

The Neural Correlates of Cue-Induced Craving in Cocaine-Dependent Women

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Objective: Drug use reminders are associated with localized changes in brain activity related to intense drug wanting or craving in cocaine-dependent men. While cocaine dependence is prevalent and disabling in women, and certain clinically relevant sex differences exist, there is an absence of knowledge related to the neural correlates of cocaine craving in cocaine-dependent women.

Method: The differential neural response to imagery depicting cocaine use and neutral imagery was defined by using [¹⁵O]H₂O positron emission tomography (PET) imaging in eight cocaine-dependent women. Results were compared with a matched group of eight cocaine-dependent men.

Results: Cocaine-related imagery was associated with relative increases in cocaine craving and increases in regional cerebral blood flow in the superior temporal gyrus, dorsal anterior and posterior cingulate cortex, nucleus accumbens area, and

the central sulcus. Compared with the results of an identical PET study in matched cocaine-dependent men, conditioned cocaine craving in women was associated with less activation of the amygdala, insula, orbitofrontal cortex, and ventral cingulate cortex and greater activation of the central sulcus and widely distributed frontal cortical areas.

Conclusions: These findings suggest the presence of sex differences in the functional anatomy of cue-induced cocaine craving associated with drug dependence. Such differences may reflect sex differences in conditioned associations to cocaine use, in affective and other corollaries of cocaine craving, or in their volitional regulation and may underlie apparent sex differences in the effects of cocaine abstinence and the expectations of treatment outcome. Some support for the need for sex-specific strategies for treatment of cocaine dependence is also furnished by the findings of this study.

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Women represent one-third of an estimated 720,000 individuals in the United States who used crack cocaine in the year 2000. Among these were 0.1% of women between 15 and 44 years of age (1). Male and female cocaine abusers may differ in clinically important dimensions, since cocaine-dependent women seek drug rehabilitation for different reasons and respond differently to treatment (2–5). Such differences have prompted the suggested need for sex-specific treatments and further suggest sex differences in the neurobiology of cocaine dependence. Modern clinical neuroscience has significantly advanced knowledge related to the neurobiology of cocaine use, dependence, and addiction but has maintained a nearly exclusive focus on male cocaine abusers, largely neglecting the significant prevalence and impact of cocaine abuse and dependence in women. The present study used functional brain imaging to identify the changes in distributed neural activity that link cocaine use reminders to enhanced drug seeking and use behaviors in cocaine-dependent women.

Cocaine dependence represents a chronically relapsing disorder. Intense drug wanting or craving precipitated by drug use reminders or cues is widely recognized as a major precipitant of relapsing drug abuse (6). In vivo functional

neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have identified a functional anatomy of cue-induced drug craving. Cocaine craving provoked by prototypical drug use scenarios or mental imagery of personal drug use results in significant increases in neural activity in circumscribed brain areas in abstinent cocaine-dependent individuals. Such areas of cocaine craving-related activation include prominent limbic and paralimbic brain regions such as the amygdala, anterior cingulate, orbitofrontal cortex, insular cortex, and the nucleus accumbens (7–13). The majority of these imaging studies have focused only on men as subjects, while fewer have examined a mixed-sex sample; none have investigated cocaine craving in an exclusive sample of cocaine-dependent women. Several functional brain imaging studies unrelated to drug craving have, however, compared female and male cocaine-dependent groups and reported significant sex differences. Male, but not female, cocaine-dependent subjects exhibited frontal cortical perfusion abnormalities (14). Relative to men, cocaine-dependent women exhibited less evidence of neuronal damage in frontal cortical gray and white matter by in vivo magnetic resonance

TABLE 1. Demographic and Clinical Characteristics of Female and Male Cocaine-Dependent Subjects Who Underwent PET Imaging to Assess Neural Correlates of Cue-Induced Cocaine Craving

| Characteristic | Female Subjects With Cocaine Dependence (N=8) | | Male Subjects With Cocaine Dependence (N=8) ^a | |
|---|---|-------|--|------|
| | Mean | SD | Mean | SD |
| Age (years) | 41.0 | 4.2 | 30.8 | 1.0 |
| Drug item score from the Addiction Severity Index | 0.24 | 0.12 | 0.26 | 0.08 |
| Duration of cocaine abstinence (days) | 7.1 | 4.7 | 6.4 | 3.9 |
| Craving frequency ^b | 3.8 | 2.0 | 7.2 | 7.7 |
| Questionnaire for Mental Imagery score ^c | 61 | 27 | 61 | 18 |
| Craving response ^d | 4.8 | 2.9 | 6.4 | 3.1 |
| | N | % | N | % |
| Handedness | | | | |
| Right | 8 | 100.0 | 7 | 87.5 |
| Left | 0 | 0.0 | 1 | 12.5 |

^a Data for five of eight subjects from Kilts et al. (11).

^b Daily frequency of experienced cocaine craving in the 7 days preceding study entry.

^c Measure of ability to create mental images.

^d Intensity of urge to use cocaine rated by subject on an 11-point Likert scale; higher scores indicate greater craving.

spectroscopy (15). Together, these studies suggest that women may have less frontal abnormalities associated with cocaine dependence than do men.

The primary goal of this study was to extend in vivo functional brain imaging studies of cocaine craving to the understudied, yet prevalent, cohort of female cocaine abusers. A secondary objective was to conduct an initial investigation of possible sex differences in the functional anatomy of cue-induced cocaine craving associated with cocaine dependence. The recent report of significant sex differences in drug craving reactivity to cocaine use cues, with a higher proportion of men reporting craving responses (16), supports the possibility of sex differences in craving-related neural activations. Hypotheses guiding this study included that cocaine-dependent women would exhibit lesser limbic activations to drug cues, perhaps associated with a more robust prefrontal cortical cue response.

Method

Subjects

Eight healthy African American women (age 35–46 years) participated as study volunteers. Subjects fulfilled DSM-IV criteria for cocaine dependence and no other axis I disorders as ascertained by the Structured Clinical Interview for DSM-IV (SCID). Six of eight subjects were currently in an outpatient drug treatment program at the Atlanta Veterans Administration (VA) Medical Center. Study subjects did not fulfill dependence criteria for any other psychoactive substance. Subjects had been abstinent from cocaine use for 1–14 days as determined by self-report and verified by urinalysis. None of the subjects had a prior or current history of other psychiatric or neurological disorders, and all were

devoid of current medical illness or medications. All of the subjects reported the presence of frequent periods of cocaine craving in the prior 30-day period and endorsed the experience of cocaine craving associated with drug use reminders. After thorough description of the study protocol and associated risks, subjects provided written informed consent to participate in an experimental protocol approved by the Emory University Human Investigation and Radiation Safety Committees and the Research and Development Committee of the Atlanta VA Medical Center. The comparison group of eight male cocaine-dependent subjects represented data from five men from a prior PET study of cue-induced cocaine craving (11) and three new subjects to generate female and male patient groups matched for age, ethnicity, mental imagery ability, duration of cocaine abstinence, absence of other axis I or axis II diagnoses, and severity of addiction (Table 1).

Induction of Cocaine Craving

Cue-induced cocaine craving was provoked by script-guided mental imagery of personal acts and sensations associated with cocaine use (11). Scripts were also constructed for a drug-neutral autobiographical experience by modification of a standardized beach or forest scene and a drug-neutral anger experience (11). All scripts were constructed by using a modified version of the Vietnam Stressful Scene Construction Questionnaire (17). Scripts were audiotaped in the first person, present tense, and edited to a standardized length of approximately 60 seconds. A representative cocaine use script is illustrated below.

It's Friday afternoon. I just got some cash and I can hardly wait 'cause I'm on my way to buy some dope. Once I separate the money out, some of it to my kids and some of it to bills, I'll have plenty left over to buy some stuff. Mmmmm...just thinking about gettin' high makes my stomach churn, and as I drive over I start thinking about how good it's going to feel to take that first hit. My heart starts beating faster as I get out of the car and walk up to the door to make the buy. Right away I can tell that its really good stuff—it's hard and yellow, just like butter. Oh, I can hardly wait to get where I am going to smoke it and as I drive over to my friend's place I grit my teeth and clench my jaw in anticipation. I get there just as fast as I can, lock up my car, and knock on the door. Finally someone lets me in, and I tell 'em to get their stem. I can feel myself breathing faster as I put the rock on the stem and I feel hot all over. With my eyes wide open I take my lighter out of my pocket, put it to the stem, and get ready to take that first, good blast.

PET Image Acquisition

State-related regional cerebral blood flow (rCBF) was determined with the ECAT 951 PET scanner (Siemens, Knoxville, Tenn.) following the bolus intravenous administration of 45 mCi of [¹⁵O]H₂O. Each participant was scanned eight times in a single imaging session, twice for each of four conditions: rest (eyes closed and ears unoccluded), neutral imagery script presentation, anger imagery script presentation, and cocaine use imagery script presentation (11). A fixed order of condition presentation was used. Scripts were presented binaurally via earphones with instructions to listen to the script and then mentally reenact the scene described. [¹⁵O]H₂O administration was coincident with the end of each script, and 90-second single frame PET studies were initiated by the detection of head radioactivity. Following offset of the scanner, state changes induced by script-guided mental imagery were self-rated using 11-point Likert scales with 0 corresponding to "none, not at all" and 10 corresponding to "a great deal" (11). Subjects rated the urge to use cocaine, vividness

TABLE 2. Location of rCBF Changes Associated With Cue-Induced Cocaine Craving Versus Neutral Imagery in Eight Female and Eight Male Subjects With Cocaine Dependence

| Group rCBF Change and Region | Brodmann's | | Number of Voxels | Talairach Coordinates ^a | | |
|--|------------|---------|------------------|------------------------------------|-----|-----|
| | Area | Voxel t | | x | y | z |
| Relative increase in female subjects (cocaine use imagery > neutral imagery) | | | | | | |
| Precentral gyrus | 4 | 4.25 | 120 | 57 | -9 | 54 |
| Superior temporal gyrus | 38 | 3.56 | 56 | -48 | -9 | -16 |
| | | 3.21 | 46 | -34 | 9 | -24 |
| Postcentral gyrus | 1, 2 | 3.45 | 78 | -34 | -24 | 31 |
| Dorsal anterior cingulate cortex | | 3.41 | 119 | 8 | 18 | 45 |
| Posterior cingulate gyrus | 31 | 2.98 | 29 | 2 | -31 | 35 |
| Superior temporal gyrus | 41 | 2.96 | 14 | 48 | -31 | 11 |
| Postcentral gyrus | 4 | 2.79 | 8 | 18 | -32 | 62 |
| Nucleus accumbens area | | 2.75 | 5 | 12 | 11 | -4 |
| Relative increase in male subjects (cocaine use imagery > neutral imagery) | | | | | | |
| Amygdala | | 5.23 | 367 | 22 | -8 | -10 |
| Nucleus accumbens area | | 3.11 | 11 | 6 | 7 | -10 |
| Inferior frontal gyrus | 47 | 4.48 | 284 | -34 | 22 | -16 |
| Caudate nucleus | | 3.71 | 84 | -4 | 8 | 5 |
| Periamygdaloid cortex | | 3.49 | 118 | -24 | 4 | -30 |
| Anterior cingulate cortex | 24 | 3.44 | 52 | 2 | 37 | 7 |
| Anterior insula | | 3.27 | 73 | -40 | 18 | 5 |
| Insula | | 3.22 | 77 | -32 | -5 | 11 |
| Amygdala | | 3.19 | 46 | -20 | -1 | -10 |
| Relative decrease in female subjects (neutral imagery > cocaine use imagery) | | | | | | |
| Fusiform gyrus | 19 | 3.59 | 219 | -28 | -59 | -9 |
| Cerebellum/parahippocampal gyrus | | | 204 | 12 | -47 | -8 |
| Cerebellum | | 3.37 | 123 | -22 | -34 | -17 |
| Cuneus | 17 | 3.17 | 217 | 20 | -89 | 8 |
| Amygdala | | 3.06 | 14 | 18 | -6 | -10 |
| Middle occipital gyrus | 39 | 3.02 | 66 | 40 | -64 | 7 |
| Relative decrease in male subjects (neutral imagery > cocaine use imagery) | | | | | | |
| Precuneus | 7 | 3.22 | 151 | -28 | -72 | 37 |
| Angular gyrus | 39 | 2.96 | 35 | 42 | -64 | 33 |
| Middle frontal gyrus | 8 | 2.94 | 16 | 22 | 31 | 39 |
| Precentral gyrus | 6 | 2.88 | 9 | 59 | -1 | 22 |

^a Distance (in millimeters) from the midsagittal plane (x coordinates, negative values refer to effects in the left hemisphere), anterior/posterior to the anterior commissure (y coordinates), and superior/inferior to the anterior/posterior commissure plane (z coordinates).

of the mental image, and their feelings of anger, sadness, happiness, and sense of being "high."

PET Image Processing and Analysis

PET image postprocessing and statistical analysis were conducted by using statistical parametric mapping (SPM 99) (Wellcome Department of Cognitive Neurology, <http://www.fil.ion.ucl.ac.uk/spm>). Images for each subject were aligned to the first scan acquired, and a mean image for each subject was then spatially normalized to a reference standard centered in Talairach space (18). The normalization parameters were applied to the individual scans, and the scans were smoothed by Gaussian filtering to a final isotropic resolution of 9 mm full width at half maximum. Task-related activations were identified by the use of a general linear model (19) to calculate difference images reflecting the relative changes in rCBF between the conditions or within conditions between the sexes. Statistically significant task-related activations exceeded a voxel intensity threshold of $p < 0.005$ (uncorrected for multiple comparisons) and a cluster threshold of five contiguous voxels.

Results

Subjective Responses to Cocaine Use Imagery

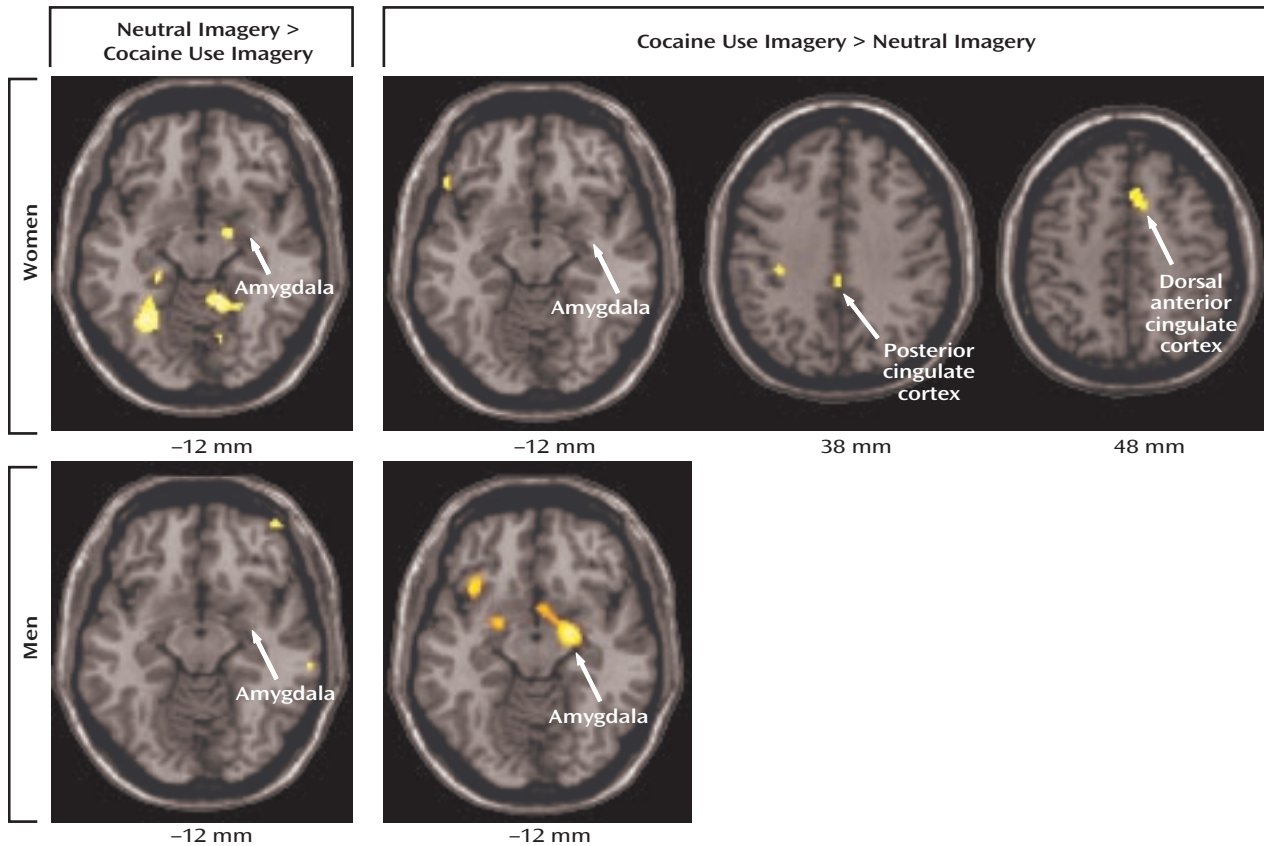
Relative to neutral mental imagery, imagery describing individual cocaine use resulted in significant increases in the urge to use cocaine (mean=4.8, SD=2.9) ($t=4.7$, $df=7$, $p < 0.005$). An increased urge to use cocaine following

script-guided mental imagery of cocaine use was reported by seven of the eight research volunteers. Cocaine use imagery did not produce changes in self-rated feelings of anger, sadness, happiness, or a sense of being "high." Relative to the neutral imagery, imagery describing an individual anger-related experience resulted in significant increases in self-rated anger in eight of eight subjects (mean=5.9, SD=2.5) ($t=5.6$, $df=7$, $p < 0.005$). Anger induction via script-guided imagery was also associated with an increase in the self-rated urge to use cocaine (mean=2.6, SD=1.8) ($t=2.5$, $df=7$, $p < 0.05$) compared with the neutral imagery (mean=0.75, SD=1.6). All script-guided mental images were rated as being highly vivid.

rCBF Response to Cocaine Use Imagery

Relative to images acquired during mental imagery of drug-neutral experiences, cocaine use imagery by cocaine-dependent women was associated with increases in rCBF in widely distributed sites, including the central sulcus, rostral superior temporal gyrus, dorsal anterior and posterior cingulate cortex, and the nucleus accumbens area (Table 2). The same experimental paradigm and contrast of conditions in a matched sample of cocaine-dependent men revealed a cocaine use imagery-related activation of the amygdala and adjoining ventral striatum,

FIGURE 1. rCBF Changes Associated With Cue-Induced Cocaine Craving Versus Neutral Imagery in Eight Female and Eight Male Subjects With Cocaine Dependence^a



^a Values at the bottom of the images refer to the inferior/superior distance from the commissural line.

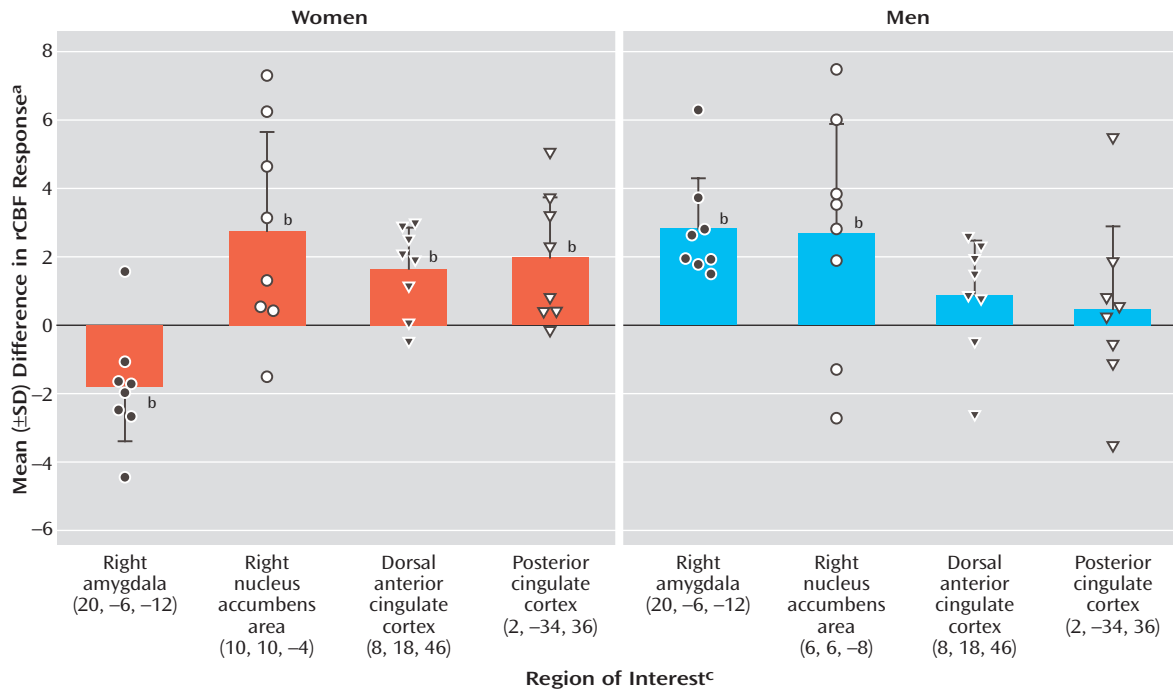
dorsal striatum, and paralimbic cortex (ventral anterior cingulate cortex, insula, orbitofrontal cortex) (Figure 1, Table 2). For the female subjects, the reverse contrast of these mental imagery conditions indicated cocaine cue-related decreases in rCBF in visual areas including the fusiform gyrus and occipital cortex, the right amygdala (Figure 2), and an area extending from the cerebellum into the adjoining right parahippocampal gyrus (Table 2). Relative to anger imagery, cocaine use imagery was associated with increased rCBF in the right insula, dorsal anterior and posterior cingulate cortex, right nucleus accumbens area, left putamen, pons, and cerebellum (Table 3).

A voxel-wise analysis of group effects for the contrast of cocaine use imagery and drug-neutral imagery indicated a greater activation ($p < 0.005$, uncorrected, activation ≥ 5 voxels) in cocaine-dependent men versus women in the right amygdala ($x=20, y=-6, z=-10$ mm) (Figure 3), left inferior frontal gyrus (Brodmann's area 47; $x=-34, y=25, z=-15$ mm), left insula ($x=-34, y=-3, z=9$ mm), right postcentral gyrus (Brodmann's area 2; $x=46, y=-20, z=-25$ mm), left lingual gyrus (Brodmann's area 19; $x=-30, y=-59, z=-5$ mm), and left caudate nucleus ($x=-4, y=6, z=7$ mm). Cocaine-dependent women, compared with men, exhibited a greater activation ($p < 0.005$, uncorrected, activation ≥ 5 voxels) to cocaine cues in the right precentral gyrus (Brodmann's area 6; $x=57, y=-3, z=22$ mm), left inferior frontal gyrus (Brodmann's area 44; $x=-42, y=3, z=26$ mm), middle frontal gyrus (Brodmann's area 9; $x=-30, y=29, z=34$ mm), medial frontal gyrus (Brodmann's area 6; $x=-18, y=12, z=44$ mm), and posterior cingulate gyrus (Brodmann's area 31; $x=2, y=-23, z=40$ mm).

Discussion

The results of this PET neuroactivation analysis suggest that cue-induced cocaine craving in cocaine-dependent women is associated with distributed activations in the central sulcus, temporal cortex, dorsal anterior and posterior cingulate cortex, and a right ventral striatal area that includes the nucleus accumbens. These cocaine craving-related activations survived correction for activations related to the use of guided mental imagery for craving induction (drug-neutral imagery condition) as well as activations related to the arousing, affective, and mnemonic corollaries of induced drug craving (anger imagery condition). Possible functional attributes of these cocaine cue-related activations include mental imagery of motor and somatosensory representations of cocaine use associated with precentral and postcentral gyrus activations. The posterior cingulate activation may relate to the retrieval of

FIGURE 2. rCBF Changes Associated With Cue-Induced Cocaine Craving Versus Neutral Imagery in Regions of Interest of Eight Female and Eight Male Subjects With Cocaine Dependence



^a Cocaine use imagery relative to the neutral imagery for a volume of interest comprising a single voxel (nucleus accumbens area) or a sphere with a radius of 5 mm (amygdala, posterior cingulate cortex, and dorsal anterior cingulate cortex). Individual symbols represent the rCBF difference for each subject for a given volume of interest.

^b Significant difference in rCBF between conditions ($p < 0.005$, uncorrected for multiple comparisons).

^c Values in parentheses represent Talairach coordinates.

vivid autobiographical memories (20). Additionally, a parametric [^{15}O]H $_2\text{O}$ PET study of reward value for chocolate implicated the posterior cingulate cortex in the processing of incentive salience, perhaps further encoding the desire to forego a stimulus even though it is deemed pleasurable (21). The cocaine cue-induced activation of the posterior cingulate cortex may thus relate to processes involved in establishing the momentary difference between wanting to use cocaine and the mental representation of liking cocaine. The additional relationship of posterior cingulate activation to mood state changes (22) does not explain its association with cocaine use imagery, since emotions of anger, sadness, and happiness were negligibly affected by cocaine use imagery. The observation that posterior cingulate cortex activation persisted when the cocaine use cue condition was contrasted with the anger cue condition (Table 3) suggests further that it is related to incentive processing rather than to autobiographical memory recall or emotion processing. The rostral superior temporal gyrus is a paralimbic association cortex area involved in multimodal object processing and the analysis of speech-like sounds (23). Its role in cue-induced cocaine craving in cocaine-dependent women is not obvious but may relate to monitoring emotional experiences (24) to the drug use cue.

The nucleus accumbens, a component of the ventral striatum, has been convincingly implicated in the pro-

TABLE 3. Regions of Significant rCBF Increases^a Associated With Cue-Induced Cocaine Craving Versus Anger-Inducing Imagery in Eight Female Subjects With Cocaine Dependence

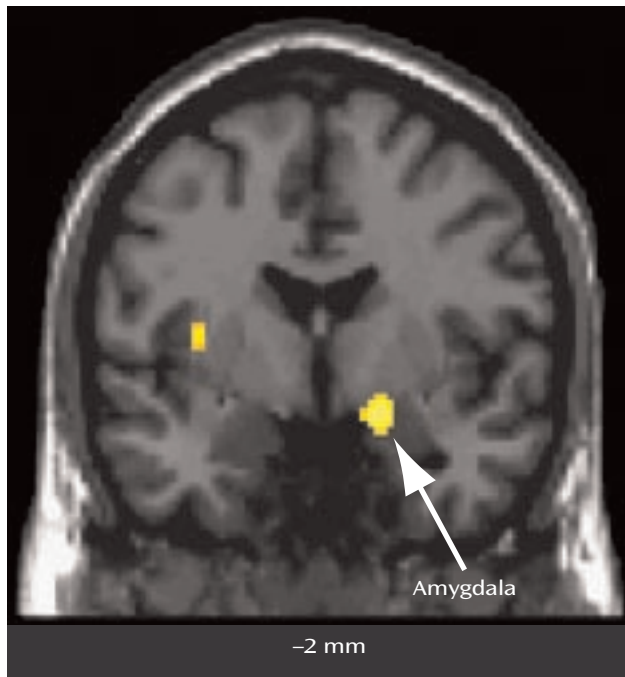
| Region | Brodmann's Area | Voxel t | Number of Voxels | Talairach Coordinates ^b | | |
|----------------------------------|-----------------|---------|------------------|------------------------------------|-----|-----|
| | | | | x | y | z |
| Precentral gyrus | 6 | 3.68 | 56 | 51 | 0 | 30 |
| Insula | | 3.66 | 102 | 44 | 12 | 12 |
| Cerebellum | | 3.64 | 316 | -8 | -70 | -32 |
| Dorsal anterior cingulate cortex | | 3.58 | 70 | -14 | 6 | 37 |
| Putamen | | 3.18 | 61 | -24 | -9 | 13 |
| Posterior cingulate gyrus | 23 | 3.16 | 7 | 16 | -18 | 27 |
| Nucleus accumbens area | | 2.88 | 16 | 14 | 11 | -6 |

^a Change in rCBF associated with cocaine use imagery greater than that associated with anger imagery ($p < 0.005$, uncorrected).

^b Distance (in millimeters) from the midsagittal plane (x coordinates, negative values refer to effects in the left hemisphere), anterior/posterior to the anterior commissure (y coordinates), and superior/inferior to the anterior/posterior commissure plane (z coordinates).

cessing of anticipated and attained rewards (25–27), perhaps particularly when reward probability is unpredictable (28). The cocaine cue-induced activation of the right nucleus accumbens area in this study seems plausibly related to the heightened expectation of cocaine reward when conditioned drug craving increases cocaine-seeking behaviors. It is of interest that cocaine craving related to

FIGURE 3. Greater Right Amygdala Activation Associated With Cue-Induced Cocaine Craving in Eight Male Relative to Eight Female Subjects With Cocaine Dependence^a



^a Voxel $t=5.34$ ($p<0.05$, corrected). The value at the bottom refers to the inferior/superior distance from the commissural line.

cocaine use imagery was also associated with activation of the right nucleus accumbens in a separate PET study of identical design in cocaine-dependent men (11), and a matched male sample (Table 2, Figure 2). Cocaine-induced cocaine craving was also associated with nucleus accumbens activation (29). However, ventral striatal activation to drug cues has not been noted in prior PET and fMRI studies in cocaine-dependent subjects (7–9, 12, 13). This difference in study findings may relate to differences in the nature of the drug cue used to provoke craving or the craving response. Similar to the results of a previous fMRI study of incentive cues in a monetary incentive delay task (30), the cocaine cue used in this study was associated with activation of a dorsal anterior cingulate cortex site. This site contributes to the valuation of incentive cues (31), and may, with the ventral striatum, guide reward-based decision making (32). These findings support the involvement of a neural circuit comprising the nucleus accumbens and dorsal anterior and posterior cingulate cortex in the evaluation of cocaine use cues as behavioral incentives, the process of defining their anticipated reward value biased by the motivation state to attain a cocaine reward, and the selection of choice behaviors.

Cocaine craving provoked by cocaine use imagery was also associated with decreases, relative to the neutral imagery condition, in visual processing areas, the cerebellum, and right amygdala. A recent study of opiate craving induced by script-guided imagery of autobiographical

drug use in opiate-dependent subjects similarly noted a relative decrease in rCBF in the striate and extrastriate cortex (33). The finding of a cocaine cue-induced decrease in amygdala activity in cocaine-dependent women is particularly noteworthy, since a cue-induced activation of the amygdala is commonly observed in male and predominantly male samples of cocaine-dependent subjects (7, 8, 11). The differential effect of sex on amygdala response associated with cue-induced cocaine craving was confirmed in a direct voxel-wise comparison (Figure 3). The interpretation for this sex difference—that drug use imagery represents a strongly conditioned cocaine cue in men but not women—seems unlikely with the comparable craving response in both sexes. An alternative interpretation for the observed sex difference in amygdala response is that the women studied formed distinct conditioned associations with drug use compared with men, leading to distinct conditioned neural responses to cocaine cues. A recently completed PET study of rape-related posttraumatic stress disorder (PTSD) in women indicated that rape trauma imagery was similarly associated with a significant decrease in right amygdala activity (unpublished 2003 study of CD Kiltz et al.). Perhaps the decreased amygdala activity associated here with cocaine use imagery in cocaine-dependent women reflects the association of trauma with past cocaine use. While none of the female subjects fulfilled DSM-IV criteria for PTSD, four of eight subjects reported past major traumas (e.g., rape, childhood physical and sexual abuse) in the PTSD subsection of the SCID. While the presence of a trauma history clearly does not establish the specific association of trauma with past cocaine use, it does perhaps increase the probability of such a learned association. While a preferential relationship between stressors (e.g., prostitution, heading a single-parent household, abusive relationships) and cocaine abuse for women needs to be systematically investigated, it has been proposed that the neurobiology of other psychiatric diagnoses such as major depression is strongly influenced by past trauma experiences (34).

We assessed whether the conditioned decreased amygdala response to cocaine cues in cocaine-dependent women is attributable to feedback from a brain area possibly involved in cognitive control of drug-seeking behavior. The dorsal anterior cingulate cortex or cognitive subdivision of the anterior cingulate cortex has been proposed to subserve executive functions related to error detection (35), monitoring competition between responses (36), and inhibiting goal-inappropriate behavior (37), in addition to decision-making (32) and motor planning (38) related to reward processing. The dorsal anterior cingulate cortex also has been implicated in animal models in the modulation of cocaine cue-induced relapse of drug taking (39). A role of the dorsal anterior cingulate cortex in the response to drug cues in cocaine-dependent women may thus relate to computing conditional probabilities of the rela-

tionship of the drug cue to drug availability, and if low then to dampen the response of areas involved in cue analysis. Some evidence for a negative correlation between the amygdala and dorsal anterior cingulate cortex response to cocaine use imagery was observed ($r=-0.68$, $df=6$, $p<0.07$), suggesting that the latter response reflects an executive control of the cue valuation functions of the amygdala. The use of [^{15}O]H $_2\text{O}$ PET studies precluded the assessment of the relative time course of the amygdala and dorsal anterior cingulate cortex responses, a relationship perhaps revealing of a regulatory role of the dorsal anterior cingulate cortex.

A secondary objective of this study was to compare in cocaine-dependent women and men the location of neural activations related to cue-induced cocaine craving. The assembled comparison sample of matched cocaine-dependent men indicated cocaine craving-related activations in a network of limbic, paralimbic, and striatal areas. Common craving-related activations for the female and male subjects were observed and included the right nucleus accumbens area, dorsal anterior cingulate cortex, and left superior temporal gyrus. These common activations suggest that both sexes process cocaine use memories as incentive cues guiding reward-based decision making (32). Observed sex differences suggest, however, that the neural correlates of cue-induced cocaine craving associated with cocaine dependence differ between men and women. As discussed, cocaine-dependent men, but not women, exhibited bilateral amygdala activation in response to the mental reenactment of cocaine use. Men, but not women, also exhibited craving-related paralimbic activations in the insula, ventral anterior cingulate, and orbital frontal cortex. The lack of paralimbic activations associated with conditioned craving responses in cocaine-dependent women may be reflective of the lack of amygdala activation to cocaine cues, since the amygdala has extensive reciprocal connections with the paralimbic cortex (40). The comparative lack of amygdala and paralimbic brain activations to a cocaine cue in women may underlie observed sex differences in craving reactivity to drug cues (16), or sex differences in its emotional (41) or other corollary states, in cocaine-dependent individuals. Anterior cingulate activation by cocaine cues of a more ventral and anterior region representing its affective subdivision (42, 43) has been consistently reported for male cocaine-dependent subjects (8, 9, 11, 13). This response may however precede the onset of cocaine craving (12) and may rather relate to the regulation of emotional responses (44) to cocaine cues. The direct voxel-wise comparison of female and male subjects provided some evidence for sex differences in the frontal cortical response to cocaine cues, with women having greater responses. This difference may relate to evidence from *in vivo* single photon emission computed tomography (14) and magnetic resonance spectroscopy

(15) studies suggesting lesser frontal cortical abnormalities in cocaine-dependent women.

In addition to a neutral imagery condition, cocaine use imagery was compared with an anger imagery condition to correct for activations related to the arousing, attention-grabbing, and episodic memory properties of cocaine use imagery (11). Retained activations, relative to comparisons to the neutral imagery condition, related to cue-induced cocaine craving included the dorsal anterior and posterior cingulate cortex, nucleus accumbens, and precentral gyrus. These results support the selective role of these brain regions in cue-induced cocaine craving, specifically related to the processing of cocaine cues as incentive stimuli for reward-directed decision making.

Limitations of this study include a relatively small sample size and the inclusion of two female subjects that were not currently in drug treatment programs. Conclusions related to possible sex differences in the neural correlates of cue-induced drug craving associated with cocaine dependence should be considered as highly preliminary. Group differences other than sex (e.g., social development, early and current trauma) undoubtedly contributed to observed differences in neural activations related to cocaine craving. The same craving induction and PET image acquisition paradigm was used for the female and male subjects. However, apparent sex differences also have to be interpreted in light of the fact that the reproducibility of craving-related activations in a same-sex population using the same craving induction protocol has not been determined.

Women represent a significant proportion of cocaine abusers in the United States yet have been essentially ignored as the subject of functional brain imaging studies of the addiction process. If this applied technology represents an important step in defining the neurobiological bases of addiction (45), then this step must be taken with study designs that include female cocaine abusers. The results of this study highlight craving-related and distributed activations along the central sulcus, temporal pole, cingulate cortex, and nucleus accumbens in cocaine-dependent women. Commonalities and potential differences between the sexes in the brain's response to cocaine use reminders may be important in defining the need for, and guiding the development of, sex-specific treatment strategies for minimizing relapse in cocaine-dependent individuals.

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