

Original Investigation

Functional, Structural, and Emotional Correlates of Impaired Insight in Cocaine Addiction

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IMPORTANCE Individuals with cocaine use disorder (CUD) have difficulty monitoring ongoing behavior, possibly stemming from dysfunction of brain regions mediating insight and self-awareness.

OBJECTIVE To investigate the neural correlates of impaired insight in addiction using a combined functional magnetic resonance imaging and voxel-based morphometry approach.


DESIGN, SETTING, AND PARTICIPANTS This multimodal imaging study was performed at the Clinical Research Center at Brookhaven National Laboratory. The study included 33 CUD cases and 20 healthy controls.

MAIN OUTCOMES AND MEASURES Functional magnetic resonance imaging, voxel-based morphometry, Levels of Emotional Awareness Scale, and drug use variables.

RESULTS Compared with the other 2 study groups, the impaired insight CUD group had lower error-induced rostral anterior cingulate cortex (rACC) activity as associated with more frequent cocaine use, less gray matter within the rACC, and lower Levels of Emotional Awareness Scale scores.

CONCLUSIONS AND RELEVANCE These results point to rACC functional and structural abnormalities and diminished emotional awareness in a subpopulation of CUD cases characterized by impaired insight. Because the rACC has been implicated in appraising the affective and motivational significance of errors and other types of self-referential processing, functional and structural abnormalities in this region could result in lessened concern (frequently ascribed to minimization and denial) about behavioral outcomes that could potentially culminate in increased drug use. Treatments that target this CUD subgroup could focus on enhancing the salience of errors (eg, lapses).

JAMA Psychiatry. 2014;71(1):61-70. doi:10.1001/jamapsychiatry.2013.2833
Published online November 20, 2013.

 Supplemental content at
jamapsychiatry.com

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Drug-addicted individuals often take drugs despite conscious, well-intentioned plans to abstain. Although this practice is often viewed as a deficiency in will power, we recently suggested that a core symptom of drug addiction is dysfunction of brain regions that underlie insight and self-awareness.¹ Because impaired insight is marked by reduced sensitivity to negative outcomes, poorer treatment outcome, and lowered treatment adherence across various neuropsychiatric disorders (eg, schizophrenia and neurologic insults),² we reasoned that this deficit could also have important implications for addiction. Discrepancies between self-reports and objective indices of behavior³⁻⁵ and compromised monitoring of ongoing behavior^{6,7} as associated with more severe drug-seeking behavior⁷ provided the preliminary evidence for impaired insight in addiction. We investi-

gated the neural correlates of impaired insight in addiction using a combined functional magnetic resonance imaging (fMRI) and voxel-based morphometry (VBM) approach.

We hypothesized key roles for brain regions underlying self-monitoring, self-awareness, interoception, and error-related processing, especially the anterior cingulate cortex (ACC) and the anterior insula. The ACC is classically implicated in the neural response to errors⁸ and in cognitive control more generally,⁹ subserving functions that include performance monitoring,¹⁰ conflict monitoring,¹¹ error detection,¹² and the prediction of posterror slowing.¹³ Abnormal (especially, hypoactive) ACC activity has been documented on selective attention and inhibitory control tasks in users of various addictive substances.¹⁴ We recently found that ACC deficits extend to emotionally salient tasks in addiction, with indi-

viduals with cocaine use disorder (CUD) showing hypoactivations in the dorsal ACC (dACC) and rostral ACC (rACC) during a drug Stroop task.¹⁵ Of particular relevance, the ACC also participates in consciously mediated behavior. The ACC forms part of a network that is hypoactive during vegetative states, minimally conscious states, seizures, and sleep,¹⁶ and damage to the ventromedial prefrontal cortex (PFC) and adjacent ACC is associated with unawareness of one's social impairment.¹⁷ In cannabis users, dACC (extending into the rACC) hypoactivity was associated with unaware errors on an error awareness task.¹⁸ In further agreement, a study of Alzheimer disease¹⁹ found that patients unaware of their illness-related deficits had reduced activity in the dACC and rACC-PFC region during a go/no-go task. Insula involvement was hypothesized because of its central role in interoception,^{20,21} implicated in conscious drug craving in addicted individuals²²⁻²⁴ and error awareness in health.^{25,26} In one study²⁷ that targeted both regions, insula and ACC error-related activity during a go/no-go task was associated with individual differences in absentmindedness, a concept related to self-monitoring and awareness.

Using a previously developed choice task that assesses self-monitoring of behavior,^{7,28} participants in the current study were grouped by insight. In parallel, participants underwent fMRI while performing an event-related color-word Stroop task.²⁹ Errors on this classic inhibitory control task could have implications for insight because of the need to self-monitor behavior (eg, on error commission); of additional relevance, errors reliably engage the ACC and insula, including during Stroop tasks³⁰⁻³⁵ and other inhibitory control tasks.³⁶⁻⁴¹ During these same scanning sessions, structural MRI was collected. Compared with healthy controls and unimpaired insight CUD (uCUD) cases, we hypothesized that impaired insight CUD (iCUD) cases would show abnormal ACC and insula functional activity during error processing and gray matter integrity (with the latter resting on previous studies⁴²⁻⁴⁵ in which CUD had reduced gray matter volume in the ACC and/or insula) and that these functional and/or structural abnormalities would correlate with increased drug use. We further hypothesized that iCUD would show diminished self-awareness of one's own emotional experiences, assessed with the Levels of Emotional Awareness Scale (LEAS).⁴⁶ Inclusion of the LEAS was important to validate our insight measure; it was also intended to extend the insight concept in addiction beyond compromised behavioral monitoring (eg, error or choice awareness) and into more complex socioemotional and interpersonal scenarios.

Methods

Participants

The Institutional Review Board of Stony Brook University approved this project. Our main sample included 33 CUD cases and 20 controls, all right-handed and native English speakers; all provided written informed consent to participate. A psychiatric interview (see the eAppendix in the Supplement) determined that all CUD cases met *DSM-IV* criteria for current cocaine dependence (n = 28) or cocaine dependence in early

(n = 3) or sustained (n = 2) remission⁴⁷⁻⁴⁹ (Table 1 provides current dependence and remission partitioning; the eAppendix in the Supplement provides current and past comorbidities). A triage urine panel for drugs of abuse was conducted in all participants immediately before all other study procedures (ie, not on a separate screening day) (Table 1 provides cocaine urine status partitioning). Urine test results positive for drugs other than cocaine in CUD cases and positive urine screen results for any drugs in controls were exclusionary (see the eAppendix in the Supplement for additional discussion of this variable and for additional exclusion criteria).

Study Procedures

Insight Assessment

Insight was assessed using established, validated procedures^{7,28} (the eAppendix in the Supplement provides a comprehensive description). In brief, participants performed a probabilistic learning choice task, providing their objective preference for viewing standardized⁵⁰ pleasant (eg, infants), unpleasant (eg, disfigurement), neutral (eg, household objects), and in-house⁵ cocaine images. After the task, participants' most selected picture category (actual choice) was compared with participants' awareness of this choice (self-report of which picture category was chosen most frequently). The CUD cases who showed agreement between their behavior and self-reports formed the uCUD group (n = 18); those showing disagreement between these measures formed the iCUD group (n = 15). All included controls (n = 20) were selected to have intact insight (only 7 controls with completed study procedures had impaired insight, requiring future investigation with larger samples; see the eAppendix in the Supplement for additional discussion of these controls). This task's relevance to insight is in assessing whether CUD cases have explicit knowledge (awareness) about their drug-seeking behavior. Because human instrumental learning (under conditions similar to the current task) is encoded as explicit causal knowledge,⁵¹⁻⁵³ choice on this task is likely goal driven (ie, not governed by habitual, implicit responding) (see the eAppendix in the Supplement for additional discussion).

Inhibitory Control Task

Participants performed 3 runs of an event-related fMRI color-word Stroop task, with instructions to press for the ink color of color-words (red, blue, yellow, and green) printed in their congruent or incongruent colors. Each task run contained 12 incongruent events (totaling 36 such events per participant) and 188 congruent events (totaling 564 such events per participant). Participants committed a mean of 20.4 (range, 1-74), 25.6 (range, 2-119), and 24.0 (range, 1-73) total errors (ie, summed across congruent and incongruent trials) during runs 1, 2, and 3, respectively (combined mean [SD], 23.4 [16.6]). No word or color of an incongruent stimulus mirrored the preceding congruent color-word; otherwise, stimuli were presented randomly. Each word was presented for 1300 milliseconds, which was also the time allotted for response (intertrial interval, 350 milliseconds); participants were not given performance feedback. Remuneration for task completion was \$25 (fixed). This Stroop task version was adapted from a previous

Table 1. Demographic Characteristics and Drug Use of All Study Participants^a

Variable	Between-Group Test	Insight Cocaine Use Disorder Cases ^b		Intact Insight Controls ^b (n = 20)
		Impaired (n = 15)	Intact (n = 18)	
Sex				
Male	$\chi^2 = 0.4$	13	15	18
Female		2	3	2
Race				
African American	$\chi^2 = 1.0$	10	11	15
White		4	5	4
Other ^c		1	2	1
Age, y	$F = 1.9$	44.1 (8.1)	43.0 (8.6)	39.6 (5.5)
Educational level, y	$F = 2.9$	12.2 (1.4)	12.8 (1.5)	13.3 (1.0)
Verbal IQ: Wide Range Achievement Test III scaled score ⁴⁷	$F = 2.4$	96.9 (10.1)	91.9 (13.7)	100.6 (11.7)
Nonverbal IQ: WASI Matrix Reasoning Scale score ⁴⁸	$F = 0.2$	10.2 (6.0)	11.1 (2.3)	10.9 (2.6)
Depression: Beck Depression Inventory II score ⁴⁹	Kruskal-Wallis $H = 23.5^d$	10.5 (6.0) ^e	9.4 (8.5) ^e	1.7 (3.2) ^{f,g}
Socioeconomic status: Hollingshead Index	$F = 1.9$	28.8 (5.3)	35.7 (12.3)	34.7 (10.6)
Cigarette smokers (current or past/nonsmokers)	$\chi^2 = 20.4^d$	11/4 ^e	16/2 ^e	4/16 ^{f,g}
Daily cigarettes (current smokers: n = 9/13/2)	$F = 0.0$	7.4 (2.5)	7.3 (5.7)	7.0 (4.2)
Time since last cigarette smoking (within 4 h/>4 h)	$\chi^2 = 5.4$	5/4	3/10	2/0
Cocaine diagnosis status: current/remission	$\chi^2 = 0.1$	13/2	15/3	...
Cocaine urine status: positive/negative (immediately before fMRI)	$\chi^2 = 3.5$	7/8	3/15	...
Treatment-seeking status: no/yes	$\chi^2 = 3.9$	11/4	7/11	...
Cocaine				
Age at onset, y	$t = 1.7$	29.1 (7.3)	24.7 (7.3)	...
Duration of use, y	$t = 1.8$	11.6 (6.8)	16.5 (8.2)	...
Past month use, d/wk	$z = -2.0$	1.9 (1.9)	0.8 (1.4)	...
Past month use, \$	$t = 0.8$	42.3 (53.1)	28.0 (43.3)	...
Current abstinence, median (range)	$z = -1.8$	4 (0-548)	31 (0-1825)	...
Longest abstinence, median (range)	$z = -1.1$	210 (18-2920)	1003.5 (21-3650)	...
Withdrawal symptoms: CSSA (range, 0-126)	$t = 0.4$	14.9 (10.0)	16.4 (12.0)	...
Severity of Dependence Scale score (range, 0-15)	$t = 0.0$	8.1 (3.3)	8.1 (3.6)	...
Cocaine Craving Questionnaire score (range, 0-45)	$t = 2.9^h$	20.7 (12.2) ^g	10.3 (8.5) ^f	...

Abbreviations: CSSA, Cocaine Selective Severity Assessment Scale; ellipsis, not applicable; fMRI, functional magnetic resonance imaging; WASI, Wechsler Abbreviated Scale of Intelligence.

^a With the exception of cocaine craving, impaired insight and intact insight cases were generally well matched on drug use variables; any factors that did differ among groups (depression, cigarette smoking history, or craving) did not explain our results as described in the eAppendix in the Supplement.

^b Data are presented as frequencies or mean (SD). Ellipses indicate lack of data in controls.

^c Race: other (Hispanic or Asian).

^d $P < .001$.

^e Mean value significantly differs from that of controls.

^f Mean value significantly differs from that of impaired insight cocaine use disorder cases.

^g Mean value significantly differs from that of intact insight cocaine use disorder cases.

^h $P < .05$.

neuroimaging study⁵⁴ and is comprehensively described elsewhere (including a descriptive task schematic).^{30,55} Table 2 gives the behavioral data.

MRI Data Acquisition | The MRI scanning was performed on a 4-T whole-body scanner (Varian/Siemens MRI scanner). The blood oxygenation level-dependent (BOLD) fMRI responses were measured as a function of time using a T2*-weighted, single-shot, gradient-echo planar sequence (echo time, 20 milliseconds; repetition time, 1600 milliseconds; in-plane resolution, 3.125 × 3.125 mm²; slice thickness, 4 mm; gap, 1 mm; typically 33 coronal slices; field of vision, 20 cm; matrix size, 64 × 64; flip angle, 90°; bandwidth with ramp sampling, 200 kHz; 207 time points; and 4 dummy scans to avoid nonequilibrium effects in the fMRI signal). Anatomical images were col-

lected using a T1-weighted 3-dimensional modified driven equilibrium Fourier transform sequence⁵⁷ and a modified T2-weighted hyperecho sequence.⁵⁸

MRI Data Processing | Image processing and analysis were performed with Statistical Parametric Mapping, version 8 (SPM8) (Wellcome Trust Centre for Neuroimaging). Image reconstruction was performed using an iterative phase correction method that produces minimal signal-loss artifacts in echoplanar images.⁵⁹ A 6-parameter rigid body transformation (3 rotations and 3 translations) was used for image realignment and correction of head motion. Criteria for acceptable motion were 2-mm displacement and 2° rotation. The realigned data sets were spatially normalized to the standard Montreal Neurological Institute stereotactic space using a 12-parameter af-

Table 2. Performance on the Color-Word Stroop fMRI Task Across All Study Participants^a

Variable	Mean (SE)			
	F (Between Groups)	Insight Cocaine Use Disorder Cases		Intact Insight Controls (n = 20)
		Impaired (n = 15)	Intact (n = 18)	
Accuracy, % correct				
All trials	1.1	0.74 (0.03)	0.69 (0.04)	0.76 (0.03)
Congruent trials	2.8	0.92 (0.02)	0.87 (0.03)	0.93 (0.01)
Incongruent trials	0.6	0.57 (0.06)	0.51 (0.07)	0.59 (0.05)
Incongruent minus congruent trials	0.1	-0.35 (0.06)	-0.36 (0.06)	-0.33 (0.04)
Reaction time, milliseconds				
All trials	0.1	804.5 (20.2)	795.4 (16.8)	797.6 (16.7)
Congruent trials	0.5	686.4 (20.0)	707.3 (20.4)	685.3 (15.9)
Incongruent trials	0.8	922.6 (25.1)	883.5 (18.5)	909.8 (21.8)
Incongruent minus congruent trials	2.6	236.2 (20.7)	176.3 (19.8)	224.5 (18.7)
Postconflict slowing, milliseconds	0.6	968.1 (34.7)	926.1 (21.2)	938.9 (24.2)
Posterror slowing (all trials), milliseconds	1.5	14.8 (11.7)	57.4 (20.2)	46.3 (16.6)

Abbreviation: fMRI, functional magnetic resonance imaging.

^a Task accuracy, reaction time, postconflict slowing (slowing after an incongruent, correct trial), and posterror slowing (slowing after an error) were computed for all participants (see Supplement for further description). Although no group differences were significant, there was an interesting trend for impaired insight cocaine participants compared with the other groups to show lower posterror slowing ($P < .10$), suggested previously as a measure of error awareness.⁵⁶ Overall, however, these behavioral results suggest that the groups were well matched on task performance and that the MRI group differences described in the Results are not attributable to differences in task-related motivation or interest.

fine transformation⁶⁰ and a voxel size of $3 \times 3 \times 3$ mm. An 8-mm full width at half maximum gaussian kernel spatially smoothed the data.

BOLD-fMRI Analyses | A general linear model,⁶¹ which included 6 motion regressors (3 translations and 3 rotations) and 1 task condition regressor convolved with a canonical hemodynamic response function and a high-pass (cutoff frequency, 1/90 seconds) filter, was used to calculate individual BOLD-fMRI maps. Specifically, our design matrix included 1 regressor collapsed across both error trials (congruent incorrect and incongruent incorrect), leaving both correct trials (congruent correct and incongruent correct) to serve as the active, implicit baseline; this implicit baseline was chosen because the task contained mostly correct events. Thus, the β -weights for this incorrect (error) regressor equated to a contrast functionally equivalent to incorrect greater than “everything else” (insofar as everything else consisted entirely of correct events), reflecting task-related error processing remaining after the variance related to correct events was removed. For analyses pertaining to a second design matrix that modeled the incongruent events, see eFigure 2 in the Supplement. Because error is contrasted with an active baseline (correct) and not a neutral baseline (eg, fixation), BOLD signal values below 0 do not necessarily reflect deactivations.

At the second level, we conducted a whole-brain 1-way analysis of variance (ANOVA) in SPM8. Because our regions of interest (ROIs) were relatively large (ACC and insula) and following the recommendation that broader, more diffuse activations are best detected by lower thresholds,⁶² we specified a height threshold of $P < .005$ voxel level-uncorrected threshold ($T = 2.68$), a common threshold in psychiatric neuroscience research. We then used a Monte Carlo procedure⁶³ (similar to AlphaSim) to identify the number of contiguous voxels necessary for a $P < .05$ cluster-corrected threshold (ie, given our imaging parameters and a height threshold of $T = 2.68$), which was calculated to be 26 contiguous voxels. One-

sample t tests were then conducted on the same first-level contrasts to confirm that the regions that differed between groups were indeed engaged during the task. To focus these latter analyses, results were masked by the respective between-group ANOVA contrasts (for results of unmasked 1-sample t tests across all participants, see eTable 1 and eTable 2 in the Supplement). Nevertheless, to protect against type I error, statistical significance for these 1-sample t tests was set at $P < .05$ family-wise voxel level-corrected threshold. The mean BOLD signals from peaks that met both criteria were extracted as spherical volumes (3-mm radius) to inspect for outliers and for use in correlation analyses (see below). MRICron corroborated anatomical specificity.

Structure

A VBM analysis was conducted with the VBM toolbox (version 8) (C. Gaser, Department of Psychiatry, University of Jena, Jena, Germany; <http://dbm.neuro.uni-jena.de/vbm/>), which combines spatial normalization, tissue segmentation, and bias correction into a unified model. The modified driven-equilibrium Fourier transform scans, which produce especially precise characterization of gray matter tissue,⁶⁴ were first spatially normalized to standard proportional stereotaxic space (voxel size, $1 \times 1 \times 1$ mm) and segmented into gray matter, white matter, and cerebrospinal fluid tissue classes according to a priori tissue probability maps.^{65,66} A hidden Markov random field⁶⁷ maximized segmentation accuracy. Jacobian modulation compensated for the effect of spatial normalization and restored the original absolute gray matter volume in the gray matter segments. Three uCUD cases had unusable structural scans; for these participants, structural scans during a 6-month follow-up session were substituted (note that removing these 3 participants did not change any VBM results). After smoothing the normalized and modulated gray matter segments with a 10-mm³ full width at half maximum gaussian kernel, we estimated a 1-way analysis of covariance, with age and total brain volume included as covariates of no interest.^{42,43,68-71} We first

performed whole-brain analyses, consistent with the functional approach. As an additional test of group differences, we defined spherical ROIs (3-mm radius) at the coordinates from the functional data that were observed for both the between-group ANOVA and 1-sample *t* tests. These firmly a priori ROIs were then analyzed in SPSS statistical software (SPSS Inc).

LEAS Scores

Participants were presented with 20 emotionally charged interpersonal scenarios and answered how each person involved would likely feel. For example, “You and your best friend are in the same line of work. There is a prize given annually to the best performance of the year. The two of you work hard to win the prize. One night the winner is announced: your friend. How would you feel? How would your friend feel?” Scoring followed a validated coding scheme (higher scores equal higher self-awareness of one’s own emotion).⁴⁶ Previously, lower LEAS scores were associated with reduced rACC activity during trauma recall in patients with posttraumatic stress disorder relative to controls who had also experienced trauma.⁷² Because only 15 participants from our main sample had LEAS data (ie, this measure was not yet in place when the fMRI protocol commenced), data from 20 additional participants (who did not complete the fMRI component) were included in the LEAS analyses to maximize sample size. Importantly, the 15 participants overlapping between both protocols did not differ from the rest of the main sample and did not differ from these new 20 participants on any Table 1 demographics (all $P > .05$), suggesting that these 20 new participants were comparable to the main sample. An analysis of covariance tested for between-group differences while controlling for age (ie, one anticipates LEAS scores to increase with age and development⁷³) and verbal IQ (ie, to produce effective written responses, one anticipates LEAS scores to increase with higher verbal IQ⁴⁶). The LEAS scorer was masked to insight and participant grouping.

Correlation Analyses

We first tested for functional-structural correspondence (correlations) among regions that showed parallel between-group differences for both methods. We then tested correlations between functional activations or gray matter (that also first showed between-group differences) with the 12 cocaine use variables from Table 1. Significance for these drug use correlations was set at $P < .01$ to minimize type I error. Because only 15 total participants from our main sample had LEAS data as described above, we were unable to inspect correlations with this measure.

Results

Function

Whole-brain SPM8 analyses revealed iCUD cases to have less error greater than correct activations compared with the other 2 study groups in the rACC (Figure 1A). Although this cluster extended dorsally to include additional ACC subregions (Table 3), a 1-sample *t* test in the iCUD group revealed that this

between-group difference was driven by error greater than correct lower activations in this group specifically in the rACC (ie, not in the entire ACC cluster; note that one peak coordinate overlapped across both analytical approaches [$x = 12, y = 44, z = 13$; Table 3]). No other between-group differences reached significance.

Structure

Although whole-brain between-group differences were non-significant, we extracted 2 ROIs corresponding to the peak rACC functional coordinate that emerged using both the whole-brain between-group ANOVA and 1-sample *t* tests ($x = 12, y = 44, z = 13$; Table 3; extracted on both the ipsilateral and contralateral sides). The iCUD group had reduced gray matter compared with the other study groups in the contralateral rACC ROI (planned comparison: $F_{1,50} = 4.7, P = .04$) (Figure 1C).

LEAS Scores

The iCUD group scored lower on the LEAS (total score) than the other 2 study groups (planned comparison: $F_{1,31} = 4.3, P = .048$) (Figure 1D), suggesting decreased self-awareness of one’s own emotion in the iCUD group.

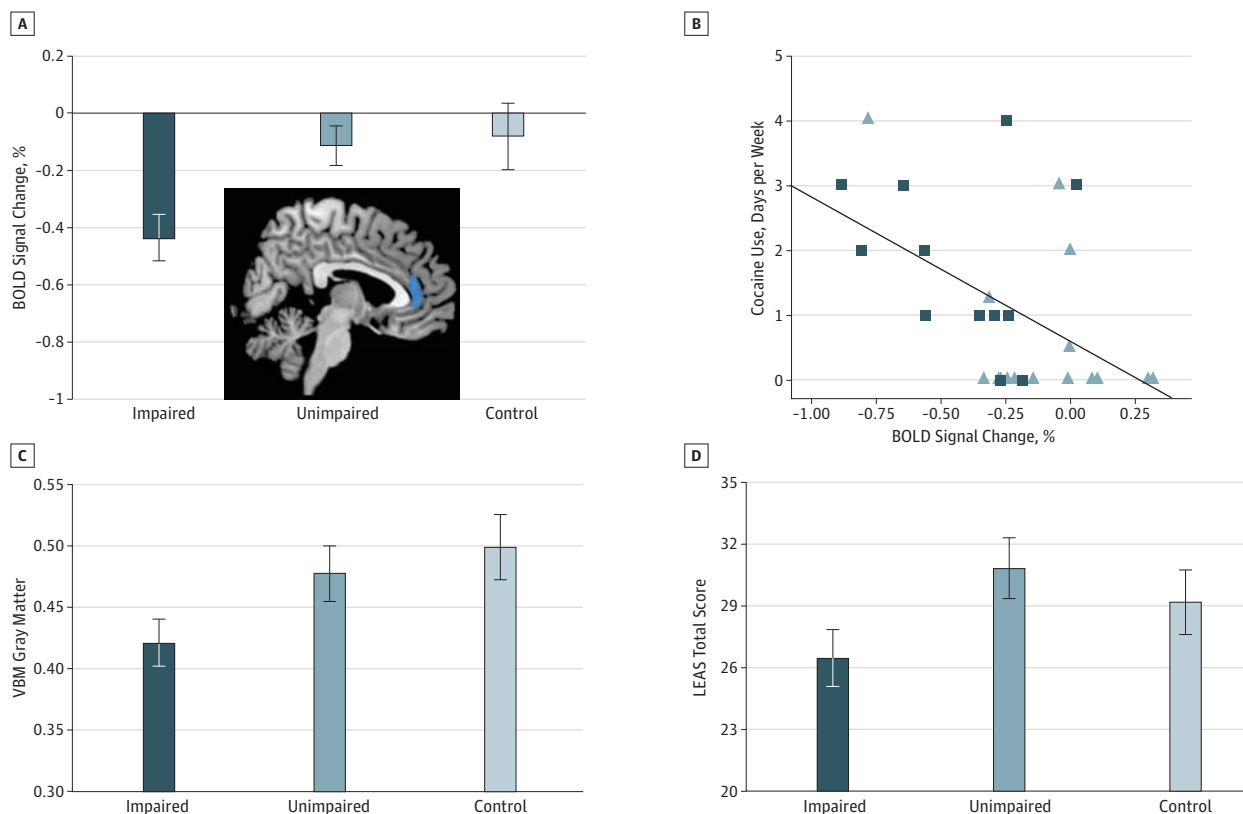
Correlations

The lower the error greater than correct activity in the extracted rACC cluster, the more frequently (days per week in the last 30 days) cocaine was used in all CUD cases (Figure 1B). The other drug use variables did not correlate with rACC activity or structure; structure and function also did not correlate.

Discussion

Our data provide novel evidence that impaired insight is associated with rACC dysfunction in cocaine addiction. Compared with controls and even uCUD cases (both with intact insight), iCUD cases had lowered rACC error greater than correct activity during a classic inhibitory control task (the pattern of response in the uCUD group more closely resembled that of controls) and gray matter volume, effects not attributable to between-group differences in demographic characteristics and drug use (see the eAppendix in the Supplement). Given the task’s active task baseline (correct trials), our functional results indicate that the iCUD group had disproportionately reduced activity to error events; in contrast, the other 2 groups had relative equivalence of these trial types (see eFigure 1 in the Supplement for time-series plots, which provide visual evidence that rACC error-related activity, even when not directly contrasted with correct responses, is decreased in iCUD cases). Interestingly, the rACC (extending into medial PFC) has been previously associated with insight-related compromises in patients with schizophrenia,⁷⁴ cannabis use disorder,¹⁸ and Alzheimer disease¹⁹; notably, only the rACC extending to the medial PFC was implicated in all 3 disorders (Figure 2). Also potentially relevant to insight, this brain area is activated during the experience of negative self-conscious emotions⁷⁵⁻⁷⁷ and during other activities relevant to social cognition (eg, self-knowledge, person perception, and mentalizing^{78,79}).

Figure 1. Brain and Levels of Emotional Awareness Scales Analyses



A, Reduced error greater than correct rostral anterior cingulate cortex (rACC) mean blood oxygenation level-dependent (BOLD) signal change in the 15 impaired insight cocaine use disorder (iCUD) cases compared with the other 2 study groups (18 unimpaired insight cocaine use disorder cases and 20 healthy controls) during the color-word Stroop task (with corresponding image, which for display purposes only was thresholded at $2.4 \leq T \leq 7.0$ and masked by an anatomical ACC region of interest) ($P_{corrected} < .05$ for impaired less than others). B, This reduced error-related rACC activity correlated with more frequent drug

use in the last 30 days in all CUD participants ($r = -0.50, P = .007$). In parallel and compared with the other study groups, impaired iCUD cases had lower (C) voxel-based morphometry (VBM) gray matter volume in the same rACC region and (D) emotional awareness (Levels of Emotional Awareness Scale [LEAS] scores) ($P < .05$ for impaired less than others) for both (C) and (D). Error bars indicate SEs. Note that BOLD signal values below 0 do not necessarily reflect deactivations (because the contrast with error is not with a fixation baseline but rather with an implicit, active baseline of correct trials; see Methods).

Table 3. Color-Word Stroop Task Between-Group Differences During Error^a

Region	BA	Side	Voxels	Peak T	Peak P	x	y	z
Impaired insight less than others								
Rostral anterior cingulate cortex	32, 24, 11	B	231	3.4	<.001	-6 -3 12 12	38 38 44 44	-5 16 25 13
Precentral gyrus	6	R	82	3.0	.002	30	7	52
Controls greater than cocaine use disorder cases								
Inferior								
Parietal lobe	40	R	137	4.2	<.001	30	-46	46
Frontal gyrus: triangularis	45	L	41	3.1	.002	-39 -51	23 23	22 16

Abbreviations: B, bilateral; BA, Brodmann area.

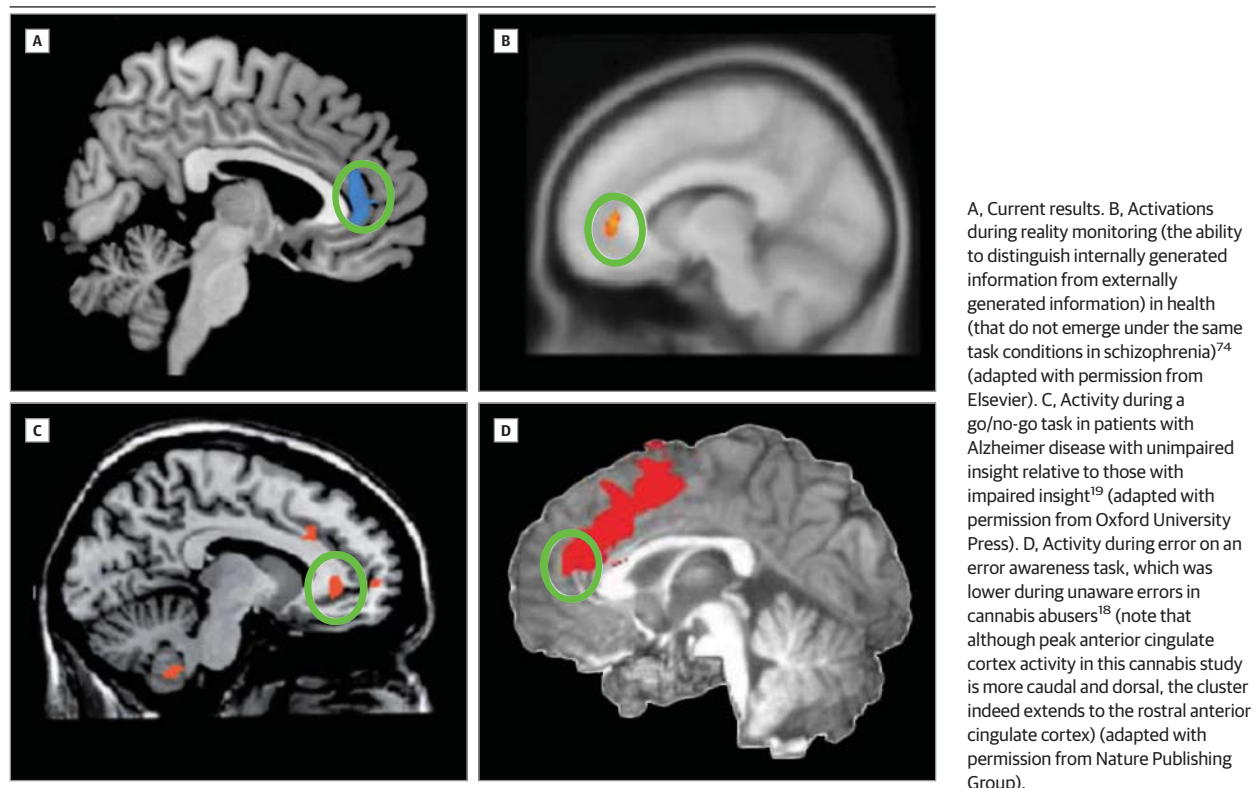
^a Analyses are 1-way analyses of variance, thresholded at $P < .05$ corrected ($P < .005$ voxel uncorrected and 26 voxels); bolded coordinates were also

observed using 1-sample t tests ($P < .05$ for family-wise voxel level-corrected threshold, masked by the respective between-group analysis of variance contrasts).

Another notable finding was a correlation between lower rACC functional activity to error and more frequent cocaine use. Because iCUD and uCUD did not differ on days of current

abstinence, current use frequency, or cocaine urine status (Table 1), this association is unlikely attributable to the residual effects of recent cocaine use (ie, acute drug effects) and

Figure 2. Rostral Anterior Cingulate Cortex Involvement in Neuropsychiatric Illnesses Characterized by Impaired Insight



might instead reflect addiction-related symptoms—an interpretation consistent with previous research. In one relevant study,⁸⁰ less cocaine use per week correlated with greater activation in the rACC during a modified Stroop task; because this study was conducted in CUD participants who had approximately 23 days of cocaine abstinence, results suggest that, similarly to the current study, the rACC–drug use association is more likely marking an addiction-related deficit (not short-term drug use). If future studies determine that iCUD cases (with associated rACC dysfunction) also have worse clinical outcomes as we anticipate, then treatments targeting rACC functioning could have clinical viability. This region showed cue-reactivity reductions to pharmacotherapeutic interventions in cigarette smokers^{81,82} and was suggested through meta-analysis as a marker of treatment response in major depression.⁸³ Conversely, future studies should also uncover the mechanisms of continued drug use in uCUD cases, themselves a highly interesting CUD subgroup insofar as they had preserved rACC function and structure while still meeting criteria for addiction. One potential explanation could be that, although uCUD cases report lower craving overall (Table 1), there is tighter correspondence between their craving and drug-seeking behavior (see eFigure 3 in the Supplement).

In parallel to these rACC results, the dACC and insula had informative null results, which were not attributable to the inability of the current task to activate these regions (see eTable 1 and eTable 2 in the Supplement). Although both the dACC and rACC participate in error-related processing, the dACC is involved in error detection and is closely interconnected with

higher-order frontal brain regions involved in adaptive behavior (eg, lateral PFC), whereas the rACC is involved in generating the (presumably negative) affective response that occurs shortly after error commission and is interconnected with several limbic brain regions (eg, amygdala, hypothalamus, and insula).³⁶ The insula is involved in forming an interoceptive representation of one's subjective feeling state,²⁰ participating in drug craving in addiction^{22–24} and error awareness in health.^{25,26} Null effects in the dACC and the insula could collectively indicate that although iCUD cases can recognize (both cognitively and interoceptively) that an error has occurred, this error might fail to elicit the appropriate emotional significance. This interpretation is bolstered by previous findings indicating that error-induced rACC activity tracks autonomic arousal,³⁵ increases when error salience is amplified (eg, when attached to monetary loss),³⁷ and participates in learning optimal task strategies.⁸⁴ Given that iCUD cases also had reduced LEAS scores, our results could indicate that this compromised salience tagging of negative emotional events may generalize to other emotional contexts (ie, extending beyond task-related errors into more complex socioemotional scenarios of potential relevance to drug-taking behavior). For example, one could speculate that for iCUD cases attempting to remain abstinent, a lapse (error) may not elicit the requisite salience or aversive valence, increasing the probability of subsequent full relapse into frequent drug use—well anticipated from our negative correlation between rACC activity and current cocaine use.

A limitation of this study is the relatively small sample size for VBM, possibly explaining the lack of whole-brain results.

Although in subsequent ROI analyses we accordingly restricted gray matter group comparisons to the region that first showed (corrected) functional effects (rACC), future studies with larger samples should replicate these results. Another limitation is that we cannot determine the precise neurobiological mechanisms underlying the decreased rACC error response; structure, although a plausible mediator,⁷¹ did not directly correlate with function. An alternative possibility could involve abnormalities in anterior frontal cortex cerebral blood flow in CUD cases, as suggested by previous perfusion fMRI studies⁸⁵; because such frontal blood flow abnormalities are seemingly more pronounced in men than women,⁸⁶ future studies should also replicate these effects in samples that include more women. Future studies could also use novel tasks that target functioning of other insight- and self-awareness-related regions not observed in this study (eg, anterior insula²⁰ but also somatosensory cortex⁸⁷).

In conclusion, because the rACC has been implicated in appraising the affective and motivational significance of errors and self-referential processing and given the association of impaired insight with diminished emotional self-awareness

(LEAS), functional and structural abnormalities in this region could be expressed behaviorally as lessened concern regarding behavioral outcomes, potentially resulting in increased drug use. The current research therefore challenges the long-held clinical assumption that impaired insight in addiction is simply a manifestation of minimization and denial; instead, such impaired insight may stem from functional and structural abnormalities of the rACC. Our results extend prior research on compromised error awareness and processing^{6,18,88} and gray matter abnormalities^{42,43,69} in drug addiction, offering the intriguing suggestion that impaired insight may drive such effects. Our results also raise the possibility that a specific CUD subgroup (iCUD) might benefit from therapeutic interventions directed at enhancing the neuropsychological mechanisms underlying insight and self-awareness¹ (eg, self-relevant [tailored] motivational interventions^{89,90}). More broadly, our results can inform other neuropsychiatric disorders (eg, anosognosia, alexithymia, schizophrenia, and mania),⁹¹ similarly characterized by impaired insight and disadvantageous, unwanted, or inappropriate behaviors (eg, leading to violence or self-harm).

ARTICLE INFORMATION

Submitted for Publication: November 9, 2012; final revision received April 22, 2013; accepted June 4, 2013.

Published Online: November 20, 2013.
doi:10.1001/jamapsychiatry.2013.2833.

Author Contributions: Drs Moeller and Goldstein had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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Acquisition of data: Parvaz, Tomasi, Goldstein.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Moeller.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Moeller, Konova, Parvaz.
Obtained funding: Moeller, Goldstein.
Administrative, technical, and material support: Parvaz, Tomasi, Lane, Fort, Goldstein.
Study supervision: Moeller, Tomasi, Goldstein.

Conflict of Interest Disclosures: None report.

Funding/Support: This research was supported by grants 1R01DA023579 (Dr Goldstein), 1F32DA030017-01 (Dr Moeller), and 1F32DA033088 (Dr Parvaz) from the National Institute on Drug Abuse.

Role of the Sponsor: The National Institute on Drug Abuse had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: Michail Misyrlis, MS, Thomas Maloney, PhD, and Patricia A. Woicik, PhD, provided additional administrative, technical, or material support. Nelly Alia-Klein, PhD, performed psychiatric interviews as needed. Gene-Jack Wang, MD, performed medical screens as needed.

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