Psychophysiological prediction of choice: relevance to insight and drug addiction

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An important goal of addiction research and treatment is to predict behavioural responses to drug-related stimuli. This goal is especially important for patients with impaired insight, which can interfere with therapeutic interventions and potentially invalidate self-report questionnaires. This research tested (i) whether event-related potentials, specifically the late positive potential, predict choice to view cocaine images in cocaine addiction; and (ii) whether such behaviour prediction differs by insight (operationalized in this study as self-awareness of image choice). Fifty-nine cocaine abusers and 32 healthy controls provided data for the following laboratory components that were completed in a fixed-sequence (to establish prediction): (i) event-related potential recordings while passively viewing pleasant, unpleasant, neutral and cocaine images, during which early (400–1000 ms) and late (1000–2000 ms) window late positive potentials were collected; (ii) self-reported arousal ratings for each picture; and (iii) two previously validated tasks: one to assess choice for viewing these same images, and the other to group cocaine abusers by insight. Results showed that pleasant-related late positive potentials and arousal ratings predicted pleasant choice (the choice to view pleasant pictures) in all subjects, validating the method. In the cocaine abusers, the predictive ability of the late positive potentials and arousal ratings depended on insight. Cocaine-related late positive potentials better predicted cocaine image choice in cocaine abusers with impaired insight. Another emotion-relevant event-related potential component (the early posterior negativity) did not show these results, indicating specificity of the late positive potential. In contrast, arousal ratings better predicted respective cocaine image choice (and actual cocaine use severity) in cocaine abusers with intact insight. Taken together, the late positive potential could serve as a biomarker to help predict drug-related choice—and possibly associated behaviours (e.g. drug seeking in natural settings, relapse after treatment)—when insight (and self-report) is compromised.

Keywords: cocaine addiction; insight; choice behaviour; event-related potentials; late positive potential; unconscious motivation
Introduction

A hallmark of drug addiction is disadvantageous/impulsive decision-making (Paulus, 2007), such that addicted individuals pursue drugs and drug-related stimuli at the expense of non-drug-related goals (Goldstein and Volkow, 2011). Predicting such disadvantageous choice in drug addiction poses special challenges because drug-addicted individuals show a compromised ability to report on internal states or monitor ongoing behaviour (Goldstein et al., 2007, 2008; Hester et al., 2007; Moeller et al., 2009, 2010), possibly stemming from impairments in brain regions subserving insight and self-awareness including the insula and anterior cingulate cortex (Goldstein et al., 2009b). Such impaired insight into behaviour, commonly conceptualized as denial of (or failure to recognize) the severity of illness, compromised control of action, or unawareness of one’s social deficits (Damasio, 1994; Bechera, 2004), may interfere with therapeutic interventions, preventing patients from effectively identifying states or situations that could trigger craving or induce relapse. Impaired insight in drug addiction also calls into question the use of self-report to predict behaviour. Indeed, conscious processes (e.g. self-reported craving) often only weakly predict future behaviour such as relapse (Miller and Gold, 1994) or drug-biased attention (Field et al., 2009), necessitating the use of objective prediction measures that do not rely on introspection.

Here, we tested the validity of the scalp-recorded event-related potential, more specifically, the late positive potential—a non-lateralized midline event-related potential component that appears ~300 ms after presentation of arousing stimuli—in predicting drug choice behaviour. The late positive potential directly indexes early and rapid changes in neural activity and is thought to be driven by motivational salience [not explainable by stimulus novelty, low-level perceptual differences or expectation violations (Hajcak et al., 2010)]. The neurobiological genesis of the late positive potential, principally localized to occipital and posterior parietal cortex, may reflect downstream processes stemming from increased activation of the amygdala, possibly mediated by phasic increases in norepinephrine via the brainstem’s locus coeruleus (Hajcak et al., 2010). Another possibility is that the late positive potential reflects the engagement of higher order fronto-parietal attention networks (Moratti et al., 2004). Importantly, previous studies have indicated that this electrophysiological measure tracks increased stimulus significance in cocaine addiction: late positive potentials elicited during passive viewing of cocaine-related pictures are enhanced in cocaine abusers [similar in magnitude to those elicited by pleasant and unpleasant images, but higher in magnitude than neutral images (Dunning et al., 2011)] and are associated with current drug use (Dunning et al., 2011) and craving (Franken et al., 2008). These studies led us to expect that cocaine-elicited late positive potentials would positively predict drug-biased choice behaviour. To measure such drug-biased choice without the need for acute cocaine administration (i.e. so that it can be measured even in abstaining or treatment-seeking drug-addicted individuals), we recently developed neuropsychological drug choice tasks, where choice to view cocaine-associated pictures is compared with choice to view positively, negatively or neutrally valenced pictures; higher cocaine-related choice is associated with higher frequency of actual cocaine use (Moeller et al., 2009). By providing an opportunity for an actual decision to be made, these choice tasks extend paradigms of drug-biased attention [a neurocognitive change where attention is preferentially allocated to drug-related stimuli at the expense of control stimuli (Franken et al., 2000; Mogg and Bradley, 2002; Duka and Townshend, 2004; Hester et al., 2006)] that also predicts relapse in abstaining individuals (Marissen et al., 2006). Effective prediction of non-conscious, disadvantageous choice could also have broad significance extending beyond drug addiction, having the potential to inform (i) other neuropsychiatric disorders (e.g. anosognosia, schizophrenia or mania; Orfei et al., 2008) that are similarly characterized by impaired insight and disadvantageous, unwanted or inappropriate behaviours (e.g. leading to violence or other types of harm to self and/or others); and (ii) more basic questions of the mechanisms underlying unconscious behaviour in disease states and possibly even in health.

The following hypotheses were tested: (i) that late positive potentials elicited by salient pictures would predict—independently of self-reports (Tomarken, 1995; Nosek et al., 2011)—subjects’ choice to view these same salient pictures: pleasant or unpleasant images in individuals with cocaine use disorder and healthy controls, and cocaine images uniquely in the cocaine subjects (both when compared with a neutral picture baseline); and (ii) given the strong coupling between choice and implicit measures of objective preferences when insight into these preferences is lacking (Galdi et al., 2008, 2012), that the objective late positive potential would predict cocaine image choice especially in cocaine subjects with impaired insight (operationalyzed as compromised self-awareness of the images that were most frequently chosen for viewing). In contrast, because self-reports predict choice when preference is known (Galdi et al., 2008, 2012), we hypothesized that self-reports (e.g. ratings of picture arousal) would predict cocaine image choice in cocaine subjects with intact insight (operationalyzed as intact self-awareness of the images that were most frequently chosen for viewing). The parallel associations with measures of current addiction severity were also expected. To establish specificity of results to late positive potentials, we also tested an additional event-related potential component that pertains to emotional processing (the early posterior negativity) (Supplementary material).

Materials and methods

Subjects

The study sample included 59 cocaine subjects and 32 healthy controls, all right-handed and native English speakers. Subjects were recruited through newspaper advertisements, word-of-mouth and local treatment facilities. All provided written consent to participate in accordance with Stony Brook University’s Institutional Review Board. Exclusion criteria were as follows: (i) head trauma with loss of consciousness exceeding 30 min; (ii) neurological, medical or psychiatric disorder that required hospitalization or regular monitoring;
Interview established that the cocaine subjects met criteria for current cocaine dependence \((n = 52)\), or cocaine dependence in partial \((n = 4)\) or fully sustained \((n = 3)\) remission. Twenty-two cocaine subjects had used cocaine within 72 h of the study as confirmed by urine analysis; the remaining 37 cocaine subjects tested negative for cocaine in urine (23 cocaine subjects were recruited from inpatient treatment facilities where cocaine use is prohibited, and the other 14 had not used cocaine within 72 h of the study) (see Table 1 for drug use variables). Note that despite not actively using cocaine, treatment-seeking individuals can still meet current dependence criteria according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. In addition to cocaine diagnosis, current comorbidities were identified in five cocaine subjects and included marijuana abuse \((n = 1)\), opiate dependence \((n = 2)\), and alcohol abuse \((n = 1)\) or dependence \((n = 1)\). Past comorbidities in the cocaine subjects included fully sustained remission for alcohol use disorder \((n = 23)\), marijuana abuse \((n = 27)\), opiate dependence \((n = 2)\), major depression disorder \((n = 8)\) or post-traumatic stress disorder \((n = 3)\). In addition, 48 cocaine subjects and six controls reported current cigarette smoking (Table 1), and three cocaine subjects met criteria for antisocial personality disorder. Because high lifetime comorbidity rates commonly occur in cocaine addiction (Rounsaville et al., 1991), including subjects with these comorbid disorders enhances generalizability of results and understanding of the addiction process.

**Study procedures**

Study procedures encompassed four steps below, all completed in a fixed sequence (to establish prediction): (i) passive picture viewing...
Stimuli and psychophysiological recordings

Subjects underwent recordings of event-related potentials as they passively viewed four types of images (30 images per picture category, each viewed for 2000 ms). Three image types were selected from the International Affective Picture System (Lang et al., 2008), commonly used in affective and psychiatric neuroscience given their extensive standardization vis-à-vis valence and arousal ratings. These included 30 International Affective Picture System images each from the categories of pleasant (e.g. nude images: mean normative valence of 7.6 ± 1.6; mean normative arousal of 5.7 ± 2.4), unpleasant (e.g. violent images: mean normative valence of 2.4 ± 1.5; mean normative arousal of 5.9 ± 2.2) and neutral (e.g. household objects: mean normative valence of 5.3 ± 1.3; mean normative arousal of 2.8 ± 1.9) (Lang et al., 2008). The fourth image type depicted cocaine and individuals preparing, using or simulating use of cocaine as previously described (Moeller et al., 2009, 2010; Dunning et al., 2011). Continuous EEG (Neuroscan) and electro-oculogram recordings were obtained throughout using a 64 silver-silver chloride electrode cap positioned according to the International 10/20 System (Klem et al., 1999). All recordings were performed using a fronto-central electrode as ground. Electrodes were placed above and below the left eye to record vertical eye movements, and placed on the outer canthi of both eyes to record horizontal eye movements. The EEG was digitized at a rate of 500 Hz and amplified with a gain of 250, and a band-pass filter of 0–70 Hz. The amplifiers were calibrated prior to each recording. Electrode impedances did not exceed 10 kΩ for any electrodes used in the analysis.

All bioelectric signals were analysed off-line using Statistical Parametric Mapping (SPM8) for magnetoencephalography/electroencephalography (MEG/EEG) (Wellcome Department of Cognitive Neurology, London, UK: www.fil.ion.ucl.ac.uk/spm/) and custom MATLAB code (The MathWorks). Data were filtered with low and high cut-offs of 0.01 and 30 Hz, respectively, and were then re-referenced to the averaged electrical activity from all 64 scalp sites. The artefact rejection procedure identified a voltage step of >75 µV between sample points and a peak-to-peak voltage difference of 150 µV within an epoch. Additional artefacts were identified through visual inspection and subsequently rejected. Robust averaging was also used to remove artefacts (Wager et al., 2005). The event-related potentials were constructed by separately averaging trials based on picture type: pleasant, unpleasant, neutral and cocaine pictures. Because previous findings have indicated that drug-specific late positive potentials are maximal at fronto-central recording sites (Littek and Franken, 2007; Franken et al., 2008), the late positive potential for each picture type was defined as the average activity at the Cz, FC2, FC1, FC2 and Fz electrodes. Following previous principle components analysis (Foti et al., 2009) and our own previous work in cocaine subjects (Dunning et al., 2011), late positive potentials were defined at early (400–1000 ms) and late (1000–2000 ms) windows after picture onset (see Fig. 1 for event-related potential waveforms). The average activity in the 200 ms window prior to picture onset served as the baseline. See the online Supplementary material for description and analysis of the additional event-related potential component analysed, the early posterior negativity, where we show that the associations with choice as described below were specific to the late positive potential.

Picture ratings

Immediately following these event-related potential recordings, subjects rated each picture’s arousal (‘rate how strong of an emotional response you had to this picture’), the closest self-report analogue to the late positive potential (Hajcak et al., 2010). Arousal ratings were collected with a computerized version of the Self-Assessment Manikin (Bradley and Lang, 1994), for which subjects chose the numbers ‘1’ through to ‘9’ (higher rating = higher arousal).

Picture choice task

Immediately following the event-related potentials and picture ratings, subjects completed a choice task that assessed their objective preference for viewing these same International Affective Picture System and cocaine images. In brief, subjects chose with continued button pressing between two fully visible side-by-side images from the four picture categories described above [for complete task information and example figure, see Moeller et al. (2009)]. Choice for a desired image enlarged this chosen image to fully cover the screen, which subjects could view for the trial duration of 5000 ms by continued button pressing; 500 ms of non-response, however, returned the side-by-side image display. The total number of button presses for each picture category was summed across 70 choice trials, yielding an objective measure of picture choice that reflected the extent to which subjects were willing to work for viewing images of each picture category (higher score = higher choice).

Insight assessment

A different choice task with probabilistic contingencies enabled insight assessment. Subjects indicated choice for viewing these same International Affective Picture System and cocaine images with a single button press for pictures hidden under flipped-over cards, arranged in four decks (for complete task information and example figure, see Moeller et al. (2009)). Immediately after subjects chose from a particular ‘deck’ on each trial, an image was revealed that covered the entire screen for 2000 ms of passive viewing. Two task design features reduced certainty of choice to enable insight assessment. First, each deck contained 26 (out of a total of 30) pictures from a particular category (e.g. pleasant), allowing pictures from other categories to be interspersed within each deck (Moeller et al., 2009). Second, at the conclusion of each run (which occurred when subjects selected from a particular deck for a total of eight times), deck location of the four picture categories shifted. The total number of cards selected per picture category across four task runs was summed, yielding a second objective measure of choice that was then compared with awareness of choice below. These sums were not analysed as dependent variables, instead only used to assess insight.

Immediately at the conclusion of this task, subjects pressed a button corresponding to one of the four picture categories to indicate what they perceived was their most selected picture type. Following previous procedures (Moeller et al., 2010), we compared subjects’ self-report of choice behaviour with their actual choice behaviour (i.e. subjects’ most selected picture category versus what they perceived was their most selected picture category). Cocaine subjects who showed correspondence between these subjective and objective measures (e.g. executing the highest number of presses for pleasant images and responding ‘pleasant’ to the question mentioned above) were classified as having ‘intact insight’ (n = 33), whereas cocaine subjects lacking correspondence (e.g. executing the highest number of presses for pleasant images and responding ‘cocaine’ to the question mentioned above) were classified as having ‘impaired insight’ (n = 26). In this way, the measure taps into self-awareness in a context where subjects have the opportunity to engage in an addiction-related behaviour, therefore relevant to insight. However, we note that this measure does not assess all aspects of ‘clinical insight’ as classically defined in psychiatry (i.e. the ability to recognize and correctly assess...
the nature and severity of one's own impairment). Cocaine subjects with any magnitude of discrepancy (≥1) were considered impaired (see Supplementary material for preliminary results that consider the magnitude of the discrepancy in modulating late positive potential-choice associations). We selected all control subjects reported in the analyses below (n = 32) to have intact insight; our analyses did not include 13 additional control subjects with impaired insight because this low sample size could have yielded unstable regression coefficients given the multiple predictors (i.e. we endeavoured to keep the ‘subject to variable’ ratio > 10:1). Nevertheless, we conducted exploratory analyses when including these 13 additional subjects as reported in the Supplementary material. Our previous findings suggested that insight impairment in cocaine addiction as currently operationalized was not mediated by impairments of incidental memory and executive functioning, verbal learning and memory, or non-verbal intelligence (Moeller et al., 2010).

Statistical analyses

Residual scores were created for the pleasant, unpleasant and cocaine pictures, each controlling for the baseline neutral pictures (i.e. the variance associated with the neutral variable was removed through linear regression); such residuals were computed for late positive potentials, self-reports and choice. We also computed parallel residual scores for the cocaine pictures controlling for the pleasant pictures, thus juxtaposing two motivationally salient contexts in cocaine subjects (Goldstein and Volkow, 2011). Hereafter, these newly created residual scores are referred to as pleasant > neutral, unpleasant > neutral, cocaine > neutral and cocaine > pleasant, respectively. Similarly derived residual scores were analysed in a previous study of addicted individuals and healthy controls that also used a combined emotional pictures/physiological approach (Lubman et al., 2009). These residual scores were used in all subsequent analyses (for results of the raw, unresidualized variables, see Supplementary material).

Our primary analyses were multiple regressions, such that late positive potentials and arousal ratings were entered simultaneously to predict choice, thus establishing each predictor’s unique contribution. Regressions were first conducted across all subjects to validate the method (e.g. all subjects were expected to show correspondence between pleasant-related late positive potentials and pleasant-related choice), and then conducted separately by insight in cocaine subjects (e.g. impaired insight cocaine subjects were expected to show the highest correspondence between cocaine-related late positive potentials and cocaine-related choice). Moderation by insight was also tested as appropriate. In separate multiple regressions, these same variables were entered to predict select measures of current addiction.

Figure 1 Event-related potential waveforms, separately by study group (impaired insight cocaine subjects, intact insight cocaine subjects, and healthy control subjects) and by electrode placement site (Fz, Cz and Pz).
severity in cocaine subjects. Because these addiction severity variables contained extreme outliers, the relevant multiple regressions were conducted with variables that were first rank-transformed, thus equivalent to Spearman correlations (except for the cocaine selective severity assessment, which was normally distributed and therefore examined with standard regressions). Similar to the rationale for predicting cocaine choice, regressions were first conducted across all cocaine subjects and then separately by insight.

In addition to these primary regressions, analyses were conducted to help bolster conclusions about insight. First, we wanted to rule out the alternative hypothesis that compared with those with intact insight, the cocaine subjects with impaired insight considered the cocaine pictures to be less salient. For this purpose, we conducted mixed 4 (Picture Contrast: pleasant > neutral, unpleasant > neutral, cocaine > neutral, cocaine > pleasant) × 3 (Group: impaired insight cocaine, intact insight cocaine, healthy controls) ANOVAs to inspect for between-group differences in the early and late positive potentials, picture arousal and picture choice (four total mixed ANOVAs). Following a significant omnibus picture contrast × group interaction, as indicated by the multivariate statistic Wilk’s λ (which protects against violations of sphericity), we conducted four univariate ANOVAs (for each of the four picture contrasts) that separately tested for between-group differences, followed by Bonferroni-corrected pairwise comparisons.

Second, we wanted to test the hypothesis that impaired insight pertains to these subjects’ particular disease (cocaine addiction), and does not simply reflect a more general compromise in monitoring choice. For this purpose, we tested whether impaired insight was driven by an inability to monitor cocaine choice in particular, compared with an inability to monitor choice of the other three categories. The null hypothesis among the impaired insight cocaine subjects would be that compromised ability to monitor choice would be equally driven by all four picture categories (i.e. 25% of the time). Thus, in a chi-square analysis, we set the expected n of the cocaine pictures to 6.5 and the expected n for the other three combined picture categories to 19.5 (6.5 × 3; current number of impaired insight subjects: n = 26; therefore, expected subjects per picture category: n = 6.5). To inspect the three salient picture categories more directly, we also tested for an inability to monitor cocaine choice when including only the pleasant, unpleasant, and cocaine images (therefore testing against a different percentage (33.3%)). Testing against the null hypothesis in these analyses could be considered a conservative approach, as one might expect choice of cocaine stimuli to be a more salient experience than choice of pleasant or unpleasant stimuli. Indeed, drugs and drug-related stimuli assume heightened salience in addiction at the expense of other positive reinforcers (reviewed in Goldstein and Volkow, 2011), while punishing stimuli no longer carry sufficient salience to deter compulsive drug-seeking (reviewed in Everitt et al., 2008). Such heightened salience (e.g. as occurs when comparing a higher money condition against a lower money condition) is typically associated with better performance [e.g. enhanced recognition for scenes (Adcock et al., 2006), increased emotional (drug) Stroop accuracy (Goldstein et al., 2009a; Moeller et al., 2012)]. As further justification for testing against the null hypothesis, preliminary paired t-tests were conducted in the impaired insight subjects, where the raw pleasant and unpleasant late positive potentials (both windows) were each compared against the raw drug late positive potentials (both windows). These analyses revealed no within-subjects differences between the drug late positive potentials and the other salient picture late positive potentials (all P > 0.1).

Third, we controlled for clinical variables potentially of high pertinence to insight (cocaine urine status, cocaine craving, treatment-seeking status, self-reported current cocaine abstinence and antisocial personality disorder), even if no differences were observed between the groups on these variables. Cocaine urine status objectively indexes recent cocaine abstinence and was shown to modulate late positive potentials in a previous study of cocaine subjects that did not explore insight or associations with cocaine picture choice (Dunning et al., 2011). Cocaine craving was examined with two variables, separately controlled in the analyses: (i) response to the question (asked after arousal), ‘Rate how much you want (or do not want) cocaine in response to this picture,’ which used the same self-assessment manikin response scale as for arousal ratings (range: 1–9, with higher number signifying greater wanting); and (ii) response on the cocaine craving questionnaire (Table 1). Treatment-seeking status and cocaine urine status were dichotomous variables (yes/no); self-reported cocaine abstinence was a continuous variable (number of days). Consideration of antisocial personality disorder, also measured dichotomously (yes/no), is reported in the Supplementary material.

Given the high number of correlations and the associated concern for enhanced Type I error, statistical significance for the regression analyses was set at P < 0.01; however, the associations that were hypothesized a priori (late positive potentials predicting respective choice behaviour) were considered significant at the more commonly used P < 0.05 threshold. Non-regression analyses (e.g. between-group analyses, tests of slopes, indirect effects, etc.) were similarly considered significant at P < 0.05. Data were excluded from one subject (from the impaired insight group) with excessively noisy event-related potentials and from another subject (from the intact insight group) with extreme scores on a neuropsychological battery (not reported here).

**Results**

**Late positive potential and arousal prediction of picture choice (Table 2)**

**Prediction of pleasant and unpleasant choice**

Pleasant > neutral late positive potentials predicted respective choice across all subjects, but only in the late (1000–2000 ms) late positive potential window (β = 0.22; P < 0.05; Fig. 2A). This late-window late positive potential explained unique variance beyond self-reported arousal, which also predicted choice in all subjects (β = 0.30; P < 0.01; Table 2). Moreover, this late positive potential-choice association remained significant after controlling for cigarette smoking history (β = 0.22; P < 0.05) or depression (β = 0.25; P < 0.05), which differed between cocaine subjects and controls (Table 1). Unpleasant > neutral late positive potentials did not predict respective choice, likely because these images, while salient, were infrequently chosen. Nevertheless, the pleasant > neutral findings in all subjects validate the method of using late positive potentials (and arousal ratings) to predict choice.

**Prediction of cocaine choice**

Cocaine > neutral arousal ratings, but not late positive potentials, predicted respective choice in both cocaine subgroups (Table 2). Of greater interest, dissociations in the prediction of choice were observed for the more rigorous analysis, where we compared the two motivationally salient contexts (cocaine with pleasant pictures). Here, cocaine > pleasant late positive potentials predicted...
was itself associated with cocaine potential-choice associations, the cocaine-craving questionnaire. Note that although not attenuating the late positive potential interaction reached significance during both late positive potential windows [early: $F(1,48) = 4.3; P < 0.05$; late: $F(1,48) = 4.1; P < 0.05$], such that cocaine > pleasant late positive potentials better predicted respective choice in impaired insight cocaine subjects. The insight x arousal interaction also reached significance in these two analyses $F(1,48) > 7.8; P < 0.01$, such that cocaine > pleasant late positive potentials continued to predict respective choice only in impaired insight cocaine subjects (early window: Fig. 2B; late window: Fig. 2C). Both early and late window cocaine > pleasant late positive potentials continued to predict respective choice only in the impaired insight cocaine subjects even when controlling for respective cocaine picture wanting ($\beta > 0.43; P < 0.05$), the cocaine-craving questionnaire ($\beta > 0.39; P < 0.05$), cocaine urine status ($\beta > 0.45; P < 0.05$), treatment-seeking status ($\beta > 0.39; P < 0.05$) and current cocaine abstinence ($\beta > 0.48; P < 0.05$). These analyses suggest that the mechanism underlying late positive potential-cocaine choice prediction in impaired insight cocaine subjects is independent from conscious craving or other important clinical variables that might be expected to impact insight or general cognitive functioning. Note that although not attenuating the late positive potential-choice associations, the cocaine-craving questionnaire was itself associated with cocaine > neutral and cocaine > pleasant choice in all cocaine subjects ($\beta > 0.45; P < 0.001$). The other variables (cocaine wanting, cocaine urine status and treatment-seeking status) were not significantly associated with choice at the $P < 0.01$ threshold, either across all cocaine subjects or when split by insight.

Importantly, the magnitude of these cocaine > pleasant late positive potential-choice correlations significantly differed between the two cocaine subgroups during both late positive potential windows: early (impaired: $\beta = 0.44$; intact: $\beta = -0.18$; correlation difference: $Z = 2.3; P < 0.05$) and late (impaired: $\beta = 0.51$; intact: $\beta = -0.13$; correlation difference: $Z = 2.5; P < 0.01$). To provide further evidence for this differing late positive potential-choice association as a function of cocaine subgroup, we tested insight as a moderator in these regressions. Specifically, across all cocaine subjects, using the cocaine > pleasant scores and separately for both late positive potential windows, we entered late positive potentials, arousal ratings, insight, the insight x late positive potential interaction, and the insight x arousal interaction to predict choice. The insight x late positive potential interaction reached significance during both late positive potential windows [early: $F(1,48) = 4.3; P < 0.05$; late: $F(1,48) = 4.1; P < 0.05$], such that cocaine > pleasant late positive potentials better predicted respective choice in impaired insight cocaine subjects. The insight x arousal interaction also reached significance in these two analyses $F(1,48) > 7.8; P < 0.01$, such that cocaine > pleasant late positive potentials continued to predict respective choice only in impaired insight cocaine subjects (early window: Fig. 2B; late window: Fig. 2C). Both early and late window cocaine > pleasant late positive potentials continued to predict respective choice only in the impaired insight cocaine subjects even when controlling for respective cocaine picture wanting ($\beta > 0.43; P < 0.05$), the cocaine-craving questionnaire ($\beta > 0.39; P < 0.05$), cocaine urine status ($\beta > 0.45; P < 0.05$), treatment-seeking status ($\beta > 0.39; P < 0.05$) and current cocaine abstinence ($\beta > 0.48; P < 0.05$). These analyses suggest that the mechanism underlying late positive potential-cocaine choice prediction in impaired insight cocaine subjects is independent from conscious craving or other important clinical variables that might be expected to impact insight or general cognitive functioning. Note that although not attenuating the late positive potential-choice associations, the cocaine-craving questionnaire was itself associated with cocaine > neutral and cocaine > pleasant choice in all cocaine subjects ($\beta > 0.45; P < 0.001$). The other variables (cocaine wanting, cocaine urine status and treatment-seeking status) were not significantly associated with choice at the $P < 0.01$ threshold, either across all cocaine subjects or when split by insight.

Figure 2 Scatterplots showing prediction of choice behaviour and drug use by late positive potentials and arousal. Across all subjects ($n = 89$), (A) association between pleasant > neutral late positive potential (late window: 1000–2000 ms) and pleasant > neutral choice. For impaired insight cocaine subjects ($n = 25$) (solid line) and intact insight cocaine subjects ($n = 32$) (dashed line), associations between cocaine > pleasant choice with (B) early window (400–1000 ms) respective late positive potentials (significant only for impaired insight); (C) late window (1000–2000 ms) respective late positive potentials (significant only for intact insight) and (D) respective arousal ratings (significant only for intact insight). Also for the cocaine subjects only, associations between amount spent on cocaine per use and (E) cocaine > pleasant arousal (significant only for intact insight), and (F) cocaine > neutral arousal (significant only for intact insight). Except for E and F (where due to outliers in the amount spent on cocaine per use, variables are rank-transformed), abscissa and ordinate values are continuous, standardized residuals. To clarify presentation, the abscissa variable (late positive potential or arousal) is further corrected for the other variable (late positive potential or arousal). LPP = late positive potential.
Table 2  Standardized regression coefficients for the predictive effects of early-window (400–1000 ms) and late-window (1000–2000 ms) late positive potentials and self-reports on respective choice behaviour

<table>
<thead>
<tr>
<th>Picture choice</th>
<th>All subjects (n = 89)</th>
<th>Impaired insight cocaine (n = 25)</th>
<th>Intact insight cocaine (n = 32)</th>
<th>Healthy controls (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \beta_{late positive potential} )</td>
<td>( \beta_{rate} )</td>
<td>( \beta_{late positive potential} )</td>
<td>( \beta_{rate} )</td>
</tr>
<tr>
<td>Pleasant &gt; neutral</td>
<td>Early late positive potential</td>
<td>0.15</td>
<td>0.30*</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>Late late positive potential</td>
<td>0.22**</td>
<td>0.30*</td>
<td>0.28</td>
</tr>
<tr>
<td>Unpleasant &gt; neutral</td>
<td>Early late positive potential</td>
<td>0.16</td>
<td>0.16</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>Late late positive potential</td>
<td>0.08</td>
<td>0.17</td>
<td>0.18</td>
</tr>
<tr>
<td>Cocaine &gt; neutral</td>
<td>Early late positive potential</td>
<td>-0.09</td>
<td>0.56*</td>
<td>0.37***</td>
</tr>
<tr>
<td></td>
<td>Late late positive potential</td>
<td>-0.04</td>
<td>0.55*</td>
<td>0.37***</td>
</tr>
<tr>
<td>Cocaine &gt; pleasant</td>
<td>Early late positive potential</td>
<td>-0.07</td>
<td>0.57*</td>
<td>0.44**</td>
</tr>
<tr>
<td></td>
<td>Late late positive potential</td>
<td>-0.03</td>
<td>0.56*</td>
<td>0.51*</td>
</tr>
</tbody>
</table>

Late positive potentials and arousal were entered as simultaneous predictors in each multiple regression, conducted for the combined sample and then separately for each study group.

*Significant association \((P < 0.01)\), and not driven by outliers.

**Significant association at the reduced statistical threshold for late positive potential-choice associations \((P < 0.05)\), and not driven by outliers.

***Initially significant association at the reduced statistical threshold for late positive potential-choice associations \((P < 0.05)\), but did not survive correction for outliers; \(\beta_{late positive potential} = \) standardized regression coefficient for the late positive potential, \(\beta_{rate} = \) standardized regression coefficient for the arousal rating, with each coefficient controlling for the effect of the other.

arousal ratings better predicted respective choice in intact insight cocaine subjects (Fig. 2D).

Late positive potential and arousal associations with current addiction severity (Table 3)

Buttressing these choice results, associations between the arousal ratings and current addiction severity variables only reached significance in the intact insight cocaine subjects. In this subgroup only, arousal was associated with shorter current abstinence, more days per week of cocaine use, and more money spent per use on cocaine (Table 3). Arousal ratings were better predictors of money spent per use on cocaine in intact insight cocaine subjects than impaired insight cocaine subjects (both cocaine > neutral and cocaine > pleasant contrasts, controlling for both late positive potential windows: correlation differences: \(Z > 2.5; P < 0.05\) (Fig. 2E and F). We again tested insight as a moderator across all cocaine subjects, entering late positive potentials, arousal, insight, the insight \(\times\) late positive potential interaction, and the insight \(\times\) arousal interaction to predict money spent per use on cocaine. Four such analyses were conducted (i.e. cocaine > neutral and cocaine > pleasant, controlling for early and late late positive potential windows). The insight \(\times\) arousal interaction was significant in all four analyses \(F(1,34) > 10.0; P < 0.01\). The insight \(\times\) late positive potential interactions were not significant \((P > 0.1)\).

Although late positive potentials were not directly associated with addiction severity variables in either of the cocaine subgroups, withdrawal symptoms [as assessed by the Cocaine Selective Severity Assessment scale (total score), Table 1] were associated with cocaine > pleasant choice in impaired insight cocaine subjects \((\beta = 0.57; P < 0.01)\), which in turn was predicted by the respective late-window late positive potential in this subgroup \((\beta = 0.57; P < 0.01)\). In tandem, these results could indicate an indirect effect of late positive potential on withdrawal/addiction severity in impaired insight cocaine subjects. This was further suggested by a trend Sobel (mediation) test in this subgroup \((Z = 1.82; P < 0.07;\) Fig. 3A). The intact insight cocaine subjects showed no evidence for this path (Fig. 3B). Taken together, these results support the double dissociation results obtained when predicting cocaine choice behaviour (better prediction by late positive potentials in the impaired insight cocaine subjects; better prediction by self-report in the intact insight cocaine subjects), now extending such results to measures of current addiction severity.

Between-group analyses

Early and late late positive potentials

Late positive potential results were similar for the early and late windows. Both picture contrast \(\times\) group interactions reached significance [Wilk’s \(\lambda: F(6,168) > 2.5; P < 0.05\)], such that group differences were observed only for the cocaine > pleasant contrast \([F(2,86) > 7.6; P < 0.01]\). In the early late positive potential window, impaired insight cocaine subjects had higher cocaine > pleasant late positive potentials than the other two groups (who did not differ) (Fig. 4A); in the late window, both...
Table 3  Standardized regression coefficients for the predictive effects of early-window (400–1000 ms) and late-window (1000–2000 ms) late positive potentials and self-reports on current addiction severity variables, separately for each cocaine study group

<table>
<thead>
<tr>
<th>Current addiction severity variables</th>
<th>All cocaine</th>
<th>Impaired insight cocaine</th>
<th>Intact insight cocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta_{LPP}$</td>
<td>$\beta_{Rate}$</td>
<td>$\beta_{LPP}$</td>
</tr>
<tr>
<td>Cocaine use: amount spent/week</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early cocaine &gt; neutral LPP</td>
<td>0.08</td>
<td>0.02</td>
<td>0.11</td>
</tr>
<tr>
<td>Late cocaine &gt; neutral LPP</td>
<td>0.02</td>
<td>0.02</td>
<td>0.11</td>
</tr>
<tr>
<td>Early cocaine &gt; pleasant LPP</td>
<td>0.19</td>
<td>0.10</td>
<td>0.07</td>
</tr>
<tr>
<td>Late cocaine &gt; pleasant LPP</td>
<td>0.18</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>Cocaine selective severity assessment total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early cocaine &gt; neutral LPP</td>
<td>0.08</td>
<td>0.12</td>
<td>0.13</td>
</tr>
<tr>
<td>Late cocaine &gt; neutral LPP</td>
<td>0.06</td>
<td>0.12</td>
<td>0.08</td>
</tr>
<tr>
<td>Early cocaine &gt; pleasant LPP</td>
<td>0.08</td>
<td>0.09</td>
<td>0.07</td>
</tr>
<tr>
<td>Late cocaine &gt; pleasant LPP</td>
<td>0.08</td>
<td>0.10</td>
<td>0.16</td>
</tr>
<tr>
<td>Severity of dependence scale total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early cocaine &gt; neutral LPP</td>
<td>0.12</td>
<td>0.07</td>
<td>0.00</td>
</tr>
<tr>
<td>Late cocaine &gt; neutral LPP</td>
<td>0.05</td>
<td>0.07</td>
<td>0.10</td>
</tr>
<tr>
<td>Early cocaine &gt; pleasant LPP</td>
<td>0.12</td>
<td>0.06</td>
<td>0.05</td>
</tr>
<tr>
<td>Late cocaine &gt; pleasant LPP</td>
<td>0.10</td>
<td>0.07</td>
<td>0.02</td>
</tr>
<tr>
<td>Cocaine craving total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early cocaine &gt; neutral LPP</td>
<td>0.01</td>
<td>0.32</td>
<td>0.00</td>
</tr>
<tr>
<td>Late cocaine &gt; neutral LPP</td>
<td>0.14</td>
<td>0.31</td>
<td>0.13</td>
</tr>
<tr>
<td>Early cocaine &gt; pleasant LPP</td>
<td>0.19</td>
<td>0.33</td>
<td>0.11</td>
</tr>
<tr>
<td>Late cocaine &gt; pleasant LPP</td>
<td>0.11</td>
<td>0.31</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Late positive potentials and arousal were entered as simultaneous predictors in each multiple regression, conducted separately for the two cocaine subgroups.

$^*$Significant association ($P < 0.01$), and not driven by outliers.

$LPP = \text{standardized regression coefficient for the late positive potential} ; Rate = \text{standardized regression coefficient for the arousal rating}$, with each coefficient controlling for the effect of other; all regressions except those for the normally distributed cocaine selective severity assessment used rank-transformed variables due to the presence of extreme outliers; LPP = late positive potential.

cocaine subgroups (who did not differ) had higher cocaine > pleasant late positive potentials than healthy controls (Fig. 4B). Thus, impaired insight cocaine subjects did not have lower cocaine-related late positive potentials than intact insight cocaine subjects, indicating that the insight measure is not driven by insufficient motivation, compromised task engagement or inattention. If any of these factors were responsible for the inability of the impaired insight cocaine subjects to effectively monitor their choice behaviour, then one would expect cocaine-related late positive potentials to be lower in this subgroup.

Arousal

The significant picture contrast $\times$ group interaction for arousal [Wilk's $\lambda$: $F(6,158)=3.9; P < 0.01$] was driven by significant group differences for the two cocaine contrasts [$F(2,81)>11.4$; $P < 0.001$; both cocaine groups > controls; Fig. 4C], but lack of significant group differences for the other two contrasts ($P > 0.6$). Thus, as to be expected, cocaine-related arousal was higher in both cocaine subgroups than controls.

Choice

The picture contrast $\times$ group interaction for choice did not reach significance [Wilk's $\lambda$: $F(6,158)=1.9; P > 0.08$; Fig. 4D]. Therefore, although inspection of the means indicates a potential difference in cocaine-related choice especially between intact insight cocaine subjects and controls, no follow-up comparisons were computed.

Unawareness of cocaine choice as driving insight impairment

Chi-square analysis showed that among the impaired insight cocaine subjects, unawareness of cocaine choice was responsible for
the insight deficit at a greater-than-chance likelihood (unawareness of cocaine choice responsible for insight impairment: 42.3% compared with expected 25.0%; unawaresness of other pictures responsible for insight impairment: 57.7% compared with expected 75.0%) \( \chi^2(1, n = 26) = 4.2; P < 0.05 \) (see also Supplementary Fig. 1). When restricting this test to cocaine, pleasant, and unpleasant pictures (with expected 33.3% for each category), cocaine choice continued to drive the insight deficit at a greater-than-chance likelihood \( \chi^2(1, n = 17) = 8.9; P < 0.05 \). 

**Discussion**

Despite extensive evidence (compiled over more than a decade) showing that late positive potentials co-vary with stimuli salience (Cuthbert et al., 2000; Schupp et al., 2000; Hajcak et al., 2010), their ability to predict choice behaviour was previously unknown. Our results show for the first time that late positive potentials, electrophysiological measures that track emotional experience (e.g. arousal), predicted subsequent behavioural choice in both health and disease states [with similar effect sizes (correlations) for each of the three subgroups]. Interestingly, this prediction was specific to the pleasant stimuli and was observed during sustained (late late positive potential) but not initial (early late positive potential) emotional processing of such stimuli. This finding is consistent with a previous study of healthy individuals that similarly revealed a later but not earlier late positive potential to be associated with behaviour (better recognition memory for pictures) (Koenig and Mecklinger, 2008). In this study, pleasant > neutral choice was also predicted by respective arousal ratings. However, there were no significant differences between the groups in rating the pleasant (or unpleasant) images on arousal. This null finding, although in agreement with our prior study using a subset of these same subjects (Moeller et al., 2009), is generally discordant with other studies that have used similar stimuli in addicted individuals. In these studies, pleasant stimuli have typically elicited lower arousal ratings (Aguilar de Arcos et al., 2005, 2008; Lubman et al., 2009) and functional MRI hypoactivations of brain reward regions (e.g. dorsal and ventral striatum) (Asenio et al., 2010) in drug-addicted individuals compared with healthy controls. Importantly, however, because such self-reported arousal ratings did not attenuate the predictive ability of the late positive potentials, results of this study support the idea that self-report and physiological/neural measures assess unique and possibly complementary information (Tomarken, 1995; Falk et al., 2010).

Our study is also significant in that it identified a variable (self-awareness of choice behaviour: insight) that modulated the prediction of drug choice in addiction. In particular, late positive potentials elicited by cocaine pictures predicted cocaine-related choice in cocaine subjects whose ability to monitor this choice was impaired. Indeed, this insight impairment was driven by unawareness of choosing to view cocaine pictures (relative to the other three picture categories, and relative to the other two salient categories specifically), speaking to its relevance vis-a`-vis these subjects’ particular disease (cocaine addiction). In contrast, for cocaine subjects in whom self-awareness of choice behaviour was intact, self-report (arousal ratings) predicted respective choice. These results suggest a double dissociation between late positive potential and self-report for predicting choice as a function of insight. Similar dissociation was observed when investigating the severity of addiction (e.g. uniquely and more prominently in intact insight cocaine subjects, arousal ratings were directly associated with money spent per use on cocaine). This dissociation is consistent with recent theory and research on implicit measures as recently reviewed (Nosek et al., 2011). In particular, the predictive validity of more implicit, bottom-up measures (note that late positive potentials have indeed been suggested to depend on bottom-up/implicit processes (Hajcak et al., 2010)) seems to be enhanced by a number of moderating factors including reduced ‘motivation’ (e.g. fewer self-presentation concerns about reporting a biased reaction to drug stimuli), ‘ability’ (e.g. less self-control), and/or ‘awareness’ (e.g. more ambivalence/less certainty about one’s own reactions to drug-related stimuli). In contrast, when motivation, ability and awareness are high, the predictive balance is shifted in favour of explicit measures (such
that conscious feelings/self-reports become more likely to guide choices, as was the case in our intact group). In this light, the lack of late positive potential-choice associations in the intact group becomes less surprising. Importantly, because these differential associations were most prominently observed using the cocaine > pleasant contrast, our results may have particular relevance to theories of addiction postulating that drug-addicted individuals pursue drugs and drug-related stimuli over other non-drug-related goals and reinforcers (Goldstein and Volkow, 2011). Unlike the classical drug > neutral contrast that has typically been the focus of previous late positive potential studies (Franken et al., 2008), a contrast between two competing reinforcers may be necessary to provide variability in choice that can be predicted by the respective late positive potentials. Specificity of results to a contrast involving the pleasant stimuli is also consistent with previous research in which future clinical outcome was predicted by blunted response to pleasant stimuli [late positive potentials (Versace et al., 2012) or self-reported valence ratings (Lubman et al., 2009)]. Notably, our double dissociation results indicate that insight could potentially inform the discussion on when self-reports can validly be used to predict important drug-relevant outcomes in addiction (Perkins, 2009), helping to ensure the efficient allocation of scarce clinical resources. Specifically, in the addicted individuals for whom self-awareness is intact, prediction of disadvantageous behaviour may be amenable to conveniently administered self-report assessments (e.g. arousal ratings when exposed to drug stimuli). In contrast, those individuals for whom the capacity to identify or report on internal states is diminished may benefit from objectively measured late positive potentials as a method of predicting disadvantageous behaviour—and possibly even treatment outcome and relapse as remains to be tested in future studies.

Limitations of this study include the following: (i) the current insight measure is largely categorical and does not assess all components of ‘clinical insight’ (i.e. it is restricted to behavioural self-awareness during a single task). Although we explored the magnitude of insight impairment among cocaine subjects already classified as impaired (Supplementary material), a fully quantitative index of insight may improve behaviour prediction. Moreover, although we anticipate that the current insight measure will...
correlate with more general clinical insight (and possibly with other variables such as self-monitoring), our method requires further validation with such measures; (ii) because the same stimuli were used in all four tasks, the possibility of habituation or priming should be accounted for in future studies, possibly through use of different affective pictures for different study components and/or through use of an objective measure of arousal (e.g. skin conductance response) that could corroborate and complement the results of both late positive potentials and self-reported arousal. However, habituation would have likely reduced the predictive association between late positive potential and choice, producing null results. Possible effects of priming were also lessened by our statistical approach: by entering arousal as a simultaneous predictor in the multiple regressions, we showed that the predictive effect of the late positive potentials was above and beyond that of arousal. In addition, the impaired insight group did not report higher arousal than the intact group (Fig. 4C), suggesting that this subgroup was not differentially primed; (iii) cocaine-related late positive potentials were indirectly associated with measures of current addiction severity in impaired insight cocaine subjects. Future clinical intervention studies may therefore benefit from including cocaine-related choice as an intermediary step; (iv) the precise process mediating the enhanced predictive effectiveness of late positive potentials in impaired insight cocaine subjects (and enhanced predictive effectiveness of self-reports in the intact subjects) requires further study. For example, the respective contributions of motivation, ability and awareness as reviewed above (Nosek et al., 2011) remain to be disentangled. Furthermore, the relationship between salience and insight should be examined more closely: a targeted 2 × 2 design could evaluate whether/how these factors influence one another and whether/how they independently or interactively contribute to late positive potential magnitude and/or choice; (v) although we conducted preliminary analyses (described in the Supplementary material) with impaired insight control subjects and when excluding subjects with antisocial personality disorder, their respective low n’s preclude drawing conclusions about their unique contributions to results, and these variables remain to be separately studied. Other variables that could impact motivational salience and/or awareness (e.g. borderline personality or other Axis II disorders) similarly remain to be evaluated in future studies with larger sample sizes; and (vi) this study included mostly males and only cocaine subjects (most of whom were current users). Therefore, future studies will need to generalize these results to females, and to individuals dependent on other addictive drugs (the latter using stimuli tailored to the particular substance of interest). In addition, although our sample was comprised of 38% treatment-seekers (therefore showing that our results are not limited to active users), future studies are needed to evaluate whether drug choice and insight on our task predict prospective clinical outcome in individuals with longer abstinence periods.

In conclusion, our results support the novel hypothesis that a psychophysiological scalp-recorded measure (the late positive potential) predicts choice behaviour as modulated by self-awareness. These findings contribute to previous efforts to use neural activity to ascertain choice (Tusche et al., 2010), while extending such findings to a clinically relevant psychopathology (cocaine addiction). By using late positive potentials to predict objective cocaine choice behaviour, these findings extend previously revealed correlations between event-related potentials and self-reported craving (Franken et al., 2003, 2008), and indicate that cocaine-elicited late positive potentials can be added to the repertoire of event-related potential/EEG profiles that have been used to predict drug-relevant variables in cocaine subjects (e.g. distinct patterns of alpha, beta, delta and theta features predicting the amount of time in treatment (Prichep et al., 1999) or the P300 predicting relapse (Bauer, 1997)). Because EEGs are relatively inexpensive (compared with other neuroimaging techniques), portable (e.g. they can now be transported and implemented via backpack), and non-invasive, it is becoming increasingly feasible to deploy this methodology at clinical intervention sites (or other sites of court-mandated confinement, such as prisons). Insofar as such results were not significant for another event-related potential component indexing emotional processing (the early posterior negativity; Supplementary material), late positive potentials could serve as a biomarker to help predict disadvantageous drug-related choice and possibly associated behaviours (e.g. drug seeking in natural settings, relapse after treatment) especially when insight (and self-report) is compromised. More generally, late positive potentials could provide an important assessment tool to help forecast disadvantageous behaviours not only in drug addiction but also in other psychopathologies similarly characterized by compromised self-awareness, and that are also associated with disadvantageous or unwelcome behaviours (e.g. binge eating and intermittent explosive disorder).

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Supplementary material

Supplementary material is available at Brain online.
References


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