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Compromised sensitivity to monetary reward in current cocaine users: an ERP study

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Abstract

We studied modulation of the P300 by monetary reward expected to be received on a sustained attention task in 18 individuals with current cocaine use disorders (CUD) and 18 control subjects. Results in the controls revealed sensitivity to money as measured with P300 amplitude and speed of behavioral response and their intercorrelations. In contrast, despite generally faster P300 waveforms and higher self-reported interest in the task, CUD did not display these responses to money vs. non-reward; at the behavioral level, this impairment correlated with frequency of recent cocaine use. These preliminary results suggest a compromised sensitivity to a secondary reinforcer in CUD. This deficit, that needs to be replicated in larger samples of currently active vs. abstaining CUD, may underlie the compromised ability to advantageously modify behavior in response to changing inner motivations and environmental contingencies.

Keywords

Cocaine addiction; early withdrawal; current drug abuse; P300; reward processing; monetary reward; secondary reinforcement; inhibitory control

Drug addiction is a complex disease characterized by recurrent drug intoxication, craving, bingeing, withdrawal and relapse as modulated by genetic, developmental, experiential and environmental factors. Neurobiological research has traditionally highlighted the role in drug addiction of the mesocorticolimbic dopaminergic reward circuitry (Goldstein & Volkow, 2002; Volkow, Fowler, Wang, & Swanson, 2004) and indeed impairments in the processing of *drug reward* and drug-related cues have been frequently studied (Childress, et al., 1999; Di Chiara & Imperato, 1988). Recently, neuroimaging studies have highlighted a compromise in the processing of *non-drug* reward in drug-addicted individuals. For example, cocaine addicted but not healthy control individuals showed less activation of corticolimbic brain areas when viewing an erotic video than when exposed to a cocaine video (Garavan, et al., 2000).

In a more recent functional magnetic resonance imaging (fMRI) study, we similarly reported that neuronal and behavioral sensitivity to a more abstract monetary reward was compromised in cocaine addiction (Goldstein, et al., 2007a; Goldstein, et al., 2007b). Specifically, whereas controls reported valuing higher amounts of money more than lower amounts, more than half

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of the individuals with cocaine use disorders (iwCUD=CUD) rated the value of all abstract monetary amounts equally (\$10=\$1000) (Goldstein, et al., 2007b). In parallel, CUD demonstrated reduced prefrontal cortical responsivity to differences between other monetary amounts (45¢, 1¢ and 0¢) received for accurate performance on a sustained attention fMRI task (Goldstein, et al., 2007a). These altered prefrontal cortical responses to money (that encompassed the lateral orbitofrontal cortex, anterior cingulate cortex, and dorsolateral prefrontal cortex) were associated with the blunted subjective sensitivity to reward gradients as measured with a simple rating scale (Goldstein, et al., 2007b) and with poorer self-reported inhibitory control as measured with a personality questionnaire (Goldstein, et al., 2007a) in CUD. Using the same sustained attention task and monetary reward quantities (45¢, 1¢ and 0¢) while recording event-related potentials (ERPs), we replicated the impact of monetary reward on neural responses in healthy young adults (Goldstein, et al., 2006): while the contingent negative variation was unaffected by money, P300 amplitude (most pronounced at the Pz electrode) was significantly larger for 45¢ than the 1¢ and 0¢ conditions. This effect corresponded to the monotonically positive subjective ratings of interest and excitement on the task (45¢>1¢>0¢).

Others have also systematically varied monetary amounts to study the role of the P300 in processing the incentive value of reinforcers. For example, P300 amplitude was larger to positive monetary feedback (3¢) than to non-reward (0¢) in healthy young adults on a complex forced-choice guessing task (Hajcak, Holroyd, Moser, & Simons, 2005). Using another guessing task in young adults, the P300 was similarly modulated by the magnitude of monetary feedback (large: 32–40¢ > small: 6–11¢) received for both wins and losses (Yeung & Sanfey, 2004). Taken together, these recent results bolster the role of the P300 in processing salient stimuli (Squires, Donchin, Herning, & McCarthy, 1977), such as stimuli with high emotional value, informative feedback or target stimuli (Johnson, 1988; Picton, 1992; Pritchard, 1981). This role of the P300 in processing reinforcer salience has recently been reviewed and interpreted to represent a norepinephrine-induced phasic enhancement of neural activity in the neocortex (including the prefrontal cortex) as a function of task-relevant information processing (Nieuwenhuis, Aston-Jones, & Cohen, 2005).

In drug addiction, the role of the P300 as a potential phenotypic marker has long been recognized (Begleiter & Porjesz, 1990). More specifically, using the oddball paradigm the P300 amplitude has been shown to be mostly decreased in cocaine addiction, as predictive of relapse (Bauer, 1997) and attributed to the effects of abstinence or withdrawal (Kouri, Lukas, & Mendelson, 1996; Noldy & Carlen, 1997), history of conduct disorders (Bauer, 2001), or impulsivity (Moeller, et al., 2004). Similarly, the P300 latency has been reported to be delayed in individuals with cocaine or cocaine and alcohol dependence (Biggins, MacKay, Clark, & Fein, 1997), although opposite results were reported for experienced intravenous users who had used cocaine within 48 hours of admission to an inpatient unit (Noldy & Carlen, 1997).

A gap in the literature pertains to the use of the P300 to study response to reward vs. non-reward in drug addiction. An exception is a study where males with a family history of alcoholism did not show the expected greater P300 amplitude and shorter latency to a performance-contingent monetary incentive on a visual discrimination task (Ramsey & Finn, 1997). Given the paucity of such studies, our current goal was to inspect the P300's modulation by monetary reward in CUD. We hypothesized that compared to age-matched healthy control individuals, the P300 will not discriminate between monetary reward and a neutral non-reward in individuals with current use (non treatment-seeking CUD). Documentation of such a P300 compromise could add to the understanding of the changes in the neocortical role in reinforcer salience expectation in drug addiction. Because P300 monetary magnitude effects are largest at posterior midline sites (Hajcak, Holroyd, Moser, & Simons, 2005; Yeung & Sanfey, 2004) and given similar results in our prior ERP study as described above (Goldstein, et al., 2006),

we focused the current analyses on the Pz electrode; results of the other midline electrodes are reported for completeness.

Methods

Participants

Thirty-six medically healthy right-handed subjects participated in this study, 18 individuals with current CUD and 18 healthy control subjects. There were no statistically significant differences between the two study groups in distributions of sex and race or in age, education, and socioeconomic status (Table 1). Although we excluded subjects with severe levels of self-reported state depression (Beck, Steer, & Brown, 1996) (scores: >29, N=2), this variable and history of cigarette smoking differed between the CUD and healthy controls (Table 1); their possible confounding effects on results were examined as described under Analyses and Results.

Subjects were recruited using advertisements in local newspapers and by word-of mouth. A full physical and neurological examination ensured the following inclusion criteria were met for all subjects: absence of 1) head trauma with loss of consciousness; 2) current neurological or any medical disease that required hospitalization or regular monitoring (note that subjects were not tested for HIV); and 3) except for psychostimulants (cocaine or amphetamine / methamphetamine) in the CUD subjects, urine screens for other drugs or their metabolites (phencyclidine, benzodiazepines, cannabis, opiates, and barbiturates) had to be negative. All CUD had a history of using cocaine for at least 3.5 days a week, for at least six months (the smoked route was used by 17 subjects; one subject used the intranasal administration instead). All healthy control subjects denied regular drug use.

In addition, a licensed clinical psychologist conducted an in-depth, 1–3 hour, psychiatric (diagnostic) interview in all subjects. This interview included the: (1) Structured Clinical Interview for DSM-IV Axis I Disorders (First, Spitzer, Gibbon, & Williams, 1996; Ventura, Liberman, Green, Shaner, & Mintz, 1998) - Nonpatient Edition or Patient Edition for control or CUD subjects, respectively; (2) Addiction Severity Index (McLellan, et al., 1992), a semistructured interview that collects data in seven problem areas (medical, employment, legal, alcohol, other drug use, family–social functioning, and psychological status) to provide an estimate of the severity of the drug abuse problems and a detailed assessment for recent and lifetime history of use of various drugs including alcohol; (3) 18-item Cocaine Selective Severity Assessment Scale (Kampman, et al., 1998) conducted to evaluate cocaine abstinence/withdrawal signs and symptoms (i.e., sleep impairment, anxiety, energy levels, craving, and depressive symptoms) 24 hours within time of interview; and (4) 5-item Cocaine Craving Questionnaire (Tiffany, Singleton, Haertzen, & Henningfield, 1993) and the 3-item Severity of Dependence Scale (Gossop, Griffiths, Powis, & Strang, 1992).

Based on this extended interview, all CUD subjects met DSM-IV criteria for current Cocaine Dependence (N=15) or Abuse (N=2). One cocaine abuser, who admitted to weekly use of cocaine, did not meet current abuse or dependence criteria, but met DSM-IV criteria for past polysubstance abuse (with cocaine as the primary drug). All CUD subjects self-reported using cocaine within 96 hours of the study (Table 1). Recent cocaine use was indeed confirmed by the urine screen results (urine was positive for cocaine on study day in all CUD subjects. These results indicate cocaine use within 72 hours of testing, which is the maximum resolution provided by the urine screen; results for the CUD subjects whose urine was negative for cocaine on study day will be reported separately). Current abuse of alcohol or cannabis was reported in two CUD subjects; urine was negative for cannabis in all subjects. Current abuse or dependence on other drugs was denied and corroborated by the pre-scan urine tests in all but one subject (urine was positive for both cocaine and amphetamine/methamphetamine) (see

Table 1 for drug use variables in all CUD subjects). Despite of their current use status, none of the study participants was intoxicated on study day (as determined by this extended clinical interview). Other current or past psychiatric co-morbidities were identified in seven CUD subjects and included major depression disorder (N=5), post-traumatic stress disorder (N=2), antisocial personality disorder (N=1), and pathological gambling (N=1) (2 CUD subjects met criteria for more than one of these disorders). Subjects did not require medications for these conditions as ascertained by the above-described interviews. Subjects were fully informed of all study procedures and provided written consent for their involvement in this study in accordance with the local Institutional Review Board.

Task

In the current study, we used a monetary reward paradigm that has been previously described (Goldstein, et al., 2007a; Goldstein, et al., 2007c). In brief, there were six sequences/blocks each consisting of all three blocked monetary reward conditions: 45¢, 1¢, 0¢ (that is, each monetary condition appeared for a total of six times). These 63 sec monetary conditions were pseudo-randomized and separated by a 35 sec fixation cross to preclude carry over effects. During each of these monetary conditions, there were 9 “Go” and 9 “No-go” trials, which were pseudo-randomized across all trials (no more than three of same type). Two distinct abstract (fractal) images (Thut, et al., 1997) served as the “Go” and “No-go” warning stimuli [S1: this expectation stimulus elicited the P300, see Figure 2 top in (Goldstein, et al., 2006)]¹. Trial sequence was as follows: fixation screen (1000 msec) followed by one of the two fractal images (visual angle = 4.5°, 500 msec) followed by another fixation screen (1000 msec), and terminating in a target stimulus (S2) in the form of a red square (visual angle = 4.5°, 500 msec) [see Figure 1B in (Goldstein, et al., 2007c)]. A response window overlapped with the full presentation of S2. A fixation point remained in the center of the screen for the duration of each 3500 msec trial. All text was in a ROM 2 font.

The subjects were instructed to press a button (using the thumb of the right hand) on a response pad with speed and accuracy upon seeing S2 after a “Go” S1 stimulus and to not press the button upon seeing S2 after a “No-go” S1 stimulus. Incorrect responses were trials where subjects pressed the button instead of refraining from responding (errors of commission) or did not press the button instead of pressing it (errors of omission) [subjects in our prior fMRI study committed on average less than one error of commission for each of these three monetary conditions (Goldstein, et al., 2007a); therefore, these two error types were combined in all current analyses]. Feedback was presented (visual angle = 2.25°, 500 msec) immediately after the offset of S2; here the amount of money earned for correct responses/non-responses was: \$0.45, \$0.01, or \$0.00. For incorrect responses/non-responses, which happened in less than 8% of trials across all subjects as further described in Results, subjects saw an “X” and did not receive remuneration. Feedback was thus contingent on behavior (i.e., it was not a priori determined). Together with a screen that displayed the monetary reward contingency at each experimental condition onset (visual angle = 1.5°, 5000 msec), subjects were aware of the reward contingencies throughout the task (at the start of each monetary block and at the end of each single trial).

Choice of these three monetary conditions was based on our previous fMRI study (Goldstein, et al., 2007a) where we selected these specific levels of reinforcement based on our goal to examine expectation of *real* money (calculations were therefore based on the monetary amount available to pay each study volunteer and the number of trials required for fMRI). Within these constraints, we further aimed to inspect differences between the highest and lowest rewards

¹Note that in our previous study these two fractal images had no significant differential effects on the selected ERP components, which included the P300 (Goldstein et al., 2006).

possible and also to incorporate a baseline non-reward condition (0¢). Similarly to the previous study, subjects were paid up to \$50 for completion of this task (Table 1).

Procedure

Participants were fitted with electrodes and positioned in a cushioned chair. An LCD panel was placed 115 centimeters from the subject's face. Instructions were provided and followed by a short training session, where no money could be earned (stimuli presented during this training session were the same as those presented during the experimental conditions). At the end of the experiment, subjects were informed of their monetary gain and were given that exact amount at the completion of the study day (note that there was no difference between the groups in total monetary gain on this task, Table 1).

Psychophysiological Recording and Data Reduction

Continuous recordings of the electroencephalogram (EEG, Neuroscan Inc., Sterling USA) and electro-oculogram (EOG) were obtained in all experimental conditions using a 64 silver-silver chloride electrodes cap positioned according to the International 10/20 System (Klem, Luders, Jasper, & Elger, 1999). All recordings were performed using a fronto-central electrode as ground, and electronically linked mastoid electrodes as reference. Electrodes were placed above and below the left eye to record vertical eye movements. The EEG was digitized at a rate of 1000 Hz and amplified with a gain of 250, and a band pass filter of 0 to 70 Hz. The amplifiers were calibrated prior to each recording. Electrode impedances were at or below 10 kilo-ohms for all electrodes used in the analysis.

Behavioral Measures and Self-Reported Scales

Reaction time (RT) and performance accuracy were recorded during all task trials and conditions. Further, upon task completion, participants were asked to rate their interest (Scale 1, ranged from 0–7: boring to interesting, respectively), excitement (Scale 2, 0–7: dull to exciting) and frustration (Scale 3, 0–7: extremely frustrating to not at all frustrating) for all three monetary conditions.

Analyses

Event-Related Potentials—The digitized, continuous EEG was transformed using a DC offset algorithm and was divided into epochs extending from 200 msec before the onset of S1 to 1800 msec after. A linear detrend algorithm was applied to the epoched EEG and after baseline correction (using the 200 msec before S1 onset), epochs were inspected and those containing amplitudes greater than 75 μ V or less than -75μ V were rejected to eliminate EOG and movement artifacts. After rejections, there was a minimum of 16 epochs per averaged waveform. Separate averages were composed (across sequences/blocks) for “Go” and “No-go” stimuli (S1) separately for the three money conditions (45¢, 1¢ and 0¢) for a total of six waveforms per subject. Grand average waveforms (across all study subjects) were also created for each monetary condition and on these averaged waveforms a P300 component was defined as the largest positive peak (relative to the pre-S1 baseline) in a latency window occurring 280–600 msec after S1. The P300 component for each individual subject was then defined as the largest positive peak ± 75 msec of the grand averaged P300 peak; the time point at which the P300 reached its maximal amplitude was selected as the P300 latency. We focus on the estimations conducted for the midline parietal electrode, Pz, which showed the most pronounced P300 response to money in previous studies (Goldstein, et al., 2006; Yeung & Sanfey, 2004). Nevertheless, before conducting the planned $2 \times 3 \times 2$ mixed ANOVA [Trial (“Go”, “No-go”), Money (45¢, 1¢, 0¢) and Group (CUD, Control)] on the Pz amplitude and latency data, we also report a similar analysis with Site as an additional factor (frontal: Fz; central: Cz; parietal: Pz).

Behavior: Reaction Time, Accuracy, and Post Task Rating Scales—Reaction time (msec) and percent of correct responses were averaged across all trials for each monetary condition. Percent accuracy was analyzed with a $2 \times 3 \times 2$ (Trial by Money by Group) mixed ANOVA. Reaction time and the three post-task rating scales (interest, excitement and frustration) were analyzed using a 3×2 (Money by Group) ANOVA.

In all these analyses (behavior and P300), in cases where the assumption of Sphericity was not met (as tested by Mauchly's Test of Sphericity), the Greenhouse-Geisser correction was used. Significant effects were followed with paired (within group) or independent (between group) t-tests; for performance accuracy and all rating scales (which were not normally distributed), the equivalent non-parametric tests were used (paired: Wilcoxon; or independent: Mann-Whitney U). Planned comparisons were conducted across all dependent variables to test our main hypothesis (45¢ does not equal to 0¢ in the control but not CUD subjects).

Correlations—The ERP variables were correlated with all behavioral variables separately across all monetary conditions or for their respective differential scores (e.g., 45¢ minus 0¢). Pearson correlations were performed for RT while Spearman correlations were performed for all other behavioral variables (the parametric correlations were performed for normally distributed variables, while the nonparametric correlations were performed for skewed variables). We also performed correlations (parametric or non-parametric as appropriate) between the main ERP and behavioral dependent variables with depression, which significantly differed between the groups (Table 1). If significant, depression was used as a covariate in the appropriate ANOVA (Stevens, 1992). The dichotomous smoking status, which also differed between the groups, was inspected with t-tests. Moreover, for all current smokers (14 CUD and three controls), we also inspected potential impact on results of current cigarette smoking frequency (number of cigarettes a day: mean $\pm$ SEM, 11.1 $\pm$ 1.7) and time since last use (seven subjects smoked a cigarette $\leq$ 4 hours before the study and 10 subjects smoked $>$ 4 hours before the study). Finally, we conducted correlations between the selected ERP and behavioral variables with the drug use measures listed in Table 1. To protect against Type I error, a significance level of 0.01 was used for all correlations. Otherwise, $p < 0.05$ was considered significant.

Results

P300 at the three midline electrodes

Results of the $2 \times 3 \times 3 \times 2$ mixed ANOVA [Trial ("Go", "No-go"), Money (45¢, 1¢, 0¢), Site (Fz, Cz, Pz) and Group (CUD, Control)] revealed the expected Site main effect [$F(1.3,43)=9.5$, $p < 0.01$] and Site by Trial interaction [$F(1.7,57.6)=20.0$, $p < 0.0001$], whereby P300 amplitudes were higher for Pz (and Cz) than Fz ($Pz=Cz > Fz$), especially during the 'Go' trials. This analysis also revealed a Group main effect [$F(1,34)=4.6$, $p < 0.05$; CUD $>$ control subjects], driven by the Fz [$F(1,34)=4.3$, $p < 0.05$] and Cz [$F(1,34)=5.7$, $p < 0.05$] electrodes but not by the Pz electrode [$F(1,34)=0.8$, $p > 0.4$]. All other multivariate effects did not reach significance [$F(2,33) < 2.0$, $p > 0.2$].

P300 at Pz

See Table 2 for the means and standard deviations of all P300 amplitudes and latencies as a function of Trial, Money, and Group. The main $2 \times 3 \times 2$ ANOVA for P300 amplitude revealed significant Trial ["Go" $>$ "No-Go"; $F(1,34)=14.4$, $p < 0.01$] and Money [45¢ $>$ 0¢, $F(2,33)=4.4$, $p < 0.05$] main effects. Although the Money by Group interaction was not significant [$F(2,33)=0.4$, $p > 0.7$], a planned contrast revealed that the monetary effect was only significant in the control but not the CUD subjects, as best demonstrated during the "Go" trials [45¢ $>$ 0¢; paired $t(17)=-2.2$, $p < 0.05$; "No-Go"; paired $t(17)=-1.8$, $p < 0.09$] (Figure 1). There were no significant

correlations between these Pz P300 “Go” amplitudes with depression, in the complete group or separately in both study subgroups (all $r < |0.38|$, $p > 0.1$). Similarly, inspected with independent t-tests separately for each monetary condition and subject group (and for the complete sample), these amplitude measures did not differ by history of cigarette smoking (all $t < |1.43|$, $p > 0.2$). For the current smokers, frequency of smoking and time since last cigarette were not associated with these amplitude measures. Thus, this differential P300 amplitude to money in the control group but not CUD subjects cannot be attributed to the differential effects of depression or cigarette smoking.

For the P300 latencies at Pz, significant Trial [“Go” < “No-Go”, $F(1,34)=23.0$, $p < 0.0001$] and Group [CUD < control; $F(1,34)=5.5$, $p < 0.05$] main effects demonstrated faster latencies for the “Go” trials and for the CUD subjects. Planned monetary contrasts did not reveal differences between the monetary conditions for any of the study groups or combined across all subjects [paired $t < |2.0|$, $p > 0.07$]. Further, both main effects remained significant after entering depression as a covariate [$F(1,33) > 6.7$, $p < 0.05$]. After entering history of cigarette smoking, the Trial by Group interaction reached significance [$F(1,33)=6.7$, $p < 0.05$], indicating faster latency in the CUD subjects for the “Go” trials only. For the current smokers, frequency of smoking and time since last cigarette were not associated with these latency measures.

Behavioral Results

See Table 2 for the means and standard deviations of RT, accuracy, and the three rating scales as a function of Trial (where relevant), Money and Group. The main $2 \times 3 \times 2$ mixed ANOVA on percent accuracy showed a Trial main effect [“No-Go” > “Go”; $F(1,34)=38.8$, $p < 0.0001$], a Money main effect ($0\text{¢} > 1\text{¢}$; $F(2,33)=4.6$, $p < 0.05$), and a Money by Trial interaction [$F(1.7,57)=14.6$, $p < 0.0001$]. Non-parametric comparisons showed that the monetary differences were driven by the “No-Go” trials, where the 1¢ condition was least accurate [$45\text{¢} = 0\text{¢} > 1\text{¢}$; $Z = -5.5$, $p < 0.0001$]; the latter is an unexpected result that requires follow-up with clear hypotheses (e.g., could it reflect increased inhibitory control requirements under conditions of relative uncertainty/frustration?). Importantly, there were no differences between the study groups in any of these comparisons. Accuracy did not correlate with depression and was also not associated with history of cigarette smoking (including frequency of smoking and time since last cigarette).

There was a significant Money linear contrast for RT (analyzed for the “Go” trials only) [$F(1,34)=5.1$, $p < 0.05$], such that there was a trend for faster RT for the highest monetary condition. Planned comparisons revealed that the control subjects were somewhat faster than the CUD subjects, a difference that reached significance for the 1¢ condition [$t(34)=2.1$, $p < 0.05$], with a trend for the 45¢ condition [$t(34)=1.8$, $p < 0.09$]. Most importantly, the 45¢ vs. 0¢ differential was only significant for the control subjects [$45\text{¢} < 0\text{¢}$; paired $t(17)=2.7$, $p < 0.05$]. Entering depression as a covariate did not impact the monetary main effect and moved the Money by Group interaction closer to significance [Quadratic within-subjects contrast, $F(1,33)=3.2$, $p < 0.09$]. History of cigarette smoking (including frequency of smoking and time since last cigarette) was not associated with RT.

Both interest and excitement rating scales showed a significant Money main effect [$45\text{¢} > 1\text{¢} \geq 0\text{¢}$; $F(1.4,46.9) > 17.2$, $p < 0.0001$] and a significant Group main effect [CUD > control; $F(1,34) > 4.5$, $p < 0.05$] (Figure 2). The Money by Group interaction was not significant. There were no significant results for ratings of frustration. When depression was entered as a covariate, results did not change for the interest ratings; the diagnosis main effect was no longer significant for the excitement ratings. Cigarette smoking (including frequency of smoking and time since last cigarette) was not associated with these rating scales.

P300-Behavioral Correlations

Because the amplitude and latency P300 group differences were noted mostly during the “Go” trials as described above (P300 at Pz section), the following correlations with behavior were focused on the “Go” trials. There was a positive correlation between the P300 amplitude differential for the 45¢ minus 0¢ condition with the respective accuracy differential in the control subjects only; the higher the P300 amplitude differential, the better the accuracy for the high monetary condition as compared to the neutral cue ($r=0.64$, $p<0.01$; Figure 3, left; this correlation remained significant after excluding the outlier on the upper right-hand corner of this figure: $r=0.61$, $p<0.01$). Similarly, a negative correlation with RT was only observed in the control subjects: the higher the P300 amplitude for the 1¢ minus 0¢ condition, the faster the respective change in RT ($r=-0.6$, $p<0.01$; Figure 3, right). Further, only for the control subjects, there was a negative correlation between latency and accuracy (this reached significance for the 0¢ condition: $r=-0.66$, $p<0.01$): the faster the P300 latency, the higher the accuracy. Controlling for depression or cigarette smoking (with partial correlations), these correlations remained significant ($r>|0.49|$, $p<0.05$). The parallel correlations in the CUD were not significant ($r<|0.29|$, $p>0.3$). None of the correlations between the P300 measures (during “Go” trials) and the rating scales survived the nominal significance level. The parallel correlations for the “No-go” trials (except with RT) were not significant ($r<|0.46|$, $p>0.06$).

Finally, we conducted analyses between these six variables (that showed P300-behavioral intercorrelations: P300 amplitude and accuracy differentials for 45¢ minus 0¢, P300 amplitude and RT differentials for 1¢ minus 0¢, and P300 latency and accuracy at 0¢ condition, all during the “Go” trials) and the selected 10 drug use variables in the CUD subjects (Table 1). One correlation reached nominal significance level: the higher the 45¢ minus 0¢ accuracy, the less frequent the cocaine use during the 12 months preceding this study ($r=-0.80$, $p<0.0001$; this correlation also reached significance for the 45¢ minus 1¢ accuracy differential, $r=-0.72$, $p=0.001$) (Figure 4). These correlations remained significant after controlling for depression and history of cigarette smoking (including current frequency and time since last use; $r>-0.66$, $p<0.01$). Parallel correlations for the “No-go” trials did not reach statistical significance ($r<|0.4|$, $p>0.1$).

Discussion

The goal of this study was to investigate the P300 modulation by sustained monetary reward vs. non-reward in adults with current CUD as compared to age-matched healthy control adults. As hypothesized, sensitivity to monetary reward was compromised in the CUD subjects: while in the control subjects the amplitude of the P300 component (recorded at Pz during expectation of reward) was higher in the 45¢ condition than the 0¢ condition, a similar P300 response to money was not significant in the CUD subjects (Figure 1). In parallel, only the control subjects reacted faster to the highest monetary condition (45¢) as compared to the neutral cue (0¢). Further, only in the control subjects these P300 amplitude differentials intercorrelated with the respective behavioral adjustments to the monetary incentive (45¢>0¢ with accuracy and 1¢>0¢ with RT, Figure 3); in the CUD subjects, the better the accuracy adjustment for the high monetary condition, the less frequent the cocaine use during the year preceding this study (Figure 4). Overall, the compromise in the P300 and behavioral responses to monetary reward in the CUD subjects could not be attributed to general decreases in P300 amplitude or latency (P300 amplitudes at Pz did not differ between the study groups and P300 latencies at Pz were *faster* in the CUD than the control subjects), differential monetary gain during the task or to the inspected individual factors (e.g., depression, history of cigarette smoking). Further, these results could not be attributed to decreased task engagement in the CUD subjects who instead reported being *more* interested in the task than the control subjects (Figure 2).

Our results in the control subjects confirm modulation of the P300 by monetary reward magnitude (Hajcak, Holroyd, Moser, & Simons, 2005; Yeung & Sanfey, 2004). Similarly, using another S1–S2 RT task, fast trials resulted in larger P300 amplitudes in a condition where healthy subjects could earn money (Otten, Gaillard, & Wientjes, 1995). Our results extend these previous studies by showing parallel reward-driven adjustments in both the P300 amplitudes and behavioral performance; their direct intercorrelations support a previously described role of the P300 in motivation (Carrillo-de-la-Pena & Cadaveira, 2000). Our results are thus consistent with the recent locus coeruleus-norepinephrine theory that predicts a covariation between the P300 and behavior (accuracy and RT) as modulated by experimental factors known to affect task-focused performance [including feedback salience used in the current study; (Nieuwenhuis, Aston-Jones, & Cohen, 2005)].

Our main results in the CUD subjects are consistent with a compromised sensitivity to monetary reward and with a potential disruption in the ability to change behavior in response to perceived inner motivational drives (i.e., impaired insight) in cocaine addiction as we previously suggested based on an fMRI study (Goldstein, et al., 2007a; Goldstein, et al., 2007b). Specifically, these conclusions are based on the apparent disparity, in the CUD subjects, between measures obtained objectively (lack of significant reward-driven P300 or behavioral adjustments) vs. those relying on subjective self-report (reward-driven interest in the task). In general, these results are consistent with ERP studies showing compromised P300 sensitivity to other neuropsychological tasks in CUD (Bauer, 1997; Bauer, 2001; Biggins, MacKay, Clark, & Fein, 1997; Kouri, Lukas, & Mendelson, 1996; Moeller, et al., 2004; Noldy & Carlen, 1997). This P300 compromise is also observed in other types of drug addiction and indeed it may be a marker for addiction susceptibility. For example, a compromised P300 response - specifically to incentives - has been documented not only in individuals with alcohol addiction (Porjesz, Begleiter, Bihari, & Kissin, 1987) but also in non-addicted individuals with a family history of alcoholism (Ramsey & Finn, 1997).

Of note are the correlations in the CUD subjects between reward-driven behavioral performance and frequency of shorter-term (1 year) cocaine use. These correlations suggest that recent cocaine self-administration (as documented by positive urine results in all CUD subjects) could also contribute to the faster P300 latencies and higher self-reported task interest in the CUD as compared to the control group. This account remains to be experimentally tested (e.g., with test-retest longitudinal designs); however, it is consistent with studies where stimulants such as caffeine (Kawamura, Maeda, Nakamura, Morita, & Nakazawa, 1996; Martin & Garfield, 2006) and methylphenidate (Ozdag, Yorbik, Ulas, Hamamcioglu, & Vural, 2004; Seifert, Scheuerpflug, Zilles, Fallgatter, & Warnke, 2003) decreased P300 latency.

Limitations of this study include the following: (1) the blocked nature of the experimental design allowed us to study sustained responses to monetary reward. However, it may have also introduced habituation effects that need to be studied separately; (2) future studies could compare additional or more disparate reward conditions (e.g., \$2 vs. \$1 vs. 10¢ or use a logarithmic formula to choose the different levels of reward) and also add monetary loss (Branston, El-Dereby, & McGlone, 2005; Yeung, Holroyd, & Cohen, 2005; Yeung & Sanfey, 2004); (3) in the current study we a priori focused on the P300, an ERP component previously associated with the processing of reward value; the study of other ERP components, such as the N2 (to be elicited with appropriate/non-equiprobable conflict/inhibitory control tasks), could prove crucial in understanding impairments in inhibitory control/impulsivity in drug addicted individuals. Also, future studies could employ other analyses (e.g., with LORETA) to refine the location of the neuroanatomical generators that are sensitive to reward salience; (4) performance variability was restricted (at ceiling) by the current simple task (chosen to sustain attention similarly in all three reward conditions). Tailoring the paradigm to observe accuracy differences (e.g., by decreasing ratio of “No-go” to “Go” trials) would allow for a

more sensitive investigation of the ERP error-related signal changes as previously reported in alcoholism (Kamarajan, et al., 2005; Pfefferbaum, Rosenbloom, & Ford, 1987); (5) future studies need to establish reliability of these results by increasing sample size and studying different subgroups within CUD (e.g., comparing current users vs. individuals with longer-term withdrawal/abstinence periods or treatment-seekers). The impact of comorbid psychopathologies in drug addicted individuals also remains to be explored; although preliminary analyses indicated no significant differences in our main dependent variables between the seven CUD subjects with other comorbid disorders and the 11 CUD subjects without such comorbidity, this effect needs to be systematically studied in larger sample sizes.

In summary, the current results demonstrate compromised sensitivity to monetary reward (as compared to non-reward) at both the behavioral (RT) and neural (P300 at Pz, where P300 is most pronounced) levels in adults with current CUD as compared to age-matched healthy control subjects. This compromise was evident despite using a higher than usual monetary incentive (\$50 vs. <\$10 in many other studies) and although reward was contingent on behavior (and not a priori determined as in studies that use guessing tasks). This compromise was also evident despite faster P300 latency and enhanced self-reported interest in the task in the CUD as compared to the control subjects. Because we further controlled for all other stimulus properties (the 0¢ condition was identical to the 45¢ condition in all properties but the amount of expected reward), we cannot attribute this specific compromise to a generalized impairment in information processing. Instead, we attribute this compromise to specific deficits in the neural network that underlies reinforcement learning (i.e., sensitivity to changing reinforcement contingencies to control goal-directed behavior). A potential candidate encompasses the anterior prefrontal cortex that showed a similar compromise when cocaine addicted individuals were expecting monetary reward in our previous fMRI study (Goldstein, et al., 2007a).

Despite this specific compromise in responding to reward vs. non-reward as documented in the current study, contingency management (use of reinforcers) improves retention and associated abstinence outcomes in cocaine and methamphetamine abusers (Petry, et al., 2005). This indicates that abstinent drug abusers are able to respond to reinforcers in well-structured and constrained environments that also incorporate treatment programs. However, these behaviors may not generalize to the everyday environments of drug addicted individuals, where external or predictable reinforcement for advantageous behaviors are not readily available. It is therefore possible that alternative treatment modalities (e.g., targeting improvements in reinforcement learning, inhibitory control or advantageous decision-making in the absence of overt reward) may help minimize longer-term relapse in drug addiction.

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Figure 1.

Grand averaged waveforms for control subjects (top) and individuals with current cocaine use disorders (bottom) reflecting 200 msec before to 800 msec after the target stimulus (S1) for each monetary reward condition (45¢, 1¢, 0¢) during the 'Go' trials (N=18 in each group).

Figure 2.

Average post-task subjective ratings for interest and excitement for control subjects and individuals with current cocaine use disorders as a function of monetary reward condition (45¢, 1¢, 0¢). Error bars represent standard error of the mean (N=18 in each group).

Figure 3.

Correlations between the P300 and behavioral dependent variables. Left: positive correlation ($R^2=.32$, $p<.01$, regression line in bold; $R^2=.23$, $p<.01$ when one outlier is removed) between the P300 amplitude differential for the 45¢ minus 0¢ monetary conditions and the respective percent accuracy differential in healthy control subjects (white circles) but not individuals with current cocaine use disorders (black circles). Right: negative correlation ($R^2=.36$, $p<.01$, regression line in bold) between the P300 amplitude differential for the 1¢ minus 0¢ monetary conditions and the respective differential reaction time in healthy control subjects (white circles) but not individuals with current cocaine use disorders (black circles) ($N=18$ in each group).

Figure 4.

Correlations between accuracy differentials on the monetary incentive task and cocaine use. Left: negative correlation ($R^2=.53$, $p<.01$) between frequency of cocaine use in the last year and the differential accuracy for the 45¢ minus 0¢ monetary conditions in individuals with current cocaine use disorders (black circles). Right: negative correlation ($R^2=.47$, $p<.01$) between frequency of cocaine use in the last year and the differential accuracy for the 45¢ minus 1¢ monetary conditions in individuals with current cocaine use disorders (black circles) ($N=18$).

Table 1
Demographic Characteristics and Drug Use by Study Subjects

	Cocaine (N=18)	Comparison (N=18)
Gender (male/female)	11/7	12/6
Ethnicity (African-American/Caucasian/Hispanic/Asian)	16/2/0/0	9/6/2/1
First language (English/other)	18/0	17/1
History of cigarette smoking (current or past/never) [‡]	15/3	4/14
Education (years)	13.4 (1.9)	13.8 (1.7)
Age (years)	43.8 (6.0)	39.9 (8.0)
Handedness: Laterality Quotient (Oldfield, 1971)	0.93 (0.1)	0.90 (0.2)
Socio-economic status (Hollingshead, 1975)	31.4 (12.7)	37.2 (11.5)
Non-verbal intellectual functioning: Wechsler Abbreviated Scale of Intelligence: Matrix Reasoning scaled score (Wechsler, 1999)	9.6 (3.0)	10.8 (2.5)
Self-reported state depression (Beck, Steer, & Brown, 1996) [†]	8.5 (6.7)	3.4 (4.3)
Monetary gain on the event-related potential task (\$)	48.0 (2.2)	48.1 (1.7)
Age at onset of cocaine use (years)	22.6 (6.0)	--
Duration of use (years)	18.5 (5.0)	--
Frequency of use (days/week) last 30 days	3.8 (2.0)	--
Frequency of use (days/week) last 12 months (N=17)	3.8 (2.2)	--
Current use in \$ per use (min – max, median) (N=15)	20–360 (60)	--
Duration of current abstinence (days) (min – max, median)	0–4, 1.5	--
Length of longest abstinence (days) (min – max, median)	0–5110, 365	--
Total score on the Cocaine Selective Severity Assessment Scale (measure of withdrawal symptoms) (0–126) (N=17)	16.7 (11.0)	--
Severity of Dependence Scale (0–15) (N=17)	6.4 (3.3)	--
Cocaine Craving Questionnaire (0–45) (N=16)	17.8 (10.1)	--

[†] $t(34)=2.7$, $p<0.05$;

[‡] $\chi^2(1)=13.5$, $p<0.0001$

Note: min is minimum; max is maximum. Values are frequencies for categorical variables or mean (standard deviation) for continuous variables; for group differences in the categorical variables, χ^2 was used, for the continuous variables independent t-tests were used.

Table 2

The P300 Amplitude and Latency at Pz and Behavioral (reaction time, accuracy, and self-reported ratings) Dependent Variables for All Study Subjects as a Function of Group, Monetary Reward, and Trial Type ('Go' vs. 'No-Go').

	Cocaine (N=18)			Comparison (N=18)		
	\$0.00	\$0.01	\$0.45	\$0.00	\$0.01	\$0.45
Go: amplitude (μ V)	6.7 (4.0)	7.3 (4.0)	7.5 (4.0)	5.8 (4.2)	6.3 (4.0)	7.0 (3.4)
No-Go: amplitude (μ V)	5.6 (3.6)	4.9 (2.8)	5.9 (2.8)	4.2 (2.7)	4.6 (2.7)	5.0 (3.3)
Go: latency (msec)	376.5 (63.5)	368.8 (63.9)	349.8 (47.0)	423.4 (62.5)	412.6 (52.7)	414.6 (64.4)
No-Go: latency (msec)	436.1 (80.5)	415.9 (85.4)	431.9 (85.9)	452.0 (76.0)	431.6 (69.6)	465.5 (68.0)
Reaction time (Go)	254.1 (47.7)	257.4 (41.8)	252.1 (44.5)	236.2 (40.4)	231.0 (34.8)	227.0 (39.6)
Percent correct (Go)	.94 (.05)	.94 (.04)	.93 (.08)	.92 (.08)	.93 (.06)	.92 (.06)
Percent correct (No-Go)	.996 (.01)	.96 (.004)	.99 (.02)	.997 (.007)	.96 (.00)	.99 (.01)
Interest ratings	4.3 (2.5)	4.9 (2.0)	5.9 (1.5)	2.8 (2.0)	3.4 (1.6)	4.4 (1.7)
Excitement ratings	4.4 (2.1)	4.7 (2.0)	6.0 (1.5)	3.3 (2.1)	3.7 (1.8)	4.4 (1.8)
Frustration ratings	5.3 (2.1)	5.2 (2.0)	5.2 (2.4)	4.9 (1.9)	4.8 (2.0)	5.3 (1.9)