Supporting Information

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SI Text

Task. Each word trial was comprised of a 500-ms fixation cross, a 2,000-ms word presentation (for word reading), a 500-ms response window (to measure accuracy, errors, and reaction time), and a 500-ms feedback slide. Given the long separation between word reading and button press (2,000 ms) to reduce working-memory demands, conflict was not expected (this delay also decreased variability in reaction time) (1). Each word condition was performed under one of three counterbalanced monetary-reward amounts ($0.50, $0.25, or $0.00), gained for correct performance for up to $75 received at the completion of this study.

Methylphenidate Effect on Additional Task-Related Ratings. In addition to craving and using the same procedures and timing (reported in *Text*), task ratings were obtained for motivation to gain money (how much do you want money right now?), sleepiness (how sleepy are you right now?), interest in task (how interested are you in the task right now?), and performance (how well did you perform on the preceding task?). A 2 (medication) × 3 (repetition) × 2 (group) ANOVA for sleepiness showed a repetition main effect ($F_{1.6,37.8} = 7.8$, $P < 0.01$) driven by decreased sleepiness from baseline to both other repetitions and a medication by repetition linear within-subjects interaction ($F_{1,24} = 5.8$, $P < 0.05$) driven by more robust decreases in sleepiness from baseline to the other two measures with methylphenidate (MPH; $Z > -2.9$, $P < 0.01$) than placebo ($Z < -1.8$, $P > 0.07$) (Fig. S4*B*). In people with cocaine-use dependence (CUD), MPH decreased sleepiness even before the task ($Z = -2.0$, $P < 0.05$), and indeed, CUD reported more sleepiness than controls but only during placebo and before the drug-word task ($Z = -2.2$, $P < 0.05$). On closer inspection, there was a trend for the task itself to decrease sleepiness in CUD (comparing baseline with ratings acquired immediately after the task during placebo; $Z = 1.9$, $P = 0.057$). Interestingly, confidence ratings acquired after the task showed enhanced ratings with MPH for CUD (6.9 ± 1.8 vs. 8.1 ± 1.4, $Z = -2.1$, $P < 0.05$) but not controls (7.5 ± 2.1 vs. 7.8 ± 2.2, $Z = -0.7$, $P > 0.5$). Thus, MPH decreased sleepiness and increased performance-confidence ratings in the CUD. There were no significant effects for the money- or task-interest ratings ($F < 2.3$, $P > 0.1$).

MPH Effect on Profile of Mood States and Cardiovascular Measures. Profile of mood (POM) states (on a scale of 0–10, how do you feel right now on the following dimensions: alert, anxious, annoyed, control, depressed, distrustful, hallucinations, happy, high, mood, restless, tired, sexual desire, MPH desire, and MPH control) were obtained three times: at baseline (just before medication administration), before functional MRI (fMRI) (45 min postmedication), and after fMRI (120 min postmedication). Heart-rate measures coincided with all POM ratings and were also obtained a fourth time as part of medical clearance after fMRI. Blood-pressure ratings were taken at baseline and after fMRI to coincide with the fourth heart-rate reading (Fig. S1).

POM state ratings. A 2 (medication) × 3 (repetition) × 2 (group) ANOVA showed no significant effects for restlessness, fatigue, depressed mood, feeling annoyed, and sexual and MPH desire. Compared with controls, CUD reported lower alertness, mood, control, happiness, and MPH control and higher anxiety, hallucinations, and MPH desire (group main effects: $F_{1,25} > 4.3$, $P < 0.05$). A repetition main effect for happiness showed a decrease in self-reported happiness from first to second repetition ($F_{2,24} = 3.5$, $P < 0.05$; recovering at third repetition). A repetition by group linear within-subjects interaction ($F_{1,25} = 6.3$, $P < 0.05$) for distrustfulness showed that higher distrustfulness in CUD than controls (reaching significance during MPH; first repetition: $Z = -2.7$, $P < 0.05$) decreased from first to third repetition during MPH ($Z = -2.1$, $P < 0.05$) but not placebo ($Z = -1.3$, $P > 0.2$). A repetition within-subjects linear contrast (first < third; $F_{1,25} = 5.6$, $P < 0.05$) and a repetition by group linear within-subjects interaction ($F_{1,25} = 5.8$, $P < 0.05$) for hallucinations showed a trend for more hallucinations at third than first repetition during placebo ($Z = -1.7$, $P = 0.08$) but not MPH ($Z = -1.0$, $P > 0.3$). Thus, MPH reduced the self-report of these psychiatric symptoms during fMRI in the CUD.

Reports for high showed a medication main effect (MPH > placebo; $F_{1,25} = 5.5$, $P < 0.05$), as driven by increases during the last repetition (120 min after medication; $Z = -2.1$, $P < 0.05$) across both study groups (Fig. S4*C*). Because there was a trend for a similar increase in self-reported high in the CUD during placebo (comparing the last with the second repetition; $Z = -1.6$, $P = 0.1$), results could be attributed to the task itself. Nevertheless, MPH may have an enhancing effect and an interaction with the drug-word task on self-reported high, but this remains to be examined in future studies.

Heart rate. A 2 (medication) × 4 (repetition: baseline/before fMRI, 45 min post-MPH, 120 min post-MPH, and post-fMRI session) × 2 (group) ANOVA showed a medication main effect (MPH > placebo; $F_{1,25} = 20.7$, $P < 0.0001$), a medication by repetition within-subjects quadratic interaction ($F_{1,25} = 4.7$, $P < 0.05$), and a three-way within-subjects linear interaction ($F_{1,25} = 4.4$, $P < 0.05$) (Fig. S7*A*). The group main effect was not significant. Follow-up paired t tests (within each medication condition separately) showed heart-rate increases during MPH (differences reached significance between the first and second repetitions; $t_{12} = -2.9$, $P < 0.05$) and decreases during placebo (differences reached significance between the first and third repetitions; $t_{12} = 2.3$, $P < 0.05$) as driven by controls. Furthermore, comparing MPH with placebo showed higher heart rate during the first and second repetitions in CUD ($t_{12} > 2.7$, $P < 0.05$) but not controls, who, instead, showed a difference during the last two repetitions ($t_{13} > 2.7$, $P < 0.05$). Thus, MPH increased heart rate in the control subjects, who showed decreases in heart rate as a function of time (and task) on the placebo day. In the CUD, heart rate was higher on MPH than placebo date during readings that preceded the task or medication administration. This result may be attributed to randomization issues that would dissipate in larger sample sizes (e.g., although not statistically significant, most CUD had MPH for their first study, whereas most controls had placebo as their first study: MPH as first day of study in 7/13 CUD vs. 5/14 controls; $\chi^2_1 = 0.9$, $P > 0.3$).

Systolic blood pressure. A 2 (medication) × 2 (repetition: baseline/before fMRI and post-fMRI session) × 2 (group) ANOVA showed a repetition main effect (second > first; $F_{1,25} = 27.3$, $P < 0.0001$) and a group main effect (CUD > controls; $F_{1,25} = 5.0$, $P < 0.05$) (Fig. S7*B*). Although interaction effects were not significant, follow-up t tests showed that the group differences were driven by postsession measures during MPH ($t_{25} = 2.6$, $P < 0.05$). Thus, the fMRI session (which included the drug-word task) enhanced systolic blood pressure in all subjects, and this enhancement was largest in the CUD during MPH day.

Diastolic blood pressure. A similar 2 × 2 × 2 ANOVA again showed a repetition main effect (second > first; $F_{1,25} = 41.7$, $P < 0.0001$) and a repetition by medication interaction ($F_{1,25} = 7.5$, $P = 0.011$) driven by higher diastolic blood-pressure increases during MPH (Fig. S7*C*). Follow-up t tests showed that MPH increased the postsession diastolic blood-pressure measures in CUD ($t_{12} =$

2.6, $P < 0.05$) but not controls ($t_{13} = -0.5$, $P = 0.7$). Similarly to systolic blood pressure, the groups differed in postsession measures during MPH only ($t_{25} = 3.3$, $P < 0.01$). Thus, diastolic blood pressure increased as a function of session in all subjects, but this effect was lowest in CUD at placebo day ($t_{12} = -2.0$, $P = 0.069$) and highest in CUD during the MPH day.

Controlling for Cardiovascular Measures and Sleepiness. Controlling for postsession MPH-enhanced cardiovascular measures (systolic and diastolic blood pressure and heart rate) and self-reported sleepiness, the caudal-dorsal anterior cingulate cortex (cdACC) three-way interaction was still significant ($F_{1,24} > 4.3$, $P = 0.05$). For rostroventral ACC/medial orbitofrontal cortex (rvACC/mOFC), when controlling for sleepiness, the medication main effect was still significant ($F_{1,23} > 7.2$, $P < 0.05$). Controlling for systolic or diastolic blood pressure, the rvACC/mOFC medication by group interaction reached significance ($F_{1,24} > 4.5$, $P < 0.05$). Heart rate could not be used as covariate (interaction with group) and was also not associated with rvACC/mOFC ($r < |0.26|$, $P > 0.2$). It was, therefore, not used in these covariate analyses. Controlling for these four measures (sleepiness and cardiovascular measures), the correlation between accuracy and rvACC/mOFC (Fig. 1*D*) was still significant ($r > 0.55$, $P < 0.01$).

Plasma MPH Concentration. Venous blood was drawn to quantify plasma concentrations of MPH before and at 45 and 120 min after MPH (or placebo) using capillary GC/MS (2). Levels of MPH were at nondetectable levels during all placebo measures and before MPH administration on the MPH day. For the MPH day 2 later measures, a 2 (repetition) × 2 (group) ANOVA showed a repetition main effect (120 > 45 min, $F_{1,25} = 35.4$, $P < 0.0001$), whereas all other effects were not significant ($F < 2.8$, $P > 0.1$). Thus, MPH plasma concentration was highest during the last time point but did not differ by group, and there was no interaction between repetitions with group (Table S1).

Effect of the Monetary Manipulation. A 2 (medication) × 2 (group) ANOVA showed no significant group differences in the amount of money earned on the task (CUD = \$66.6 ± 1.4 vs. controls = \$68.9 ± 1.4, $F_{1,25} = 1.4$, $P > 0.3$). All other effects were similarly not significant ($F < 1.0$, $P > 0.3$). Indeed, in separate 2 (medication) × 2 (\$0.50 and \$0.00; the intermediate money condition, \$0.25, was excluded for clarity and simplicity) × 2 (group) ANOVA analyses, there were no main effects or interactions with money on any of the behavioral performance measures in this sample ($F < 2.4$, $P > 0.1$). Lack of a behavioral effect was not reflected in posttask self-ratings, where all subjects rated the higher monetary condition as more valuable than the no money condition (4.9 ± 0.6 vs. 0.4 ± 0.2, respectively, $F_{1,25} = 51.7$, $P < 0.0001$); none of the other effects reached significance ($F < 3.2$, $P > 0.09$). These ratings were performed immediately after the word-value ratings, using a previously described scale (3). A similar whole-brain ANOVA did not reveal any money effects (main or interaction effects) at the selected statistical threshold ($P < 0.05$ cluster-level corrected and $P < 0.001$ voxel-level uncorrected with 20 contiguous voxels; there were no significant results even when reducing the threshold to $P < 0.05$ cluster-level corrected and $P < 0.005$ voxel-level uncorrected with 10 contiguous voxels). We, therefore, focused all current analyses on the averaged word conditions. Nevertheless, the impact of MPH on the processing of this secondary reinforcer remains to be inspected with larger sample sizes.

Brain–Behavior Correlations. Correlation analyses with our a priori regions of interest (ROIs; SPSS analyses with signal change derived from the coordinates in Table 1 and Fig. 1) showed the rvACC/mOFC to correlate with task accuracy and errors of omission for the drug words during both MPH and placebo (all $r_S > |0.54|$, $P < 0.01$; correlations for neutral words were similar, although not reaching nominal significance level, $r_S < |0.48|$, $P < 0.05$). Correlations between these behavioral measures with the cdACC were observed for the neutral words during placebo ($r_S > |0.50|$, $P < 0.01$; correlations for drug words and during MPH were similar, although not reaching nominal significance level, $r_S < |0.49|$, $P = 0.01$). There was also a correlation between the cdACC with errors of commission for neutral words during MPH ($r_S = -0.54$, $P < 0.01$).

ROI Correlations with Drug Use in CUD. ROI analyses showed that the cdACC correlated with lifetime use of marijuana (neutral words during MPH, $r_S = -0.74$, $P < 0.01$) and alcohol (drug and neutral words during placebo, $r_S > -0.71$, $P < 0.01$; correlation with lifetime cocaine use was similar, although not reaching nominal significance level; drug words during placebo, $r_S = -0.36$, $P = 0.064$). The rvACC/mOFC correlated with cocaine use in the last 30 d (neutral words during placebo, $r_S = -0.69$, $P < 0.01$). All correlations were also visible (but not as strong) for all other respective conditions (e.g., during placebo and MPH and drug- and neutral-word conditions). Thus, the higher the cdACC activations, the lower the lifetime use of marijuana and alcohol (with a similar trend for cocaine). For the rvACC/mOFC, the effect was more specific to recent drug use such that the more the deactivations, the more the recent cocaine use.

Excluding the CUD with comorbid current heroin dependence did not change the cdACC three-way interaction ($F_{1,24} = 7.6$, $P = 0.011$), the rvACC/mOFC medication main effect ($F_{1,24} = 10.7$, $P < 0.01$), the medication main effect for errors of commission ($F_{1,24} = 6.0$, $P < 0.05$), or the rvACC/mOFC correlation with accuracy ($r = 0.53$, $P < 0.01$).

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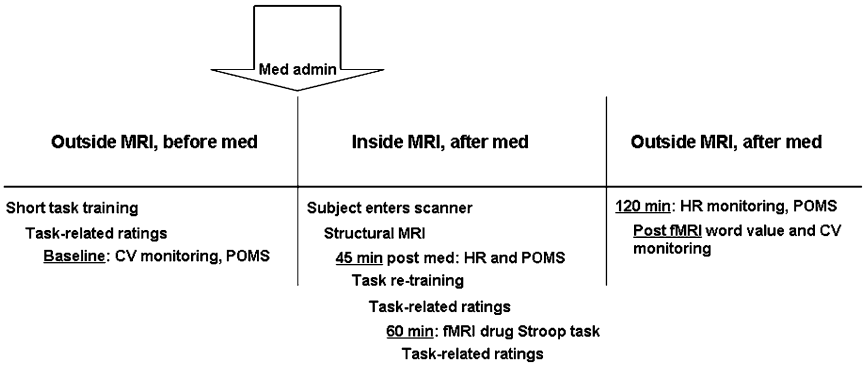

Fig. S1. Study procedures. MRI, magnetic resonance imaging; Med, medication (20 mg oral methylphenidate or placebo); CV, cardiovascular (heart rate and blood pressure); HR, heart rate; POMS, profile of moods state; fMRI, functional MRI.

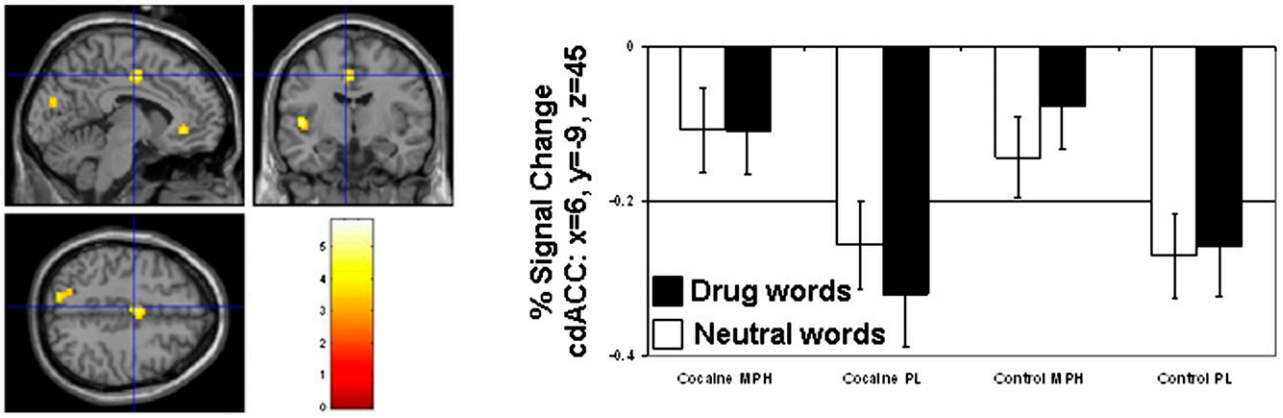

Fig. S2. Neuroimaging results in peak cdACC coordinate. Variable is mean percent blood oxygen level-dependent (BOLD) signal change from a fixation baseline as a function of drug vs. neutral words on the drug-word fMRI task in the peak cdACC coordinate (x = 6, y = −9, z = 45) that showed the expected medication effect ($F_{1,25}$ = 14.2, P = 0.001). Cocaine (n = 13); control (n = 14). MPH, methylphenidate; PL, placebo.

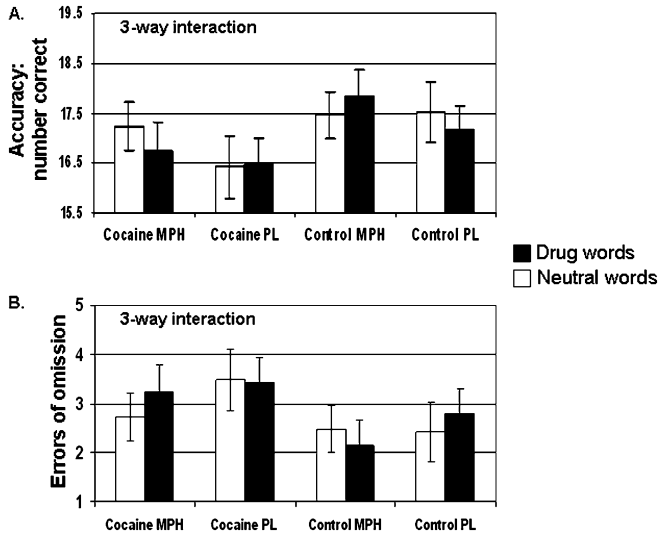

Fig. S3. Behavioral results for task accuracy and errors of omission. Error bars represent SEM. Cocaine (n = 13); control (n = 14). MPH, methylphenidate; PL, placebo.

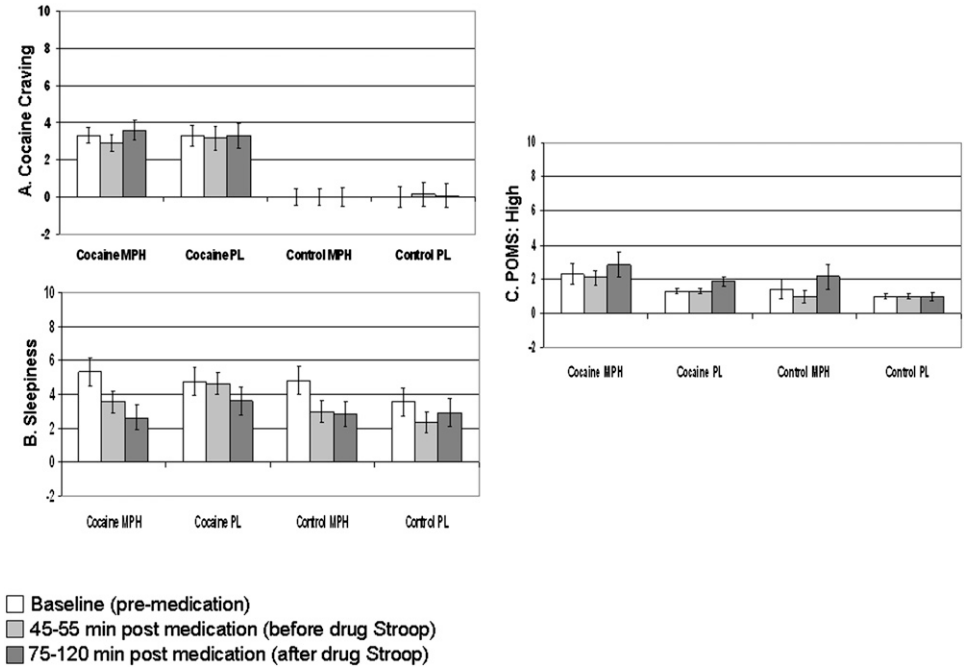

Fig. S4. MPH effects on task-related ratings and POMS. Error bars represent SEM. Cocaine (n = 13); control (n = 14). MPH, methylphenidate; PL, placebo.

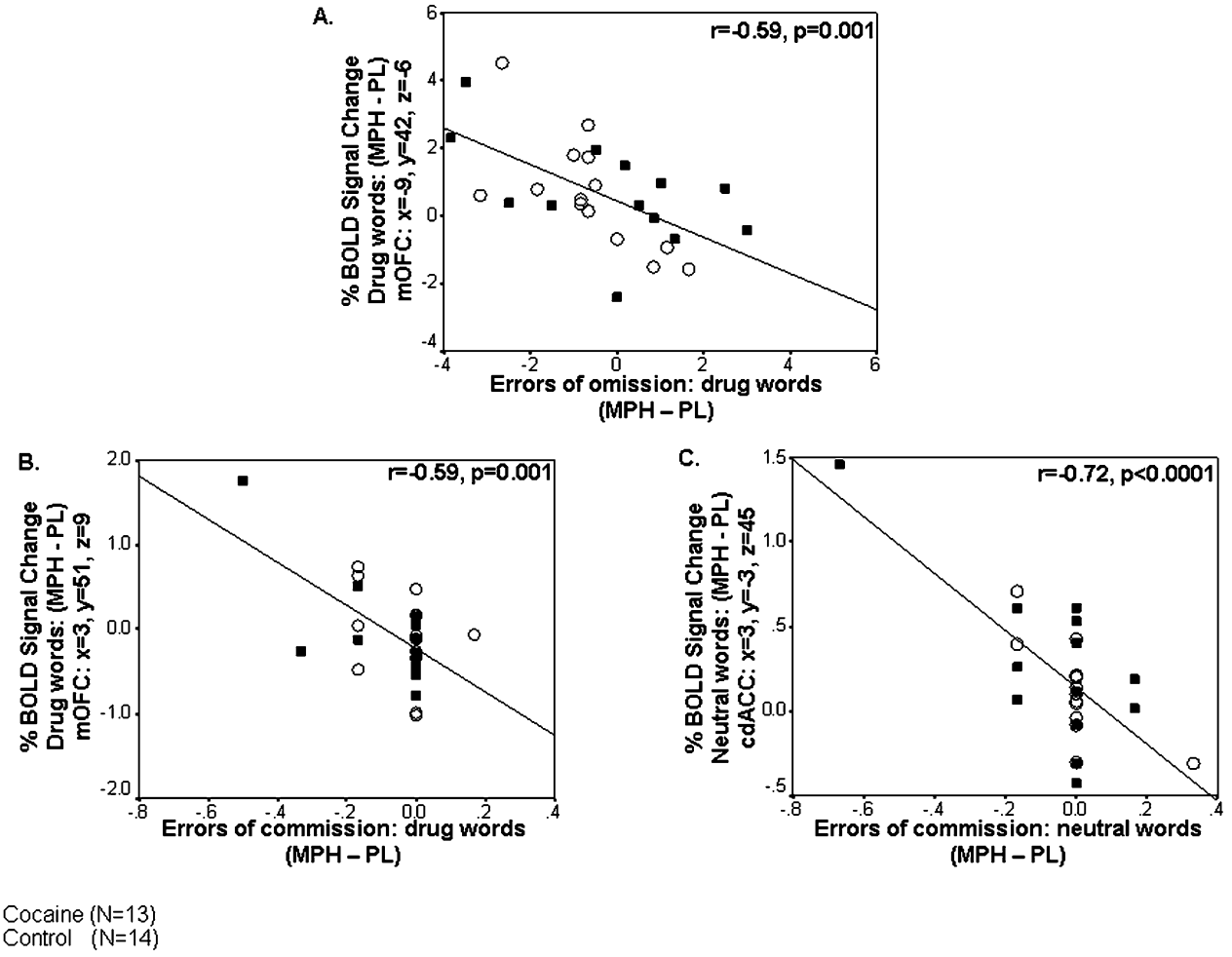

Fig. S5. MPH-driven behavioral-fMRI enhancements intercorrelate. Correlations are between percent BOLD signal change (MPH − placebo) with the respective behavioral measures for (*A*) rvACC/mOFC ($x = -9$, $y = 42$, $z = -6$) and errors of omission during drug words, (*B*) rvACC/mOFC ($x = 3$, $y = 51$, $z = 9$) and errors of commission during drug words, and (*C*) cdACC ($x = 3$, $y = -3$, $z = 45$) and errors of commission during neutral words. Note that, for the cdACC ROI, the correlation was still significant after exclusion of an outlier ($r_S = -0.46$, $P < 0.05$) as confirmed by whole-brain analyses for a more posterior peak cluster ($x = 9$, $y = -18$, $z = 45$, 38 voxels, $Z = 4.5$, $P < 0.01$ cluster-level corrected with small-volume correction). In all correlations, the behavioral measure was used as seed value regressed against the respective fMRI contrast maps in whole-brain simple-regression analyses.

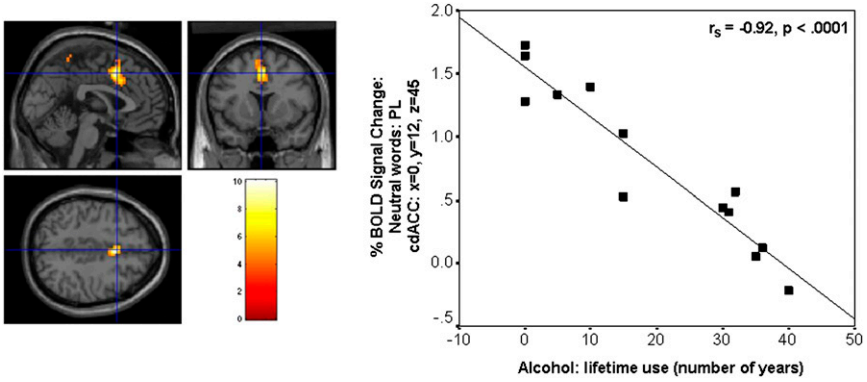

Fig. S6. Whole-brain correlation between cdACC and lifetime alcohol use in 13 CUD. Correlation is between percent BOLD signal change in the cdACC (to neutral words from a fixation baseline during placebo; $x = 0$, $y = 12$, $z = 45$) with lifetime alcohol use (similar ROI correlations were observed for lifetime marijuana and cocaine use).

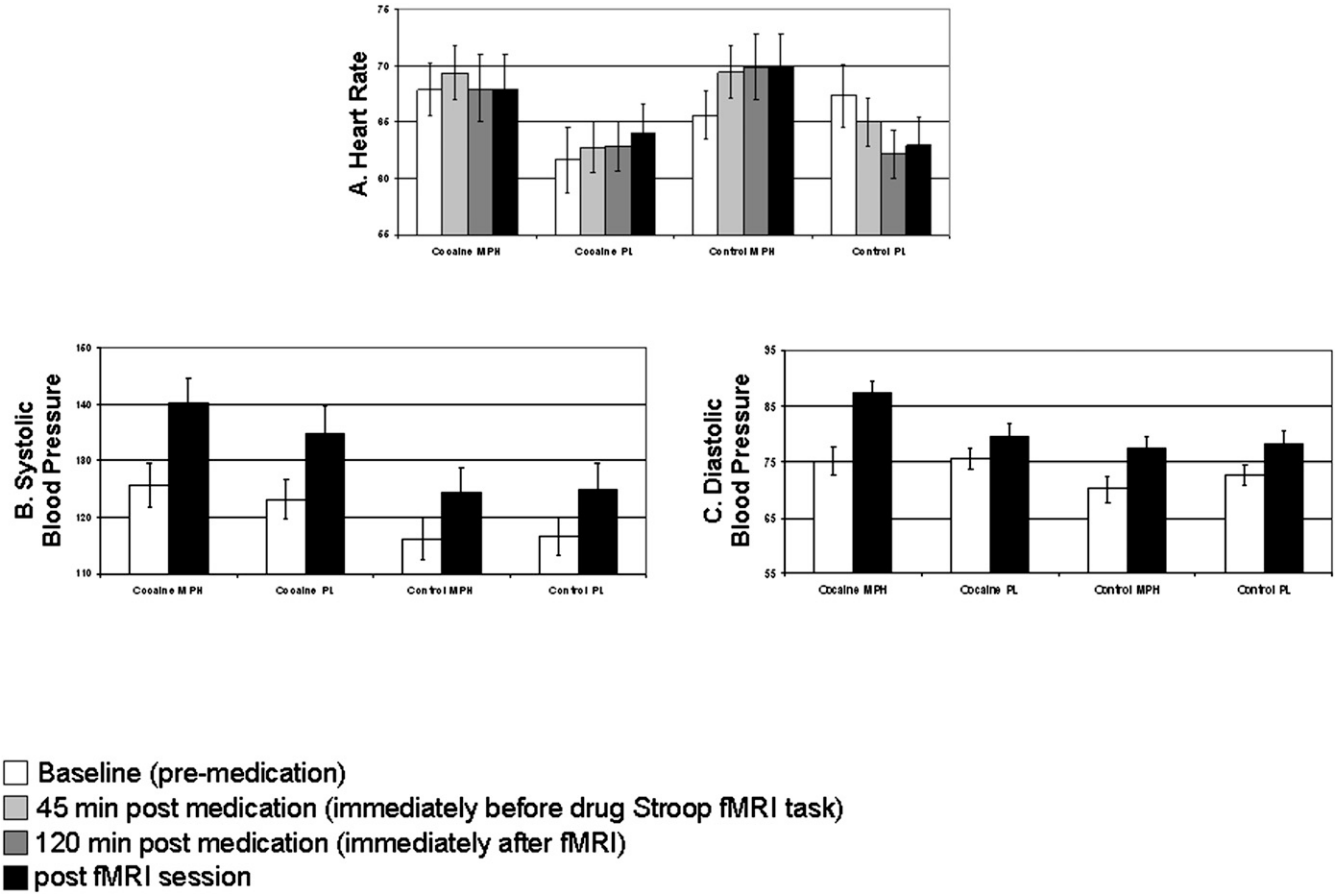

Fig. S7. MPH effects on cardiovascular measures: heart rate and systolic and diastolic blood pressure. Error bars represent SEM. Cocaine (n = 13); control (n = 14). MPH, methylphenidate; PL, placebo.

Table S1. Demographics and drug use of all study subjects

	Test	Control (n = 14)	CUD (n = 13)
Gender: male/female	$\chi^2_1 = 1.1$	14/0	12/1
Race: African-American/Caucasian/Asian	$\chi^2_2 = 1.8$	9/4/1	11/2/0
Age (y)	$t_{25} = 2.5$*	38.8 ± 6.2	46.2 ± 8.7
Education (y)	$t_{25} = -1.7$	13.9 ± 1.3	12.9 ± 1.9
Verbal intelligence quotient (IQ): Wide-Range Achievement Test III—Reading Scale (4)	$t_{25} = -1.5$	99.8 ± 11.4	93.6 ± 9.8
Nonverbal IQ: WASI—Matrix Reasoning Scale (5)	$t_{25} = 0.7$	10.8 ± 3.8	9.9 ± 2.8
Socioeconomic status: Hollingshead Index	$t_{25} = -0.7$	39.9 ± 9.0	37.5 ± 8.1
Height (in)	$t_{25} = -0.3$	70.3 ± 3.4	69.9 ± 2.9
Weight (lb)	$t_{23.0} = -1.6$	186.6 ± 22.9	174.4 ± 15.7
Baseline heart rate (screen)	$t_{25} = 0.4$	65.3 ± 11.0	66.8 ± 8.2
Baseline systolic blood pressure	$t_{25} = 1.5$	124.4 ± 6.6	129.8 ± 11.9
Baseline diastolic blood pressure	$t_{25} = -0.5$	76.7 ± 8.8	74.8 ± 10.6
MPH in plasma 45 min post-MPH administration (ng/mL)	$F_{1,25} = 2.8$	0.92 ± 1.3	1.77 ± 2.2
MPH in plasma 120 min post-MPH administration (ng/mL)	$F_{1,25} = 2.8$	4.5 ± 2.2	6.0 ± 3.8
Mean depression: Beck Depression Inventory II (6)	$Z = -3.5^{\dagger}$	1.5 ± 3.1	8.0 ± 4.7
Cigarette smokers (current or past/nonsmokers)	$\chi^2_1 = 10.7^{\dagger}$	2/12	10/3
Cocaine lifetime use (y)	$Z = -4.8^{\dagger}$	0.0 ± 0.0	17.9 ± 9.4
Cocaine past-month use (d/mo)	$Z = -4.8^{\dagger}$	0.0 ± 0.0	13.6 ± 9.9
Alcohol lifetime use (y)	$Z = -2.3$*	4.9 ± 7.7	19.2 ± 15.3
Alcohol past-month use (d/mo)	$Z = -2.7^{\dagger}$	0.9 ± 1.5	4.3 ± 4.3
Marijuana lifetime use (y)	$Z = -3.4^{\dagger}$	1.1 ± 0.4	7.6 ± 9.2
Marijuana past-month use (d/mo)	$Z = -1.0$	0.0 ± 0.0	0.08 ± 0.3

χ^2 tests were used for categorical variables, Mann-Whitney U tests were used for all continuous nonnormally distributed variables, and t tests were used for all other variables. For MPH in plasma, an ANOVA was used as described in *Text*. Values are frequencies or means ± SD. All subjects denied any use of heroin, methadone, other opiates/analgesics, barbiturates, sedatives/hypnotics/tranquilizers, amphetamines, hallucinogens, or inhalants (an exception was a young CUD subject who reported 15 d of heroin use in the last 30 d but no lifetime heroin use). CUD, individuals with cocaine-use disorders; WASI, Wechsler Abbreviated Scale of Intelligence.

*$P < 0.05$.

†$P < 0.01$.

Table S2. Group differences: drug-word fMRI task

	BA	Side	Number of voxels	Z	P cluster-level corrected	x	y	z
Controls > CUD								
Middle frontal gyrus	6	R	29	7.1	0.000	21	15	60
Insula		R	31	5.8	0.000	36	9	3
Fornix		L	24	5.7	0.000	−6	−24	18
Cerebellum		M	79	6.5	0.000	0	−45	−6
Inferior parietal lobule	39	R	46	6.1	0.000	33	−66	12
Fusiform gyrus	18, 19	R	23	6.0	0.000	27	−78	−12
Lingual gyrus	17, 18	L	293	7.8	0.000	−12	−87	0
		R				6	−87	3
Controls < CUD								
Precentral gyrus	4, 6	L	103	7.1	0.000	−51	−3	27
Superior frontal gyrus	6	L	20	5.7	0.000	−21	−9	57
Precuneus, superior parietal lobule	7	L	61	7.1	0.000	−12	−60	51
Angular gyrus	19, 39	R	35	6.8	0.000	42	−69	30
Cerebellum		R	24	5.6	0.000	18	−69	−18
Cuneus	18, 19	L	89	>7.1	0.000	−15	−84	30

All results: $P < 0.05$ cluster-level corrected (family-wise error corrected), 20 voxels minimum. BA, Brodmann Area; CUD, individuals with cocaine-use disorders; L, left; R, right; M, middle.