Brain Perfusion Is Abnormal in Cocaine-Dependent Polydrug Users: A Study Using Technetium-99m-HMPAO and ASPECT

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Cocaine abuse is widespread and has been associated with serious neurovascular complications. We studied a group of cocaine-dependent polydrug users with ^{99m}Tc-HMPAO and high-resolution SPECT and compared their perfusion pattern to cerebral perfusion in a group of older control subjects. Sixteen of 18 cocaine-dependent polydrug users had abnormal perfusion characterized primarily as small focal defects involving inferoparietal, temporal, and anterofrontal cortex and basal ganglia. Psychometric testing was abnormal in all 18 cocaine-dependent subjects. No relation was found between the severity of SPECT abnormalities and mode of administration or frequency or length of cocaine use. All 15 older normal subjects had normal cerebral perfusion. While the focal perfusion abnormalities to the cortex and basal ganglia could be explained by the profound vasoconstrictor effects of cocaine, the combinational use of multiple substances including cannabis and alcohol may play a contributory role. This study documents the high incidence of functional brain abnormalities in cocaine-dependent chronic polydrug users without corresponding abnormalities on imaging studies of cerebral anatomy and morphology.

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Cocaine use has reached epidemic proportions in the United States (*1*) and has been linked to serious neurologic, cardiovascular, and obstetrical complications (*2–4*). Catastrophic neurovascular damage including subarachnoid and intracerebral hemorrhage and infarction has been associated with severe abuse but is a rare occurence (*5*). Alterations in cerebral blood flow and metabolism without infarction or hemorrhage have been reported in cocaine users when positron emission tomography has been used as a biologic probe (*6*). Abnormalities have been observed even among asymptomatic social cocaine users when functional brain imaging has been performed with ^{123}I-isopropyl iodoamphetamine and standard rotating gamma camera tomography (SPECT) (*7*). The recent availability of high spatial resolution SPECT systems (*8*) and ^{99m}Tc-labeled brain perfusion tracers (*9,10*) offer the opportunity to better define these perfusion defects as to size, location, and overall pattern. Subjects who were diagnosed as currently cocaine-dependent were studied using a high-resolution dedicated brain imaging system (ASPECT) and ^{99m}Tc-hexamethylenepropyleneamine oxime (HMPAO). We compared the perfusion pattern in these subjects to that derived from a group of well-studied normal older control subjects.

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METHODS

Study Population

We studied 18 male, polydrug users with a mean age of 31.7 yr (range 22–42 yr). Subjects were recruited through advertisements in local newspapers. All subjects were interviewed and examined by a physician, and laboratory studies were performed to rule out medical illness. None exhibited evidence of cardiovascular or neurologic disease, and all subjects tested negatively for the HIV antibody. Drug histories were obtained via: (1) a medical history interview with a physician; (2) written drug history questionnaires; and (3) the orally administered Structured Clinical Interview for DSM-III-R. To insure consistency, these three procedures were performed or reviewed by the examining physician. Eleven subjects had magnetic resonance (MR) scans. Eight MR studies were normal, two showed single, less than 0.5 mm, nonspecific foci of high signal on long TR/TE images (Patients 9 and 12, Table 1) and one showed mild diffuse brain shrinkage (Patient 18).

Subject demographics are described in Table 1. All subjects met DSM-III-R criteria for current (<5 yr) cocaine abuse or dependence. They used an average of 2.2 g of cocaine per week (range 0.25–9). Seven subjects used an intravenous route 100% of the time, six subjects freebased their cocaine, one inhaled it, three used a combination of freebasing and inhalation, and one freebased 95% of the time and used an intravenous route the other 5%. They had an average history of cocaine use of 7.7 ± 1.3 yr (range 2–20). Eighteen subjects used alcohol currently, with 7/18 meeting current abuse or dependence criteria. Seven subjects used opioids currently, and all seven met current dependence criteria. Nine subjects used marijuana currently but did not meet current abuse or dependence criteria. Six subjects used

TABLE 1
Subject Characteristics

Subject Number	Age	Cocaine dose per week (gms)	Route	History of cocaine abuse or dependence	Other drugs used Past (> 5 years)	Other drugs used Present (< 5 years)	Urine drug screen on scan day	Neuropsychological Deficit Severity Rating	Neuropsychological Deficit Cognitive Ability	ASPECT Results
1	34	3 to 4	Inhalation	20 years	ETOH, Opioids, +CB	ETOH, CB	cocaine	1	I, O, SM, VR	BG(L), F, T, Pa
2	36	3 to 4.5	snort	approx 2.5 years	ETOH, +CB Sed, Stim, Hal	*ETOH, CB	cocaine, cannabinoids	1	CN, O, S, SM, VL	T, Pa
3	34	1	Inhalation	3 years	ETOH, CB Stim, Hal	ETOH	cocaine	2	CA, O, P, VR	BG(R), F, T, Pa
4	32	1 to 1.5	Inhalation/ snort	2 years	no past substance dependence/abuse or use	ETOH, CB	cocaine, cannabinoids	2	O, P, PD, S, SL, SR, VL, VR,	BG, F, T, Pa
5	31	0.5	Inhalation	8 years	*ETOH, +CB Stim, Hal	*ETOH	cocaine	1	CA, O, P, PD	BG, Th(L), F, T, Pa
6	35	0.5 to 1	Inhalation	7 years	*ETOH, CB	*ETOH Sed, Hal, NSD	cocaine benzodiazepine	1	O, PD, SL, VR	F, T, Pa
7	35	5.4	Inhalation, IV (5%)	4 years	*ETOH, Opioids, *CB, Sed, Stim, Hal, Butyl nitrate	*ETOH *Stim (not into CB)	cocaine	1	CA, O, P, SL	T(R), Pa
8	32	0.5	Inhalation, snort	4 years	ETOH, *CB Stim, Hal	*ETOH, CB	cocaine	1	CA, O, P, SL, SM, VL	BG(R), F(R), T, Pa
9	42	1 to 2	Inhalation	13 years	ETOH, CB Sed	ETOH, CB	negative (s/o history)	2	CA, P, SM, SR	Normal
10	23	6 to 9	Inhalation, snort	4 years	ETOH, CB	+ETOH, CB Sed	negative (s/o history)	1	SL	F(R), T, Pa
11	30	0.25 to 2	Inhalation	5 years	CB, Hal	ETOH, CB	cocaine	1	SL, SM	Normal
12	36	0.5	IV, snort Inhalation	6 yrs	ETOH, *Opioids, *CB, *Sed, *Stim, +Hal	ETOH, *Opioids CB	Not administered	1	A, SL, SM	BG(L), F(L), T, Pa(L)
13	42	2.5-5	IV, Inhalation	4 yrs	*ETOH, *Opioids, *CB, *Sed, *Stim, +Hal	ETOH, *Opioids	Not administered	1	VR(T), SL	BG(L), F(L), Pa(L)
14	32	3.5	IV, Inhalation	5 yrs	+ETOH, *Opioids, *CB, *Sed, Stim, +Hal	ETOH, *Opioids, CB, Sed Glue, Butyl nitrate	Not administered	2	CA, O, P, PD, SL	BG, F, T(L), Pa(L)
15	35	2	IV, snort Inhalation	17 yrs	*ETOH, *Opioids, *CB, *Sed, *Stim, *Hal, +NSD, +Butyl nitrate	ETOH, *Opioids Sed	Not administered	1	O, S, SL, VL	BG(L), F(L), T, Pa
16	35	0.5	IV, Inhalation, snort	12 years	ETOH, *Opioids, CB, Sed, Hal	ETOH, *Opioids, Sed	Not administered	1	O, S, SL, VL	BG, Th(R), F, T, Pa(L)
17	32	1 to 1.5	IV, Inhalation, snort	5 years	*ETOH, *Opioids, +CB, +Sed, Stim, Hal, NSD, Butyl nitrate MDA	*ETOH, *Opioids, +Sed	Not administered	2	O, S, SL, SM, VL	BG(L), F, T, Pa(L)
18	33	1	IV, snort, Inhalation	10 years	*ETOH, *Opioids, *CB, *Sed, *Stim, *Hal, *Glue, *Butyl nitrate, *MDA, *Steroid X	ETOH, *Opioids	Not administered	1	SL, VL	F, T, Pa

KEY: * meets criteria for DSM-IIIR substance abuse; + meets criteria for DSM-IIIR substance Dependence

ETOH = Alcohol
CB = Cannabis
Sed = Sedative
Stim = Stimulant
Hal = Hallucinogen
NSD = Nitrous oxide

0 = no deficit
1 = mild deficit
2 = moderate deficit
3 = severe deficit

A = Attention
CA = Concept Attainment
CN = Color Naming
I = Inhibition
O = Organization
P = Perseveration
PD = Perceptual Distortion
S = Segregation
SL = Spatial Learning
SM = Set Maintenance
SR = Spatial Retrieval
VL = Verbal Learning
VR = Verbal Retrieval

BG = Basal Ganglia
Th = Thalamus
F = Frontal
T = Temporal
Pa = Parietal

sedatives currently, and one met current abuse criteria. One subject used stimulants currently but did not meet criteria for current abuse or dependence. One subject had a current history of hallucinogen and nitrous oxide use, and one subject had a current history for use of glue and butyl nitrate; neither met abuse or dependence criteria.

All subjects reported using cocaine from 1 to 16 days prior to the SPECT study day. Urine drug screening was performed on eleven subjects on the study day, nine of which were positive for cocaine metabolites. Two subjects had negative drug screens and denied using cocaine for at least 9 to 16 days prior to the scan.

All subjects were given a battery of neuropsychologic tests designed to test attention, memory, and higher order cognitive functions. The test battery included the Wechsler Memory Scale subtests of Digit Span and Visual Reproduction, the Stroop Color-Word Test, the Rey-Osterreith Complex Figure Test, the California Verbal Learning Test, the Wisconsin Card Sorting Test, and the Luria 3-step Motor Sequence Test.

An older control group also was selected who reported no previous or current abuse of alcohol nor previous or current use of cocaine, cannabis, stimulants, or opioids. The mean age of the older control subjects was 68.0 yr (range 53–79 yr). Six subjects were males and nine were female. The subjects underwent a general physical examination and an extensive neurologic interview and examination. None had histories of neurologic, psychiatric, or cardiovascular diseases, and all had normal neurologic examinations. Each subject underwent a global assessment of memory and orientation, the Mini-Mental Status Test, and each took cognitive tests that included the Stroop Color-Word Test, Verbal Fluency Test, Wechsler Vocabulary Test, Luria Mental Rotation Test, Rey-Osterreith Complex Figure Test, Logical Memory Test subset of the Wechsler Memory Scale, and the Wisconsin Card Sorting Test.

Imaging Protocol

The ASPECT brain imager uses a single stationary annular sodium iodide crystal with an inside diameter of 31 cm and a thickness of 8 cm. The collimator system is made up of three parallel-hole collimators that are rotated incrementally so that the gamma rays projected onto the inner surface of the crystal are collected. The system uses an array of 63 photomultiplier tubes and has a system resolution in air using capillary line sources of 8.2 mm at the center and 7.3 mm at 9 cm from the center for ^{99m}Tc (*8*). The sensitivity in air is 7.8 cps per μCi for a point source at the center and is uniform throughout the 21.4 cm diameter by 10.7 cm axial field of view.

Brain perfusion SPECT was performed beginning 10 min following the intravenous injection of 20 mCi of ^{99m}Tc-HMPAO (Ceretec, Amersham, Ltd., Amersham, England). Data were acquired for 30 min on an ASPECT system (Digital Scintigraphics,

Inc., Boston, MA) in 120 projections with a 360-degree rotation of the collimators. Two pulse-height analyzer windows were employed, one set at 140 ± 14 keV and one set to acquire scatter information from 112 to 126 keV. After the completion of acquisition, the collimator and crystal corrections were performed on each data set. The combined set of projections was then calculated by subtracting 90% of the scatter projections, filtered to remove the forward scatter component from the photopeak projections. The projections were prefiltered using a Butterworth filter (cutoff = 0.175 cycles per pixel; power factor = 20). The reconstructed slices were attenuation corrected and displayed on a 128 × 128 matrix (1.67 × 1.67 mm pixel size) as a set of 64 slices (1.67 mm slice thickness). Coronal, sagittal, and rotating three-dimensional displays were calculated from these slices.

Images were interpreted independently by three reviewers blinded to the clinical information. A final interpretation was reached by consensus in cases of disagreement. Transaxial and coronal images were displayed using a standard yellow-red color table for delineation of brain anatomy (see Fig. 1A) and a linear color table referenced to the maximum activity in the cerebellum for identification of perfusion defects; cortical regions less than 60% of the maximum cerebellar activity as determined from computer-generated isocount maps of ^{99m}Tc-HMPAO activity (see Fig. 1B) were reported as abnormal. The defect was described as small if it involved less than 1 cm of cortex and large if a single perfusion defect involved a centimeter or more of cortex. Perfusion defects were reported as to location: frontal, temporal, parietal and occipital lobes, basal ganglia, thalamus, and cerebellum. The extent, location, and severity of the defects were then compared to drug use and the results of the neuropsychologic tests.

RESULTS

Sixteen of 18 cocaine-dependent polydrug users had abnormal brain perfusion patterns (Fig. 1). Focal perfusion abnormalities were most frequently seen in the inferior parietal cortex (16/18), temporal cortex (15/18 patients), anterofrontal cortex (14/18 patients), and basal ganglia (11/18 patients) (Table 1). Abnormalities were not seen in the cerebellum or occipital cortex and only two abnormalities were reported in the thalamus. Defects appeared as small, well-defined focal areas of reduced tracer uptake in 15 patients, with additional large perfusion deficits in 11 of these subjects, and large focal defects alone in one subject. We found no relation between the number of large or small SPECT abnormalities and mode of administration, frequency or length of use, concomitant alcohol or other substance abuse. The two subjects with normal SPECT studies had freebased cocaine at least one to two times per week for 6–10 yr, reported only occasional cannabis use in the past, were rated moderately to severely cocaine-dependent, and reported only infrequent alcohol use. One of these subjects tested negatively for cocaine metabolites and both tested negatively for cannabis metabolites at the time of the SPECT study.

Psychometric tests were abnormal in all subjects (Table 1). Of the 18 subjects, 13 had mild and 5 had moderate deficits. The more frequent neuropsychologic defects involved spatial learning (13/18), organization (12/18), perseveration (7/18), set maintenance (7/18), verbal learning (7/18), and concept attainment (6/18). While these abnormalities were consistent with perfusion abnormalities to the frontal and temporoparietal association cortex, a more detailed comparison between the site of the perfusion defect and the character of the neuropsychologic defect could not be made because of the size of the patient population.

All 15 older control subjects had normal cerebral perfusion patterns on ^{99m}Tc-HMPAO SPECT imaging (Fig. 2) and all performed normally on neuropsychologic tests.

DISCUSSION

Cocaine is a potent vasoconstrictor. When used as a local anesthetic, it produces central nervous system adrenergic stimulation by blocking the presynaptic reuptake of norepinephrine and dopamine (*11*). Its use has been associated with a number of cardiovascular complications as well as with vasoconstriction of the coronary arteries and a drop in coronary blood flow (*3, 12–17*). While cocaine is the drug most frequently involved in drug-related emergency room visits (*18*), only 47 cases of stroke have been reported in the literature (*5*). Since cocaine acts as a vasoconstrictor and causes elevated blood pressure and heart rate, most of these strokes are associated with intracranial and subarachnoid hemorrhage.

Functional imaging of the brain using radiotracers that reflect cerebral metabolism and blood flow provides the first opportunity to evaluate the functional abnormalities that may presage the anatomic and morphologic damage that is reflected on transmission CT and MR imaging. Our study indicates a high incidence of regional cerebral blood flow abnormalities in cocaine-dependent polydrug users. High-resolution SPECT is useful in identifying the pattern of these alterations in cerebral blood flow. The defects tend to be focal, well-demarcated reductions in cortical perfusion, often less than 1 cm in length. The temporal, inferior parietal, and anterior frontal cortex were the most frequently involved areas of the brain. Volkow et al. observed abnormalities in regional cerebral blood flow primarily in the prefrontal cortex using large regions of interest that may not have detected small defects (*6*). London et al. observed that glucose metabolism was reduced over the entire cerebral cortex as well as the mid-brain and thalamus after the acute administration of cocaine (*20*). We were able to define widespread focal, usually small, perfusion abnormalities in our chronic cocaine polydrug users perhaps because of the high spatial resolution of our system.

Cortical perfusion defects may be the result of vasospasm either due directly to the effect of cocaine on smooth muscle or indirectly by potentiating the physiologic response to cocaine (*19*). The defects probably represent at least some degree of irreversible ischemia since Volkow et al. found no improvement in perfusion using $H_2{}^{15}O$ PET in chronic users after cocaine withdrawal (*6*). If the ob-

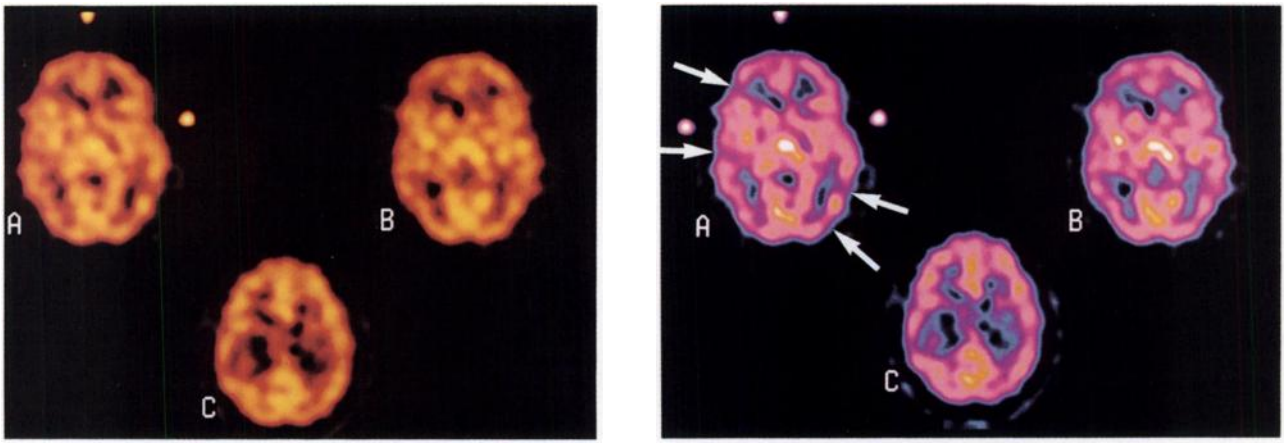

FIGURE 1. Transaxial ^{99m}Tc-HMPAO SPECT in a subject reporting recent use of cocaine with standard hot-body (yellow-red) color scale (left) and the isocount map as described in the text (right) 2 cm (A), 4 cm (B), and 6 cm (C) above the orbitomeatal line. There are multiple small focal perfusion defects involving the right inferior parietal, left temporal, and left frontal cortex (arrows). There is also asymmetric basal ganglia uptake decreased on the right. The left hemisphere is on the reader's left.

served perfusion defects represent regions of structural damage, they must be below the resolution of conventional imaging techniques, since we found normal or nonspecific findings on MR imaging in our subjects and Tumeh et al. observed cortical perfusion defects in chronic cocaine users who had normal CT studies.

Perfusion abnormalities involving the basal ganglia were found in 11/18 of our patients. It has been proposed that the cocaine receptor is associated with dopamine uptake and metabolism (*21,22*). Since dopamine receptors are heavily concentrated in the basal ganglia, alterations in receptor function and dopamine metabolism may affect cerebral blood flow and, therefore, be a factor in the high incidence of basal ganglia abnormalities that we observed on ^{99m}Tc-HMPAO SPECT.

Most of our cocaine-dependent subjects were using other substances, principally alcohol, cannabis and, in seven patients, opioids. Abnormalities in regional cerebral blood flow have been reported in chronic alcoholics with ^{99m}Tc-HMPAO SPECT. Decreased glucose metabolism has been observed after morphine administration (*23*). Concomitant substance abuse among cocaine users occurs with a very high frequency and it is extremely difficult to isolate a population of patients who are only using cocaine. The acute administration of cocaine has been associated with reduced cerebral glucose utilization (*20*) and reduced coronary blood flow (*12*). Given its potent vasoconstrictor effect, it is highly likely that cocaine was at least a contributory factor in the development of focal perfusion defects in our patients.

We used an older population as a control group for several reasons. Attempts to recruit age-matched controls were unsuccessful because we could not reliably exclude subjects with previous substance use. The older population, on the other hand, was well studied, carefully screened, and were unlikely to have used cocaine based on

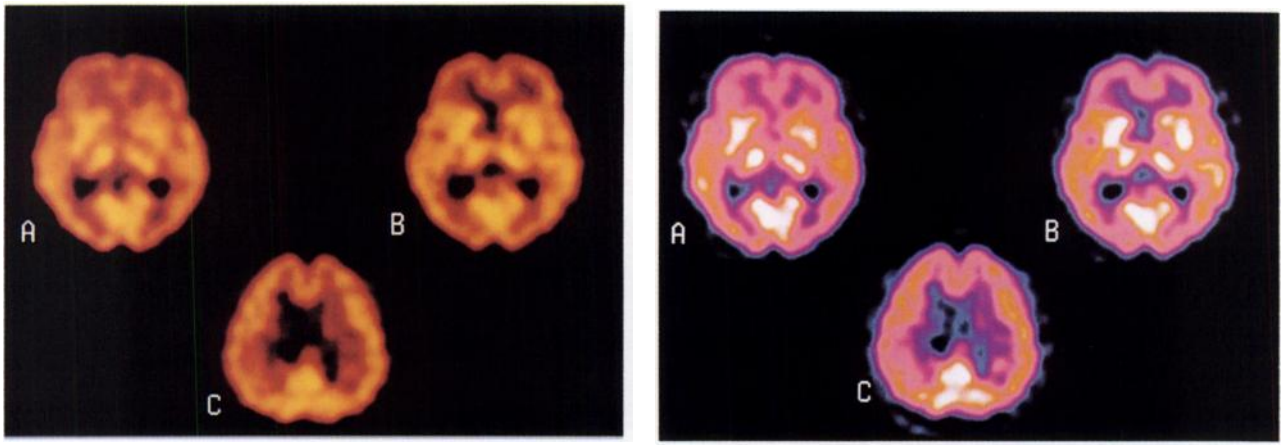

FIGURE 2. Transaxial ^{99m}Tc-HMPAO SPECT in an older control subject with standard hot-body (yellow-red) color scale (left) and isocount map as described in text (right) obtained 2 cm (A), 4 cm (B), and 6 cm (C) above the orbitomeatal line. Cerebral perfusion is normal. The left hemisphere is on the reader's left.

their age. Since all control subjects had normal perfusion, we need only assume that their cerebral blood flow was normal when they were within the age-range of the cocaine polydrug users, an assumption supported by other studies.

This study demonstrates a high incidence of focal cortical perfusion defects in HIV-negative, cocaine polydrug users. This pattern should be recognized in patients having brain perfusion SPECT for other reasons and should serve as a warning that, despite normal or near normal MRI studies, substance abuse is associated with a very high incidence of functional abnormalities of the brain.

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