Gender Differences in Cerebral Perfusion in Cocaine Abuse: Technetium-99m-HMPAO SPECT Study of Drug-Abusing Women

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Cocaine abuse continues to be a major public health concern, with a variety of medical and neurologic sequelae. Previous studies have demonstrated abnormalities in cerebral perfusion in chronic cocaine abusers and after acute administration of cocaine. Although women are becoming increasingly represented among drug abusers, few studies have included women. To the authors' knowledge, none has compared cerebral perfusion in asymptomatic women with that in men. **Methods:** The cerebral perfusion of 13 cocaine-dependent women, 4 of whom were also heroin dependent, was studied with ^{99m}Tc hexamethylpropyleneamine oxime (HMPAO) SPECT. These women were compared with 13 cocaine-dependent men and 26 healthy control subjects. Structural brain lesions and neurologic abnormalities were excluded by MRI and neurologic evaluation. Perfusion studies were interpreted in a standardized fashion by reviewers blinded to clinical information. **Results:** It was found that cocaine-dependent women were much less likely to have abnormal study findings than cocaine-dependent men ($p = 0.003$) and were indistinguishable from normal women ($p = 1.0$). However, the results in both women and men who concurrently used heroin plus cocaine were all abnormal. Perfusion abnormalities tended to be located in anterior brain structures, such as the frontal and temporal cortex and the basal ganglia. **Conclusion:** These data suggest that cocaine-dependent women have fewer abnormalities in cerebral perfusion than cocaine-dependent men, but that concurrent abuse of heroin and cocaine is associated with more perfusion abnormalities in both sexes.

Key Words: cerebrovascular circulation; brain; cocaine; heroin; SPECT

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Cocaine abuse continues at epidemic levels both in the general population and among concurrent heroin-dependent persons (*1*). The most recent national household survey found 1.3 million Americans to be current cocaine users, with one half of those noted to be frequent users (*2*). It was reported that 9.2% of all women had used cocaine at least once, with 0.6% reporting frequent use. For women between the ages of 26 and 34 yr, 20.7% reported using cocaine at least once, with 1.1% reporting frequent use. These numbers are likely to be gross underestimates of drug abuse because homeless, transient and incarcerated persons were not surveyed.

Cocaine use has been associated with a number of serious medical and neurologic disorders (*3,4*), most prominently cardiovascular (*5,6*) and cerebrovascular (*7,8*), and an increased incidence of human immunodeficiency virus (HIV) infection, especially among cocaine- and heroin-dependent persons who self-administer the drugs intravenously (*9*). The acute cerebrovascular complications of cocaine use have become increasingly recognized and include ischemic stroke (*10–12*), intracerebral and subarachnoid hemorrhage (*8,13*) and vasculopathy (*14*). In addition to acute clinical complications of cocaine abuse, the authors (*15–18*) and others (*19–22*) found evidence of abnormal cerebral perfusion, unrelated to structural brainlesions, in a large percentage of otherwise healthy, asymptomatic cocaine- and polydrug-using men.

With ^{99m}Tc-hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO), a lipophilic radiopharmaceutical with rapid and stable brain uptake in proportion to cerebral perfusion (*23,24*), the authors showed that alterations in SPECT perfusion patterns are often indistinguishable from patterns seen in early acquired immunodeficiency syndrome dementia complex (*17*) and that abnormalities improve with short-term abstinence and buprenorphine treatment of cocaine addiction (*18*). Others used PET to demonstrate alterations in both cerebral perfusion (*25*), metabolism (*26–28*) and dopamine receptor function (*29,30*) in similar patients. In addition, both PET (*31*) and SPECT (*32*) have been used to study acute administration of cocaine, which revealed global hypometabolism and regional hypoperfusion.

However, in this, as in many areas of medical research (*33,34*), previous work has focused almost entirely on men. Although a preliminary report from this laboratory (*15*)

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included studies of women with abnormalities, not all of these patients had complete psychiatric, neurologic and substance abuse classification. Indeed, several of these patients were evaluated with specific neurologic problems, making these results difficult to interpret. Given probable gender differences in both cardiovascular and cerebrovascular pathophysiology, any attempt to understand the mechanism behind cocaine-associated cerebral perfusion changes should address their reproducibility across gender. An attempt to address this question led to the design of this study specifically to address possible gender differences.

METHODS

Patient Recruitment and Evaluation

A total of 52 subjects participated in this study. All studies were approved by the Institutional Review Committees of the Brigham and Women's Hospital (Boston) and McLean Hospital (Belmont, MA), and informed consent was obtained for each study in each case.

Thirteen cocaine-dependent women (mean age ± s.d. = 34.6 ± 4.6 yr) were recruited through advertisements in local newspapers. Each underwent extensive medical and neurologic examination, brain MRI, routine blood work and HIV antibody testing to rule out medical or neurologic illness. Exclusion criteria consisted of any significant medical or neurologic condition, including epilepsy, migraine, unexplained loss of consciousness or severe head trauma. All results of medical, psychiatric and clinical laboratory evaluations, including HIV testing, were unremarkable. All MRI studies were also normal, without atrophy, with the exception of a previously unrecognized cerebellar hemispheric infarction in one patient. Drug and alcohol histories were obtained by (1) a medical history interview with a physician, (2) written drug history questionnaires and (3) the orally administered Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition-revised (DSM-III-R) (*35*). Nine of the 13 exclusively used cocaine and met DSM-III-R Axis I diagnostic criteria for cocaine dependence; the remaining 4 were both cocaine and heroin dependent. None met DSM-III-R criteria for any other Axis I diagnosis (with the exception of nicotine dependence), including depression. Many reported sporadic use of other illicit drugs, but none met criteria for abuse or dependence. Urine drug screens taken on the day of SPECT imaging were positive for cocaine in all women and positive for opiates in the four codependent women. Two women also tested positively for phencyclidine.

For comparison purposes, subjects were matched for age, amount and duration of cocaine and heroin use and history of alcohol use with 13 cocaine-dependent men (32.4 ± 6.7 yr) who were part of a previous study (*16*). These men were recruited through similar advertisements and had undergone a screening procedure and testing identical to that of the women. All were likewise normal, and all tested negative for the HIV antibody. Urine drug screens on the day of SPECT imaging revealed the presence of cocaine in all nine men tested, with only one other substance, marijuana, detected in one man. The four heroin- and cocaine-dependent men, part of a drug treatment program, were free of all drugs at the time of imaging.

These cohorts of drug-abusing women and men did not significantly differ with respect to age, race, body mass index, amount of cocaine use, amount or duration of heroin use, route of administration of cocaine or heroin or level of alcohol use (Table 1). The women reported a significantly longer duration of cocaine use (15.3 ± 4.8 yr vs. 8.2 ± 6.2 yr, $p = 0.005$). A difference in the total amount of cocaine, although greater in women than in men, did not reach statistical significance.

TABLE 1
Covariates of Interest in Cocaine-Using Subjects*

	Women	Men	p Value
Cocaine-dependent subjects, total	13	13	—
Cocaine dependent only	9	9	—
Heroin and cocaine dependent	4	4	—
Age (yr)	34.6 (4.6)	32.4 (6.7)	0.37
Race (number black/white)	6/7	5/8	0.74
Body mass index (kg/m^2)	24.34 (4.74)	24.88 (3.72)	0.75
Alcohol use score (0–3)†	1.7 (1.1)	1.5 (1)	0.72
Cocaine use			
Amount (g/wk)	6.6 (7.3)	3.3 (2.9)	0.09
Duration (yr)	15.3 (4.8)	8.2 (6.2)	0.005
Heroin use			
Amount (bags/day)	1.6 (2.9)	2.4 (3.9)	0.88
Duration (yr)	4.3 (8)	3.7 (7.1)	1.0
Route of drug administration (% intravenous)	38.5	38.5	1.0
Urine drug screen on day of SPECT			
Cocaine	13	9	—
Phencyclidine	2	0	—
Opiates	4	0	—
Marijuana	0	1	—

*Mean (s.d.).
†Alcohol use: 0, no use; 1, mild/moderate use; 2, abuse; 3, dependence.

Control Subjects

Twenty-six healthy controls, 13 women (56.3 ± 5.1 yr) and 13 men (62.9 ± 8.7 yr), participating in an ongoing study of aging, were evaluated. Each underwent medical and neurologic evaluations similar to those of the cocaine-abusing subjects, and none demonstrated abnormalities. In addition, each underwent extensive neuropsychologic evaluation, described elsewhere (*16*), to exclude subtle dementing illness; the results were normal in all cases.

Imaging Protocol

Patients were studied using a digital ASPECT system (Digital Scintigraphics, Inc., Boston, MA) with a single-crystal sodium iodide ring detector and three collimators designed to view the patient's head from three angles simultaneously. The system has a resolution in air using capillary line sources of 6.8 mm at the center and 5.9 mm at 9 cm from the center for ^{99m}Tc. All patients were injected with 20 mCi of ^{99m}Tc-HMPAO (Ceretec, Amersham, Ltd., UK) while sitting or lying supine in a dimly lit room with eyes open. Acquisition of images began 10 min after injection and lasted from 30 to 40 min (15–20 sec per projection) in 120 projections with a 360° rotation of the collimators. Two pulse-height analyzer windows were used, one set at 140 ± 14 keV and one set to acquire scatter information from 112 to 126 keV. The combined set of projections was then calculated by subtracting 90% of the scatter projections and prefiltered to remove the forward-scatter component from the photopeak projections using a Butterworth filter (cutoff = 1.05 cycles/cm; power factor = 20). Data were corrected for attenuation using an attenuation factor of 0.15 cm, reconstructed in the axial plane parallel to the orbitomeatal line and displayed on a 128 × 128 matrix (1.67 × 1.67-mm pixel size) as a set of 20 slices (5.01-mm slice thickness).

MRI scans were acquired using a 1.5-Signa system (General Electric Co., Milwaukee, WI). A standard spin-echo imaging protocol (TR = 3000 msec, TE = 30 or 80 msec, NEX = 0.5) with a slice thickness of 3 mm, 256 × 192 matrix and 24 cm field of view, was used in each case.

Each SPECT study was viewed on a video display terminal and consisted of transaxial image sets, made up of 20 slices, each 5.01 mm thick as a result of summing three 1.67 mm slices. A gradient 16-component color scale was used to display each image set; white represented the maximum of reconstructed activity. The color display level for each patient was individually scaled so that the cerebellar nuclei were white (greater than 90% of the maximum activity), thereby normalizing each data set to the activity in the cerebellum. An area was considered abnormal if a decrease in regional cerebral blood flow to less than 60% of maximum, at least 8 mm in width, was seen completely traversing the cortical shell on at least two contiguous slices. This cutoff was chosen to remain consistent with several previous studies involving cocaine-dependent men (*16–18*). On the color scale, this represented a change from white or orange to blue. Basal ganglia were considered abnormal if peak activity was below 60% of maximum or if there was an asymmetry of at least one color level between left and right.

All 52 images sets were interpreted in random order during two consecutive reading sessions. Three investigators (B.L.H., B.G. and J.M.L.) simultaneously examined each image set without knowledge of the clinical class. Individual abnormalities for each patient were recorded on a database by region, number and size of defects. All abnormalities were either agreed on by all investigators or determined by consensus. A study was considered to be abnormal if more than one perfusion defect was identified.

Statistical Analysis

Fisher's exact test was used for the comparison of categorical outcome of SPECT results among various subgroups. Student's t-test and the Mann-Whitney U-test was used to test for differences in a number of covariates (gender, age, race, body mass index, alcohol use, amount and duration of cocaine and heroin use and route of administration of cocaine) between groups. Multivariate analyses of variance and covariance were used to evaluate both gender differences and group differences in location of SPECT abnormalities and the effects of the covariates. Multiple logistic-regression models were developed to evaluate the effect of covariates on binary categorical outcome simultaneously and to look for evidence of effect modification. Mean values are reported (± s.d.). All reported p values are two sided.

RESULTS

A reduction was found in the proportion of abnormal studies in drug-abusing women compared with that in men. The results in 5 of 13 drug-abusing women were abnormal compared with those in 12 of 13 men ($p = 0.011$). On the other hand, normal controls were indistinguishable by gender, with the findings in 2 of 13 women and 4 of 13 men considered abnormal ($p = 0.322$). Comparing drug-abusing women with normal women, no significant difference could be found between the two groups ($p = 0.378$). Categorizing drug use as exclusively cocaine (EC) or heroin and cocaine (HC), of the nine EC women, only one result was abnormal compared with eight of nine in men with a similar drug-using profile ($p = 0.003$). In fact, compared with normal women (2 of 11 abnormal), EC women did not significantly differ ($p = 1.0$). Considering HC users, all four women and all four men in this category had abnormalities. This group of women differed significantly from normal women ($p = 0.006$) and from EC women ($p = 0.007$). A similar comparison for men revealed no significant differences between the two groups of drug users ($p = 1.0$) (Fig. 1).

Analysis of the number of perfusion abnormalities with respect to gender also showed striking differences. Drug-abusing women had an average of 2.0 ± 2.52 defects, which was less than that in drug-abusing men with 6.08 ± 5.98 defects ($p = 0.04$) and similar to that in normal women with 0.69 ± 1.32 defects ($p = 0.12$). EC women had an average of 0.56 ± 0.73 defects, similar to that in normal women ($p = 0.74$) but much less than that in HC women with 5.25 ± 1.89 defects ($p = 0.005$) and EC men with 3.67 ± 2.87 defects ($p = 0.005$). Comparing HC women with HC men (11.5 ± 8.02 defects), no significant gender difference was found at this level of drug use ($p = 0.08$). No evidence for a gender difference was detected between normal controls, with women averaging 0.69 ± 1.32 defects and men averaging 1.23 ± 1.74 defects ($p = 0.44$). Although the categorical outcome was not affected by race, there was a trend toward more perfusion defects in the white patients (5.6 ± 5.88 defects) than in black patients (1.91 ± 2.07 defects; $p = 0.06$). However, race was not a significant independent variable in any model tested, and there was no evidence of sex × race interaction.

Multivariate analysis of variance and analysis of covari-

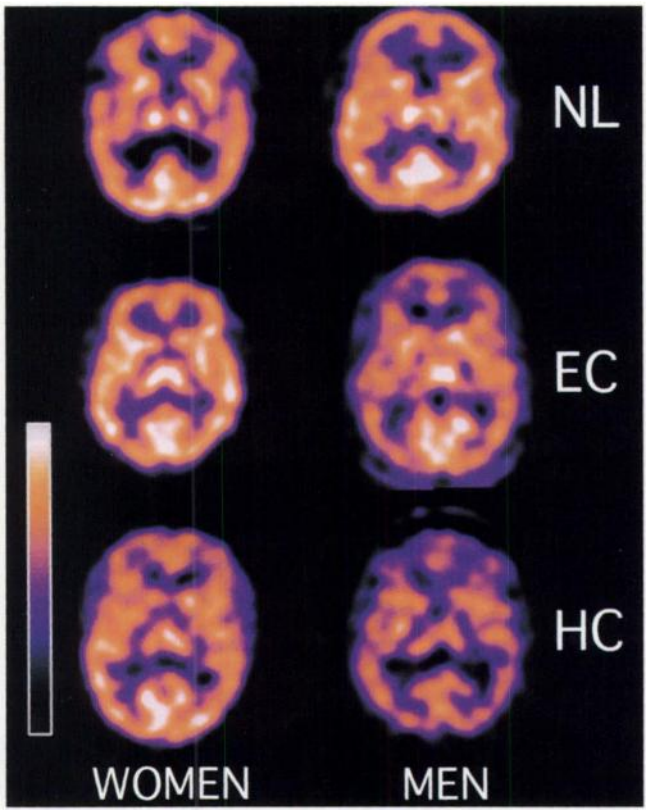

FIGURE 1. Comparison of brain SPECT images of women and men in each clinical category. Comparable midcortical slice (5-mm thick), including basal ganglia, thalamus, frontal, temporal, parietal and visual cortex. NL = normal control; EC = exclusive cocaine user; HC = concurrent cocaine and heroin user.

ance showed that, controlling for the significant effect of sex on the result ($F = 8.64$, $p = 0.0074$), the use of heroin was an independent and significant predictor of outcome ($F = 17.38$, $p = 0.0004$). The entire model ($F = 13.01$, $p = 0.0002$) was extremely suggestive of an association of male sex and concomitant use of cocaine and heroin with increasing number of perfusion defects. The route of administration of cocaine was independently significantly predictive of outcome ($F = 7.27$, $p = 0.0126$) but, because of covariance with the use of heroin, did not add to the strength of the model ($F = 0.06$, $p = 0.8$). No other covariate, including age, amount or duration of cocaine or heroin use or alcohol use was found to be independently significant or helpful in terms of the model.

There was a predilection for defects of the frontal cortex (50% vs. 19%, $p = 0.02$), temporal cortex (73% vs. 35%, $p = 0.006$) and basal ganglia (38% vs. 8%, $p = 0.009$) in cocaine users compared with normals. A nonsignificant trend was seen for parietal cortex defects (27% vs. 8%, $p = 0.07$). The differences were even more significant when HC users were compared with normals. However, comparing women cocaine users with men, men showed a higher frequency of frontal (56% vs. 0%, $p = 0.015$) and parietal (56% vs. 0%, $p = 0.015$) defects and a nonsignificant trend toward a higher frequency of temporal abnormalities (78% vs. 44%, $p = 0.17$). The side of the defects (left or right) was not a distinguishing factor among any of the groups (Fig. 2).

As an internal measure of the reliability of these methods for visually classifying these scans, the sensitivity and specificity were determined using categorical rating of normal controls compared with the subject men. Using these data, a sensitivity of 92% and a specificity of 77% were calculated.

DISCUSSION

Cocaine-dependent women, compared with men, exhibit strikingly fewer abnormalities in cerebral perfusion, both in terms of the number of defects per patient and in the proportion of patients affected. When exclusive use of cocaine is considered, the differences between women and men are even more apparent. However, in persons with concurrent cocaine and heroin abuse, gender differences become less apparent, with women and men exhibiting abnormalities of cerebral perfusion.

These gender differences cannot be explained by differences in a number of covariates such as age, race, body mass index, alcohol use, amount of cocaine use, amount or duration of heroin use or route of drug administration. In fact, women used more cocaine ($p = 0.09$) for a longer period ($p = 0.005$) than did men. This raises the possibility of selection bias in choosing these subjects. Although entry into the study was not conditional on the specific amount or duration of these drugs, it is possible that women are somehow "protected" in various ways from the harmful

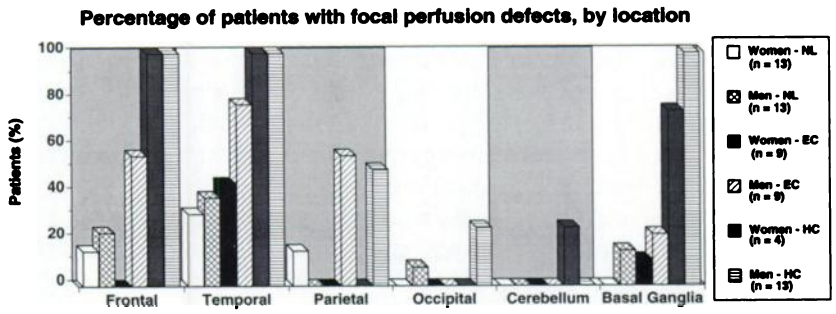

FIGURE 2. Percentage of patients in each category with focal cerebral perfusion abnormalities by brain region.

effects of these substances. As such, more "healthy" or resilient women may have been studied, i.e., those less likely to exhibit cerebral perfusion abnormalities.

In addition, these results cannot be explained on the basis of differences in any other known cause of altered cerebral perfusion because no medical or neurologic disorders were revealed despite a thorough diagnostic evaluation. All patients tested negative for the HIV antibody. Structural abnormalities in cerebral anatomy did not underlie perfusion defects in either group of patients. All patients underwent MRI, which revealed only one abnormality, a previously unrecognized cerebellar hemisphere infarction in one women, which matched a cerebellar perfusion defect. This defect was discounted from the analysis.

Another possibility is that these results could be explained by differences in body fat and thus the distribution and metabolism of drugs or radiotracer. Women tend to have a higher fat content than men, which can be represented by the body mass index (*36*). Gender differences in the rates of metabolism of various compounds have been appreciated for a number of years (*37,38*). HMPAO is a lipophilic compound and, as such, may have a differential distribution based on gender. This could lead to differences in the determination of relative global perfusion but would be unlikely to explain differences in regional differences in perfusion. At any rate, as no difference in mean body mass index was found between these drug-abusing women and men, it is unlikely that these mechanisms underlie these results.

Drug abuse often occurs in conjunction with other psychiatric disorders, potentially confounding any study that attempts to look at drug effects in isolation (*39*). Several groups have reported alterations in cerebral perfusion and metabolism related to clinical depression (*40,41*). In a PET study that considered only cocaine users not currently depressed, no abnormalities in regional cerebral metabolism were found (*29*). Although depression often confounds the picture in substance abuse, all of these cocaine-dependent women and men screened negatively for major affective disorders, and yet perfusion abnormalities were still found in a large percentage of subjects.

The authors are unaware of any established gender differences in cerebral perfusion for either normals or for any disease state. In fact, few studies of cerebral perfusion have highlighted women (*42,43*). The possibility that these data may reflect a general gender difference in cerebral perfusion patterns certainly exists. However, the fact that the normal controls (women and men) did not significantly differ as a function of gender suggests that this is unlikely.

The methods used for rating datasets were designed ad hoc to "cast a wide net" to distinguish subtle perfusion defects between groups more effectively. The evaluation of this technique in reference to cocaine-dependent men found it to be sensitive (92%), with some reduction in specificity (77%), showing that a few normal control men were classified as "abnormal." As apparent from Figure 2, most of these abnormalities were in the temporal lobe; an area notoriously difficult to evaluate because of its convolutions and axis relative to the rest of the brain. However, this demonstrates the necessity of additionally considering continuous data, such as the total defect count and the importance of employing consistent cutoff criteria, when evaluating multiple small perfusion defect pathologic conditions, especially in the temporal lobe.

One area of concern is the previous SPECT studies of cocaine-abusing patients that did include women. Although only two such studies (*15,44*) were found, one was from the authors' own laboratory (*15*), involving 12 subjects, 7 of whom were women, all with abnormal scans. Several points need clarification regarding these findings. This was a preliminary study and was not an attempt to compare women with men in a systematic way. The technique, using iodoamphetamine as a radiotracer and a low-resolution camera, was different. Most importantly, however, these subjects were not a cohort of asymptomatic cocaine-dependent women. Some were referred for SPECT imaging because of neurologic abnormalities, such as recent seizure. These subjects did not undergo the rigorous screening and evaluation to rule out these and other abnormalities and concurrent drug abuse that was described for the current cohort. In addition, no drug screening was performed at the time of imaging to rule out concurrent drug use. The previous results were a "work in progress" which was reported to suggest that cocaine abuse could be associated with SPECT abnormalities, providing the basis for more rigorous and specific investigation.

The nature of the perfusion abnormalities exhibited by drug-dependent patients remains unclear. Despite the increasingly recognized association between cocaine use and stroke, both ischemic and hemorrhagic, there has been no direct evidence of routine blood vessel abnormalities in this patient population. Although there have been occasional pathologic reports of cerebral vasculitis (*14*), this seems uncommon, and no other more common vasculopathy has been reported. However, cocaine appears to have a powerful effect at the calcium L channel, magnifying the effect of contractile stimuli at this site (*45*). Acute administration of cocaine has been reported to result in vasospasm in coronary arteries in humans (*6,46*) and in cerebral arteries in animals (*47,48*). Vasospasm has been posited as an explanation for some symptomatic cerebrovascular complications of cocaine use (*4*). Indeed, acute intravenous administration of cocaine in humans has produced focal reductions in cerebral perfusion, as measured by SPECT (*32*), and global reduction in cerebral glucose metabolism, as measured by PET (*31*). The coupling of metabolic and perfusion defects seen by Volkow et al. (*27*) led this group to consider vasospasm rather than infarction a likely mechanism. However, because abnormalities detected by a variety of imaging modalities persist beyond a period of acute or even recent administration of cocaine, it seems unlikely that vasospasm is the only explanation, especially vasospasm on normal blood vessels. Other evidence showing

unaltered coupling of regional cerebral perfusion and metabolism in acute cocaine administration in rats further argues against the role of vasospasm in acute neurologic events (*49*).

Given the predilection for frontal cortex and basal ganglia that was found for perfusion (*15–18*) and that Volkow et al. (*25,28*) found for metabolic abnormalities in cocaine-abusing patients, these areas may be the sites of physiologically important metabolic disturbances in these patients. The neurotransmitter dopamine is thought to play a critical role in cocaine addiction, with the reinforcing properties of cocaine believed to be related to activation of cocaine receptors on the dopamine transporter that blocks reuptake of dopamine (*50,51*). Depletion of brain dopamine in chronic cocaine abuse may be equally important in producing drug craving and dependency (*52*). PET studies in humans have shown reduced striatal postsynaptic dopamine receptor binding (*30*) and reduced striatal presynaptic dopamine precursor uptake (*29*) in chronic cocaine abusers. In addition, there is PET evidence of preferential uptake of cocaine, associated with the dopamine reuptake site in the striatum of normal humans and baboons (*53*). As dopamine receptors abound both in the striatum and in the mesolimbic and mesocortial pathways (*54*), this circuitry has been implicated as central in mediating the addictive properties of cocaine (*39,50*). These are precisely the areas in which the bulk of perfusion abnormalities was found in these patients.

The finding that women, and perhaps men, who abuse cocaine are much more likely to exhibit perfusion abnormalities with concurrent use of heroin has not been previously reported. However, this observation is in agreement with animal models of drug interaction. Wang et al. (*55*) showed that a combination of cocaine and methamphetamine induced basilar artery vasospasm in rabbits; each drug alone had little or no effect. London et al. (*56*), using fluorodeoxyglucose-PET in humans, found that acute administration of morphine resulted in focal areas of cerebral hypometabolism similar to what they observed in acute cocaine administration. However, perfusion studies specifically evaluating the chronic effects of heroin abuse have not been performed. Although opiate abuse alone has been associated with cerebral vasculitis, the total amount of cerebrovascular disease seems to be much less than that seen with cocaine use (*57*). This may relate to opiates' lack of systemic vasopressor effects. However, because perhaps 75% of all opiate users concurrently use cocaine (*1*), this distinction is often difficult to make in individual patients.

The reason why cocaine-abusing women may have fewer cerebral perfusion abnormalities can only be postulated at this point. An intriguing hypothesis stems from lines of evidence regarding both gender differences in atherosclerosis and the cause of vasospasm. It is suspected that women, especially premenopausal women, such as those in this study, have less atherosclerotic disease, including less cerebrovascular disease, than age-matched men (*58*). As the risk of vascular disease increases with age (*58*), especially after surgical menopause (*59*), and may be attenuated by postmenopausal estrogen replacement therapy (*60,61*), a protective effect of estrogens has been postulated (*62*). Furthermore, although a matter of some debate, a number of groups believe that atherosclerosis is a prerequisite for arterial spasm (*63–66*), which in turn may predispose to further arterial damage (*67*). However, most of this work comes from the study of coronary arteries, and little work has been done regarding pure cerebral vasospasm. At any rate, taken as a whole, it is possible that estrogens partially protect women from mild atherosclerosis and, thus, from cocaine-associated cerebral vasospasm. The addition of heroin, and perhaps other drugs, may overcome this protective effect.

Gender differences with respect to drug abuse have been reported. Human studies address differences in demographics and psychiatric comorbidity (*68*). Studies in the rat support a reduction in cocaine toxicity in females, which seems to be related more to the presence of estrogens than the absence of testosterone (*69–71*). Although these data do not address the question of cerebral perfusion in humans, they do support the findings in this cohort of premenopausal women.

Fortunately, these perfusion abnormalities may not all be permanent. Despite reports of irreversible defects in perfusion (*20,21,25*) and metabolism (*28*), changing patterns of glucose metabolism are seen in different periods of cocaine withdrawal (*26*). In addition, the authors showed improvement in perfusion patterns in men undergoing cocaine treatment with buprenorphine (*18*). Although this may reflect either abstinence or an effect of buprenorphine, which has itself been shown to increase cerebral blood flow, this evidence suggested that these perfusion abnormalities result from, rather than are a cause of, substance abuse. CT evidence also suggests that structural changes, in this case cerebral atrophy, may follow moderate use of cocaine (*72*).

This evidence, showing that women who exclusively use cocaine are often indistinguishable from normals while those who also use heroin have abnormal findings, further strengthens this effect hypothesis. This may speak to the need for early treatment of cocaine-dependent women, possible gender differences in response to treatment and possible differences in perfusion pattern response to perturbation and to treatment.

In summary, cocaine-dependent women have fewer abnormalities in cerebral perfusion than comparable men and are indistinguishable from a control group of older women. When cocaine- and heroin-dependent women are considered, however, abnormalities previously noted in men are also found in women. How these abnormalities respond to time and to drug addiction treatment is unknown.

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