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Sex Differences in Medial and Lateral Orbitofrontal Cortex Hypoperfusion in Cocaine-Dependent Men and Women

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Abstract

Background— The different clinical trajectories of cocaine-dependent men and women may be a consequence of distinct neurobiological substrates. Hypoperfusion of the orbitofrontal cortex (OFC) has previously been reported in individuals addicted to cocaine and has been posited as a biological mediator of relapse due to impulsivity or impaired decision making.

Objective— This study assessed regional cerebral blood flow (rCBF) between abstinent cocaine-dependent men and women and sex-matched healthy controls.

Methods— Cocaine-dependent subjects were abstinent from cocaine for 11 to 28 days and had no other major mental health or substance use disorders. rCBF was assessed with single photon emission computed tomography after administration of a placebo saline infusion. A resting scan was also obtained in a subset of cocaine-dependent and control men.

Results— In the 35 cocaine-dependent and 37 healthy control subjects examined, a sex-by-group effect was observed for the left lateral ($P = 0.001$), right lateral ($P = 0.002$), and medial ($P < 0.02$) OFC. Cocaine-dependent men demonstrated significantly lower right and left lateral, but not medial, OFC rCBF compared with sex-matched healthy controls after placebo infusion ($P \leq 0.001$). Similar bilateral OFC decreases were observed in male cocaine-dependent subjects at rest. In contrast, cocaine-dependent women showed lower rCBF in the medial, but not lateral, OFC relative to sex-matched healthy controls after placebo infusion ($P < 0.01$). Male cocaine-dependent subjects also showed decreased rCBF ($P < 0.01$) in the bilateral anterolateral temporal cortex and anterior cingulate, whereas decreased rCBF was observed in female cocaine-dependent subjects in the bilateral superior frontal gyri. Large and diffuse areas of increased rCBF were observed after placebo infusion in cocaine-dependent men, but not in women, relative to sex-matched healthy controls.

Conclusions— rCBF appears to be reduced in the bilateral OFC in cocaine-dependent men and in the medial OFC in cocaine-dependent women. Sex differences in the medial and lateral OFC rCBF may be relevant to understanding relapse characteristics differentiating men and women addicted to cocaine.

Keywords

cocaine-related disorders; female; gender; orbitofrontal cortex; single-photon emission-computed tomography

INTRODUCTION

Epidemiologic, etiologic, and clinical differences have been observed between men and women suffering from cocaine addiction. Women are less likely to be diagnosed with cocaine use disorders¹ and tend to initiate use of cocaine at an older age than do men.^{2,3} Women dependent on cocaine express more craving when exposed to cocaine cues,^{4,5} and experience a heightened vulnerability to the physical, psychiatric, and social consequences of substance use.⁶ In light of the growing literature demonstrating discrete differences in the brains of men and women, neurobiological substrates may underlie the different clinical trajectories of men and women with addictive disorders.^{7,8} In nonaddicted subjects, for example, investigators have reported sex differences in brain structure,⁹ basal measures of brain functioning,^{10,11} and functional measures of neural responding.¹² Several studies have now documented basal neural differences in cocaine-dependent men and women, including a relative absence of cerebral perfusion defects,¹³ less frontal cortex neuronal loss,¹⁴ and better white-matter blood flow¹⁵ in women relative to men. Women dependent on cocaine also differ from similarly dependent men in their neural response to cue-induced craving¹⁶ and stress.¹⁷

One of the most consistent findings in substance use disorders, and particularly in cocaine-dependent individuals, is reduced activity of the orbitofrontal cortex (OFC) in the addicted population.^{18–20} The OFC assesses the motivational value of prospective rewards, assuring that stimuli most advantageous to survival are chosen and that stimuli most detrimental to survival are avoided. Persons with damaged cortex in the region of the OFC tend to make both rapid and irresponsible decisions, although memory, learning, language, and attention are preserved. In the presence of such lesions, established behaviors are not altered in response to a reversal of reward contingencies²¹ and decision making does not appropriately reflect long-term consequences.²²

Volkow et al^{23–25} have reported that men addicted to cocaine, methamphetamine, or alcohol exhibit decreased energy utilization in the OFC, suggesting that the heightened impulsivity and impaired decision making observed in the addicted person may be a consequence of attenuated OFC activity.^{18–20} Alterations in OFC energy utilization or regional cerebral blood flow (rCBF) have also been reported in individuals with substance use disorders during decision-making tasks.^{26,27} Consistent with Volkow et al,²⁴ we have observed a decrease in right and left lateral OFC rCBF after saline infusion in 10 cocaine-dependent men relative to sex-matched healthy controls.²⁸ Lower medial^{29,30} and right lateral³⁰ OFC gray-matter tissue density has also been observed in cocaine-dependent individuals relative to healthy controls. However, other investigators have not reported a similar perfusion deficit in this addicted population.^{31,32} Because decreased perfusion of the OFC is frequently cited as the biological underpinning of the impulsiveness and impaired decision making ubiquitous in addicted individuals, confirmation of this finding is essential.

In a previous study using single photon emission computed tomography (SPECT) and t-image analytic techniques, we reported that the lateral OFC deficits observed in cocaine-dependent male subjects²⁸ did not extend to the female subjects.³³ Because the presence or absence of OFC deficits in female cocaine-dependent subjects may have important clinical implications, we further assessed potential sex differences in OFC rCBF in cocaine-

dependent subjects by directly comparing the OFC rCBF response after saline infusion in an expanded pool of male and female cocaine-only addicted subjects and sex- and age-similar healthy controls using statistical parametric mapping (SPM). Our saline infusion data were derived from a single-blind study designed to compare procaine-induced rCBF changes to placebo (saline). As procaine can be anxiogenic, we further considered that the attenuated OFC rCBF after saline infusion in our previous report of male subjects might have reflected group differences in the anticipation of a possible procaine administration. A third additional SPECT scan was therefore also obtained in a subset of male cocaine-dependent and control subjects while at rest.

SUBJECTS AND METHODS

Subjects

Twenty-eight cocaine-dependent men, 10 cocaine-dependent women, 18 healthy male controls, and 19 healthy female controls were studied. Three cocaine-dependent men were excluded owing to methodologic problems during scanning. Subjects were 24 to 45 years old (per study criteria), and underwent a medical history and physical examination, the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* Structured Clinical Interview,³⁴ clinical laboratory tests, urine drug screen, electrocardiogram, and clinical magnetic resonance imaging (MRI). Lifetime cocaine and other substance use history was obtained from cocaine-dependent subjects using the Timeline Follow-Back interview.³⁵ After complete description of the study to the subjects, written informed consent was obtained. Subjects were financially compensated for their participation. Approval for the study was obtained from the institutional review board of the University of Texas Southwestern Medical Center and the VA North Texas Health Care System, both in Dallas, Texas.

Cocaine-dependent subjects were recruited from persons requesting treatment for cocaine dependence in Dallas, Texas, at the VA Medical Center, Homeward Bound, Inc., and The Salvation Army. Addicted subjects were hospitalized as soon as possible after their last reported use of cocaine and remained in a structured residential unit until the study was completed. Exclusion criteria included present use of any central nervous system (CNS) active medications; a lifetime history for affective, anxiety, or schizophrenic disorder or organic brain syndrome experienced before the onset of a substance abuse diagnosis or after a period of at least 3 months' abstinence; a substance use disorder (other than cocaine or nicotine) within the previous 12 months; or a lifetime history of withdrawal from alcohol, sedative-hypnotics, or opioids. All women were premenopausal, and a negative pregnancy test was obtained in all female subjects before SPECT scanning.

Exclusion criteria for healthy controls included the medical criteria as noted for the cocaine-dependent subjects, as well as a lifetime history of any other *DSM-IV* Axis I disorder (except nicotine or caffeine abuse or dependence). Healthy controls with a first-degree relative with an Axis I disorder or ≥ 2 second-degree relatives with a substance use disorder were also excluded.

Study Sessions

Study sessions were held at the Nuclear Medicine Center at the University of Texas Southwestern Medical Center. Cocaine-dependent men and women were both studied at a mean time point of 3 weeks' abstinence (range, 11–28 days) at the time of the saline study. Saline administration was conducted as part of a study of the effects of procaine on rCBF. Every subject received both a saline and a procaine infusion. Saline administration was performed at ~12:00 PM and procaine was administered 48 hours later.²⁸ Due to the strong

subjective response to procaine, a fixed-order, single-blind design was employed, with saline always administered on the first study day. (The findings from the procaine scan performed on the second study day are not reported here.) After 30 minutes of rest following IV catheter insertion, a Symptom Checklist 90-R (SCL 90-R)³⁶ or Brief Symptom Inventory (BSI)³⁷ was obtained (basal measure). Two minutes later, saline was administered over 2 minutes followed by 20 mCi of technetium 99m hexamethyl-propyleneamine-oxime (^{99m}Tc-HMPAO) (Nycomed/Amersham, Princeton, New Jersey) over 30 seconds and 10-mL saline flush over 30 seconds. Infusion took place behind a curtain, and subjects were not aware of the exact time of the infusion. Four minutes after completion of the final infusion, the SCL 90-R/BSI was repeated. The SPECT scan was obtained 90 minutes after saline infusion. This perfusion image represents rCBF at the time of radiotracer administration and not at the time of the scan.

The SCL 90-R was used with the first 30 subjects, and the BSI for all subsequent subjects. The BSI uses 53 of the 90 questions in the SCL 90-R, shortening the time of questioning. Both questionnaires assess the same 9 dimensions plus 3 summary measures of symptom severity: positive symptom distress index (PSDI, severity of response); positive symptom total (PST, frequency of response); and global severity index (GSI, severity by frequency of response). To allow the joint analyses of both questionnaires in our study, we extracted the 53 BSI questions from the subjects who received the SCL 90-R. Raw nontransformed scores were used because our time frame of questioning has not been empirically validated.

We considered that the rCBF response after saline infusion could reflect the anticipation of possibly receiving procaine. A third “at rest” study was therefore obtained in a subset of subjects. The paradigm was exactly the same as that described for the saline infusion, except that subjects were informed that no medication would be administered. Fourteen addicted subjects (13 men, 1 woman) and 15 controls (10 men, 5 women) participated in the resting scan. Because only 1 addicted female subject was included in this third scan, only the results for the male subjects are reported. The third scan was obtained 5 to 7 days after the procaine scan in 11 addicted male subjects and 5 male controls. Five of the controls returned for a third scan between 8 and 70 months after their saline scan. Two addicted men were restudied 3 to 4 years after their saline scan when they were readmitted for cocaine use. These 2 men were 5 to 10 weeks abstinent at the time of their resting scan.

SPECT Imaging

SPECT images were acquired with a PRISM 3000S 3-headed SPECT camera (Picker International, Cleveland, Ohio) and using ultra high-resolution fan-beam collimators (reconstructed resolution of 6.5 mm) in a 128 × 128 matrix in 3° increments. 20mCi of ^{99m}Tc-HMPAO was administered for each scan, and total scan duration was 20 minutes. Image reconstruction was performed in the transverse domain using back-projection with a ramp filter. Voxels in reconstructed images were 1.9 mm³. Reconstructed images were smoothed with a fourth-order Butterworth 3-dimensional filter, and attenuation was corrected using a Chang first-order method with ellipse size adjusted for each slice.

Statistical Analysis

Demographic and Clinical Data—Data were analyzed with Statistical Package for the Social Sciences (SPSS) software, version 13.0 (SPSS Inc., Chicago, Illinois). Parametric statistics were used to examine the demographic characteristics of the sample and the substance use metrics of the addicted groups. Nominal data were analyzed via χ^2 crosstabs analysis.

Image Analysis—Image analyses comprised 3 different activities: normalization, coregistration, and subtraction. SPECT images were resliced to 2 mm³ voxels, coregistered to Talairach space,³⁸ and normalized to whole brain counts. Analyses of change in rCBF were measured relative to global cerebral blood flow. Thus, higher rCBF in the control group relative to the addicted group may reflect higher rCBF in the control group, lower rCBF in the addicted group, or some of both. Images were smoothed from their original resolution of 6.5 mm to a final resolution of 10 mm. Areas differing between addicted subjects and controls were overlaid on an MRI model in Talairach space. Voxel-wise analyses of saline-induced effects on rCBF were analyzed using SPM2 (Wellcome Department of Cognitive Neurology, University College, London, England) with a statistical threshold of $P < 0.01$ for voxel z scores and a cluster size no smaller than 50 voxels. Mean relative rCBF in 18 selected clusters was exported to SPSS to examine sex-by-group differences and the regions of interest (ROIs) relationships with subjective measures.

The selected clusters were chosen based on our a priori hypothesis, their relevance to the addictive disorders, and/or their prominence in the SPM analysis. Because of the numerous regions of increased rCBF in the cocaine-dependent men relative to the male controls (see “Results” section), we selected areas for ROI analysis from this comparison based on a concept proposed by Gusnard et al.³⁹ They posit that the “resting” brain is involved in a number of mental processes, including self-referential attention and the awareness of one’s own physiological state and environmental milieu. Based primarily on findings from neuroimaging studies, Gusnard et al suggest these areas of basal activity include the dorsal medial, ventral medial, posterior medial, and posterior lateral cortices. Three of these areas—the posterior cingulate (representing the posterior medial cortex), the mesial OFC (representing the ventral medial cortex), and the right mesial aspect of the superior frontal gyrus and left middle frontal gyrus (representing the dorsal medial cortex)—were observed in our male comparison and therefore selected for ROI analysis. The right caudate was chosen from this comparison because of its significance in the addictive disorders.

Cluster Analysis—To explore sex-by-group (control and cocaine-dependent) differences, cluster boundaries for specific ROIs identified by the SPM comparisons were identified and the mean counts per voxel within each cluster were determined for each subject. Because of the high degree of intercorrelation between several of the selected ROIs (data not shown), a factor analysis with varimax rotation and Kaiser normalization was calculated across these regions with the goal of data reduction. The resultant rCBF factors were summarized by composite regression factors. Items were included with factor loadings of ≥ 0.5 .

rCBF Response to Saline—A 1-way analysis of variance was conducted between the 4 groups (addicted male subjects, male controls, addicted female subjects, female controls) for the 18 identified ROIs. Significance was assessed at a Bonferroni adjusted α of 0.003 (0.05/18). Post hoc paired comparisons were made using the Tukey test, with P values of 0.05 considered significant. An analysis of covariance (ANCOVA) was performed to account for the effects of age.

Subjective Responses to Saline—Nonparametric methods were employed because the BSI data did not meet the assumptions of normality and homoscedasticity. The Mann-Whitney U test of independent samples was employed to assess between-group (ie, addicted male subjects vs male controls) differences on the 9 BSI domains and 3 summary factors. Comparisons were performed for basal and net BSI change (BSI after saline – basal BSI) scores. Within-group (all subjects, males vs females, and sex-by-group) comparisons of BSI scores before and after saline infusion were conducted with the Wilcoxon signed rank test. To control for the type I error rate, significance was assessed at a Bonferroni adjusted α of 0.004 (0.05/12).

Correlational Analysis—A Spearman rank correlation was conducted between the 5 analytically derived factors and 12 BSI scores, using a Bonferroni adjusted α of 0.0008 (0.05/60). Correlations between the 5 ROI factors and 4 measures of drug use history were performed with a Pearson product moment correlation, using a Bonferroni adjusted α of 0.0025 (0.05/20).

RESULTS

Demographic and Clinical Characteristics

The cocaine-dependent men and women in this study were more likely to be African American than were controls (Table I). Addicted men were significantly older than male controls ($t_{41} = 3.60$; $P < 0.001$), although the mean age difference between the 2 groups was only 6 years. Male and female cocaine-dependent subjects revealed no significant differences in recent and lifetime cocaine use, although women reported significantly more “days used” in the 90 days preceding treatment ($P = 0.007$). Lifetime nicotine consumption was greater for cocaine-dependent subjects than for controls. Nicotine use in the female cocaine-dependent group was skewed by 1 woman who reported 90 pack-years of smoking.

rCBF Response to Saline

Male Controls Versus Male Cocaine-Dependent Subjects—The rCBF response after saline infusion was compared between sex-matched cocaine-dependent and control subjects ($P < 0.01$) (Figure 1). Regions of difference are described by cluster size and uncorrected z scores. Cocaine-dependent men showed a decrease in rCBF, relative to male controls, in the right lateral OFC and anterolateral temporal cortex (cluster size = 1337; $z = 5.04$; $P < 0.001$) and left lateral OFC and anterolateral temporal cortex (cluster size = 877; $z = 4.17$; $P < 0.001$) (Figures 1 and 2). Addicted male subjects also revealed a decrease in the rostral anterior cingulate rCBF compared with male controls (cluster size = 231; $z = 3.50$; $P < 0.001$).

In contrast to the relatively isolated regions of decreased rCBF, cocaine-dependent subjects showed large and diffuse areas of increased rCBF relative to controls (Figure 3). These regions included the posterior cingulate, left and right superior frontal gyrus, middle frontal gyrus, medial OFC, cerebellum, right thalamus, and a large area on the left incorporating the left insula, Brodman area (BA) 41, thalamus, parahippo-campus, and putamen.

Female Controls Versus Female Cocaine-Dependent Subjects—Female cocaine-dependent subjects showed decreases (Figures 1 and 4) relative to sex-matched controls, in the medial OFC (primarily BA 11) (cluster size = 410; $z = 3.67$; $P < 0.001$), right (cluster size = 410; $z = 3.67$; $P < 0.001$) and left (cluster size = 409; $z = 3.67$; $P < 0.001$) superior frontal gyrus, and the right (cluster size = 201; $z = 2.88$; $P < 0.002$) and left (cluster size = 201; $z = 3.38$; $P < 0.001$) parietal cortex.

Increases in rCBF after saline infusion in the addicted subjects relative to the control female group were isolated and circumscribed compared with that of males (Figure 3). Relative increases in rCBF were observed in a region comprising the right middle frontal gyrus and extending into the superior aspect of the anterolateral temporal cortex (cluster size = 1538; $z = 3.55$; $P < 0.001$) and a similar region on the left (cluster size = 1334; $z = 3.71$; $P < 0.001$), anterior cingulate (cluster size = 218; $z = 3.35$; $P < 0.001$), left postcentral gyrus (cluster size = 156; $z = 2.81$; $P < 0.002$), and several regions in the cerebellum.

ROI Analyses—Eighteen ROIs were selected to assess sex-by-group comparisons (see “Methods” section) (Tables II and III). Differences were observed between all clusters,

although 5 regions did not meet our more rigorous Bonferroni adjusted α of 0.003. Post hoc analyses demonstrated expected differences in the male and female group comparisons in all regions, and in no case did a cluster identified in the male comparison differ between females and visa versa. Of particular relevance to our a priori hypothesis was the decreased rCBF in right and left lateral OFC in the male cocaine-dependent subjects ($P \leq 0.001$), but not the female cocaine-dependent subjects, and decreased rCBF in the medial OFC in the addicted female subjects ($P < 0.02$), but not in the addicted male subjects. Male controls and female controls did not significantly differ in any of the selected ROIs. Because the cocaine-dependent men were significantly older than the male controls, an ANCOVA was performed between the 10 selected male ROIs. The right and left lateral OFC and anterolateral temporal cortices, as well as the right posterior cingulate, remained different at $P < 0.005$. The other 5 regions were significant at $P < 0.05$. To assess the role of cigarette use on the results, correlations of the selected clusters with cigarette pack-years were performed within both the male and female cocaine-dependent groups. There were no significant correlations between pack-years and cluster rCBF.

ROI Factor Analysis—Five factors emerged from the factor analysis of the 18 selected ROIs. Two ROIs—the anterior cingulate (from female comparison) and the right caudate (from male comparison)—were deleted from the model because they did not meet our minimum item loading criteria. The 5 factors (FAC1–FAC5) explained 72.6% of the total variance: FAC1 = 19.0%; FAC2 = 16.1%; FAC3 = 14.7%; FAC4 = 12.9%; and FAC5 = 9.9% (Table IV). Item loading by sex was consistent for all 5 factors. The direction of the loading (increase or decrease) was consistent for all factors except FAC5.

rCBF Response During Rest

In each resting scan, mean counts per voxel were obtained for the 10 ROIs described previously in the male comparison after saline infusion (Table V). There was a significant correlation between the left ($r = 0.94$; $P < 0.001$) and right ($r = 0.88$; $P < 0.001$) lateral OFC rCBF in the saline and resting scans. With the exception of the left middle frontal gyrus ($r = 0.14$) and the right caudate ($r = 0.54$), all other saline and resting scan ROIs were significantly correlated ($r > 0.6$; $P < 0.005$) (Table V). Independent t tests between these 10 ROIs revealed 3 regions that met our adjusted α of $P < 0.005$: the left ($t = 4.95$; $P < 0.001$) and right ($t = 3.61$; $P = 0.002$) lateral OFC and the right posterior cingulate ($t = 3.71$; $P = 0.002$). Statistical trends were noted in the right anterolateral temporal cortex, anterior cingulate, and right superior frontal gyrus.

Subjective Response to Saline

Brief Symptom Inventory—Before saline administration, male cocaine-dependent subjects demonstrated significantly higher ($P < 0.004$) BSI scores than did male controls on GSI, PSDI, and obsessive compulsive, phobic anxiety, and psychoticism indexes (Table VI). Only paranoid ideation was significantly higher in female cocaine-dependent subjects relative to female controls ($P < 0.01$), although somatization, GSI, and PSDI revealed strong trends toward significance. BSI scores before and after saline administration revealed no within-group differences in total (all subjects), by group, or in sex-by-group.

Correlation Between BSI and ROI Factors—In the combined male group, 6 significant relationships (all, $P < 0.001$) were observed between FAC1 and obsessive compulsive ($\rho = -0.517$), depression ($\rho = -0.494$), psychoticism ($\rho = -0.492$), GSI ($\rho = -0.578$), PST ($\rho = -0.534$), and PSDI ($\rho = -0.622$). Although not statistically significant, strong trends were noted between FAC1 and phobic anxiety ($\rho = -0.475$) and paranoid ideation ($\rho = -0.488$). These relationships appeared to be secondary to the higher BSI scores and lower FAC1 scores in the cocaine-dependent men, as significant correlations were not

evident within either male group when considered separately. To determine if subjective assessments influenced observed differences between cluster rCBF, the 5 regions in FAC1 were assessed with ANCOVA for these 6 significant BSI measures. After ANCOVA, all of the group differences persisted ($P < 0.005$), suggesting that the rCBF differences were not attributable to the subjects' emotional state.

The combined female group did not show significant correlations between FAC1 and any BSI measures ($\rho = -0.005$ to -0.334). Correlations were also observed at a less restricted level of significance ($P < 0.01$) between FAC1 and phobic anxiety ($\rho = 0.475$; $P < 0.002$) and paranoid ideation ($\rho = 0.488$; $P < 0.001$) and FAC4 and phobic anxiety ($\rho = 0.417$; $P = 0.005$) in the male sample, and FAC2 and obsessive compulsive ($\rho = 0.495$; $P = 0.006$), GSI ($\rho = 0.494$; $P < 0.007$), and PST ($\rho = 0.508$; $P < 0.005$) in the female sample.

Relationship Between Cocaine Use and ROI Factors

There were no significant relationships between the 5 ROI factors and drug use metrics in the total patient sample or by sex (Table I). The only noteworthy trend was between FAC3 and "days used" in the 90 days before treatment ($r = -0.433$) for the total group.

DISCUSSION

Our findings support previous reports of decreased OFC activity in substance-dependent subjects. We have further isolated the decrease in OFC rCBF to the bilateral OFC in male, but not in female, cocaine-dependent subjects. In contrast, a decrease in medial OFC is observed in female, but not in male, cocaine-dependent subjects. Increases in rCBF following saline were also sex-specific, with diffuse regions of increased rCBF observed in male, but not in female, cocaine-dependent subjects relative to sex-matched healthy controls.

The anatomical distinctions between the medial and lateral OFC may have clinical relevance. Bolla et al,⁴⁰ for example, examined healthy subjects with positron emission tomography during performance of a gambling task.⁴¹ Whereas male subjects activated the bilateral OFC, women activated the medial OFC, suggesting sex differences in OFC responsiveness and/or utilization during a decision-making task. Elliott et al⁴² have suggested that the medial OFC is involved in the assessment of reward value, based on the familiarity, or "rightness," of a stimuli. In contrast, the lateral OFC is primarily involved in the suppression of previously rewarded responses. O'Doherty et al,⁴³ for example, describe a functional MRI 2-choice response reversal task in healthy subjects in which medial OFC activation correlated with the amount of money won (eg, reward value, or "rightness") and activation of the lateral OFC correlated with the amount of money lost. Lateral OFC activation associated with monetary loss presumably reflected a change in response contingencies.

A decrease in the perfusion of medial OFC may leave female cocaine-dependent subjects less responsive to the rewarding effects (or "rightness") of a stimulus (reward insensitivity). This may produce a muted response to the rewarding effects of cocaine, nondrug rewards, or both. In male cocaine-dependent subjects, a perfusion deficit in the lateral OFC may attenuate their ability to alter behaviors in response to changing contingencies; that is, they would not respond appropriately to the adverse outcomes of stimuli (ie, cocaine) previously associated with reward (punishment insensitivity).

Volkow et al^{24,44-46} reported a decrease in glucose metabolism in the lateral and/or medial OFC of abstinent cocaine-dependent men at rest, although the OFC anatomical region was not consistently defined. Although our work supports these findings in the lateral OFC, we

did not observe a similar decrease in the medial OFC in men. Tucker et al³² and Ernst et al¹⁵ also showed regional perfusion differences in male and female cocaine-addicted subjects during rest. However, Tucker et al only identified broad areas of increased (in female cocaine-dependent subjects relative to controls) and decreased (in male cocaine-dependent subjects relative to controls) perfusion, and neither encompassed the OFC. Methodologic differences between these studies make comparison with ours difficult, including the assessment of patients with much shorter (4 days³²) or longer (>4 months¹⁵) periods of abstinence, the possible inclusion of subjects taking CNS active medications, and ROIs that were manually defined.¹⁵

Other studies support our general findings that cocaine-dependent women show less neural disruption than their male counterparts, although these studies did not isolate specific differences in OFC activation in cocaine-dependent men and women. Using SPECT imaging, for example, Levin et al¹³ found deficits in the frontal, temporal, and basal ganglia regions in cocaine-dependent men but not in cocaine-dependent women. Compared to sex-matched controls, male cocaine-dependent subjects showed a higher frequency of frontal “defects” (56%) than did female cocaine-dependent subjects (0%). Similarly, King et al⁴⁷ found that whereas the electroencephalogram (EEG) of male cocaine-dependent subjects significantly differed from controls, the EEG of female cocaine-dependent subjects did not differ from sex-matched controls. Female cocaine-dependent subjects also showed less neuronal injury and glial activation in the frontal cortex compared with their male counterparts.¹⁴ Sex differences between cocaine-dependent men and women may result from premorbid differences or the menstrual/estrous-related pharmacokinetic⁴⁸ or pharmacodynamic^{48–51} effects of cocaine.

Increased cerebral perfusion has previously been reported in the frontal, temporo-parietal, and/or parietal regions of cocaine-dependent men and women relative to controls.^{15,52} In our study, areas associated with heightened self-awareness (ie, dorsal medial, posterior medial, and ventral medial cortex³⁹) were significantly elevated in the male (but not in the female) cocaine-dependent subjects, suggesting that the males may have been more focused on their internal states and external environment. This may have been due to either a basal hyper-awareness or in expectation of procaine administration. However, rCBF measures of the dorsal and ventral medial cortex (FAC4) did not correlate with BSI measures (except phobic anxiety) before saline administration.

Methodologic strengths of our study include a carefully selected patient and control population, excluding many confounds common in substance abuse research. Cocaine-dependent subjects were studied during a restricted period of verified abstinence, thus avoiding the rapid fluctuations in neural activity that occur during the first few days of cocaine abstinence as well as the more gradual changes that may develop with extended abstinence. The cocaine-dependent group excluded subjects with a lifetime history of other Axis I disorders and had limited histories of other drug use.

Methodologic weaknesses include the administration of saline, which may have increased anxiety during ligand uptake. However, similar findings were observed in the right and left lateral OFC during rest. Other potential weaknesses included the assessment of comparatively few addicted female subjects relative to controls, although 9 of the 10 female cocaine-dependent subjects showed medial OFC rCBF below the mean of the female controls. The imbalance in the number of female controls and addicted female subjects reflects the difficulty in recruiting cocaine-using-only female participants. All recruited female controls were included in the analysis based on the concept that our power to find differences would be greatest with the largest number of subjects per group. Because we

confined subjects to a specific period of abstinence, menstrual phase was not controlled. Nevertheless, the within-group findings in the female subjects were relatively consistent.

Limits of spatial resolution and the ability to only determine relative measures of limbic activation are inherent in our SPECT methodology and camera. However, the reported differences were quite large and well within our limits of resolution, and our finding that OFC rCBF is lower in cocaine-dependent subjects relative to controls is similar to the reports of others using absolute measures of energy utilization.²⁴ It should also be noted that the SPECT technique utilized assessed relative, not absolute, differences between groups. Although both gray²⁹ and white^{53,54} matter are reduced in cocaine-dependent subjects relative to controls, no discrete structural lesions (by MRI) were observed in any of the subjects in this study. However, structural changes in gray and/or white matter may, at least in part, explain the decreases in rCBF observed in the cocaine-dependent group. Groups were not matched on other potential confounds, such as nicotine use, race, or socioeconomic status.

Lastly, we had previously reported that OFC rCBF did not differ between 10 female cocaine-dependent subjects and matched female controls when assessed by *t*-image analysis.³³ A retrospective analysis of this comparison, again performed by *t*-image analysis, showed a difference in medial OFC rCBF when the *P* value was increased to 0.05 (from 0.01). Thus, differences from our previous report may be secondary to the image analytic technique utilized or the increased power of a larger number of female controls.

A general finding in the present study is that addicted male subjects demonstrate greater neurobiological disruption relative to addicted female subjects. These observations are consistent with much of the existing literature reviewed previously in this article. Yet, clinical studies suggest women run a more severe course of substance dependence compared with men.^{55–57} These seemingly disparate findings may suggest a disconnect between imaging assessments of CNS dysfunction and the presumed associated addictive behaviors. Alternately, patient populations meeting the rigorous study inclusion and exclusion criteria of neuroimaging studies may not appropriately reflect clinical populations. A third interpretation is that medial OFC perfusion deficits may result in heightened psychopathology relative to lateral OFC deficits, thus worsening the course of addiction in cocaine-dependent women relative to men.

CONCLUSIONS

Lowered OFC perfusion in cocaine-dependent subjects appears to be in sex-specific anatomically discrete regions. Distinct roles have been suggested for the mesial and lateral OFC in signaling reward value. Future studies are required to replicate these findings in male and female cocaine-dependent subjects and to assess the relevance of sex-specific differences in OFC rCBF to their clinical presentation and course.

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Figure 1. Decreases in regional cerebral blood flow in (A) male and (B) female cocaine-dependent subjects compared with healthy sex-matched controls. Talairach coordinate (z-axis) noted. L = left; lat = lateral; OFC = orbitofrontal cortex; AC = anterior cingulate; R = right; sup = superior.

Figure 2.

Counts per voxel in right and left lateral orbitofrontal cortex (OFC) of male and female cocaine-dependent and healthy control subjects. Horizontal lines denote mean for group. Left column represents counts of left lateral OFC; right column represents counts of right lateral OFC.

A. Male Cocaine-Addicted Compared to Male Control Subjects

B. Female Cocaine-Addicted Compared to Female Control Subjects

Figure 3.

Increases in regional cerebral blood flow in (A) male and (B) female cocaine-dependent subjects relative to healthy sex-matched controls. Talairach coordinate (z-axis for transverse, y-axis for sagittal) noted. Post = posterior; vent = ventral; L = left; R = right.

Figure 4. Counts per voxel in the medial orbitofrontal cortex (OFC) of male and female cocaine-dependent and healthy control subjects. Horizontal lines denote mean for group.

Table 1

Demographic and clinical characteristics of male and female cocaine-dependent individuals and healthy controls by subject group.

Variable	Male Control (n = 18)	Male Cocaine (n = 25)	Female Control (n = 19)	Female Cocaine (n = 10)	Test Statistic			
					F	t	χ^2	DF
Age, mean (SD), y	33 (7)	39 (4)	33 (7)	36 (7)	5.4			3,68
Race, no. (%)							29.3	9
White	11 (61)	4 (16)	11 (58)	3 (30)				
Black	2 (11)	20 (80)	4 (21)	7 (70)				
Hispanic	3 (17)	1 (4)	3 (16)	0				
Asian	2 (11)	0	1 (5)	0				
Cigarette pack-years, mean (SD)	0.04 (0.2)	9 (9)	0.1 (0.3)	21 (30)	9.17			3,66
Cocaine use, mean (SD)								
Days used in 90 days		46 (27)		75 (25)		2.88		32
Years used		13 (5)		10 (8)		1.46		32
Dollars spent—lifetime		\$212,000 (\$411,000)		\$225,000 (\$305,000)				
Days used—lifetime		1714 (1438)		1945 (1828)		0.40		33
Days abstinent at testing		19 (4)		20 (4)		0.59		33

DF = degrees of freedom.

Table II

Areas of decreased regional cerebral blood flow after saline administration in male and female cocaine-dependent and healthy control subjects (mean [SD] counts per voxel).

Region of Interest	One-Way ANOVA					Post Hoc Comparisons by Sex *		
	Male Control (n = 18)	Male Cocaine (n = 25)	Female Control (n = 19)	Female Cocaine (n = 10)	F (3,68)	P	Male Control vs Cocaine	Female Control vs Cocaine
Decrease in male cocaine-dependent subjects relative to male controls (Figure 1A)								
L lateral OFC	72 (4)	65 (5)	69 (5)	68 (6)	6.1	0.001	<0.001	0.93
R lateral OFC	72 (4)	66 (5)	69 (6)	68 (6)	5.4	0.002	0.001	0.92
L anterolateral temporal cortex	71 (4)	65 (4)	70 (4)	71 (4)	10.0	<0.001	<0.001	0.99
R anterolateral temporal cortex	69 (3)	64 (5)	67 (4)	66 (5)	7.5	<0.001	<0.001	1.0
Anterior cingulate	72 (6)	66 (6)	70 (4)	70 (7)	4.8	0.004	0.004	1.0
Decrease in female cocaine-dependent subjects relative to female controls (Figure 1B)								
Medial OFC	70 (5)	71 (6)	74 (5)	66 (6)	3.6	0.017	0.99	0.01
L superior frontal gyrus	63 (4)	66 (4)	65 (4)	59 (3)	7.1	<0.001	0.13	0.004
R superior frontal gyrus	62 (3)	64 (4)	6 (4)	58 (3)	5.8	0.001	0.74	0.001

ANOVA = analysis of variance; L = left; OFC = orbitofrontal cortex; R = right.

* Determined by Tukey test.

Table III

Areas of increased regional cerebral blood flow after saline administration in male and female cocaine-dependent and healthy control subjects (mean [SD] counts per voxel).

Region of Interest	One-Way ANOVA					Post Hoc Comparisons by Sex *		
	Male Control (n = 18)	Male Cocaine (n = 25)	Female Control (n = 19)	Female Cocaine (n = 10)	F (3,68)	P	Male Control vs Cocaine	Female Control vs Cocaine
Increase in male cocaine-dependent subjects relative to male controls (Figure 3A)								
R caudate	75 (3)	80 (5)	78 (5)	78 (5)	3.3	0.02	0.001 *	1.0
Medial OFC	64 (4)	70 (6)	66 (6)	66 (6)	3.8	0.01	0.009 *	1.0
R superior frontal gyrus	79 (2)	83 (3)	80 (3)	81 (3)	6.0	0.001 †	0.001 *	0.93
L middle frontal gyrus	75 (3)	79 (4)	76 (4)	78 (4)	5.1	0.003	0.004 *	0.41
R posterior cingulate	92 (23)	97 (4)	93 (4)	94 (5)	6.0	0.001 †	0.001 *	0.98
Increase in female cocaine-dependent subjects relative to female controls (Figure 3B)								
L middle frontal cortex	66 (3)	67 (4)	64 (4)	71 (4)	7.1	<0.001 †	0.96	<0.001 *
R middle frontal cortex	64 (4)	63 (4)	62 (4)	69 (5)	6.1	<0.001 †	0.98	<0.001 *
L anterolateral temporal cortex	58 (5)	57 (4)	58 (4)	65 (5)	7.8	<0.001 †	0.82	0.003 *
R anterolateral temporal cortex	60 (4)	59 (4)	60 (4)	66 (4)	8.6	<0.001 †	0.97	0.001 *
Anterior cingulate	86 (3)	88 (4)	86 (2)	90 (4)	4.3	0.008	0.25	0.02 *

ANOVA = analysis of variance; R = right; OFC = orbitofrontal cortex; L = left.

* Statistically significant ($P = 0.05$) by Tukey test.

[†] Statistically significant ($P = 0.003$) by one-way ANOVA.

Factor (FAC) analysis of selected regions of interest (ROIs) for 35 male and female cocaine-dependent subjects and 37 healthy male and female controls.

Table IV

ROIs with FAC Loadings of ≥ 0.5	FAC Correlation Coefficients				
	FAC1	FAC2	FAC3	FAC4	FAC5
L lateral OFC (male decreased)	0.86				
R lateral OFC (male decreased)	0.79				
L anterolateral temporal cortex (male decreased)	0.72				
R anterolateral temporal cortex (male decreased)	0.72				
L middle frontal cortex (female increased)		0.85			
R middle frontal cortex (female increased)		0.89			
L anterolateral temporal cortex (female increased)		0.69			
R anterolateral temporal cortex (female increased)		0.57			
L superior frontal gyrus (female decreased)			0.82		
R superior frontal gyrus (female decreased)			0.82		
Medial OFC (female decreased)	0.52		0.54		
L middle frontal gyrus (male increased)				0.84	
R superior frontal gyrus (male increased)				0.75	
R posterior cingulate (male increased)				0.62	
Medial OFC (male increased)					-0.65
Anterior cingulate (male decreased)					0.65

L = left; OFC = orbitofrontal cortex; R = right.

Comparisons between selected regions of interest after saline administration and during rest in male cocaine-dependent and healthy control subjects.

Table V

Region of Interest	Correlation: Saline vs Rest		Mean (SD) Counts/Voxel in Resting Scan		Independent t Test Controls vs Patients	
	r	P*	Male Controls (n = 10)	Addicted Male Subjects (n = 12)	t (2,20)	P*
Decrease in cocaine-dependent males relative to male controls (Figure 1A)						
L lateral OFC	0.94	<0.001	72 (4)	62 (5)	4.95	<0.001
R lateral OFC	0.88	<0.001	69 (4)	63 (5)	3.61	0.002
L anterolateral temporal cortex	0.82	<0.001	69 (4)	66 (5)	1.63	0.12
R anterolateral temporal cortex	0.80	<0.001	65 (3)	62 (4)	2.21	0.04
Anterior cingulate	0.90	<0.001	72 (7)	65 (5)	2.97	0.008
Increase in cocaine-dependent males relative to male controls (Figure 3A)						
R caudate	0.54	0.01	77 (4)	80 (5)	1.52	0.14
Medial OFC	0.94	<0.001	64 (2)	68 (8)	1.58	0.13
R superior frontal gyrus	0.71	<0.001	81 (2)	83 (2)	2.70	0.01
L middle frontal gyrus	0.14	0.53	78 (2)	77 (3)	0.73	0.47
R posterior cingulate	0.63	0.002	95 (3)	99 (3)	3.71	0.001

L = left; OFC = orbitofrontal cortex; R = right.

* P values of <0.005 are considered significant.

Table VI

Mean (SD) Brief Symptom Inventory³⁷ scores before saline administration in male and female cocaine-dependent and healthy control subjects.

	Male Control (n = 18)	Male Cocaine (n = 25)	Female Control (n = 19)	Female Cocaine (n = 10)	Male Control vs Male Cocaine		Female Control vs Female Cocaine	
					U	P*	U	P*
Somatization	0.10 (0.15)	0.15 (0.29)	0.04 (0.08)	0.20 (0.19)	220.0	0.89	43.0	0.006
Obsessive compulsive	0.07 (0.16)	0.33 (0.35)	0.25 (0.92)	0.17 (0.28)	109.5	0.002	74.0	0.20
Interpersonal sensitivity	0.04 (0.13)	0.17 (0.30)	0.03 (0.08)	0.23 (0.36)	168.5	0.07	73.5	0.13
Depression	0.03 (0.07)	0.13 (0.25)	0.01 (0.04)	0.12 (0.25)	159.0	0.05	80.0	0.19
Anxiety	0.13 (0.19)	0.26 (0.29)	0.11 (0.15)	0.12 (0.14)	164.5	0.11	88.0	0.72
Hostility	0	0.10 (0.18)	0	0.08 (0.14)	144.0	0.005	66.5	0.01
Phobic anxiety	0	0.14 (0.20)	0.02 (0.06)	0.02 (0.06)	126.0	0.001	94.5	0.96
Paranoid ideation	0.04 (0.11)	0.30 (0.43)	0.04 (0.08)	0.22 (0.30)	137.5	0.01	46.0	0.004
Psychoticism	0.01 (0.05)	0.29 (0.42)	0.01 (0.05)	0.12 (0.21)	116.5	0.001	70.5	0.06
GSI	0.05 (0.07)	0.19 (0.21)	0.03 (0.04)	0.14 (0.16)	102.0	0.002	36.5	0.006
PST	2.6 (3.5)	8.8 (9.1)	1.6 (2.1)	6.8 (7.9)	113.5	0.005	41.0	0.01
PSDI	0.56 (0.51)	1.06 (0.57)	0.53 (0.51)	1.12 (0.74)	96.0	<0.001	44.5	0.009

U = Mann-Whitney U nonparametric test scores; GSI = global severity index; PST = positive symptom total; PSDI = positive symptom distress index.

* P values of ≤0.004 are considered significant.