Anterior cingulate cortex hypoactivations to an emotionally salient task in cocaine addiction

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Anterior cingulate cortex (ACC) hypoactivations during cognitive processing characterize drug addicted individuals as compared with healthy controls. However, impaired behavioral performance or task disengagement may be crucial factors. We hypothesized that ACC hypoactivations would be documented in groups matched for performance on an emotionally salient task. Seventeen individuals with current cocaine use disorders (CUD) and 17 demographically matched healthy controls underwent functional magnetic resonance imaging during performance of a rewarded drug cue-reactivity task previously shown to engage the ACC. Despite lack of group differences in objective or subjective task-related performance, CUD showed more ACC hypoactivations throughout this emotionally salient task. Nevertheless, intensity of emotional salience contributed to results: (*i*) CUD with the largest rostroventral ACC [Brodmann Area (BA) 10, 11, implicated in default brain function] hypoactivations to the most salient task condition (drug words during the highest available monetary reward), had the least task-induced cocaine craving; (*ii*) CUD with the largest caudal-dorsal ACC (BA 32) hypoactivations especially to the least salient task condition (neutral words with no reward) had the most frequent current cocaine use; and (*iii*) responses to the most salient task condition in both these ACC major subdivisions were positively intercorrelated in the controls only. In conclusion, ACC hypoactivations in drug users cannot be attributed to task difficulty or disengagement. Nevertheless, emotional salience modulates ACC responses in proportion to drug use severity. Interventions to strengthen ACC reactivity or interconnectivity may be beneficial in enhancing top-down monitoring and emotion regulation as a strategy to reduce impulsive and compulsive behavior in addiction.

blood-oxygen-level-dependent fMRI | salience | brain-behavior dissociation | craving | cocaine use

In the impaired response inhibition and salience attribution (I-RISA) model we have emphasized the role of the anterior cingulate (ACC) and orbitofrontal cortices (OFC) in core clinical symptoms of drug addiction that encompass attribution of enhanced salience to drug cues at the expense of the salience attributed to nondrug-related stimuli (1). Supporting this core I-RISA hypothesis, neuroimaging studies in drug addicted individuals demonstrate ACC and OFC hyperactivations during drug-related cue reactivity (2), including craving (3, 4) and hypoactivations during performance of neutrally valenced cognitive tasks (5–9). Because these hypoactivations in addicted individuals could reflect impaired performance (5–8) or decreased engagement (9), in the current study we set out to determine whether ACC hypoactivations in addiction can still be observed in groups matched for overt performance on an emotionally salient task. This is a crucial question because the clinical implications for such hypoactivations even in the absence of overt behavioral group differences may be pronounced. For example, these ACC hypoactivations could be targeted for early detection and may be amenable for intervention and prevention of relapse to compulsive drug use. Because similar ACC hypoactivations are frequently reported in other psychopathologies of cognitive function, impulsivity, and motivation [e.g., attention deficit hyperactivity disorder (10), schizophrenia (11), and depression (12)], the current results could be of broad general significance.

In particular, we were interested in the 2 major subdivisions of the ACC that are differentially recruited for the regulation of emotion, cognition, and behavior in response to salient stimuli (13): the caudal-dorsal ACC (cdACC, that is located at the edge of the posterior medial frontal cortex) implicated in performance monitoring (14) and cognitive control (15); and the rostroventral ACC (rvACC, that also extends to the ventromedial prefrontal cortex, medial OFC, and rectal gyrus) implicated in regulating autonomic functions (16), retention of extinction learning (17) and in the adaptive suppression of emotion (18). Functional neuroimaging studies in posttraumatic stress disorder (19, 20) and depression (21) have indeed implicated the cdACC in emotional conflict monitoring (22), whereas the rvACC has been implicated in emotional conflict resolution (23).

We recently developed an emotionally salient task that engages both these ACC subdivisions in cocaine addicted individuals. The cdACC was activated and the rvACC was hypoactivated (as compared with a fixation baseline) in 14 individuals with cocaine use disorders (CUD) during functional magnetic resonance imaging (fMRI) with a monetarily rewarded drug cue-reactivity task; control subjects were not included in this previous study (24). The present study further interrogates these 2 ACC subdivisions in a new cohort of CUD compared with a healthy control group matched on sex, age, education, intelligence, and socioeconomic status. Given that cocaine abusers experience persistent decreases in ACC glucose metabolism even after protracted withdrawal (25), as possibly indicative of premorbid or enduring ACC deficits, we hypothesized that both ACC subdivisions will be hypoactive in CUD as compared with performance-matched controls.

Results

Behavior. ***Task performance.*** A 2 (money: 50¢, 0¢) by 2 (word: drug, neutral) by 2 (group: control, CUD) analysis of variance (ANOVA) revealed a significant main effect for money, such that performance accuracy on this task improved as a function of monetary reward across all subjects (50¢ > 0¢, $F_{1,32} = 10.1$, $P < 0.01$). All other effects (word, group, interactions) did not reach significance in this sample ($F_{1,32} < 2.0$, $P > 0.1$). Similarly,

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Table 1. Task activations and group differences in 17 healthy control and 17 individuals with cocaine use disorders (CUD)

	x	*y*	*z*	T CUD	T Control	T Control > CUD	No. of voxels
L rvACC/mOFC BA 10, 11	−9	48	−12	−10.2	−0.3	+7.0	20
L DLPFC BA 6, 8	−42	6	45	+4.0	−7.0	−7.8	35
L DMPFC BA 6	−15	3	69	+15.0	+4.1	−7.7	20
R cdACC BA 32	6	0	45	−2.3	+10.0	+8.6	27
R inferior parietal lobule BA 40	51	−48	42	+4.1	−6.2	−7.3	37
L cerebellum	−6	−75	−39	+3.7	−7.2	−7.7	26
R middle occipital gyrus BA 19	42	−78	12	+6.6	−4.0	−7.5	27
R cuneus BA 17	12	−84	9	+9.9	−4.1	−9.9	264

$P < 0.001$ corrected (T > 9.9), 20 voxels minimum (all cluster-level corrected $P < 0.0001$). *x*, *y*, and *z* are the Talairach coordinates of the clusters in mm (location of group differences). T all subjects: + activations, − deactivations (from a fixation baseline). T control > CUD: + control > CUD, −control < CUD. BA, Brodmann's area; R, right; L, left.

there were no significant effects for reaction time (across all correct responses or across all responses) ($F_{1,32} < 1.3$, $P > 0.3$). Consistent with this matched group performance, there were no group differences in the amount of money earned on this task (Table S1).

Craving and money wanting ratings. A 4 (repetition: ratings were taken twice before, once during and once after the fMRI task) by 2 (rating: cocaine, money) by 2 (group) ANOVA showed a main effect of rating (money > cocaine, $F_{1,31} = 174.2$, $P < 0.0001$) and a rating by group interaction ($F_{1,31} = 4.8$, $P < 0.05$). This interaction was explained by higher cocaine ($Z > -2.6$, $P < 0.05$) but not money ($Z < 0.7$, $P > 0.5$) wanting in the CUD than control group (Table S1). Thus, during the fMRI task, all subjects rated wanting to gain money more than wanting cocaine, but the CUD wanted cocaine more than controls. All other effects did not reach significance ($F_{1,31} < 3.7$, $P > 0.06$). Although there were no effects for repetition in this ANOVA, we inspected a potentially more subtle task-related increase in craving in the CUD by subtracting the cocaine wanting ratings taken before the fMRI task from those taken after the task. Results showed that 6 CUD reported higher cocaine craving after the fMRI task, whereas all controls reported no change in these ratings (all scored at "0"); this was a significant difference (Table S1). There was no such difference for money wanting ratings (Table S1).

Word value ratings. A 2 (word) by 2 (group) ANOVA showed the word main effect was significant (drug < neutral, $F_{1,32} = 54.0$, $P < 0.0001$); there was no main effect for group or interaction with group ($F_{1,32} < 0.3$, $P > 0.6$). Thus, all subjects rated the drug words as more negative than the neutral words (Table S1).

To summarize, this task was emotionally salient as evidenced by both objective performance (increased accuracy to monetary reward) and subjective ratings (increased money > cocaine wanting and negative value attributed to the drug vs. neutral words) across all subjects. Importantly, although CUD reported more craving throughout the task and a further increase in craving after the fMRI task, there were no group differences in behavioral performance on this task.

Whole-Brain Activations/Hypoactivations and Correlation Analyses. For all subjects and compared with the fixation baseline, the fMRI task produced brain activation and hypoactivation patterns similar to those reported using other blocked cognitive (7, 8) and emotional tasks (19, 20) (Table 1 and Fig. S1). Most importantly, despite a lack of significant group differences in both objective and subjective task-related behavioral measures (Table S1), there were significant whole-brain blood-oxygenation-level-dependent (BOLD) fMRI differences between the groups (Table 1). Notably, these group differences included both the cdACC [Brodmann Area (BA) 32] and rvACC/medial OFC (BA 10, 11), our 2 a priori regions of interest (ROIs). These ACC subdivisions were engaged by this fMRI task in our previous study that included another cohort of CUD ($n = 14$) and no controls (24). Other regions that showed significant group differences were the left dorsolateral and dorsomedial prefrontal cortex, right inferior parietal lobule, middle occipital gyrus and cuneus, and the left cerebellum.

Follow-up ROI analyses confirmed the group main effect in all these regions ($F_{1,32} > 4.6$, $P < 0.05$), showing hypoactivations in the CUD compared with controls in both ACC subdivisions (Fig. 1). Interestingly, follow-up *t* tests showed that, in the CUD, the cdACC had the most hypoactivations in the least salient condition (neutral words at 0¢ condition; reaching significance as compared with the drug words at the 0¢ condition, $t_{16} = 2.2$, $P < 0.05$) (Fig. 1*A*). In all of the other regions, the pattern was reversed such that CUD showed higher activations than controls (Fig. S2). In addition to the group main effect, the cuneus also showed a significant money main effect ($F_{1,32} = 4.2$, $P < 0.05$) and a word by group interaction ($F_{1,32} = 5.3$, $P < 0.05$) (Fig. S2*E*).

To inspect intercorrelations between both ACC subdivisions, we performed ROI correlations that were then followed by a whole-brain simple regression analysis. The ROI analyses showed positive correlations across all subjects for the most salient condition (drug words at 50¢, $r = 0.34$, $P < 0.05$) with a similar trend for the neutral words at the same monetary condition ($r = 0.31$, $P < 0.1$). The whole-brain regression analysis, where subjects' cdACC % signal change scores to the most salient condition (from a fixation baseline) were entered as seed values against their own contrast (activation) maps during the same condition, confirmed the first correlation (with rvACC, peak voxel: $x = -3$, $y = 51$, $z = 0$, 31 voxels, $T = 3.3$, threshold: $P < 0.001$ voxelwise uncorrected with 20 voxels minimum). Follow-up analyses using this peak voxel showed this correlation to be driven by the controls ($r = 0.69$, $P < 0.01$) and not by CUD ($r = 0.21$, $P > 0.4$). The test of coincidence of these regression lines was significant ($F_{2,30} = 5.4$, $P = 0.01$), confirming that these specific ACC intercorrelations differed significantly between the study groups (this result is especially sound given that the whole-brain regression analysis was conducted across all study subjects, enhancing the possibility for uncovering similar group results but decreasing the possibility for differential group results, which were nevertheless significant in the current study).

Correlations Between the ACC and Drug Use in the CUD. No correlations were significant at the nominal significance level ($P < 0.01$). At the reduced threshold for our a priori ACC region, 2 correlations were significant: (*i*) the more the cdACC hypoactivations, the more frequent the current cocaine use (number of days used in the past 30 days, Spearman r (r_S) = −0.56, $P < 0.05$). This correlation was strongest for the least salient condition (neutral words at 0¢: $r_S = -0.47$, $P = 0.057$; the other 3

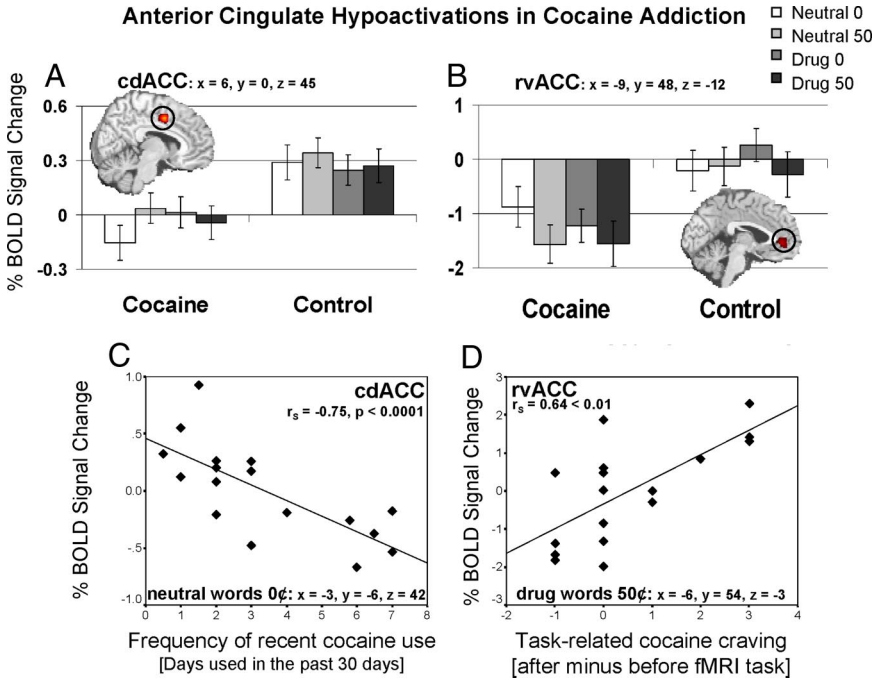

Fig. 1. Anterior cingulate hypoactivations in cocaine addicted as compared with control subjects ($n = 17$ in each group). (*A*) Mean % BOLD signal change from a fixation baseline as a function of the selected 4 task conditions in the cdACC ($x = 6$, $y = 0$, $z = 45$); (*B*) mean % BOLD signal change from a fixation baseline as a function of the selected 4 task conditions in the rvACC/mOFC ($x = -9$, $y = 48$, $z = -12$); (*C*) correlation between frequency of current cocaine use and cdACC responses to the least salient condition (neutral words at 0¢) in the CUD (derived from a whole-brain regression analysis with peak voxel at $x = -3$, $y = -6$, $z = 42$); and (*D*) correlation between task-induced craving and rvACC responses to the most salient condition (drug words at 50¢) in the CUD (derived from a whole-brain regression analysis with peak voxel at $x = -6$, $y = 54$, $z = -3$). Error bars represent standard error of the mean. The respective sagittal maps show the maxima of the selected ROIs ($P < 0.001$ familywise cluster-level corrected, 20 voxels minimum) that represent the regions that significantly differed between the groups in the second-order group ANOVA as described in *Methods*.

conditions: $r_S < -0.28$, $P < 0.3$) and it was confirmed with a whole-brain regression analysis, where the frequency of current cocaine use by individuals was entered as seed value against their own contrast maps during the least salient condition (peak voxel: $x = -3, y = -6, z = 42$, 48 voxels, $T = 4.2$, threshold: $P < 0.034$ cluster-level corrected with a small volume correction (26) and a voxelwise uncorrected level of $P < 0.005$ with 20 voxels minimum) (Fig. 1*C*); (*ii*) the rvACC showed a trend for a correlation with the fMRI-induced change in craving ($r_S = 0.36$, $P < 0.15$), which reached significance for the most salient condition (drug words at 50¢, $r_S = 0.51$, $P < 0.05$; the other 3 conditions: $r_S < 0.28$, $P < 0.3$). This correlation was also confirmed with a whole-brain regression analysis, where fMRI-induced craving change scores of individuals were entered as seed value against their own contrast maps during the most salient condition (peak voxel: $x = -6, y = 54, z = -3$, 41 voxels, $T = 3.7$, threshold: $P < 0.041$ cluster-level corrected with a small volume correction (26) and a voxelwise uncorrected level of $P < 0.005$ with 20 voxels minimum) (Fig. 1*D*).

Discussion

The I-RISA model identifies drug addiction as a neurocognitive disorder, not fully explained by self-willed choice or overt behavior of the drug addicted patient (1). Providing validity to this underlying hypothesis, our current study is the first to document that, compared with healthy control subjects and even in the absence of behavioral differences between the groups, the ACC is hypoactive as measured with BOLD-fMRI during an emotionally salient task. These findings extend previous fMRI results where ACC hypoactivations were documented in CUD as compared with controls in response to emotionally neutral cognitive tasks (9), or where performance differed on similar cognitive (5–8) or other emotionally salient tasks (27). Our current results indicate that such ACC hypoactivations cannot be fully attributed to task difficulty. Importantly, our results suggest that such ACC hypoactivations extend to tasks that are emotionally salient to CUD, suggesting that these neural responses also cannot be attributed to task disengagement. In general, these results echo previous neuroimaging studies using symptom-specific stimuli in other neurocognitive psychopathologies (e.g., depression, posttraumatic-stress disorder) (19–21). It would be interesting to evaluate whether these hypoactivations persist into longer-term abstinence as suggested by previous positron emission tomography studies (25).

Although not driven by task disengagement, emotional salience modulated these ACC responses in the CUD in proportion to drug use severity. First, the most cdACC hypoactivations in the CUD were noted during the least salient condition (neutral words at 0¢) (Fig. 1*A*), and the more these specific hypoactivations, the more frequent the recent drug use (Fig. 1*C*). These findings highlight the role of emotional and motivational factors in cdACC function (28) extending its more commonly described role in performance monitoring (14) and cognitive control (15). Further, the more the rvACC hypoactivations, specifically to the most salient condition (drug words at 50¢), the less the self-reported task-induced change in craving. This correlation is consistent with the crucial role of the rvACC in maintaining a default brain function that needs to be suspended during goal-oriented tasks (29, 30), with most suspension evidenced during the successful processing of emotionally challenging conditions [e.g., when least anxious but not anxious subjects anticipate a painful shock (18) or when sadness is provoked in healthy controls but not in depressed patients (31)]. It is therefore possible that in our study these rvACC hypoactivations

indicate the successful suspension of the cue-induced craving [elicited by the drug-related words that are conditioned to drug use in addicted individuals as we recently suggested (42)] such that task performance could be maintained at adequate levels despite the elicited desire for cocaine. Finally, in the controls only, the cdACC and rvACC were positively intercorrelated especially during the most salient task condition. Note that negative relationships between these major ACC subdivisions were previously reported in healthy controls (32). However, we examined responses to salient stimuli and not functional connectivity during rest. Importantly, absence of a similar correlation in the CUD suggests disrupted communication between both ACC major subdivisions during the processing of salient cues in drug addiction.

Other mostly cortical regions (and cerebellum) showed the opposite pattern (greater activation in CUD than in controls). These regions encompassed the dorsolateral prefrontal cortex, inferior parietal lobule, middle occipital gyrus, and cuneus, previously implicated as underlying overt behavioral group differences between CUD and controls performing other cognitive tasks (7, 8). Our current results suggest that these hyperactivations may indicate compensatory or complementary responses to the ACC hypoactivations, potentially necessary for achieving the same level of performance in the CUD as in controls. The lack of significant results for subcortical regions (e.g., dorsal and ventral striatum, amygdala, thalamus, midbrain) may have been driven by the high statistical threshold used for the whole-brain ANOVAs ($P < 0.001$ familywise corrected). This high statistical threshold was chosen as we focused on the main result of this study (robust group main effect in fMRI-BOLD responses to this task vs. lack of overt behavioral differences between the groups). The subcortical regions may show more intricate patterns of response (e.g., interactions between group and monetary reward or drug-related cues) that need to be studied separately (see for example ref. 42).

Limitations of this study include differences in race and smoking between the groups and heterogeneity in the CUD (i.e., 5/17 were negative for cocaine in urine). However, we controlled for the effects of race and cigarette smoking throughout the analyses (see *SI Text*) and thus these are unlikely to have accounted for the results. Future studies with a larger number of abstinent or treatment-seeking CUD are required to assess potential cocaine withdrawal effects in these responses. Another limitation pertains to the use of a blocked and not an event-related design. We selected a blocked design because prior behavioral studies have demonstrated that emotional/motivational stimuli become more potent when they are grouped together into blocks, rather than when intermixed with neutral trials (33).

Conclusions

We conclude that ACC hypoactivations in cocaine users cannot be attributed to task difficulty or disengagement. Further, the dissociation between overt behavioral performance and brain responses to this emotionally salient task and the absence of cdACC-rvACC functional interconnectivity may represent markers to be targeted for intervention in cocaine addiction. Interventions to strengthen the reactivity of the cdACC may be beneficial in enhancing motivation and top-down monitoring, whereas the rvACC could be targeted for enhancing craving suppression. Targeting ACC interconnectivity may be beneficial for improving similar other trait action tendencies (e.g., impulsivity) (34) that may predispose to compulsive drug use (35).

Materials and Methods

Subjects. Fifty-one right-handed native English speakers were recruited using advertisements in local newspapers and by word of mouth. Subjects underwent a full physical and neurological examination by a neurologist and a diagnostic interview by a clinical psychologist. This interview included the Structured Clinical Interview for DSM-IV Axis I Disorders (research version) (36, 37), the Addiction Severity Index (38), the Cocaine Selective Severity Assessment Scale (39), and the Cocaine Craving Questionnaire (40). All subjects were able to understand and give informed consent. Subjects were healthy individuals, not taking any medications, and further excluded for (*i*) history of head trauma or loss of consciousness (>30 min) or other neurological disease of central origin (including seizures); (*ii*) abnormal vital signs at time of screening and history of major medical conditions, encompassing cardiovascular (including high blood pressure), endocrinological (including metabolic), oncological, or autoimmune diseases; (*iii*) history of major psychiatric disorder (other than substance abuse or dependence for CUD and/or nicotine dependence for both groups); (*iv*) history of gambling as assessed with the South Oaks gambling questionnaire (cutoff <5) (41); (*v*) except for cocaine in the CUD subjects, positive urine screens for other psychoactive drugs or their metabolites (phencyclidine, benzodiazepines, cannabis, opiates, barbiturates, and inhalants); (*vi*) pregnancy as confirmed with a urine test in all female subjects; (*vii*) contraindications to the MRI study; and (*viii*) because of the verbal nature of the fMRI task (24) education of less than 12 years (or equivalent) and verbal intelligence of ≤85.

Of these 51 subjects, 38 subjects (17 CUD, 21 controls) completed the fMRI task without loss of data due to motion or technical difficulties (see later thresholds discussion; there were no group differences in these subject exclusions, $\chi^2_1 = 1.1$, $P > 0.3$). Four more controls were excluded to numerically equate the groups and for demographic matching that included sex, age, education, intellectual functioning, and socioeconomic status (Table S1). Race and history of cigarette smoking nevertheless differed between the groups. Their potential contribution to results was inspected as described in *SI Text*. Note that, of the 34 subjects included in the current study, results of 26 (15 CUD and 11 controls) were previously reported (42) as further described later (under BOLD-fMRI analyses).

All 17 CUD used crack/cocaine (mostly smoked route) in the past 30 days and met DSM-IV criteria for current cocaine dependence ($n = 15$) or abuse ($n = 2$; these 2 subjects met criteria for cocaine dependence under remission). Three of the CUD also reported current alcohol abuse ($n = 1$), moderate alcohol dependence ($n = 1$), or marijuana abuse ($n = 1$). Current use or dependence on other drugs was denied and corroborated by the prescan urine tests in all subjects (urine was positive for cocaine in 12 CUD; urine was negative for all drugs in all other subjects). Subjects were fully informed of all study procedures and risks and provided written consent in accordance with the local institutional review board.

Task. The fMRI task (developed in E-prime, Psychology Software Tools, Inc.) uses 4 counterbalanced monetary amounts (50¢, 25¢, 1¢, or 0¢), obtained for correct performance on a blocked neuropsychological task for up to $75, received at the completion of this study (Fig. S3). For simplicity and clarity, in the current manuscript we report results of 2 of these monetary conditions: the highest reward available versus no monetary gain (50¢ and 0¢). Each of these monetary amounts was received twice, under a drug versus neutral cue. The drug cues were 40 regular drug words; non-English or slang drug words were not used (as they may have not been recognized by the control subjects) (24). The neutral cues were 40 household words matched to the drug words on length, frequency in the English language (43), and part of speech (noun, adjective, adverb, verb) (24). Similarly to other fMRI tasks of emotion, the 2 word types were presented in a blocked on-off or off-on order (i.e., drug-neutral or neutral-drug) (44), counterbalanced between subjects (Fig. S3*A*). Across all 3.4-min task conditions (Fig. S3*B*), subjects had to press 1 of 4 buttons (yellow, blue, red, green) on a commercially available response pad (Cedrus brand Lumina model LP-400), matching the color of the word they had just read; word color order was pseudorandomized across all sequences (Fig. S3*C*). The task was presented via MRI-compatible goggles.

Behavioral Measures. Reaction time and accuracy data were collected across all trials using E-prime. Note that minimum accuracy was ≥50%, a threshold that was met by all 34 subjects included in this study. We also collected ratings of drug craving (''how much do you want cocaine right now?'' from not at all to very much, 0 to 10) outside the scanner (just before the task on a computer monitor) and then immediately before, once during, and at the completion of all fMRI sequences (inside the scanner this question was presented through MRI compatible goggles). A similar procedure was followed for the motivation to gain money (''how much do you want money right now?''). Finally, immediately after completion of the MRI session (and outside the scanner), all subjects rated all words on valence (''how negative or positive'' a word is, from extremely negative to extremely positive, −5 to +5). All ratings were obtained using custom programs written in C++.

MRI Data Acquisition. MRI scanning was performed on a 4T whole-body Varian/Siemens MRI scanner. The BOLD responses were measured as a function of time using a T2*-weighted single-shot gradient-echo EPI sequence (TE/TR = 20/1600 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, 128 time points, and 4 dummy scans to be discarded to avoid nonequilibrium effects in the fMRI signal). Padding was used to minimize subject motion, which was also monitored immediately after each fMRI run (45). Earplugs (−28 dB sound attenuation; Aearo Ear TaperFit 2; Aearo Company) and headphones (−30 dB sound attenuation; Commander XG MRI Audio System, Resonance Technology Inc.) were used to minimize the interference effect of scanner noise during fMRI (46). Anatomical images were collected using a T1-weighted 3D-MDEFT sequence (47) (TE/TR = 7/15 ms, 0.94 × 0.94 × 1 mm spatial resolution, axial orientation, 256 readout and 192 × 96 phase-encoding steps, 16 min scan time) and a modified T2-weigthed hyperecho sequence (48) (TE/TR = 42/10,000 ms, echo train length = 16, 256 × 256 matrix size, 30 coronal slices, 0.86 × 0.86 mm in-plane resolution, 5 mm thickness, no gap, 2 min scan time), both reviewed to rule out gross brain morphological abnormalities.

MRI Data Processing. Subsequent analyses were performed with the statistical parametric mapping package SPM2 (Wellcome Trust Centre for Neuroimaging). A 6-parameter rigid body transformation (3 rotations, 3 translations) was used for image realignment and to correct for head motion; 2 mm displacement and 2° rotation in any of the axes in any of the task sequences were used as criteria for acceptable motion. The realigned datasets were spatially normalized to the standard frame (Talairach) with a 12-parameters affine transformation (49), using a voxel size of 3 × 3 × 3 mm^3. An 8-mm full-width-half-maximum Gaussian kernel was used to smooth the data.

BOLD-fMRI Analyses. A general linear model (50) and a box-car design convolved with a canonical hemodynamic response function (HRF) and low-pass (HRF) and high-pass (cut-off frequency: 1/256 Hz) filters were used to calculate individual BOLD-fMRI maps. Four contrast maps per subject were calculated, reflecting % signal change from a fixation baseline for each of the 4 task conditions. These individual contrast maps were included in a second-order (random-effects) repeated measures ANOVA SPM2 model with 2 groups (CUD and control), 2 word conditions (drug and neutral), and 2 monetary conditions (50¢ and 0¢). Brain activation clusters with at least 20 voxels (540 mm^3) and $P < 0.001$, cluster-level corrected for multiple comparisons using the continuous random field calculation implemented in SPM2, were considered significant. This higher than usual ($P < 0.05$ corrected) statistical threshold was selected as we were particularly interested in the most robust task activations/hypoactivations and the group main effect [reported exclusively in the current manuscript; for results of interaction effects (in 30 subjects, 26 from the current sample), which necessitated a lower statistical threshold ($P < 0.005$ uncorrected) and revealed the dopaminergic midbrain, see ref. 42]. In all SPM analyses, anatomical specificity was corroborated with a coplanar stereotaxic atlas of the human brain (51).

To confirm the voxel-based analyses, functional ROIs with an isotropic volume of 27 voxels (729 mm^3) were defined at all of the significant coordinates (Table 1) to extract (with a custom program written in IDL, ITT Visual Information Solutions) the average (and variability) BOLD-fMRI signal amplitudes in these regions. These ROIs offer precise spatial localization of the functional responses as we previously reported (e.g., refs. 7 and 8). These ROI measures were used in follow-up analyses (e.g., ANOVA with Bonferroni corrections, *t* tests, correlations) conducted in SPSS 11.5 (SPSS Inc.). Statistical significance for these ROI analyses was defined at $P < 0.05$, uncorrected (note that here we only inspected the regions that were significant at $P < 0.001$ cluster-level corrected at the whole-brain analyses, providing protection against Type I error). In all analyses, the appropriate corrections were used in cases of violation of homogeneity of variance (e.g., as tested with Levene's test or Mauchly's test of sphericity).

We conducted correlations between the selected ROIs (averaged across the 4 task conditions) with 6 selected cocaine use variables (Table S1). These correlations in SPSS were inspected with a familywise corrected threshold ($P < 0.01$). These exploratory correlations were conducted to inspect associations between the brain regions that differed between the group and severity of drug use (including time since last use). For our a priori region, the ACC correlations were reported if they reached the more lenient statistical threshold ($P < 0.05$). All ROI correlations were validated with SPM whole-brain, voxel-based correlation analyses (simple regressions) as described in *Results*.

The behavioral measures were similarly analyzed. Note that all continuous and normally distributed variables were inspected with parametric tests (within groups: paired *t* test; between groups: independent t tests; correlations: Pearson *r*). Self-report measures (including depression and the nonnormally distributed cocaine use variables) were inspected with the respective nonparametric tests (Wilcoxon, Mann–Whitney U, or Spearman $r = r_S$).

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