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Subjective sensitivity to monetary gradients is associated with frontolimbic activation to reward in cocaine abusers☆

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Abstract

Drug addiction is characterized by marked disruptions in the ability to process reward. Here we evaluated in cocaine addicted and healthy control participants the subjective sensitivity to reward gradients and its association with neural responses to sustained reward. A self-report questionnaire was used to assess the former. A functional magnetic resonance imaging task that utilized monetary reward as feedback in a blocked design was used to assess the latter. Results revealed that whereas control subjects valued high money more than low money, over half of the cocaine addicted subjects valued all monetary amounts equally. This compromised subjective sensitivity to gradients in reward value was significantly correlated with higher activations to money in the lateral orbitofrontal cortex/inferior frontal gyrus (BA 47) and amygdala, and lower activations in the middle frontal gyrus (BA 6), which together explained 85% of the variability on this rating scale in the cocaine abusers only. These results provide for the first time evidence of restricted subjective sensitivity to gradients of reward in cocaine addiction and of the involvement of frontolimbic brain regions (including the orbitofrontal cortex) in this deficit.

Keywords: Crack-cocaine addiction; Mesocorticolimbic dopaminergic circuit; fMRI BOLD; Monetary incentive salience; Reward valence

1. Introduction

Animal research suggests that after chronic drug administration the value of a drug reward is increased (Ahmed and Koob, 1998; Ahmed et al., 2002) while that of a non-drug reward is decreased (Grigson and Twining, 2002). Parallel human studies have generally reached similar conclusions. For example, cocaine addicted subjects show reduced activation of corticolimbic brain areas when viewing an erotic video than when exposed to a cocaine video (Garavan et al., 2000). However, a question persists as to the perceived *subjective* value of reward in the drug addicted individual. A modified subjective value attributed to rewards in the environment may alter underlying stimulus-reinforcement association learning. This modified response to reinforcement in drug addicted individuals may in turn contribute to their cognitive-behavioral and emotional impairments that encompass decision-making (Bechara et al., 2002; Bolla et al., 2003) and discounting of delayed rewards (Kirby and Petry, 2004).

Studies of non-human primates further suggest that the subjective valuation of reward is mediated by the orbitofrontal cortex (OFC), part of the mesocorticolimbic dopaminergic circuit. In particular, OFC neurons discriminate between different rewards based on the relative preferences exhibited in overt behavior (Tremblay and Schultz, 1999). In analogous human functional neuroimaging studies in healthy subjects, the OFC responds maximally to extremes of a reward range (including best outcome versus worse outcome) (Elliott et al., 2003; O'Doherty et al., 2001), demonstrating an association with the reinforcer's relative magnitude (Knutson et al., 2000; Breiter et al., 2001) or its subjective pleasantness (Kringelbach et al., 2003). In drug addiction, we separately reported lack of a graded (i.e., relative) OFC response to monetary reward in cocaine abusers as compared to matched healthy control subjects (Goldstein et al., in press), providing experimental evidence for the central role of OFC dysfunction in reward processing

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and inhibitory control (i.e., Impaired Response Inhibition and Salience Attribution, I-RISA) in this disorder (Goldstein and Volkow, 2002). However, the role of the OFC in the *subjective* processing of different values of reward has yet to be explored.

In the current brain-behavioral study we therefore directly asked the following two questions: (1) is subjective sensitivity to reward value modified in drug addicted individuals as compared to healthy control subjects? and (2) does this change encompass the OFC (including the inferior frontal gyrus, IFG)? Given the role of the OFC in relative reward processing and its impaired function in drug addiction, we hypothesized that subjective sensitivity to *gradients* in the value of a non-drug reward will be restricted in cocaine abusers as compared to control subjects. We further hypothesized that this constrained subjective sensitivity to reward will be associated with OFC/IFG responsivity to reward.

2. Methods

2.1. Participants

Twenty-nine healthy subjects participated in the study, 16 cocaine abusers and 13 matched control subjects. There were no group differences in gender (4 females in both groups, $\chi^2(1) < 1$, $p > 0.3$), race (12 and 11 African–Americans in the cocaine and control groups, respectively, $\chi^2(1) < 1$, $p > 0.3$), and education (mean ± S.D., cocaine: 12.8 ± 2.7 years versus control: 14 ± 1.2 years, $t(21) = -1.66$, $p > 0.1$). Subjects were also matched on handedness (Oldfield, 1971), English as first language, socio-economic status (mean ± S.D., 30.9 ± 14.2 in cocaine abusers and 40.5 ± 10.8 in control subjects, $t(27) = -2$, $p > 0.05$) (Hollingshead, 1975), measures of general intellectual functioning which were within the average range for both groups, and self-reported depression (median was <2 for both groups) (Beck et al., 1996). Significant differences between the groups were observed in age (mean ± S.D., cocaine>control subjects, 42.8 ± 4.6 > 37.6 ± 6.8 years, $t(27) = 2.4$, $p < 0.05$) and percent current or past cigarette smokers (by self-report) (75% in cocaine abusers versus 23% in control subjects, $\chi^2(1) = 7.7$, $p < 0.01$). These age and smoking differences between the groups were accounted for in the analyses as described in Section 2, Section 3 and Supplementary Material.

Initial screening by phone and subsequent on site evaluation by a neurologist and a clinical psychologist ensured that the cocaine abusers were free of illnesses that required hospitalization or regular monitoring, were not using marijuana, barbiturates, amphetamines, or opiates (this was ensured by pre-scan urine tests in all subjects), and had at least a 12 month history of cocaine use (with predominant use of cocaine by smoked route). In all cocaine abusers, mean (±S.D.) age of onset and duration of cocaine use were 24.8 ± 8.04 and 17.6 ± 6.65 years, respectively. Fifteen of the 16 cocaine abusers fulfilled DSM-IV criteria for current cocaine dependence ($N = 9$) or cocaine early remission ($N = 6$), and one cocaine user who admitted to weekly use of cocaine did not meet current abuse or dependence criteria (this subject met criteria for past polysubstance abuse which included crack-cocaine). Length of abstinence from cocaine at time of study ranged from 1 to 90 days (median = 4.5 days). The nine abusers with current cocaine dependence reported using cocaine the night before the study; their urine was positive for cocaine, indicating that they had used cocaine within the previous 72 h. Mean (±S.D.) number of days of cocaine use in the subjects ($N = 13$) who consumed cocaine in the past 30 days was 9 ± 6.8 days (range 2–25 days), and mean amount of use per sitting (which in some subjects extended for >24 h) was 1.79 ± 1.4 g (range 0.19–5.13). Subjects were fully informed of the nature of the research and provided written consent for their involvement in this study in accordance with the local Institutional Review Board.

2.2. Subjective valuation of monetary reward and other behavioral measures

Using a Likert-type visual analogue rating scale, subjects were asked to "rate how valuable (i.e., how important) the following amounts of money are to you". Subjects rated 7 monetary amounts (US$ 10, US$ 20, US$ 50, US$ 100, US$ 200, US$ 500, US$ 1000) on a scale of 0–10: from not at all valuable to extremely valuable, respectively (adapted from Martin-Soelch et al., 2001). The rating for US$ 10 was subtracted from the rating for US$ 1000 (US$ 1000–10) to represent the range of Subjective Sensitivity to Gradations in monetary Reward value (SSG-R). The lower the value, the less the sensitivity (i.e., the more similar the value ratings across these highest and lowest money amounts).[1] This scale was administered twice, immediately before and after the functional magnetic resonance imaging (fMRI) task. Scores from both administrations were highly correlated in both study groups (SSG-R1 with SSG-R2, cocaine abusers: $r = 0.96$; control subjects: $r = 0.95$, both $p < 0.0001$). Because results from the second administration may reflect the effects of habituation, only results from the first scale (before MRI) are reported throughout the manuscript. After MRI, subjects were also asked to "rate what you felt about the task you just participated in". Thus, subjects rated the overall task as well as its three monetary conditions (described below) on interest (boring to interesting) and excitement (dull to exciting) using two additional visual analogue scales ranging from 0 to 7.

2.3. Sustained monetary reward fMRI task

Following training, subjects either responded (pressed a button using their dominant hand) or refrained from responding during a trigger (a red square was the target stimulus), depending on one of two preceding instruction stimuli (adapted from Thut et al., 1997) (Fig. 1). There were 9 pairs (18 trials) of press (50% go's) and no press trials within each of three identical conditions. These conditions were distinguished only by blocked levels of monetary reward received for correct performance on this forced-choice task: high money (45 cents); low money (1 cent); and no money (0 cent). Each monetary condition was of 63 s duration, preceded by a 35 s fixation cross to preclude carry over effects. Every three (different) monetary conditions constituted a run for a total of 6 runs/blocks. Each trial was of 3.5 s fixed duration (1000 ms fixation cross + 500 ms for one of two fractal images at screen center + 1000 ms fixed delay + 500 ms for the target stimulus at screen center + 500 ms feedback slide) (Fig. 1). To simulate real life incentive motivation, subjects received up to US$ 50 for this. This was a relatively substantial amount of money as it doubled the subjects' total earnings during the complete study day. This was also a meaningful (salient) amount of money because its receipt was contingent on the correctness of subjects' performance (Zink et al., 2004). The task was presented via MRI compatible goggles. Reaction time and accuracy data were collected across all trials.

2.4. MRI acquisition and processing

MRI scanning was performed on a 4T whole-body Varian/Siemens MRI scanner. Blood oxygen level dependent (BOLD) responses were measured with a T2*-weighted single-shot gradient-echo EPI sequence (TE/TR = 20/3500 ms, 4 mm slice thickness, 1 mm gap, typically 33 coronal slices, 20 cm FOV, 64 × 64 matrix size, 90°-flip angle, 200 kHz bandwidth with ramp sampling, 91 time points, 4 dummy scans). Padding was used to minimize motion, which was inside the accepted threshold of 1 mm maximum displacement (32% of the voxel size) and 1° rotation as determined immediately after each run (Caparelli et al., 2003). A T1-weighted 3D-MDEFT sequence (Lee et al., 1995) was used for structural imaging; all MRI images were inspected to rule out gross morphological brain abnormalities.

All time series were converted into SPM99 format (Wellcome Department of Cognitive Neurology, London UK). A six-parameter rigid body transformation (3 rotations, 3 translations) was used for image realignment. The realigned datasets were normalized to the Talairach frame with a 12-parameters affine transformation (Ashburner et al., 1997), using a voxel size

[1] Using an exponential algorithm, we also calculated a value that represented the line of best fit for each subject's curve: the lower the value, the flatter the curve (i.e., the more similar the value ratings across the highest and lowest money amounts, see Martin-Soelch et al., 2001). However, we chose to report SSG-R throughout the manuscript because of its better face validity.

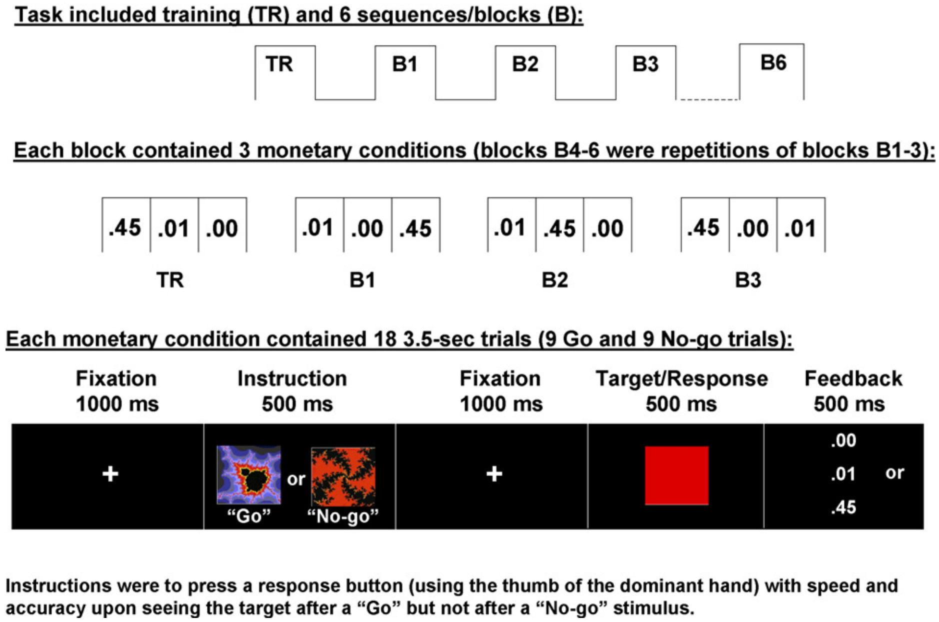

Fig. 1. Experimental paradigm for the monetary incentive task. Overall design and experimental conditions are depicted at the top; at each condition onset (conditions were separated by 35 s), a 3.5 s screen (not depicted) displayed the monetary reward (US$ 0.00, US$ 0.01, or US$ 0.45). Together with the feedback delivered at the end of each trial, this 3.5 s screen (similar in appearance to the feedback screen) guaranteed the subjects were continuously aware of the reward contingencies.

of 3 mm × 3 mm × 3 mm. An 8 mm full-width-half-maximum Gaussian kernel was used to smooth the data. A general linear model (Friston et al., 1995) and a box-car design convolved with a canonical hemodynamic response function were used to calculate the activation maps. The time series were band pass filtered with the hemodynamic response function as low pass filter and 1/750 s cut-off frequency as high-pass filter.

2.5. Data analyses

The behavioral measures were analyzed with parametric (ANOVA or *t*-tests) or non-parametric (paired: Wilcoxon Signed Ranks Test; or independent: Mann–Whitney) tests as appropriate. For the second goal of this study, independent *t*-tests were conducted in SPM99 to inspect differences in brain activation (45¢ > fixation baseline) for: (a) control subjects versus cocaine addicted individuals (reported in greater detail separately, Goldstein et al., in press); (b) control subjects versus each of the two cocaine subgroups as described below; and (c) the two cocaine subgroups. More pertinently, simple linear voxel-based (whole brain) correlation analyses were also conducted: each subject's individual averaged maps of BOLD responses to the high monetary reward (45¢ > fixation baseline) were correlated with SSG-R. In all SPM analyses, threshold was set at $p < 0.001$ (uncorrected at voxel-level, minimum 5 contiguous voxels, 135 mm^3, masked with general task activations). A small volume correction (Worsley et al., 1996) at 10 mm (the spatial extent of the correction) was used for the a priori region of interest (OFC/IFG).

Based on prior work (Tomasi et al., 2004), functional regions of interest (ROI) with a large volume of 729 mm^3 (27 voxels) were then defined at the center of the clusters that significantly correlated with SSG-R across all study subjects; within each cluster, the estimated BOLD fMRI signal was calculated and expressed as a percentage of change for the high monetary condition from baseline. Clarification of anatomical specificity was corroborated with a co-planar stereotaxic atlas of the human brain (Talairach and Tournoux, 1988). These functional ROIs take into account the functional activation of a region in response to the designated task and not only a region's absolute size (volume). These ROIs were used to confirm the whole brain analyses and to examine associations with 5 other behavioral variables (reaction time, percent correct, interest ratings, excitement ratings, and total money earned on the task). For all ROI analyses, significance was set to 0.01 to protect against Type I error (5 variables by 3 ROIs = 15 analyses).

The possibly confounding variables were inspected with correlations (for age) or *t*-tests (for smoking history and urine status) against the selected dependent variables, and used as covariates when necessary (i.e., when associations with the ROIs or SSG-R were significant).

3. Results

3.1. Subjective sensitivity to gradients of monetary reward

The group main effect on the money value rating scale was not significant (Fig. 2A). However, a difference between the study groups was revealed at a closer inspection of this scale: 56% of the cocaine abusers (versus 15% of control subjects) reported US$ 10 to be equally valuable to US$ 1000, providing ≤2 point difference[2] in rating these disparate monetary values ($\chi^2(1) = 4.5$, $p < 0.05$) (Fig. 2B). Thus, in this "flat" cocaine subgroup, paired *t*-tests between all lower versus higher monetary values were not significant ($t(8) < -1.5$, $p > 0.2$). In contrast, the ratings of the "non-flat" cocaine subgroup were monotonically positive (all $t(6) > -2.8$, $p < 0.05$), and not statistically different than those of the control subjects. Moreover, when combining all cocaine abusers and control subjects within the "non-flat" group ($N = 18$), significant differences between all monetary ratings were observed using the two other behavioral scales (45¢ > 0¢: interest and excitement $Z > -2$, $p < 0.05$; 45¢ > 1¢: excitement $Z = -2.3$, $p < 0.05$). Within the combined "flat" group ($N = 11$), there were no significant differences between these monetary ratings (all $Z < -1.6$, $p > 0.1$). Note that similar trends were not

[2] Note that we used this 2-point difference as the cut-off based on the distribution of responses on the money rating scale in the cocaine abusers and control subjects (Supplementary Material, Fig. 1s).

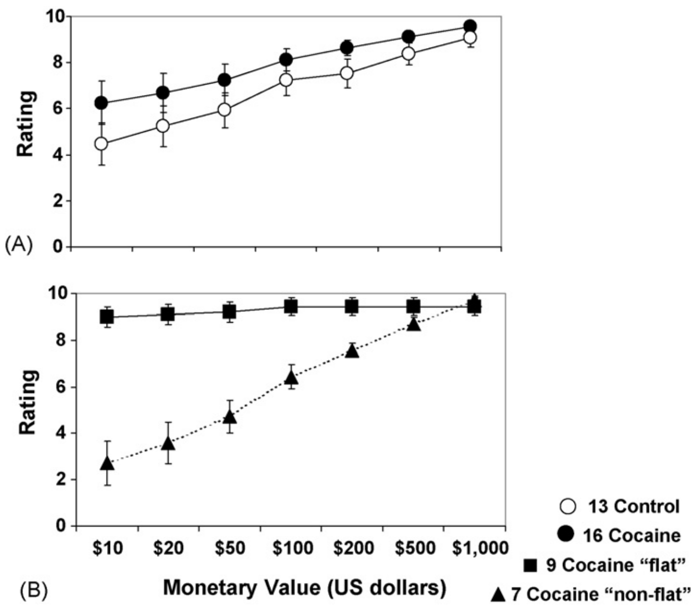

Fig. 2. Money value rating scale. (A) Subjective ratings in control subjects ($N = 13$, white) compared with cocaine abusers ($N = 16$, black). (B) Data presented for two cocaine subgroups: subjects with flat ratings on the money rating scale ($N = 9$, black squares) vs. subjects with non-flat ratings ($N = 7$, black triangles). Error bars represent standard error.

significant for the cocaine subjects only, possibly due to insufficient power (Supplementary Material, Fig. 2sA2).

3.2. fMRI-behavior correlations

Consistent with our second a priori hypothesis, results of the SPM whole brain correlation analyses revealed an inverse correlation between SSG-R with response to the high monetary reward in the left lateral OFC/IFG (BA 47, 13; $x = -33$, $y = 9$, $z = -12$, $T = 4.87$, 6 voxels) and, reducing the set threshold to $p < 0.005$ uncorrected, also in the left amygdala ($x = -27$, $y = -6$, $z = -15$, $T = 5.4$, and $x = -24$, $y = -6$, $z = -6$, $T = 3.6$, 20 voxels) (both with small volume correction at 10 mm, $p < 0.01$ cluster level corrected) (Fig. 3A). In addition, a positive correlation was observed with the right middle frontal gyrus (MFG, Fig. 3B, BA 6; $x = 33$, $y = 9$, $z = 54$, $T = 7.94$, 67 voxels). These correlations were only significant in the cocaine abusers. Results were confirmed with the ROI analyses (Fig. 3, linear regression lines; OFC/IFG: $r = -0.74$, $p = 0.001$; MFG: $r = 0.89$, $p < 0.0001$) (for the amygdala: $r = -0.80$, $p < 0.0001$; for control subjects all $r < |0.38|$, $p > 0.2$, Supplementary Material, Fig. 3s). These results were unchanged when age, cigarette smoking, and urine status as well as measures of task performance were tested with partial correlations (see Supplementary Material, Fig. 4s, for correlations between the SSG-R and OFC/IFG or MFG responses to monetary reward as a function of urine status and cigarette smoking history in the cocaine abusers). Further, in a linear regression analysis, these three ROIs explained 85% of SSG-R in the cocaine abusers ($R^2 = 0.85$, $R^2_{adj} = 0.82$, $F = 23.3(3,12)$, $p < 0.0001$) and only 17% in the control group ($R^2 = 0.17$, $R^2_{adj} = -0.11$, $F = 0.6(3,9)$, $p > 0.6$).

These results were also confirmed with ROI ANOVAs: there were main effects of group (healthy control subjects, “flat” and “non-flat” cocaine subgroups) on activations to monetary reward in the OFC/IFG and MFG ($F > 7.8$, d.f. = 2.24, $p < 0.01$) and a trend in the amygdala ($F = 4.7$, d.f. = 2.24, $p < 0.05$). The “non-flat” cocaine subjects activated the OFC/IFG less than the other two groups (that did not differ) (mean ± S.D., “non-flat”, “flat”, and control, respectively: $0.24 \pm 0.16 < 0.51 \pm 0.15 = 0.54 \pm 0.16$). The “non-flat” cocaine subjects also activated the amygdala less than the other two groups, an effect that reached significance for the contrast with the control group (mean ± S.D., “non-flat”, “flat”,

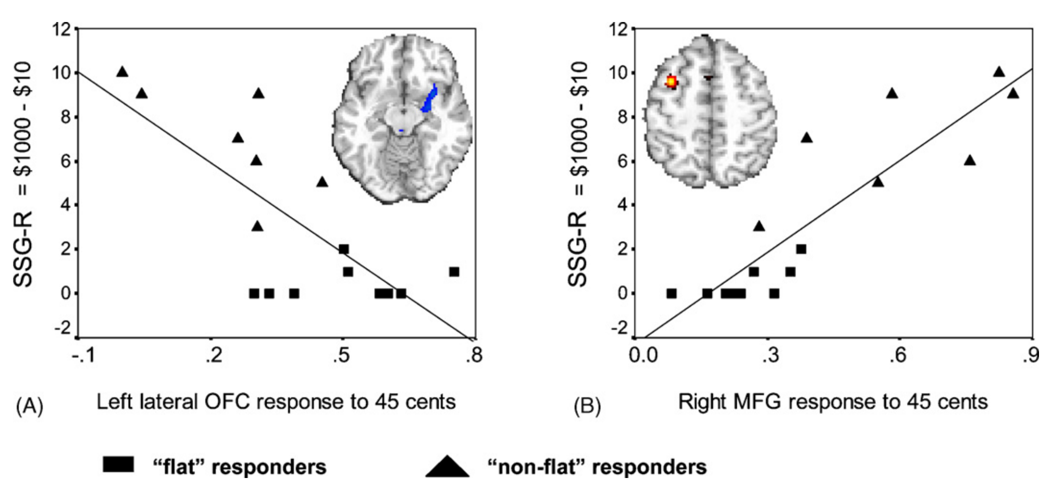

Fig. 3. Correlations between subjective sensitivity on the money value rating scale with neural responses to high reward (45 cents, as compared to a fixation baseline) in 16 cocaine abusers. SSG-R: rating of US$ 1000 minus rating of US$ 10 on the monetary value rating scale; OFC is orbitofrontal gyrus (BA 47, $Z = -12$), MFG is middle frontal gyrus (BA 6, $Z = 54$). (A) The plot shows the association with the left lateral OFC/IFG ($r = -0.74$, $p = 0.001$); the inserted statistical map of brain activation depicts the cluster location corresponding to this correlation ($x = -33$, $y = 9$, $z = -12$, $T = 4.87$, 6 voxels, with small volume correction at 10 mm, $p < 0.01$ cluster level corrected). At a more liberal threshold ($p < 0.005$ uncorrected), there was a similar correlation with the amygdala (data not shown). (B) The plot shows the association with the right MFG ($r = 0.89$, $p < 0.0001$); the inserted statistical map of brain activation depicts the cluster location corresponding to this correlation ($x = 33$, $y = 9$, $z = 54$, $T = 7.94$, 67 voxels, $p < 0.0001$ cluster level corrected). Data presented for the two cocaine subgroups: subjects with flat ratings on the money rating scale (squares) vs. subjects with non-flat ratings (triangles).

and control, respectively: $0.20 \pm 0.15 < 0.38 \pm 0.10 < 0.45 \pm 0.22$). In contrast, the "non-flat" group was indistinguishable from the control subjects in MFG activations to money (mean ± S.D., "flat", "non-flat", and control, respectively: $0.25 \pm 0.10 < 0.61 \pm 0.22 = 0.51 \pm 0.23$). Moreover, we inspected with voxel-wise analyses the differences in activations to money between all three groups. Results revealed higher left OFC/IFG response to the high money condition in the control than the combined cocaine group (Goldstein et al., in press). Similarly, the right MFG was activated to monetary reward more in the healthy control subjects (cluster peak at $x = 45$, $y = 3$, $z = 45$, $T = 5.9$, 52 voxels, $p < 0.001$ uncorrected) this time also in the cocaine "non-flat" group (cluster peak at $x = 36$, $y = 9$, $z = 57$, $T = 5.9$, 35 voxels, $p < 0.001$ uncorrected) than the cocaine "flat" group.

3.3. Effect of possible confounding variables (age, cigarette smoking, and cocaine urine status)

Except for the ROI differences, the cocaine subgroups did not differ in: task performance (Supplementary Material, Fig. 2sB2–C2); distributions of sex and race ($\chi^2(1) < 0.8$, $p > 0.4$); age, education, socio-economic status, handedness, measures of general intellectual functioning, and depression (independent *t*-tests, all $t(14, 13 \text{ for depression}) < |1.8|$, $p > 0.1$; or Mann–Whitney, all $Z < -1.9$, $p > 0.1$); and selected cocaine use variables (including duration and amount, severity of withdrawal symptoms and presence of cocaine in the urine at time of testing, cigarette smoking) (all $p > 0.1$). Nevertheless, these differences between the "flat" and "non-flat" cocaine subgroups may emerge with larger sample sizes.

There were also no significant correlations between SSG-R or the three ROIs and the continuous possible confounding variables (age, socio-economic status, days of abstinence) in the cocaine abusers (all $r < |0.36|$, $p > 0.1$) or the control subjects (all $r < |0.27|$, $p > 0.1$). Using independent *t*-tests to examine the potential effect of the categorical variables (cigarette smoking, urine status for cocaine), results were similarly null (i.e., no significant associations between smoking or urine and SSG-R or the three ROIs) in the cocaine abusers (all $t < |1.88|$, $p > 0.08$) or the control subjects (all $t < |1.70|$, $p > 0.1$). Note that covariate analyses were therefore not required (a significant association between a dependent variable and a possible confounding variable is a prerequisite for a covariate analysis) (Stevens, 1992).

4. Discussion

The notion that cocaine abusers undergo a change in their subjective value system is pervasive in public opinion. For example, it is generally assumed that drug addicted individuals will inevitability be overtaken by drug needs, disregarding consciously set and explicitly valued plans that ultimately conflict with drug use. However, scientific studies on this commonly held belief are scarce. Here we report two key findings, lending psychological and neurobiological support for a modified reward valuation in cocaine abusers.

4.1. Lower subjective sensitivity to gradients in monetary value in cocaine abusers

More than half of the cocaine abusers rated US$ 10 as equally subjectively valuable as US$ 1000 (Fig. 2B). This distinct subgroup lacked monotonically positive gradations in rating the value of money demonstrating a significantly constrained subjective sensitivity to relative monetary reward. Further, across all study subjects, these individuals also reported 0¢ and 1¢ to be as interesting and exciting as 45¢. Thus, this "flat" group displayed an overall compromised sensitivity to different amounts of money as measured by value attribution (Fig. 2) or task engagement (Supplementary Material, Fig. 2sA).

This finding may seem perplexing at first, especially in light of the frequently used delay discounting and gambling reward paradigms where time and reward contingencies are juxtaposed to examine the effects of the created conflict on decision-making/choice behavior (e.g., Bechara and Damasio, 2002; McClure et al., 2004). In contrast, in the current study subjects did not *choose* between smaller immediate versus larger delayed monetary rewards. Instead, we focused on the individual's *subjective experience* (evaluation of a non-drug reward). Our results do not rule out the possibility that other reward-related processes (e.g., emotional/motivational, behavioral/approach), and especially those more directly associated with the actual drug of abuse, could be intact or even sensitized (Cardinal and Everitt, 2004).

Overall, we interpret this constrained subjective sensitivity to reward gradients as an additional symptom of the reward threshold elevations and reward sensitivity decreases characterizing chronic drug use (Ahmed and Koob, 1998; Ahmed et al., 2002), hypothesized to result from adaptations of the reward circuit to intermittent and chronic supraphysiological stimulation by drugs (Volkow and Fowler, 2000). Preserved sensitivity (illustrated by the small squares in 4A) would allow the detection of differences between reinforcers in healthy control subjects (*monotonically positive function*). In contrast, the low sensitivity in cocaine abusers (large squares) would not permit the distinction between stimuli of different gradations but rather allow an all-or-nothing identification only of the stimuli that reach the threshold required for perception of reinforcement (*step function*). A question to be explored is whether improving subjective sensitivity to gradients in reward value could modulate choice behavior such that non-drug rewards would be chosen over drug use (see Donny et al., 2003) (Fig. 4).

4.2. The OFC/IFG in the constrained subjective sensitivity to relative monetary value

In the cocaine abusers, 85% of variance in the constrained subjective sensitivity to monetary reward gradients was attributed to lateral OFC/IFG, amygdala, and MFG responses to monetary reward (Fig. 3). Thus, the higher the left OFC/IFG and amygdala activations and the lower the right MFG responses to monetary reward, the less was the sensitivity to relative monetary value in cocaine abusers but not in control subjects.

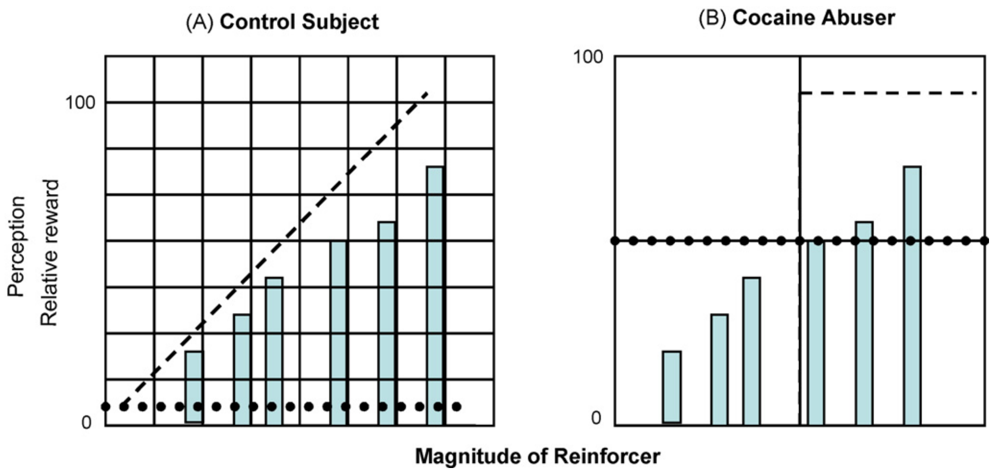

Fig. 4. Diagrammatic representation of the changes in relative and absolute reward in addiction. Dotted lines reflect the threshold for a stimulus to be perceived as reinforcing: the threshold is lower in the non-addicted (A) and higher in the drug addicted (B) individual. Dashed lines reflect the function that describes the perception of a stimulus as subjectively valuable. The high sensitivity to the reinforcers (small squares, A) allows the detection of small reinforcers and differences in magnitude between reinforcers in control subjects (*monotonically positive function*). The low sensitivity in cocaine abusers (large squares, B) does not permit the distinction between stimuli of different gradations but rather identify only those that reach the threshold required for the stimulus to be perceived as reinforcing (*step function*).

The implication of the OFC/IFG in subjective sensitivity to *gradients* in monetary value is consistent with a previously suggested role for the OFC in the processing of relative reward in the healthy state (Breiter et al., 2001; Elliott et al., 2003; Kringelbach et al., 2003; Knutson et al., 2000; O'Doherty et al., 2001). Given the additional role of the OFC in emotional suppression (Beauregard et al., 2001; Levesque et al., 2003), and the uniqueness of this brain-behavior correlation to the cocaine abusers only, findings further suggest the impact on results of competing, extraneous or idiosyncratic factors (Montague and Berns, 2002). For example, it is possible that during the performance of this fMRI task, the cocaine abusers had to actively suppress craving responses, possibly from conditioning to money as a cocaine cue. The "non-flat" cocaine subjects, who had the lowest OFC/IFG activations, may have successfully suppressed craving and were also better able than the "flat" cocaine subjects to process gradients of reward. In contrast, the "flat" responders, who had higher OFC/IFG activations to money, may have not successfully suppressed craving and were also not able to process reward gradients. This explanation may be seen as inconsistent with the pattern of results in the control subjects (who had similar OFC/IFG responses to money as the "flat" group but preserved ability to process gradients in reward) unless one recalls lack of a similar correlation between SSG-R and OFC/IFG in this healthy comparison group (Supplementary Material, Fig. 3s). Thus, higher OFC/IFG responses are not necessarily indicative of preserved reward processing in drug addicted individuals, potentially tapping different functions than in healthy control subjects (Goldstein et al., 2001).

Similar results in the amygdala, which together with the OFC constitutes part of the structural appetitive/approach network that underpins Pavlovian incentive and motivated behavior (Gottfried et al., 2003; O'Doherty et al., 2003), and is commonly associated with regulation of emotion (Hare et al., 2005), lend further support for greater task-related emotional suppression or similar competing, extraneous or idiosyncratic factors operating in the "flat" cocaine subgroup. However, because the current correlation between SSG-R and OFC/IFG was driven by the "non-flat" cocaine group (and not the "flat" cocaine group), this interpretation remains tentative. Finally, the MFG (BA 6) is traditionally considered a motor area; however it is increasingly being recognized as a region involved in cognitive control (Ridderinkhof et al., 2004) and working memory (Wager and Smith, 2003). In the current context, we suggest that its positive correlation with the subjective sensitivity to monetary gradients reflects the cognitive effort (e.g., increased attention and working memory) that is required for making decisions about the relative value of reward.

4.3. Recommendations

The findings from this study highlight the existence of subgroups within cocaine abusers with distinct functional and neurobiological deficits. Further, the monetary rating scale is simple and easy to administer. Thus, drug abusers who evidence a compromised subjective sensitivity to gradations in reward could be readily identified for tailored interventions to improve associated cognitive-emotional skills (e.g., training on attention and set shifting tasks to facilitate flexible processing of a multidimensional context; training on other learning and memory tasks to improve general value estimations and increase the relative value of non-drug related reward). Also, small amounts of reward may be effective in contingency management or relapse prevention (Petry and Martin, 2002) – at least for the distinct subgroup of cocaine abusers who does not differentiate between lower versus higher amounts of money. Studies on potential deficits in subjective gradations of negative reinforcers (punishment) would also be clinically relevant in that both positive (vouchers, privileges) and negative (incarceration) reinforcers are used in the management of the drug abuser.

4.4. Study limitations

(1) The cocaine abusers differed in age and history of cigarette smoking from the control subjects. There was also variability within the cocaine abusing group in time since last cocaine use. Therefore, we consistently monitored the effect of these possibly confounding variables throughout the study demonstrating that they did not affect results. Nevertheless, these factors may emerge as important in larger samples. For example, treatment seeking status has been shown to influence activation of the prefrontal cortex (including the OFC) to drug related cues across multiple studies (Wilson et al., 2004). (2) The sample size was relatively small; replication in larger samples is necessary for assessing generalizability of results. (3) This study cannot determine whether the blunted sensitivity to gradients of rewards antedated drug use or is the consequence of chronic drug abuse.

4.5. Conclusions

Here we report that a distinct subgroup within cocaine abusers had lower sensitivity to monetary gradations. A restricted range of subjective valuation of reward may play a mediating role in the ability to use internal cues and feedback from the environment to inhibit inappropriate (drug-escalated) behavior. Moreover, a "flattened" sensitivity to gradients in reward may predispose individuals to disadvantageous decisions (e.g., trading a car for a couple of cocaine hits). Without a relative context, drug use and its intense effects (craving and high) could become all the more overpowering. The current results therefore extend to human research the study on the reinforcement-related mechanisms that are used to guide behavior (Rolls, 2000) and which are distorted by drugs (Schoenbaum and Setlow, 2005). Our results further suggest that these deficits go beyond differences in threshold sensitivity and reinforcer devaluation when delayed, to include deficits in sensitivity to *gradations* of a reinforcer.

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Appendix A. Supplementary Material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.drugalcdep.2006.08.022.

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