Brain Atrophy and Chronic Cocaine Abuse: Background and Work in Progress

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INTRODUCTION

The crack epidemic, now a decade old, disabused neurologists of the idea that cocaine was a relatively safe drug. Acute neurologic complications of cocaine intoxication such as headaches, delirium, seizures, and strokes have now been amply delineated. Less clear is whether long-term cocaine use, uncomplicated by acute problems, can lead to structural or functional changes in the human brain. Brain atrophy is a potential consequence of alcohol abuse (Cala and Mastaglia 1980; Fox et al. 1976; Harper et al. 1988; Ron et al. 1982), inhalant abuse (Hormes et al. 1986; Rosenberg et al. 1988), and use of nonrecreational substances such as corticosteriods (Bentson et al. 1978; Gordon 1980) and valproic acid (McLachlan 1987). This chapter summarizes some earlier work linking long-term cocaine abuse to brain atrophy, and it describes an ongoing investigation of brain atrophy and dysfunction in chronic cocaine abusers using volumetric brain magnetic resonance imaging (MRI).

PRIOR STUDIES

The use of cocaine in Minneapolis and St. Paul took off in 1986, about a year after the crack epidemic arrived in New York. Admissions to Hennepin County Medical Center (HCMC) for cocaine-related illness quadrupled within a year, with neurologic complications accounting for about a tenth of these admissions. A link between brain atrophy and cocaine first surfaced in a retrospective study of patients admitted with the then relatively novel diagnosis of cocaine-related seizure (Pascual-Leone etal. 1990). This study covered 1985 to 1987, during which time 474patients were admitted to HCMC with a primary diagnosis of acute cocaine intoxication corroborated by a positive urine toxicology screen for-cocaine. Thirty-two of these patients had a first-ever seizure within 90minutes of using cocaine. Thirteen of these 32 were first-time

cocaine users. Computed tomographic (CT) head scans were performed in all 32patients with new-onset seizures. Among the 13 first-time users, there was a single abnormal scan; it showed a subarachnoid hemorrhage. Among the 19 habitual cocaine users, two scans revealed cerebral infarc-tion and 10 (53 percent) showed diffuse cerebral atrophy. All 10patients with atrophy were human immunodeficiency virus (HIV) negative. None was older than 38 years. Their experience with alcohol and other drugs could not be accurately determined.

In a second retrospective study covering a similar time interval, the focus was on brain volume, itself quantified by linear CT measurements (Pascual-Leone et al. 1991). This study included patients at HCMC and the University of Minnesota Hospital admitted with cocaine intoxication or addiction who underwent a CT scan. The presenting problem was head-ache (about half), seizure, delirium, or movement disorder. Patients with the following potentially confounding variables were excluded: polydrug or alcohol abuse (by self-report), alcohol dependence (by "Diagnostic and Statistical Manual of Mental Disorders," 3d ed. (DSM-III) criteria), HIV seropositivity, decreased serum albumin, and age less than 20 or greater than 40 years. Of the 51 patients studied, 16were first-time cocaine users. Planimetric measurements were performed on the CT scans of the first-timeand habitual cocaine groups as well as a control group of 54 patients admitted for headache with the same exclusions. There were seven mea-surements (see figure 1) plus four indices derived from these measures.

The habitual cocaine abuser group differed significantly from both the first-use and control groups on all but two of the measurements and all four indices. This finding implies cerebral atrophy in the habitual user group (table 1). There was no significant difference on any of the measures or derived indices between the first-use cocaine subgroup and the controls. There was no relationship between CT measurements and age in this two-decade age range. There was a correlation between duration of cocaine abuse and atrophy on one measure, the maximal frontal horn width, suggesting a dose-effect relationship (figure 2).

There is little additional information on the effect of cocaine abuse on human brain volume. Studies involving cocaine and CT or MRI brain imaging have featured abusers of multiple drugs (including alcohol) besides cocaine. In a study from Johns Hopkins University and the National Institute on Drug Abuse (NIDA) Addiction Research Center, three planimetric CT measures were made on a group of abusers of

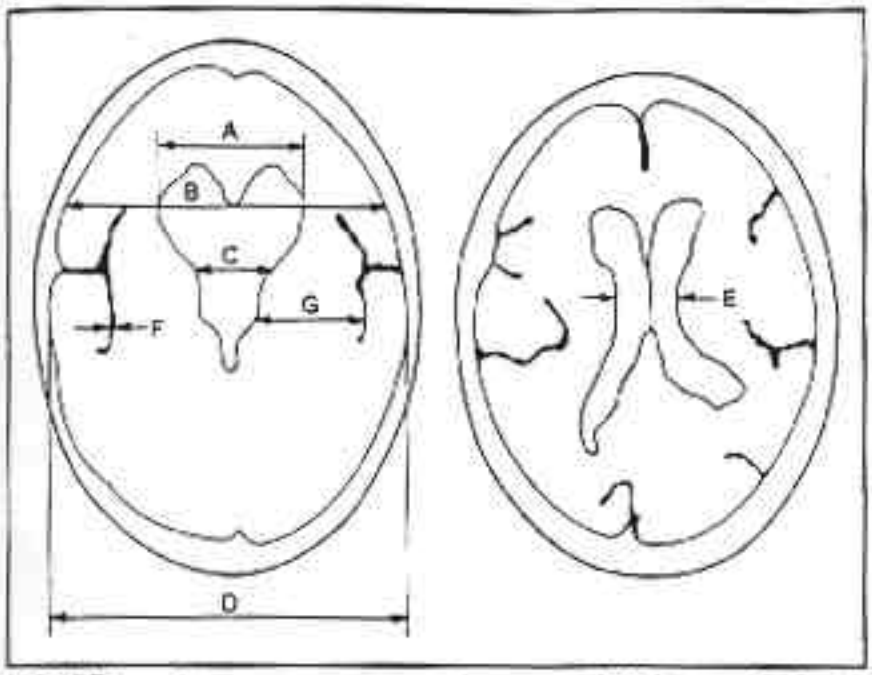

FIGURE 1. *Linear measurements taken on axial CT slices. Maximal width of the frontal horns of the lateral ventricles (A), frontal brain width (B), minimal intercaudate distance (C), maximal width of the brain (D), minimal width of the ventricular bodies (E), maximal width of the sylvian fissure (F), and mean distance between the third ventricle and the sylvian fissure (G).*

multiple substances, including cocaine (Cascella et al. 1991). A severity score was established for each drug, based on frequency and quantity of use. Substance abusers and controls differed significantly on third ventricular width, suggesting atrophy in the substance abuser group. For individual substances, however, only alcohol severity scores could be correlated with any measure of atrophy, after taking into account the effect of age.

There is a single study that includes volumetric MRI measures performed at the University of Trondheim, Norway. The study group consisted of polysubstance abusers with experience in, or abuse of, a mean of 5.3 drugs, including heavy alcohol consumption in each case (Aasley et al. 1993). There were planimetric and volumetric measures of the cerebral hemispheres and cerebellum; the substance abuser and control groups

TABLE 1. Values of the linear measurements and calculated indices of cerebral atrophy on CT in controls (N = 54) and first-time (N = 16) and habitual (N = 35) cocaine abusers.

		Cocaine abusers	
	Controls	1st time	Habitual
Max. frontal horns width (A)	3.06±0.20	3.04±0.26	3.63±0.32*
Frontal brain width (B)	10.77±0.37	10.68±0.44	10.69±0.47
Min. intercaudate distance (C)	0.83±0.14	0.80±0.22	1.14±0.32*
Max. brain width (D)	12.76±0.66	12.96±0.57	12.17±0.63
Min. ventricular bodies width (E)	2.30±0.30	2.40±0.41	2.81±0.37*
Max. sylvian fissure width (F)	0.22±0.06	0.21±0.11	0.28±0.08†
Distance third ventricle-sylvian fissure (G)	3.88±0.20	3.88±0.21	3.73±0.36‡
Frontal lobe index (A/B)	0.29±0.02	0.29±0.03	0.34±0.03*
Evans ratio (A/D)	0.24±0.02	0.23±0.02	0.28±0.03*
Bicaudate index (C/D)	0.07±0.01	0.06±0.02	0.09±0.02*
Huckman number (A+C)	3.88±0.26	3.84±0.39	4.76±0.54*

NOTE: All measurements given in cm as mean ± standard deviation.

KEY: * = $p < 0.005$ habitual cocaine addicts versus controls and versus first-time cocaine users; † = $p < 0.005$ habitual cocaine addicts versus controls, $p < 0.05$ versus first-time cocaine users; ‡ = $p < 0.05$ habitual cocaine addicts versus controls and versus first-time cocaine users; max = maximum; and min. = minimum.

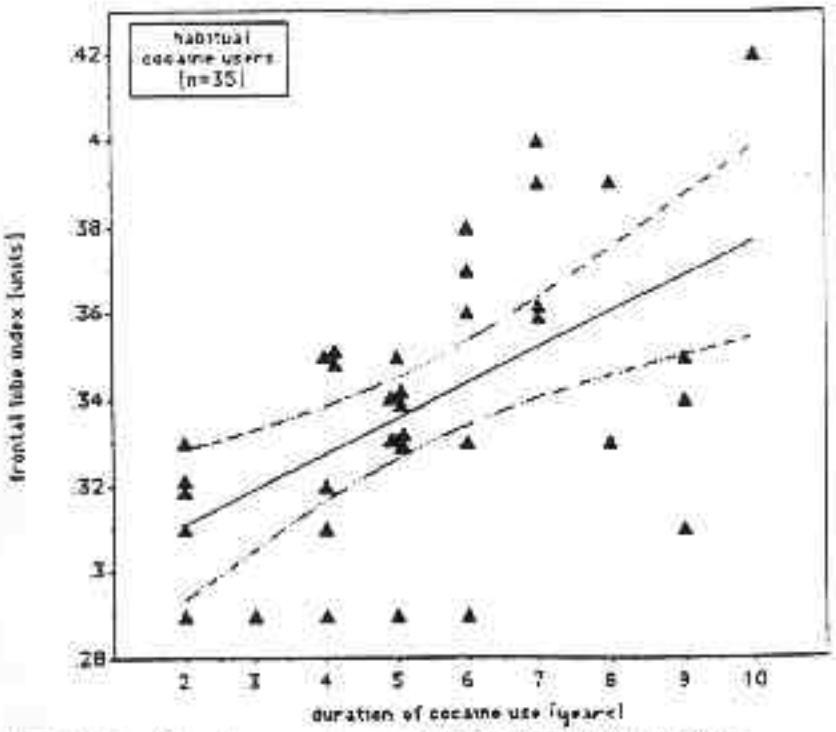

FIGURE 2. *Simple regression analysis for frontal lobe index (A/B) and duration of cocaine abuse in years in the 35 habitual cocaine abusers. Regression line and 90 percent confidence bands for the true mean of the frontal lobe index are displayed.*

differed only on a measure of the volume of the cerebellar vermis, the site of alcoholic cerebellar degeneration.

In two studies of single photon emission computed tomography (SPECT) in cocaine abusers, many subjects abused additional substances, including alcohol. In one of these, CT scans were also obtained, supplementing SPECT data (Tumeh et al. 1990). Diffuse cerebral atrophy was found in 2 of 10 subjects, one of whom used alcohol heavily. In the second SPECT study, MRI revealed diffuse cerebral atrophy in one subject of eight, whose substance abuse profile is not described (Strickland et al. 1993).

The reported HCMC studies were limited. Their retrospectivity prevented adequate control for the confounding influence of alcohol or other substances, nutritional status, and other neurologic problems

such as multiple head injuries. Brain atrophy was inferred from linear measure-ments in a single plane. No conclusions about preferential involvement of grey or white matter were possible, and no mechanism for atrophy was suggested. In other studies, alcohol appeared to be a potent confounder. It would also be important to consider whether any brain atrophy due to cocaine brings brain dysfunction in its wake, and whether either atrophy or dysfunction prove to be reversible with abstinence from cocaine.

THE BRAIN ATROPHY AND DYSFUNCTION IN CHRONIC COCAINISM (BADCO) STUDY

The BADCO Study has been undertaken to investigate brain atrophy and its functional consequences in a manner that will overcome some of the methodological problems that have afflicted earlier studies. The study is driven by four hypotheses: Long-term use of cocaine induces cerebral atrophy; atrophy has functional consequences detectable as cognitive and electrophysiological dysfunction; the pathogenic basis for atrophy is cerebral ischemia; and consequences are partially reversible with abstinence from cocaine.

Subjects are recruited among inpatients at four Twin Cities chemical dependency treatment centers. The need for inpatient treatment, defined with increasing stringency in recent years, represents the imprimatur of severe abuse. Total duration of substance abuse must be 6 months or longer. Subjects must be 20 to 40 years old, have at least a 10th grade education, and be 1 to 4 weeks out from their last substance use. Poly-substance abusers, who predominate at these treatment centers, are excluded, along with monosubstance abusers of inhalants and alcohol. Subjects are screened for potentially confounding neurologic, cardiac, metabolic, toxic, and nutritional problems with a neurologic history, physical examination, HIV antibody test, liver function tests, serum albu-min, body mass index, and urine toxicology. Total substance exposure is quantified, and an additional index of functional severity based on the Global Assessment of Function (GAF) Scale (DSM-IV) is assigned.

Subjects are divided into two experimental groups: cocaine abusers and abusers of a single other substance (monosubstance abusers) excluding cocaine, alcohol, and inhalants. (Those who abuse cocaine only are also considered monosubstance abusers.) The group of other monosubstance abusers provides a match for the cocaine abusers in terms of lifestyle. The experimental protocol involves

volumetric MRI, neuropsychological testing, electrophysiological testing and, for some cocaine abusers, SPECT or positron emission tomography (PET). In BADCO's cross-sectional wing, comparisons will be drawn between these two experi-mental groups and normative data for each element of the experimental protocol. Cross-sectional comparisons will address the first two study hypotheses. A longitudinal wing will feature a 6-month reassessment and retest of the cocaine abusers, not all of whom will have continued to abstain from cocaine. Longitudinal data will address the fourth study hypothesis. The functional imaging techniques, SPECT and PET, will be used to address the third study hypothesis.

MRI data are acquired on a 1.5 Tesla unit that also produces standard, clinically useful images. Volumetric analysis is performed using a novel three-compartment model (Bonar et al. 1993). For each subject, a "slab" of brain tissue consisting of 15 to 20 3-millimeter-thick MRI brain slices (including most of the cerebral hemispheres but excluding the posterior fossa) is analyzed. Percentages of grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) are calculated for a slab by summing across slices; a fourth (other) compartment consisting mostly of meninges and blood vessels is accounted for. The combined GM+WM compartment can be taken as a relative measure of brain volume; a small GM+WM compartment implies cerebral atrophy. The reproducibility of the method has been investigated in a group of nine normal volunteer subjects aged 20 to 40 years who were scanned two to six times over a period of several years; this group serves as the normal control group for the brain volume aspect of the study. The fractional volume of the GM+WM compartment is extremely stable over time, although the fractional volumes in the individual GM and WM compartments vary somewhat.

The neuropsychological wing of the study involves a battery of tests constructed to evaluate a broad range of cognitive abilities, with a focus on information processing speed and efficiency and on mechanisms of attention. There are tests of general intelligence, including reading ability and vocabulary, that can be expected to reflect baseline function; verbal and visual memory tasks to test immediate memory span, short-term processing, delayed retention, and rate of new learning and retrieval; tests of attention, response time, and impulsivity; tests of executive function; and tests of psychomotor function. A depression inventory is also included. This battery, of course, addresses the question of brain dys-function due to chronic cocaine abuse, and in the specific context of BADCO it permits correlation with anatomic changes revealed by MRI.

The electrophysiological arm of BADCO consists of a quantitative electroencephalogram (EEG). Recording is performed during eyes-open and eyes-closed relaxed wakefulness, as well as during a mental arith-metic task. Artifact is edited out in this system, so that lengthy epochs are available for analog-to-digital conversion and fast Fourier transform analysis. Power in each of six defined frequency bands can be derived for each electrode site. Like the neuropsychological arm of BADCO, the electrophysiological arm affords the possibility of assessing the func-tional correlates of imaging data.

Preliminary Results

For purposes of this chapter, a partial analysis of early BADCO data was undertaken. In keeping with a focus on brain atrophy, volumetric MRI data were analyzed and compared with measures of substance abuse severity. Results from the neuropsychological and electrophysiological arms are not presented.

Forty-five substance abusers have been entered to date (see table 2). Most cocaine abusers smoked crack. The other monosubstance abuser group, at present, includes predominantly opiate abusers. The cocaine abuser and other monosubstance abuser groups are very closely matched for age and education. For each substance, an approximate value for total quantity of substance used was calculated from average quantity per unit time and duration; a rating is based on a scale of 1 to 5. The GAF func-tional outcome rating is based on a scale of 10 to 100, with 100 implying no effect of substance abuse on family or social and occupational function. (Both rating scales are available upon request.) Not surprisingly, the BADCO requirement of inpatient chemical dependency treatment status produced subjects with considerable social and occupational problems. Table 2 reflects the entire BADCO population divided between groups.

MRI data are currently available from 24 cocaine abusers and 6 other monosubstance abusers. These subgroups do not differ significantly from their parent groups, as presented in table 2.

Figure 3 contains illustrative data for a single cocaine abuser who was studied twice, 6 abstinent months apart. In this figure, transaxial slice number (abscissa) is plotted against percentage of brain slab volume (ordinate). Brain slice numbers increase in a caudal-rostral direction. Summing the compartmental contributions of each slice across all

TABLE 2. BADCO Study population to date. Some cocaine abusers have no single preferred route of administration. Lifetime quantity of single substance used is scored on a scale of 1to 5. The measure of functional outcome, scored on a scale of 10 to 100, is described in the text; higher figures imply better function.

	SUBJECTS	
	Cocaine*	Other substance**
Number		
Age		
Education (y)	13.2 (11-19)	12.7 (12-14)
Duration of abuse (y)	4.7 (.6-14)	4.7 (.5-15)
Quantity used	3.2 (1-5)	3.5 (3-4)
Functional outcome	50.4 (15-70)	47.8 (30-70)

KEY: * = route of administration: smoked, 21; insufflated, 8; IV, 1.
** = heroin, 7; prescription opiates, 1; marijuana, 2; benzodiazepines, 1.

15 slices yields the overall percentage composition for each tissue compartment. The large GM contribution (solid line) at slice 25 corresponds to deep grey nuclei (thalamus and basal ganglia), the WM peak at slice 35 (dot-dash line) corresponds to the centrum semiovale, and the CSF peak at slice 33 corresponds to the lateral and third ventricles. In this subject, the GM+WM compartment is within normal limits on both occasions. The significance, if any, of the scan-to-scan variation in GM and WM composition is unclear.

In figure 4, grand means (horizontal dashes) for the GM+WM fraction (for each of 20 brain slices) are displayed for the cocaine abuser group; individual subject values are represented by small closed circles. The continuous solid line represents the slice means for the normal control group; the dashed lines correspond to plus or minus 2 standard deviations (SD). The cocaine abusers appear to be atrophic (cocaine abuser slice means are below normal control means). The atrophy implied by these preliminary data appears to be generalized. Data from separate GM and WM plots are, at this stage, inconclusive, but they suggest greater volume loss in the WM compartment.

Brain volume has been defined here as (GM+WM)/(GM+WM+ CSF+"other") across all brain slices comprising the slab; in table 3, the

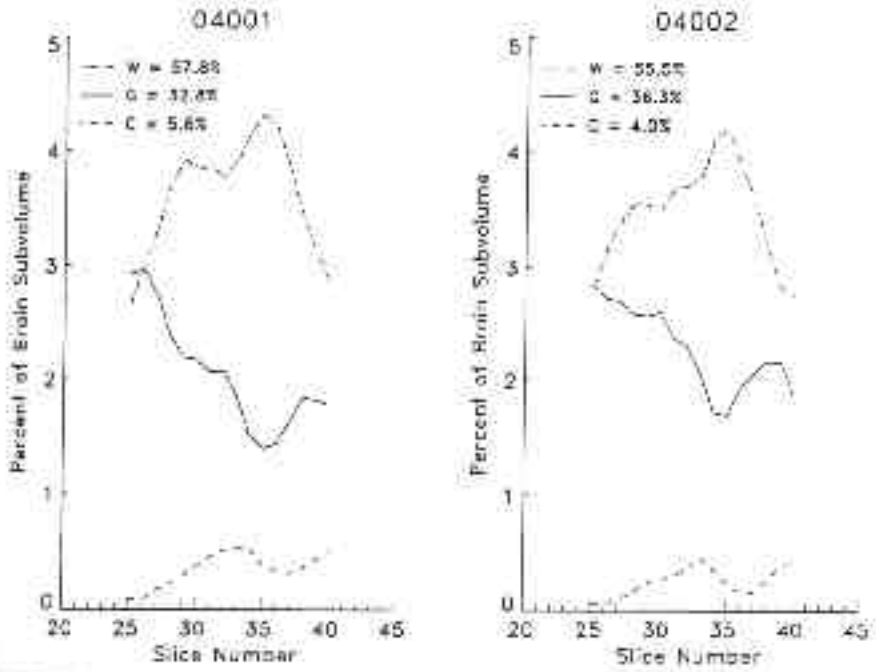

FIGURE 3. *MRI data from abstinent cocaine abuser.*

mean brain volume (SD) is shown for each experimental group and for the normal control group. Each experimental group differs significantly from the normal control group. There is no difference on this measure between the cocaine abuser and other monosubstance abuser groups. In the cocaine abuser group, there is no significant correlation between brain volume and three measures of severity of abuse: duration of abuse, quantity of substance used, and functional outcome.

Discussion

Data from the ongoing BADCO Study are preliminary and cannot at this time support any definite conclusions. There is an early indication that the cocaine abuser group will differ from normal controls on a volumetric

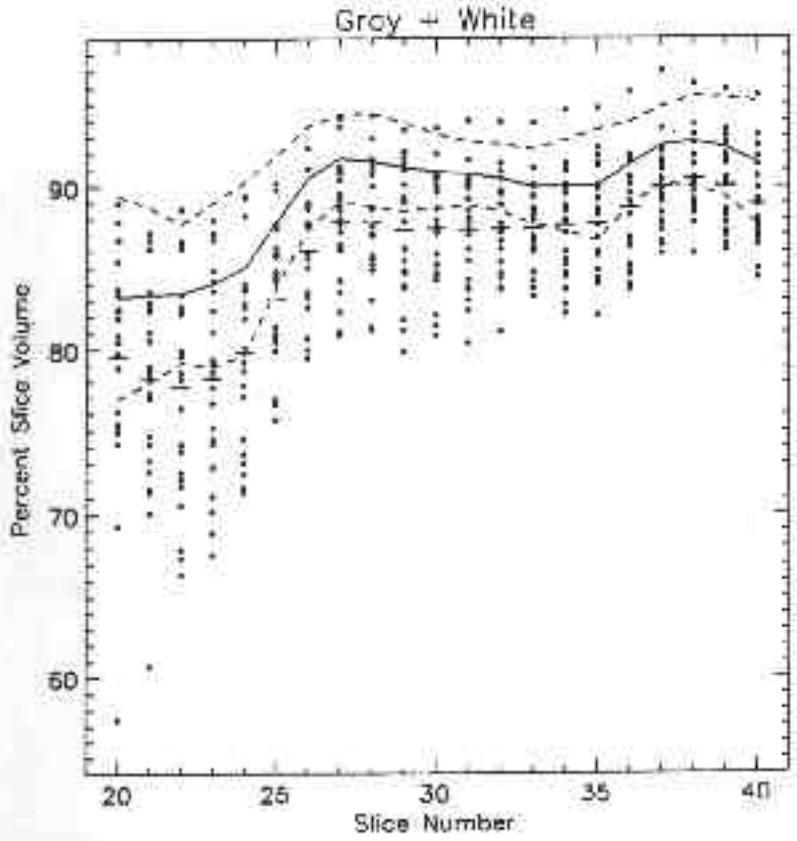

FIGURE 4. *Grand means for GM+WM fraction, cocaine abuser group.*

MRI measure of brain volume, suggesting cerebral atrophy in the cocaine abuser group and corroborating earlier retrospective studies of cocaine abusers at the same institution.

The measure of atrophy here is a relative one, with brain (WM+GM) volume expressed as a percentage of total intracranial contents. Absolute volumes in the WM and GM compartments have not yet been investi-gated, but they might provide an alternate measure if corrected for height. Atrophy appeared widespread, but it may be evenly distributed only with respect to the horizontally oriented slices that make up a slab.

TABLE 3. $p < 0.01$ for cocaine group versus normal controls and for other monosubstance abuser group versus normal controls.

BRAIN VOLUME FRACTIONS			
	White matter	Grey matter	White & grey
Cocaine (24)	0.510 (0.048)	0.350 (0.049)	0.860 (0.036)
Other (6)	0.505 (0.054)	0.353 (0.027)	0.858 (0.045)
Norms	0.539 (0.046)	0.359 (0.048)	0.898 (0.010)

The MRI technology used in this study affords the opportunity to reorient the plane of slicing. An analysis of coronally oriented slices, for exam-ple, might demonstrate atrophy that preferentially involves particular lobes. There is also the possibility of investigating specific regions rather than a whole brain slab.

If cocaine does induce cerebral atrophy, the association between cocaine and ischemic stroke provides one possible mechanism. Predominantly WM atrophy, as suggested by early results here, is in keeping with small-vessel ischemic disease. The SPECT studies already cited do show per-fusion defects in cocaine abusers, though not associated with atrophy onMRI (Strickland et al. 1993) or CT (Tumeh et al. 1990) in the great majority of cases. The correlation of SPECT with quantitative MRI, as in the BADCO Study, may be more fruitful. Radiologic evidence of small-vessel ischemic disease will also be looked for on the standard clinical MR images that are generated during volumetric MRI data acquisition. Alternatively, a direct, widespread cytotoxic effect of cocaine, for which there is no compelling evidence, may account for atrophy.

The BADCO Study's MRI data are presented here in stand-alone fashion, but the functional tests in the study, especially the neuropsychological battery, will supply critical context for any imaging findings. The idea of drug-induced brain atrophy is chilling (and shrunken cerebral hemis-pheres would make an eye-catching "this is your brain on drugs" display), but atrophy independent of functional decline may represent an anatomic curiosity, with no dire consequences for the cocaine abuser. More light will be shed on the importance of anatomic or functional changes by the longitudinal wing of the study.

The BADCO Study may find atrophy without implying a specific causal relationship to cocaine, since there is, so far, no difference in brain volume between cocaine abusers and noncocaine, nonalcohol,

noninhalant mono-substance abusers. If both groups do exhibit similar atrophy, common factors must be considered. Volumetric MRI-demonstrable atrophy may be a toxic effect of a variety of substances whose ability to cause brain volume loss was never suggested by less elaborate imaging techniques. Addiction itself, independent of the substance involved, may produce changes in the brain beyond the dopaminergic system that directly participates in addictive behavior. Minor head injuries, past nutritional deficits, stress and other lifestyle factors, and genetic influences may mediate brain volume in substance abusers.

The factors common to abusers of various single substances are no doubt well represented or even exaggerated in the polysubstance abuser, whom the BADCO Study has struggled mightily to exclude. Only a study of thepure cocaine abuser has the ability to establish causal links to cocaine. This approach can demonstrate specific actions of cocaine, uncover spe-cific deficits, and suggest specific treatments. But there are conceivable advantages to the less pure study of polysubstance abusers, aside from avoiding the logistical problem of ferreting out the uncommon single-substance abuser. If polysubstance abusers predominate at chemical dependency treatment centers, then they are worthy of study. If addiction itself might account for many of the behavioral and biological changes due to substance abuse, then fractionating addicts by substance may not help. If the social causes and consequences of the substance abuse problem in this country are similar for many substances, then a focus on cocaine may provide only a sidelight.

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