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ROLE OF THE ANTERIOR CINGULATE AND MEDIAL ORBITOFRONTAL CORTEX IN PROCESSING DRUG CUES IN COCAINE ADDICTION

R. Z. GOLDSTEIN,[a]* D. TOMASI,[a] S. RAJARAM,[b] L. A. COTTONE,[a] L. ZHANG,[b] T. MALONEY,[a] F. TELANG,[a] N. ALIA-KLEIN[a] AND N. D. VOLKOW[c]

[a]*Brookhaven National Laboratory, P.O. Box 5000, Upton, NY 11973-5000, USA*

[b]*State University of New York at Stony Brook, Stony Brook, NY 11794-4400, USA*

[c]*National Institute on Drug Abuse, Bethesda, MD 20892, USA*

Abstract—Our goal in the current report was to design a new functional magnetic resonance imaging (fMRI) task to probe the role of the anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) in processing of salient symptom-related cues during the simultaneous performance of an unrelated task in drug-addicted persons. We used a novel fMRI color-word drug Stroop task in 14 individuals with cocaine use disorders; subjects had to press for color of drug vs. matched neutral words. Although there were no accuracy or speed differences between the drug and neutral conditions in the current sample of subjects, drug words were more negatively valenced than the matched neutral words. Further, consistent with prior reports in individuals with other psychopathologies using different Stroop fMRI paradigms, our more classical color-word Stroop design revealed bilateral activations in the caudal–dorsal anterior cingulate cortex (cdACC) and hypoactivations in the rostro-ventral anterior cingulate cortex/medial orbitofrontal cortex (rACC/mOFC). A trend for larger rACC/mOFC hypoactivations to the drug than neutral words did not survive whole-brain corrections. Nevertheless, correlation analyses indicated that (1) the more the cdACC drug-related activation, the more negative the valence attributed to the drug words ($r=-0.86$, $P<0.0001$) but not neutral words; and (2) the more the rACC/mOFC hypoactivation to drug minus neutral words, the more the errors committed specifically to the drug minus neutral words ($r=0.85$, $P<0.0001$). Taken together, results suggest that this newly developed drug Stroop fMRI task may be a sensitive biobehavioral assay of the functions recruited for the regulation of responses to salient symptom-related stimuli in drug-addicted individuals. **© 2006 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: emotional Stroop interference, inhibitory control, cognitive conflict, attention bias, drug addiction, fMRI BOLD.

*Corresponding author. Tel: +1-631-344-2657; fax: +1-631-344-5260.
E-mail address: rgoldstein@bnl.gov (R. Z. Goldstein).

Abbreviations: ACC, anterior cingulate cortex; BOLD, blood-oxygenation level dependent; cdACC, caudal–dorsal anterior cingulate cortex; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; fMRI, functional magnetic resonance imaging; I-RISA, Impairments in Response Inhibition and Salience Attribution; MRI, magnetic resonance imaging; OFC, orbitofrontal cortex; rACC/mOFC, rostro-ventral anterior cingulate cortex/medial orbitofrontal cortex; ROI, region of interest; SPM, statistical parametric mapping.

A dysregulated function of the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) has been previously suggested to mediate core characteristics in drug addiction; these encompass impairments in response inhibition and salience attribution (I-RISA) where dyscontrol in a drug context and salience attributed to drug cues are hypothesized to be more pronounced than for non-drug-related stimuli (Goldstein and Volkow, 2002). However, to date, neuroimaging evidence for the role of the OFC and ACC in I-RISA in drug addiction has relied mostly on *separate* studies of salience attribution/reward processing [e.g. with a decision-making task (Bechara et al., 2002) or a cocaine-related film (Garavan et al., 2000)] vs. inhibitory control [e.g. with neutral go/no-go tasks (Kaufman et al., 2003)]. Thus, in drug-addicted individuals a *unified* functional magnetic resonance imaging (fMRI) task is yet to be developed to probe the role of the OFC and ACC in processing of salient symptom-related cues during the simultaneous performance of an unrelated and possibly conflicting task. We currently report results of such a single well-validated paradigm (Whalen et al., 1998; Bush et al., 2000), newly modified (using color-word and not counting responses) for the in-depth analysis of cue-related brain–behavioral interrelationships within drug-addicted individuals.

Thus, although closely aligned with the extensive literature in cocaine-addicted individuals on neural processes underlying both cocaine-related (i.e. emotional) cue responses (Grant et al., 1996; Childress et al., 1999; Garavan et al., 2000; Kilts et al., 2001; Wexler et al., 2001; Bonson et al., 2002) and inhibitory control (Kaufman et al., 2003; Bolla et al., 2004; Hester and Garavan, 2004), the novelty of the current task is in the combination of both emotional (i.e. non-neutral) and inhibitory control processes within a single task. This dual-task aspect is necessary for testing how the brain reacts to drug-related cues that are irrelevant to the task, but relevant to the subjects' symptomatology (i.e. drug addiction; for a similar approach in other psychopathological disorders see for example Shin et al., 2001). To the authors' best knowledge, this is the first time that a color-word emotional Stroop task is used in the fMRI environment to study context-specific processing (drug vs. matched neutral words) in drug-addicted individuals.

EXPERIMENTAL PROCEDURES

There were 14 subjects with cocaine use disorders (five female; nine African-American, three Caucasian, and two Hispanic), 43.9±5.6 years old with 12.9±2.2 years of education (mean±S.D.), all healthy as determined by physical, neurolog-

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ical and psychiatric evaluations. All subjects were right-handed, had English as first language, and were not color-blind. General intellectual functioning was average (Matrix Reasoning of the Wechsler Abbreviated Scale of Intelligence scaled score=11±4, percentile=57.1±30.0) and reading level was within the lower average range (Wide Range Achievement Test standard score=85±23, percentile=28.9±26.4). All subjects had a diagnosis of Substance Dependence (cocaine, current N=8; partial or full remission N=5) or Abuse (N=1) as determined with the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), Research Version–Patient Edition. Length of last voluntary abstinence from cocaine ranged from 1 to 96 days (median=12 days). All experiments on human subjects were conducted in accordance with the Declaration of Helsinki, http://www.wma.net, and all procedures were carried out with the adequate understanding and written consent of the subjects. Formal approval to conduct the experiments described has been obtained from the local human subjects review board.

The *drug* Stroop fMRI task used 40 drug words matched on length, frequency in the English language (Francis and Kučera, 1982), and part of speech (noun, adjective, adverb, verb) with 40 household-related items. Similarly to the counting Stroop task (Whalen et al., 1998), words were presented via magnetic resonance imaging (MRI)-compatible goggles in a blocked on–off or off–on order, pseudorandomized across all subjects (Supplementary Material, Fig. 1sB). After a long preparation period (2 s, Fig. 1sD), subjects had to press one of four response buttons (yellow, blue, red, green), matching the color of the word they had just read; word color order was pseudorandomized across all sequences. Reaction time and accuracy data were collected across all trials. After completion of the MRI session, all subjects rated all words (Table 1) on valence ("how negative or positive" a word is, from extremely negative to extremely positive, −5 to +5). Just before the fMRI task, training was conducted outside and inside the scanner, both repeated depending on performance (if <70% accuracy, range 2 to 5 training sequences, 3.4±1.1). For training we used the same paradigm but with the letter A; words were not used so as not to create subsequent habituation effects (see Fig. 1sA for task sequence).

MRI scanning was performed on a 4T whole-body MRI scanner (Varian, Palo Alto, CA, USA/Siemens, Berlin, Germany). The blood-oxygenation level dependent (BOLD) responses were measured as a function of time using a T2*-weighted single-shot gradient-echo echo-planar imaging sequence (time of echo/time of repetition=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, four dummy scans). Padding was used to minimize subject motion, which was also monitored on-line (Caparelli et al., 2003); accepted threshold was 1.5 mm displacement and 1.5° rotation. A T1-weighted 3D-MDEFT sequence was used for structural imaging performed after fMRI; all MRI images were inspected to rule out gross morphological brain abnormalities.

All time series were converted into statistical parametric mapping (SPM) format and the SPM2 package (Wellcome Department of Cognitive Neurology, London, UK) was used for subsequent analyses. A six-parameter rigid body transformation (three rotations, three 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 of 3×3×3 mm^3. 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 boxcar 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 1/520 s cutoff frequency as high-pass filter.

Table 1. All drug and neutral words used in the current study

	Stroop		Reading	
	Drug	Neutral	Drug	Neutral
1.	High	Door	Cane	Lawn
2.	Line	Wall	Dice	Soap
3.	Money	Dowel	Chip	Ball
4.	Party	Range	Cloud	Porch
5.	Rock	Desk	Hustle	Hearth
6.	Dust	Roof	Obsession	Shrubbery
7.	Habit	Shelf	Score	Bacon
8.	Smoke	Brush	Lighter	Cushion
9.	Blow	Pail	Chemical	Calendar
10.	Powder	Butter	Straw	Rosemary
11.	Dealer	Cellar	Cotton	Hammer
12.	Bowl	Sign	Base	Crop
13.	Crystal	Ceiling	Loaded	Orange
14.	Crack	Slide	Pipe	Farm
15.	Rush	Foot	Screen	Puzzle
16.	Bags	Meat	Needle	Vessel
17.	Gram	Dill	Mirror	Piano
18.	Ecstasy	Masonry	Milligram	Algorithm
19.	Withdrawal	Workbench	Eightball	Arrowhead
20.	Coke	Vase	Syringe	Fence
21.	Dime	Sink		
22.	User	Palm		
23.	Addiction	Thermostat		
24.	Ounce	Jelly		
25.	Snort	Drill		
26.	Buzzed	Outlet		
27.	Drug	Wick		
28.	Dope	Lard		
29.	Sniff	Broom		
30.	Stoned	Pillow		
31.	Binge	Table		
32.	Nostril	Armoire		
33.	Stimulant	Microwave		
34.	Freebase	Ornament		
35.	Inhale	Radio		
36.	Kilo	Rice		
37.	Overdose	Flashing		
38.	Pusher	Boiler		
39.	Speedball	Dandelion		
40.	Vial	Soot		

The Stroop words were used in the fMRI task and rated for subjective valence immediately after the scan. The Reading words were used just before the fMRI task, to establish reading speeds and prime subjects to read.

To identify significantly activated brain areas, a voxel-by-voxel statistical analysis was applied to the parameter estimates for each subject; here contrasts were created to represent the activations to the drug or neutral conditions as compared with the fixation baseline. We also created differential contrasts directly comparing the drug to the neutral conditions. Maps of BOLD signals were then averaged using a custom program written in IDL (Research Systems, Boulder, CO, USA) and included in a second-level random-effects voxel-by-voxel t-test to inspect task activations, hypoactivations, and differences between the drug and neutral conditions. Simple regression analyses using "absolute" (drug or neutral>or<baseline) or differential (drug>or<neutral) SPM contrasts were then conducted with the respective measures of behavioral performance (performance during each condition or differential scores between conditions). Note that a similar

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approach (subtraction between different task conditions and subsequent correlation analyses to dissociate function of corticolimbic brain regions) was previously reported (e.g. (Iidaka et al., 2001). A threshold of $P<0.05$ family-wise corrected was used for the main task activations/hypoactivations (*t*-tests); $P<0.01$ uncorrected was used for all voxelwise whole brain correlations; minimum cluster size was 50 contiguous voxels, 1.35 cc. Functional regions of interest (ROIs) with a volume of 729 mm^3 (cubic, 27 voxels) were defined at signal maxima and the average BOLD responses (% signal change) calculated for the a priori ROIs [rostro-ventral anterior cingulate cortex/medial orbitofrontal cortex (rACC/mOFC) and caudal–dorsal anterior cingulate cortex (cdACC)]. These ROIs were used to confirm the voxel-based correlations. Clarification of anatomical specificity was corroborated with a co-planar stereotaxic atlas of the human brain (Talairach and Tournoux, 1988).

RESULTS

Post-task valence assignments were more negative for drug as compared with neutral words (-1.3 ± 1.6 vs. 0.72 ± 0.9, paired $t(13)=-3.5$, $P<0.01$; Wilcoxon signed ranks test $Z=-2.8$, $P<0.01$); the more negative these differential ratings (drug minus neutral), the longer was the last voluntary abstinence from cocaine ($r=-0.74$, $P<0.01$). As expected (see Supplementary Material), there were no differences between the drug and neutral words in accuracy (mean±S.D.) (percent correct: 82 ± 10.1 vs. 82 ± 9.8; percent errors of omission: 18 ± 10.1 vs. 17 ± 10). Speed differences between the conditions also did not reach significance (reaction time: 248.1 ± 27.3 ms vs. 253.9 ± 20.1 ms). These results remained unchanged when excluding the one subject with drug abuse instead of drug addiction diagnosis. This subject was therefore not excluded from further analyses.

Random-effects voxelwise *t*-test results revealed that the task produced bilateral activations (task>baseline) in the cdACC, in other frontal regions, parietal lobe (precuneus and inferior parietal lobule), occipital lobe (lingual and fusiform gyrus), and in the caudate, thalamus, and cerebellum. Task hypoactivations (task < baseline) were noted in the rACC extending to the rectal gyrus/medial OFC and ventromedial prefrontal cortex (mOFC), insula, parahippocampal gyrus, and in the cuneus and lingual gyrus, all bilaterally (Fig. 1A–B, Table 2). There were no significant differences in this voxelwise pattern when directly comparing both word conditions for this group of 14 cocaine-addicted individuals (see also Supplementary Material, Fig. 2s). Nevertheless, paired *t*-tests using the ROIs within the rACC/mOFC cluster ($x=-6$, $y=42$, $Z=-9$ and $x=-6$ $y=45$ $z=-3$) revealed significantly larger hypoactivations to the drug (mean$=-1.22$ and -1.24; S.E.M.$=0.42$ and 0.31) than neutral (mean$=-0.62$ and -0.84; S.E.M.$=0.33$ and 0.32) words ($P<0.05$). Indeed, the voxelwise analyses displayed a discernable drug minus neutral difference in this region ($x=-6$, $y=42$, $z=-9$; voxels$=104$; $Z=2.8$); however, this difference did not reach the nominal significance level (cluster-level corrected) in this study sample.

Although the *average* performance accuracy or BOLD responses for drug vs. neutral words did not differ, at the individual level the drug minus neutral *differential* accuracy scores (i.e. drug controlling for neutral context) significantly correlated with the drug minus neutral differential BOLD responses in the rACC/mOFC, both in voxel-based analyses (Fig. 1C, inset, and Table 2C) and ROI analyses (Fig. 1C, linear regression). Note that these correlations were not significant when separately inspecting the drug or neutral responses, consistent with the increases in sensitivity (i.e. subject classification) when comparing a selected task condition to an active control and not a non-active baseline condition that we previously reported (Zhang et al., 2005). Further, the valence ratings for the drug (and not neutral) words (corrected for general intellectual functioning with a regression analysis) significantly correlated with BOLD responses to the drug (and not neutral) words in the cdACC in both voxel-based analyses (Fig. 1D, inset, and Table 2D) and ROI analyses (Fig. 1D, linear regression). These ROI correlations remained significant after controlling (with partial correlations) for numerous possible confounding variables (e.g. demographics and individual characteristics; drug use estimates including severity and duration of use, cigarette smoking, and length of abstinence which correlated with the cdACC, $r=0.56$, $P<0.05$; and task performance including number of training sessions; see Supplementary Material, Fig. 3s, for effect on correlations of urine status and cigarette smoking). Voxelwise correlations with accuracy and valence ratings were also observed for the parahippocampal gyrus (Table 2C) and cerebellum (Table 2D), respectively. These correlations were in the reverse direction to the respective rACC/mOFC and cdACC correlations.

Note that at the significance thresholds that we chose for these analyses, we did not observe similar correlations for reaction time as we did for the accuracy measures. However, we did not expect to find similar correlations between these measures of performance with the BOLD signal. Prior studies from our laboratory, using a different fMRI blocked-design task, showed lack of an association between these performance measures in the cocaine addicted but not control subjects; we attributed these results to impaired perception of inner motivation in drug addiction (Goldstein et al., 2007).

DISCUSSION

Cocaine-addicted individuals rated drug-related words as more negative than matched neutral words, challenging the commonly held belief—but rarely tested as an empirical hypothesis in human studies—that drug cues are positively valued by drug-addicted individuals. These results are consistent with a recent study where alcohol drinkers rated liking ethanol less than apple juice and water (Hobbs et al., 2005) and implicate at the least ambivalence toward drug cues especially for the cocaine-addicted individuals with histories of longer abstinence periods.

Consistent with prior reports (Whalen et al., 1998; Bush et al., 2000), this newly developed color-word drug Stroop fMRI task produced bilateral activations in the cdACC, in other frontal regions, parietal and occipital lobes, and in the caudate, thalamus, and cerebellum. Task hypoactivations were noted bilaterally in the rACC/mOFC,

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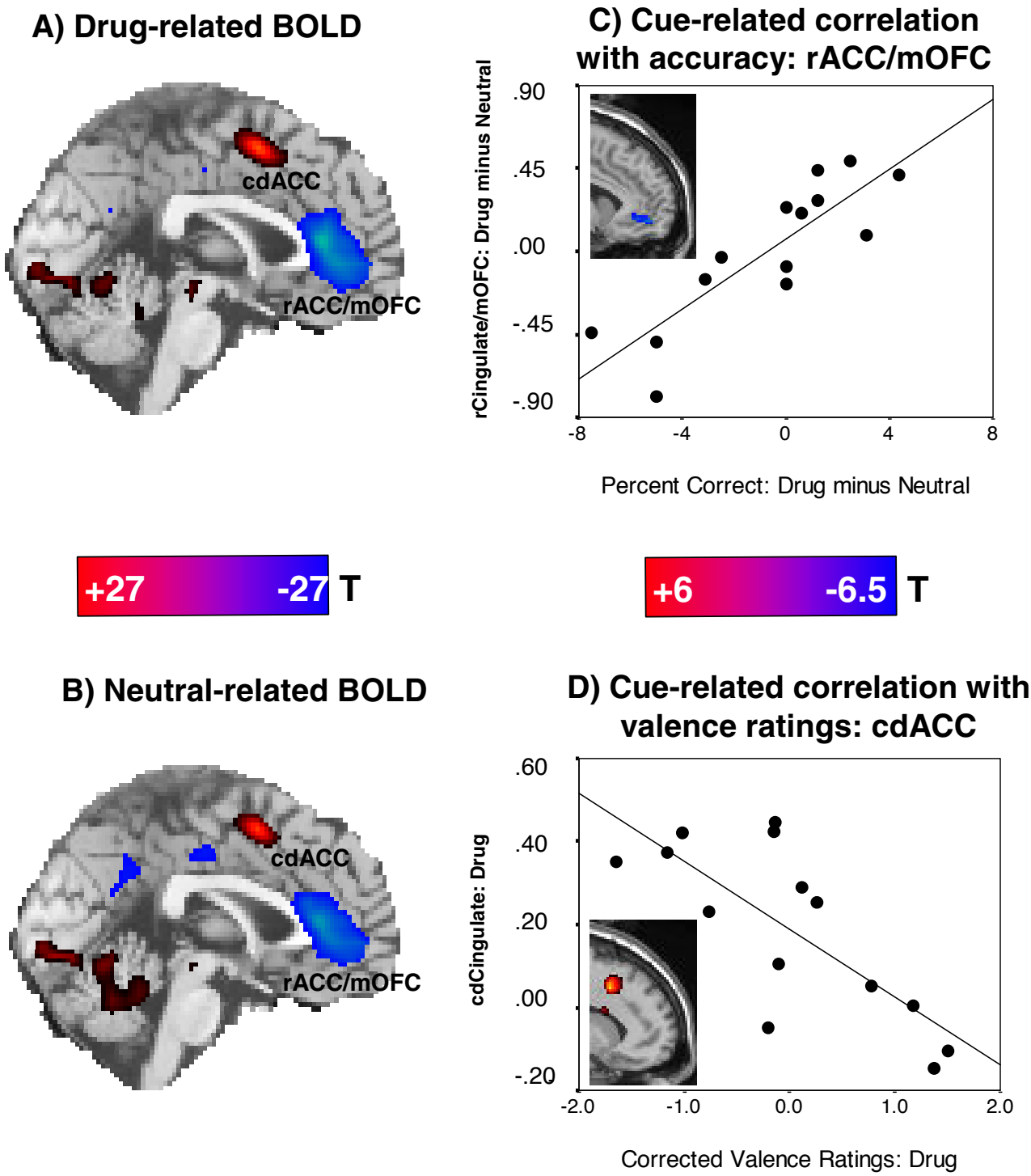

Fig. 1. Drug Stroop task: neural (BOLD) responses and correlations with behavior in 14 cocaine-addicted individuals. (A) A sagittal map is shown for cue-related activations (red: drug words>baseline) and hypoactivations (blue: drug words<baseline) ($P<0.05$ family-wise corrected; color bar represents t-scores≥7.99). (B) A sagittal map is shown for neutral activations (red: neutral words>baseline) and hypoactivations (blue: neutral words<baseline) ($P<0.05$ family-wise corrected; color bar represents t-scores≥7.99); note that there were no significant differences in this pattern when directly comparing the word conditions (drug>neutral or drug<neutral; $P<0.01$ uncorrected) for this sample (see also Supplementary Material, Fig. 2s). (C) The plot shows the association between the BOLD signal change for drug as compared with neutral words (drug>neutral) in the rACC/mOFC as a function of the respective differential performance accuracy and the corresponding linear regression line ($r=0.85$, $P<0.0001$; x=6, y=51, z=−9); the inset statistical map of brain activation depicts the cluster location corresponding to this correlation ($P<0.01$ uncorrected; color bar represents t-scores≥2.68; Table 2C). (D) The plot shows the association between the BOLD signal change for drug words as compared with baseline (drug>baseline) in the cdACC as a function of valence ratings for drug words and the corresponding linear regression line (r=−0.86, $P<0.0001$; x=12, y=15, z=42); the inset statistical map of brain activation depicts the cluster location corresponding to this correlation ($P<0.01$ uncorrected; color bar represents t-scores≥2.68; Table 2D). Minimum cluster size was 50 contiguous voxels (1.35 cc) for all voxel-by-voxel analyses.

Table 2. SPM drug Stroop task results in all 14 cocaine-addicted individuals

	BA	Side	Size	*t*	*P* cluster level	x	y	z
A. Activations								
Caudal/dorsal ACC	32	R	260	25.6	0.000	3	6	51
Inferior frontal gyrus, insula	44, 9	R	707	18.3	0.000	48	3	15
Middle frontal gyrus	10, 46	L	66	13.5	0.000	−33	42	15
Superior frontal gyrus	6	L	61	18.0	0.000	−42	3	42
Parietal lobe	7	R	222	25.0	0.000	21	−63	48
Parietal lobe	40	L	181	15.5	0.000	−39	−36	48
Occipital lobe	18, 19	R	2816	37.6	0.000	24	−69	−9
Cerebellum		R		32.3		21	−54	−21
Caudate		R	75	12.5	0.000	9	0	15
Thalamus		R		9.2		9	−12	18
B. Deactivations								
Rostral ACC/mOFC[a]	10, 11	R	1044	31.7	0.000	6	51	−9
Pregenual ACC	24, 32	R		30.7		3	36	6
Rostral ACC/mOFC[a]	10	R		28.1		3	54	0
Insula	13	R	232	15.4	0.000	33	−30	24
Insula	13	L	2516	27.9	0.000	−33	−18	18
Parahippocampal gyrus	19, 30	L		21.5		−18	−42	−3
Cuneus, lingual	18	L		23.7		−9	−78	24
C. Positive correlations between drug>neutral contrasts with drug>neutral percent correct								
Rostral ACC/mOFC[a]	10, 11	R	210	6.4	0.015	6	51	−9
Pregenual ACC/mOFC[a]	32, 10	R		5.1		12	45	−6
Subgenual ACC	24, 32	L		4.1		−6	24	−3
Rostral ACC/mOFC[a]	10, 11	L		3.8		−6	42	−12
Rostral ACC/mOFC[a]	32, 10	L		3.8		0	39	−9
Negative correlation								
Parahippocampal gyrus	19, 36, 37	L	262	5.4	0.004	−24	−45	−6
D. Negative correlations between drug contrasts with drug ratings[b]								
Caudal/dorsal ACC	32	R	472	6.0	0.000	12	15	42
Caudal/dorsal ACC	6, 8	R		4.4		9	21	51
Caudal/dorsal ACC	32, 24	L		3.8		−15	15	27
Positive correlation								
Cerebellum		R	200	4.3	0.027	21	−63	−24

Local maxima are listed for **A:** task activations (all words>baseline), **B:** hypoactivations (all words<baseline), and for whole brain correlations with **C:** performance accuracy (drug>neutral) and **D:** drug valence ratings (drug>baseline). A threshold of $P<0.05$ family-wise corrected was used for the main task activations/hypoactivations (*t*-tests); $P<0.01$ uncorrected was used for all voxel-wise whole brain correlations; minimum cluster size was 50 contiguous voxels, 1.35 cc. Brodmann's areas (BA), side (hemisphere), size (number of voxels), *t* values, *P* values (cluster level corrected) and Talairach coordinates are listed. All ACC/mOFC regions are shaded.

[a] Including rectal gyrus/medial orbitofrontal cortex and ventromedial prefrontal cortex.

[b] Corrected for general intellectual functioning.

ACC, anterior cingulate cortex; mOFC, medial orbitofrontal cortex.

insula, parahippocampal gyrus, and in the cuneus and lingual gyrus. A trend for larger rACC/mOFC hypoactivations was noted for the drug as compared with the matched neutral words in this sample of 14 cocaine-addicted individuals. This trend remains to be replicated in studies with larger sample sizes.

Further, two correlations with the prefrontal cortex were unique to the task context in this drug-addicted sample: (1) the more the rACC/mOFC hypoactivation specifically to drug vs. neutral words (drug more than neutral), the higher was the number of errors for the drug vs. neutral words (drug more than neutral). Thus, although—by design (see Supplementary Material)—mean performance did not differ between the two task conditions, erroneous performance correlated with hypoactivation in the rACC/mOFC and this effect was context specific (i.e. observed only when subtracting neutral from drug responses) (Fig. 1C); and (2) the more the cdACC activation specifically to the drug (and not neutral) words, the more negative were the valence ratings attributed to the drug (and not neutral) words (Fig. 1D). Note that our subsequent interpretations are therefore based on these significant brain–behavior correlations, not to be attributed to "reverse-inference" (Poldrack, 2006).

The "affective" rACC has been previously implicated in the assessment of the salience of emotional information

and regulation of emotional responses (Bush et al., 2000), and particularly in the suppression of task-irrelevant emotional information (Whalen et al., 1998), consistent with the mOFC role in reward processing (Elliott et al., 2000). The first correlation may therefore be consistent with the effect of emotional context on inhibitory control within the rACC/mOFC (e.g. see Shafritz et al., 2006): it is possible that the less the accuracy (more distraction) for the drug as compared with the neutral words, the greater the required rACC/mOFC suppression of an emotional reaction to the drug words in these cocaine-addicted individuals. This finding (as is the lack of significant accuracy differences between the word conditions) is also consistent with the previously documented ACC error-related hypoactivity in cocaine users and other drug using groups (Kaufman et al., 2003; Forman et al., 2004; London et al., 2005).

The "cognitive" cdACC has been previously implicated in demanding tasks that involve stimulus–response selection in the face of competing streams of information including Stroop-like tasks (Bush et al., 2000), and particularly in conflict resolution (Carter et al., 1998), encompassing emotionally valenced tasks (Davis et al., 2005). The second correlation may therefore be consistent with the demanding cognitive processes that demarcate drug cues as negatively valenced for drug-addicted individuals (e.g. overcoming the emotional load of drug words in order to assign what is perceived to be the subjectively appropriate or socially sanctioned negative valence).

Limitations of the current report include the following: (1) to adapt the emotional color-word Stroop task to fMRI, our design has deliberately removed the opportunity to test whether drug-related stimuli are processed behaviorally in a different way than neutral stimuli (see Supplementary Material for a detailed explanation; in brief, word reading was allowed for a long period and was separated from pressing for its color minimizing the conflict inherent in such a task; further, display of the response key minimized working memory demands). The adaptation to the MRI environment of this *color-word drug Stroop* task, achieved here for the first time, took precedence when designing the current task given the previous consistent documentation of the role for attentional bias to drug-related stimuli in drug-addicted individuals; in these other word or picture color-naming or button pressing behavioral paradigms, accuracy or response latency differences between drug-related and neutral matched stimuli have been reported in abusers of alcohol (Duka and Townshend, 2004) nicotine (Mogg and Bradley, 2002), heroin (Franken et al., 2000), and cocaine (Hester et al., 2006). Nevertheless, the behavioral documentation of an attentional bias using our own task design is warranted; (2) a related concern is the lack of significant differences between the drug and neutral conditions at the BOLD signal level. We postulate that such differences would be significant with larger sample sizes or when including a non-drug-addicted control group; in the latter case we would expect to document a significant condition by group interaction effect on the BOLD signal in the selected ROIs such that differences between the task conditions will be observed only in the drug using and not control group (e.g. larger hypoactivation in the rACC/mOFC to the drug than neutral condition in the drug users, as indeed suggested by preliminary paired *t*-test ROI results in the current study); and (3) use of alternating stimuli (Cox et al., 2001) instead of the current block design may have facilitated our ability to obtain significant behavioral differences between the drug and neutral conditions. This could be tested with further optimizations of the current design (e.g. rendering it event-related or non-verbal).

Overall, using a newly designed color-word drug Stroop fMRI task in 14 individuals with cocaine use disorders, results showed unique (drug-related) brain-behavior associations at the individual level. Thus, the more the cdACC activation and rACC/mOFC hypoactivation, the more negative the valence attributed and the more the errors committed *specifically in the drug context* (controlling for the neutral context), respectively. The significance of these drug-specific multimodal associations is in suggesting that the rACC/mOFC and the cdACC may uniquely contribute to different aspects of drug-related responses (distraction/decreased task accuracy) and intrusive negative *cue-related* thoughts in drug-addicted individuals. Taken together, if replicated in future studies with larger sample sizes, these results may model the on-line experience of drug-addicted individuals when facing drug cues where, despite considerable amount of cognitive effort (modulated by cdACC), unregulated emotional reactions to these salient cues are paramount and are not successfully suppressed (modulated by rACC/mOFC). The effect on results of severity and duration of drug use, and application to populations with other drug use disorders, remain to be accomplished. Prospective studies also need to explore the relevance of these findings to the progression of drug addiction and prediction of relapse [see for example use of fMRI during a decision-making task to predict relapse in methamphetamine dependent subjects (Paulus et al., 2005)].

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APPENDIX

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi: 10.1016/j.neuroscience.2006.11.024.

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