture presentation was randomized within each block, which was composed to form 2 different picture orders, counterbalanced between participants within groups.

### Procedure

After the clinical interview, participants viewed 120 pictures, with accompanying startle probes delivered binaurally through headphones. The acoustic startle probe was a 50-millisecond, 100-dB burst of white noise with instantaneous rise time, presented either 2500 or 3500 milliseconds after picture onset for 96 of the 120 trials, balanced across picture types. Two startle probes were delivered before experimentation to facilitate startle habituation. Pictures were displayed for 4 seconds, followed by a 6-second interstimulus interval. Participants were instructed to view each picture and to ignore startle probes. After this, participants rated the pictures using a computerized version of the Self-Assessment Manikin (SAM).39 Participants rated pictures on a continuum (range, 1-20) of 2 dimensions: valence (unpleasant vs pleasant) and arousal (calm vs aroused).

### PHYSIOLOGICAL DATA COLLECTION AND PROCESSING

Physiological signals were recorded using a Grass Model 12 Neurad (Grass Technologies, West Warwick, Rhode Island) acquisition system. Version 11.0 of the VPM software package39 was used to control the timing and presentation of stimuli and to collect and store the physiological data. Data processing was conducted using VPMANLOG39 and Neuroscan, version 4.3 (Compumedics USA, Charlotte, North Carolina). Facial EMG signals were amplified and filtered for 30- to 1000-Hz activity (half-amplitude cutoffs). Facial EMG signals were sampled at 1000 Hz from 2 seconds before picture onset to the end of each

### Table 1. Demographic and Basic Group Characteristics at Baseline and Follow-up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Opiate-Dependent Individual (n=33)</th>
<th>Opiate-Dependent Healthy Control (n=19)</th>
<th>Less Than Weekly (n=19)</th>
<th>At Least Weekly (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F, No.</td>
<td>16/17</td>
<td>9/10</td>
<td>10/9</td>
<td>5/7</td>
</tr>
<tr>
<td>Age, y</td>
<td>31.6 (7.6), 22-46</td>
<td>30.0 (6.8), 19-46</td>
<td>32.89 (6.0), 19-26</td>
<td>25.00 (6.6), 20-24</td>
</tr>
<tr>
<td>Beck Depression Inventory score</td>
<td>14.5 (11.0), 0-38</td>
<td>4.3 (4.7), 0-15</td>
<td>14.3 (9.7), 0-28</td>
<td>15.1 (13.4), 0-38</td>
</tr>
<tr>
<td>PANAS score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative affect</td>
<td>12.3 (3.0), 10-21</td>
<td>11.2 (1.9), 10-17</td>
<td>12.5 (3.4), 10-21</td>
<td>12.3 (2.4), 10-17</td>
</tr>
<tr>
<td>Positive affect</td>
<td>28.7 (8.5), 15-44</td>
<td>30.2 (8.2), 17-50</td>
<td>29.6 (8.8), 17-44</td>
<td>26.4 (8.3), 15-39</td>
</tr>
<tr>
<td>Substitution therapy, No.</td>
<td>14</td>
<td>10</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>14</td>
<td>10</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>19</td>
<td>9</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Dose, mean (SD), mg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>52.1 (37.1)</td>
<td>55.2 (43.7)</td>
<td>46.7 (20.8)</td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>9.6 (9.5)</td>
<td>7.3 (5.8)</td>
<td>12.5 (12.3)</td>
<td></td>
</tr>
<tr>
<td>Time since beginning regular opiate use, y</td>
<td>10.0 (5.8), 1.3-27.5</td>
<td>10.9 (6.4), 2.8-27.5</td>
<td>9.3 (5.3), 1.3-18.9</td>
<td></td>
</tr>
<tr>
<td>Short Opiate Withdrawal Scale score</td>
<td>4.5 (5.1), 0-19</td>
<td>4.9 (5.3), 0-16</td>
<td>4.6 (5.1), 0-19</td>
<td></td>
</tr>
<tr>
<td>Severity of Dependence Scale score</td>
<td>8.1 (3.3), 1-14</td>
<td>8.1 (3.6), 1-14</td>
<td>8.3 (3.9), 1-12</td>
<td></td>
</tr>
<tr>
<td>Craving score, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before experiment</td>
<td>16.0 (23.1), 0-74.5</td>
<td>10.1 (17.7), 0-67</td>
<td>26.8 (29.1), 0-74.5</td>
<td></td>
</tr>
<tr>
<td>After experiment</td>
<td>62.6 (34.0), 1-100</td>
<td>63.4 (33.3), 1.5-100</td>
<td>57.3 (37.6), 1-99</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: PANAS, Positive and Negative Affect Schedule.
picture presentation period. Activity at each facial muscle site was integrated separately (full-wave rectified), converted to microvolts, and filtered using a digital finite impulse response (50-Hz, 24 dB per roll-off 0-phase–shift low-pass filter in Neuroscan). Facial reactivity was computed as the mean EMG activity between 0 to 2 seconds after picture onset minus the mean of a 2-second prepicture baseline. The postauricular reflex was recorded, processed, and scored according to the procedures outlined by Benning and colleagues.30

Electroencephalograms (EEG) were recorded from 3 scalp sites \( (F_2, C_z, P_z) \) based on the international 10-20 system. Vertical and horizontal electrooculography was also performed. The EEG and electrooculography signals were amplified by 10,000, with high- and low-pass filters set to 0.1 Hz and 30 Hz, respectively. Data were collected at 1000 Hz from 2 seconds before picture onset (baseline period) until picture offset. The EEG data epochs were extracted between 1 second before and 1.25 seconds after probe onset, sampled at 100 Hz, converted to microvolts, and analyzed using Neuroscan, version 4.3. All channels were baseline-corrected to the mean of their 150-millisecond prestimulus period. For each probe presentation, saturated EEG and electro-oculography trials were excluded from additional analyses. An algorithm correcting for eye-movement artifacts39 using the vertical electro-oculogram channel data was then applied within participants, channels, and trials. Event-related potential waveforms were then obtained by averaging the EEG signal within each individual at each scalp site for each picture category. Only the startle-elicited P300 (or P3) component was analyzed, given that it is most sensitive to the affective qualities of foreground stimuli and is understood to reflect attentional allocation.31 To calculate the peak P3 amplitude, it was necessary to define earlier components so that the appropriate latency window could be identified on each waveform (ie, N1 [64-192 milliseconds], P2 [N1 latency until 272 milliseconds], P3 [N2 latency until 336 milliseconds], and P3 [N2 latency until 504 milliseconds]).31

**Figure 1.** Self-Assessment Manikin (SAM) valence (A) and arousal (B) ratings and corrugator supercilii (C) and zygomaticus major (D) electromyogram reactivity by picture types within baseline groups. Error bars represent 1 SEM.

### Statistical Analysis

The multivariate statistic Wilks’ Lambda test was used for repeated-measures effects to protect against violations of sphericity. Some participants were excluded from SAM analyses \( (n=2) \) owing to equipment failure, and from postauricular reflex analyses \( (n=3) \) and startle-elicited event-related potential analyses \( (n=1) \) owing to excessively noisy EMG/EEG channels. An additional 8 clinical (26%) and 6 nonclinical (33%) participants were excluded from postauricular analyses because they did not exhibit a scorable postauricular reflex, as determined by visual inspection of averaged waveforms. The percentage of nonresponders was not significantly related to group status \( (n=49; \chi^2=0.316, P=.57) \). Previous physiological research, including our own, has indicated that between 20% and 40% of participants with normal hearing do not exhibit a scorable postauricular reflex.41,42 We report startle-elicited P300 amplitude at the Pz scalp location, consistent with past research.31

Data analysis was divided into 2 phases. Baseline group differences in SAM ratings and psychophysiological variables were analyzed using 2-way, mixed-factor analyses of variance (picture type \( [4] \) × group \( [2] \)). Prediction of regular (at least weekly) heroin use at follow-up was then analyzed using logistic regression models. Missing data were excluded on a pairwise basis (ie, the maximum number of participants with complete data for the variables involved in each analysis was included in that analysis). Measures of baseline processing of pleasant compared with neutral, drug-related compared with neutral, and pleasant compared with drug-related pictures were calculated by examining residuals generated from univariate regression analyses in which the control variable (eg, responses during neutral pictures) was regressed onto the response variable (eg, response during pleasant pictures). In the subsequent logistic regressions predicting outcome, baseline treatment group (methadone or buprenorphine) was entered as the first block,
followed by indices of affective stimuli processing. Following this, 2 sets of more stringent analyses were conducted for variables that did significantly predict outcome. Given that 24 of 33 participants (72.7%) reported using heroin at baseline (in addition to opiate pharmacotherapy) and that there was a trend for the group that used heroin weekly or more often at follow-up to report greater baseline craving scores ($P < .1$), these regressions were run again with both amount of heroin used at baseline and baseline craving scores entered separately as covariates in the first block. This allowed examination of whether picture processing and response variables that significantly predicted outcomes represented epiphenomena of baseline heroin use or baseline craving scores or whether they were distinct phenomena.

## RESULTS

### BASELINE GROUP DIFFERENCES

**Self-Report**

Valence ratings differed according to group. As shown in Figure 1, both groups exhibited more positive valence ratings for pleasant compared with neutral pictures and for neutral compared with unpleasant pictures. However, the opiate-dependent group rated the drug-related pictures as significantly more pleasant, relative to neutral and pleasant pictures, than did the control group. This pattern of results was identical for arousal ratings. Whereas the control group rated the pleasant pictures as more arousing than the drug-related pictures, the opiate-dependent group rated the drug-related pictures as significantly more arousing than the pleasant pictures. Table 2 presents the mixed-factor analysis of variance results (picture $[4] \times$ group $[2]$) for self-report ratings and psychophysiological variables.

### Reflex Modulation

Consistent with previous findings, the postauricular reflex was significantly greater for pleasant compared with unpleasant pictures in the control group. However, the opiate-dependent group failed to show this effect, consistent with an inhibited response to pleasant stimuli (Figure 2).

### Event-Related Potentials

Startle-elicited P300s across groups were significantly attenuated for unpleasant, pleasant, and drug-related pictures relative to neutral pictures, suggesting that these affective and drug-related pictures captured

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Table 2. Mixed-Factor ANOVA Results for SAM Ratings and Psychophysiological Dependent Variables

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Group</th>
<th>Picture</th>
<th>Picture × Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valence$^a$</td>
<td>$F_{4,40} = 0.232$</td>
<td>$F_{4,45} = 55.202^b$</td>
<td>$F_{4,45} = 2.772^c$</td>
</tr>
<tr>
<td></td>
<td>$P &gt; N^b$</td>
<td>N $&gt; U, P, D^b$</td>
<td>Between-group differences on D/N contrast$^c$ and D/P contrast$^d$</td>
</tr>
<tr>
<td></td>
<td>$D &gt; U^b$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arousal$^a$</td>
<td>$F_{4,40} = 0.380$</td>
<td>$F_{4,45} = 38.872^b$</td>
<td>$F_{4,45} = 5.032^d$</td>
</tr>
<tr>
<td></td>
<td>$N &lt; U, P, D^b$</td>
<td>$U &gt; D^b$</td>
<td>Between-group differences on P/N contrast$^c$, D/N contrast$^d$, and D/P contrast$^b$</td>
</tr>
<tr>
<td></td>
<td>$D &gt; U^b$</td>
<td>$U &gt; D^b$</td>
<td></td>
</tr>
<tr>
<td>Corrugator activity, µV</td>
<td>$F_{3,43} = 2.927^b$</td>
<td>$F_{3,45} = 5.309^d$</td>
<td>$F_{3,45} = 2.259^c$</td>
</tr>
<tr>
<td>OD $&gt;$ control$^b$</td>
<td>$U &gt; N^d$</td>
<td></td>
<td>Between-group differences on D/P contrast$^d$</td>
</tr>
<tr>
<td>Zygomatic activity$^a$</td>
<td>$F_{3,40} = 0.195$</td>
<td>$F_{3,45} = 3.406^d$</td>
<td>$F_{3,45} = 2.646^c$</td>
</tr>
<tr>
<td></td>
<td>$P &gt; N^d$</td>
<td></td>
<td>Between-group differences on U/N contrast$^c$ and D/U contrast$^d$</td>
</tr>
<tr>
<td></td>
<td>$U &gt; N^d$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postauricular reflex, µV</td>
<td>$F_{3,43} = 2.815$</td>
<td>$F_{3,45} = 2.968^d$</td>
<td>$F_{3,45} = 3.394^d$</td>
</tr>
<tr>
<td>Control $&gt;$ OD$^b$</td>
<td>$P &gt; U^d$</td>
<td></td>
<td>Between-group differences on P/N contrast$^c$ and P/U contrast$^b$</td>
</tr>
<tr>
<td>Startle-elicited P300, µV</td>
<td>$F_{3,43} = 3.418^b$</td>
<td>$F_{3,45} = 6.69b^b$</td>
<td>$F_{3,45} = 2.269^d$</td>
</tr>
<tr>
<td></td>
<td>$N &gt; U, P, D^b$</td>
<td></td>
<td>Between-group differences on P/N contrast$^d$ and P/D contrast$^d$</td>
</tr>
</tbody>
</table>

Abbreviations: ANOVA, analysis of variance; D, drug; N, neutral; OD, opiate-dependent group; P, Pleasant; SAM, Self-Assessment Manikin; U, unpleasant.

$^a$Self-Assessment Manikin ratings and zygomatic values were transformed (not microvolts).

$^b P < .01$.

$^c P < .1$.

$^d P < .05$.  

[1] Self-Assessment Manikin ratings and zygomatic values were transformed (not microvolts).

[2] P < .01.


[4] P < .05.

As shown in Figure 1, both groups exhibited similarly enhanced corrugator reactivity during unpleasant pictures. However, the opiate-dependent group displayed significantly greater corrugator activity during pleasant compared with drug-related–picture viewing than did the control group, indicating a lack of the typical pattern of facial reactivity to pleasant stimuli (corrugator relaxation). Both groups also exhibited the normal pattern of greater zygomatic activity during pleasant pictures (Figure 1). However, the opiate-dependent group, in contrast to controls, exhibited significantly greater zygomatic reactivity to unpleasant compared with neutral pictures. Thus, though the control group exclusively responded with increased zygomatic activity to the pleasant pictures, the opiate-dependent group demonstrated a lack of differential reactivity in this usually appetitive response, responding to both pleasant and unpleasant stimuli in a similar fashion.

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Facial Expression

As shown in Figure 1, both groups exhibited similarly enhanced corrugator reactivity during unpleasant pictures. However, the opiate-dependent group displayed significantly greater corrugator activity during pleasant compared with drug-related–picture viewing than did the control group, indicating a lack of the typical pattern of facial reactivity to pleasant stimuli (corrugator relaxation). Both groups also exhibited the normal pattern of greater zygomatic activity during pleasant pictures (Figure 1). However, the opiate-dependent group, in contrast to controls, exhibited significantly greater zygomatic reactivity to unpleasant compared with neutral pictures. Thus, though the control group exclusively responded with increased zygomatic activity to the pleasant pictures, the opiate-dependent group demonstrated a lack of differential reactivity in this usually appetitive response, responding to both pleasant and unpleasant stimuli in a similar fashion.

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Reflex Modulation

Consistent with previous findings, the postauricular reflex was significantly greater for pleasant compared with unpleasant pictures in the control group. However, the opiate-dependent group failed to show this effect, consistent with an inhibited response to pleasant stimuli (Figure 2).
more attentional resources, thereby inhibiting the cortical response to the startle probe. However, the opiate-dependent group displayed significantly less P300 attenuation in response to pleasant relative to neutral pictures compared with the control group, suggesting that they did not attend as strongly to these pictures. Also, the control group displayed significantly larger P300 amplitudes during pleasant pictures than during drug-related pictures, whereas the opiate-dependent group displayed the opposite pattern, suggesting that the heroin users had a greater attentional bias toward drug-related stimuli compared with pleasant stimuli.

In summary, baseline group differences were prominent for indices of the processing of and response to pleasant and drug-related pictures. Relative to the control group, and consistent with an anhedonic response, the opiate-dependent group rated the pleasant pictures as less arousing, responded with increased corrugator activity, lacked postauricular potentiation, and had decreased startle-elicited P300 attenuation. Consistent with enhanced processing of drug cues, the opiate-dependent group also rated the drug-related pictures as more pleasant and arousing and demonstrated greater startle-elicited P300 attenuation.

Given the between-group differences in depressive symptoms, we investigated whether Beck Depression Inventory scores were related to these discrepancies in affective responding. There was no significant relationship between the Beck Depression Inventory scores and response to pleasant stimuli compared with neutral, unpleasant, or drug-related stimuli (all \( r < .183, P > .17, \) 1-tailed), both within and across groups.

**PREDICTION OF REGULAR HEROIN USE AT FOLLOW-UP**

Self-Assessment Manikin valence ratings of drug-related pictures (compared with neutral pictures: odds ratio [OR], 5.09; 95% confidence interval [CI], 1.06-24.5; \( P = .04 \)), pleasant pictures (compared with neutral pictures: OR, 0.18; 95% CI, 0.04-0.79; \( P = .02 \); compared with drug-related pictures: OR, 0.18; 95% CI, 0.04-0.86; \( P = .03 \)), and SAM arousal ratings of pleasant pictures (compared with drug-related pictures: OR, 0.26; 95% CI, 0.09-0.80; \( P = .02 \)) all significantly predicted regular heroin use at follow-up above the constant and baseline treatment model (eTable, available at http://www.archgenpsychiatry.com). For psychophysiological

![Figure 2](image-url)
variables, only the startle-elicited P300 amplitude to pleasant pictures (relative to drug-related pictures) significantly predicted regular heroin use at follow-up (OR, 4.35; 95% CI, 1.15-16.40; \( P = .03 \)). The model of SAM valence ratings of pleasant pictures (relative to neutral pictures) accounted for the most variance (44%) and had the greatest sensitivity (83.3%) and specificity (82.4%), suggesting it is the superior model. Figure 3 displays the associations between all 5 standardized SAM and startle-elicited P300 predictors and status of heroin use at follow-up.

When baseline heroin use was entered in the first block, only the SAM valence ratings of pleasant relative to neutral pictures (OR, 0.095; 95% CI, 0.01-0.75; \( P = .03 \)) and pleasant relative to drug-related pictures (OR, 0.081; 95% CI, 0.01-0.91; \( P = .04 \)) remained statistically significant predictors (eTable). The model of SAM valence ratings of pleasant (relative to drug-related) pictures accounted for marginally more variance (78.2%) and had greater specificity (94.1%), suggesting it is the superior model.

When baseline craving scores were entered into the first block, only the SAM valence ratings of pleasant relative to neutral pictures (OR, 0.095; 95% CI, 1.29-57.86; \( P = .03 \)), pleasant pictures (compared with neutral pictures: OR, 0.37; 95% CI, 0.00-0.53; \( P = .02 \)), compared with drug-related pictures: OR, 0.051; 95% CI, 0.00-0.68; \( P = .03 \)), and arousal ratings of pleasant pictures (compared with drug-related pictures: OR, 0.33; 95% CI, 0.12-0.97; \( P = .04 \)) also remained statistically significant predictors of heroin use at follow-up. The model of SAM valence ratings of pleasant relative to neutral pictures accounted for the most variance (67.3%) and had the greatest OR, sensitivity (75%), and specificity (88.2%).

Given the variable follow-up period, we conducted a number of analyses to ensure that frequency of heroin use at follow-up was not a direct consequence of later reassessment. First, using logistic regression, we found that a continuous measure of time to follow-up in months did not predict weekly heroin use \( [ \text{black triangles} ] \), within each variable, thereby depicting group differences in their relative response to either drug vs pleasant, drug vs neutral, or pleasant vs neutral stimuli.

In this study we used a multimethod approach to examine hedonic responses to natural reinforcers and drug cues in opiate addiction as well as their relationship with clinical outcomes. Across a range of response measures (ie, self-report, expressive, reflex modulation, and cortical/attentional measures), we consistently found altered processing of drug-related and pleasant pictures in opiate-dependent individuals relative to controls. In response to normally pleasant pictures (ie, pictures of natural reinforcers), the opiate-dependent group had lower self-reported arousal, increased corrugator activity, an absence of postauricular potentiation, and decreased startle-elicited P300 attenuation. The opiate-dependent group also rated the drug-related pictures as more pleasant and arousing and demonstrated greater startle-elicited P300 attenuation. Furthermore, SAM valence ratings of pleasant pictures consistently predicted regular heroin use (at least once a week) at follow-up, even after controlling for baseline craving score and heroin use.

The consistent inhibition of normal responses to pleasant pictures (as opposed to a general attenuation of responses to all affective stimuli) in the opiate-dependent group is an important finding, especially because such indices also strongly predicted ongoing regular heroin use. These data contrast with the large body of normative psychophysiological and electrophysiological research on emotional processing, demonstrating that emotionally arousing stimuli reliably elicit a variety of physiological responses.\(^{29,43}\) The results support animal evidence of increased reward thresholds in drug addiction and are consistent with Koob and Le Moal’s\(^{8,10}\) concept of allostatics as well as previous research examining subjective reports of anhedonia in addicted populations.\(^{2,5,11}\)

In addition, the drug cue findings are consistent with previous behavioral studies of attentional processing in addiction, including studies\(^{44}\) of both methadone maintained\(^ {13}\) and recently detoxified heroin addicts.\(^ {45}\) Such results support the notion that drug cues have implicit motivational salience in addicted users and capture attentional resources. Indeed, enhanced event-related potential responses to drug-related stimuli have been reported across a range of addicted populations,\(^ {14,15,46-50}\) suggesting that

**COMMENT**

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drug cues capture processing resources and influence behavior. While few other addiction studies have included a non–drug-related emotionally salient class of stimuli (eg, sexual imagery, highly aversive images) in their study design, our results support the notion that the hedonic balance between drug cues and natural reinforcers is abnormal in heroin users, with drug cues capturing relatively more attentional and hedonic resources than natural rewards.

However, one outstanding issue is if reduced sensitivity to natural reinforcers is a consequence of long-term drug exposure or opiate-substitution pharmacotherapy (as in the allostatic model), if it represents a vulnerability to addictive disorders, or if it is a combination of both. Franken et al recently reported that individuals who engage in high-risk recreational activities (skydivers) report more anhedonic symptoms than those who prefer low-risk activities (rowers). While the authors suggested that frequent exposure to “natural highs” may induce an allostatic state and subsequent anhedonia, an alternative explanation may be that individuals with relatively lower premorbid responsiveness to natural reinforcers (ie, decreased activation of reward circuitry) may be driven to experiment with high-risk, intensely hedonic experiences (such as skydiving or drug use). Indeed, while previous imaging studies in long-term heroin users reveal long-lasting decreases in dopamine D2 receptors within the striatum (suggesting down-regulation of the dopaminergic reward system with regular drug use), more recent evidence suggests that low levels of D2 receptors may increase vulnerability to drug use.

It is important to consider a number of limitations when reviewing our data. The period of reassessment for the opiate group was variable, reflecting some of the difficulties associated with conducting prospective studies in people with heroin dependence. Nevertheless, our analyses indicated that this variable was not related to heroin use at follow-up and did not affect the predictive association between reduced reward responsiveness at baseline and subsequent heroin use. An additional confounder is that the subject groups were not matched on depressive symptomatology. However, it is important to note that no participant met criteria for a current mood disorder; mood ratings (ie, positive affect, negative affect) on the day of testing did not differ significantly between the groups; and exploratory analyses indicated that depressive symptoms did not correlate with the response to pleasant stimuli relative to other classes of stimuli. Nevertheless, high rates of depressive symptoms are commonly reported in addicted populations, including those being treated with substitution pharmacotherapy.

Another limitation is the relatively small sample of heroin users, recruited primarily through advertisements, which raises issues of generalizability to the wider heroin-using population. While the sample size is consistent with other published psychophysiological investigations, our findings require replication in a larger sample, including those who are long-term abstinent. No biological assays were conducted on the day of testing to confirm recent abstinence from use of heroin or other illicit drugs. Nevertheless, participants reported that they had not used any other drugs in the past 24 hours; none appeared to be intoxicated; and all maintained their concentration for the entire experiment. Furthermore, while no biological assay was conducted to confirm heroin use during the follow-up period, previous research has noted the excellent concordance between self-reported use and urine drug testing results in heroin users engaged in treatment. Finally, it is important to note that a large number of analyses were conducted, and though we recognize that the risk of type 1 error is a factor in our study, we believe that these risks are outweighed by the benefits of fully describing the patterns observed in this unique data set, so that effects of interest can be subjected to further experimental scrutiny.

We report that heroin users undergoing opiate-substitution therapy demonstrate an inhibited response to natural reinforcers (anhedonia) across a range of response measures and that subjective ratings of pleasant pictures robustly predict regular heroin use at follow-up. Such findings are of clear clinical relevance and highlight the importance of targeting anhedonic symptoms within addiction treatment settings. Finally, our results support previous literature that demonstrated enhanced attentional processing of drug cues in opiate addiction, emphasizing the importance of effectively managing exposure to cues within relapse-prevention training. Future studies will need to examine the specificity of these findings across addictive disorders and the effectiveness of interventions that target improved hedonic responses to alternate reinforcers.

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REFERENCES


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