Brain Maturation May Be Arrested in Chronic Cocaine Addicts

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Background: *Animal and human newborn studies suggest that exposure to cocaine in utero delays glial maturation and white matter myelination. Postmortem data show that in the frontal and temporal lobes, white matter myelination continues into middle age. Recent magnetic resonance imaging (MRI) data have confirmed continued white matter volume increase in these regions, reaching a maximum at age 47.*

Methods: *Thirty-seven male cocaine dependent (CD) and 52 normal control subjects between ages 19 and 47 were evaluated with MRI. Coronal images focused on the frontal and temporal lobes were acquired using pulse sequences that maximized gray/white matter contrast.*

Results: *Highly significant positive correlations between white matter volume and age were observed in both the frontal and temporal lobes of the control group (*$r = .52$, $p = .0001$ *and* $r = .54$, $p = .0001$, *respectively); however, CD subjects did not demonstrate any age-related increase in white matter volume of the frontal (*$r = -.001$; $p = .99$*) and temporal (*$r = -.07$; $p = .67$*) lobes in this age range.*

Conclusions: *The age-related expansion in white matter volume occurring in normal control subjects was absent in CD subjects. The findings suggest that in adults, cocaine dependence may arrest normal white matter maturation in the frontal and temporal lobes of addicts who continue using cocaine.* Biol Psychiatry 2002;51:605–611 © *2002 Society of Biological Psychiatry*

Key Words: Brain, aging, maturation, cocaine, addiction, white matter, myelin, gray matter, frontal lobe, temporal lobe

Introduction

The effects of cocaine on the developing fetal and newborn brain have been an area of intense research. Animal studies indicate that in utero exposure to cocaine delays astroglia maturation (Clarke et al 1996; Whitaker-Azmitia 1998). A longitudinal magnetic resonance imaging (MRI) study on human newborns with gestational cocaine exposure demonstrated delayed white matter myelination in approximately half of the sample, which is associated with abnormal neurologic findings at 12 months of age (Ferriero 1998; Hajnal et al 1995).

Magnetic resonance imaging can investigate myelination in vivo through the use of inversion-recovery sequences that maximize brain gray/white matter contrast (Valk and van der Knaap 1989). Using this method, it was recently demonstrated that in normal male adults, the white matter volume of the frontal and temporal lobes continues to increase into the mid to late 40s, reaching the maximum volume at age 47 (Bartzokis et al 2001). These results are consistent with postmortem data showing that white matter myelination of these same regions continues into late middle age (Benes et al 1994; Yakovlev and Lecours 1967).

The ability to measure the brain's continued white matter volume expansion with MRI allows in vivo comparison of the course of brain maturation in the cocaine-dependent (CD) population and normal control subjects. We hypothesized that cocaine use interferes with this maturational process, resulting in delayed or arrested brain development in adulthood similar to the adverse effects of cocaine on brain development of animal and human newborns (Ferriero 1998).

Methods and Materials

Subjects

Male cocaine dependent (CD) and normal control subjects were included in this study. All subjects were between 19 and 47 years of age and signed written informed consents approved by the local institutional review board before study participation.

Thirty-seven CD subjects were recruited from patients admit-

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ted to inpatient and outpatient treatment programs and research clinics at a metropolitan Department of Veterans Affairs Medical Center. They were 25 to 47 years old (mean = 37.5, SD = 6.1), had relatively chronic illness (mean length of cocaine exposure = 8.8 years, SD = 6.1, range 1–30 years), and the ethnic composition was comprised of 6 Caucasians, 30 African Americans, and 1 Hispanic. All CD subjects met DSM-IV criteria for CD and self-reported use of at least $50 per week, primarily by smoking ("crack" cocaine). Length of cocaine abuse and severity of recent consumption were assessed by verbal self-report. Subjects had regular urinalysis testing, which served to corroborate self-reported date of last cocaine use.

The CD subjects were excluded if they had other psychiatric disorders of such severity as to require the use of psychoactive medications (benzodiazepines, antipsychotics, etc.); met DSM-IV criteria for dependence on opiates, benzodiazepines, or other sedative-hypnotics; or had a history of clinically significant medical conditions that could produce structural brain abnormalities (stroke, transient ischemic attack, head trauma resulting in loss of consciousness for longer than 15 min, hypertension, diabetes). Dependence on alcohol or marihuana was not an exclusion criterion; within our sample, 3 CD subjects were currently dependent on alcohol, and 13 had a past history (greater than 12 months before evaluation) of alcohol dependence. Five of the CD patients were currently dependent on marihuana, and another seven had a past history of marihuana dependence.

Fifty-five normal male subjects aged 19 to 44 were recruited from community volunteers. Selection criteria were as follows: no evidence of significant current or past psychopathology or substance dependence; no evidence of central nervous system impairment or history of medical, neurologic, or psychiatric diagnosis; self-report that no first-degree relatives have been treated for a major psychiatric disorder. The above criteria excluded 2 subjects with history of head trauma. One additional subject was excluded from analysis because he was a statistical outlier on the temporal lobe volume measure (over 4 SD greater than the mean of the remaining subjects). The remaining 52 control subjects averaged 30.6 years in age (SD = 6.8), 16.9 years of education (SD = 2.5, range 12–22), and ethnic composition comprised 32 Caucasians, 13 African Americans, 2 Hispanics, and 5 Asians.

MRI Protocol

The MRI examination used a 1.5-Tesla instrument and followed previously published methods (Bartzokis et al 1993). In brief, a coronal pilot sequence was used to align a sagittal MRI pilot sequence. The sagittal pilot sequence was then used to specify the position of the coronal image acquisition grid. The sagittal image containing the left hippocampus was used to define an oblique coronal acquisition plane perpendicular to the hippocampus. Two coronal sequences of the same brain slices were acquired: a transverse asymmetric dual spin-echo Carr-Purcell-Meiboom-Gill sequence (TR = 2500, TE = 30,90) and an inversion-recovery (IR) sequence (TR = 2500, TI = 600, TE = 30). Both sequences had two repetitions, 256 × 192 view matrix, 25 cm field of view, and produced coregistered 3-mm-thick contiguous slices. These images provide excellent multiparameter visualization of the frontal and temporal lobes.

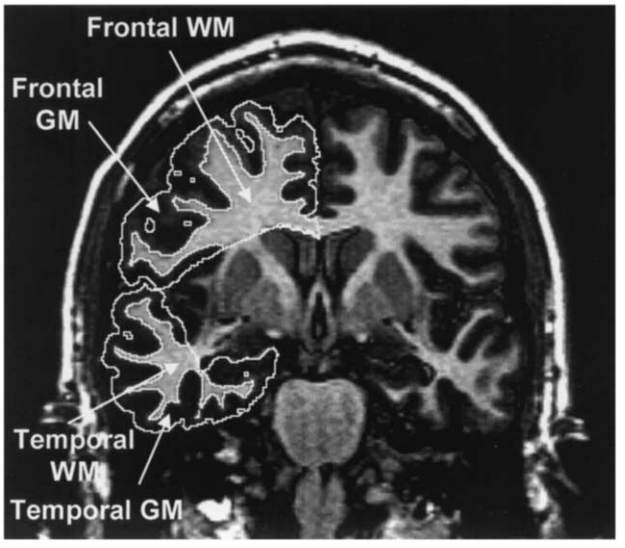

Figure 1. Oblique coronal inversion-recovery image with drawings of frontal and temporal lobe gray matter (GM) and white matter (WM) regions of interest.

Image Analysis

Imaging measures were obtained using a Macintosh configured image analysis workstation that read compact disks containing the original MRI data stored in digital format. Data from the MRI scans were analyzed using customized image analysis software. Regions of interest (ROIs) were quantified by two raters who were blind to the clinical data, using previously published methods (Bartzokis et al 1993). The raters, using a calculated T_2 image derived from the spin-echo sequence, manually traced a rough contour surrounding the brain by maintaining the cursor on the bright cerebrospinal fluid (CSF) pixels and cutting through the brain to exclude subcortical gray and white matter and insular cortex (Figure 1). All pixels with T_2 values in the CSF range ($T_2 > 130$ msec) were then eliminated from the image using the "shrink image" function of the software. Thus, the resulting ROIs contained only brain pixels. Once the brain ROI was quantified, it was pasted onto the IR image and is depicted as the outer (brain/CSF) border in Figure 1. Then the pixel intensities of the IR image were displayed in histogram form, and the gray matter histogram peak was eliminated. The resulting measure was the white matter area and is depicted as the inner (gray/white) border in Figure 1. The gray matter area was obtained by subtracting the white matter area of each lobe from the total lobe area.

A contiguous seven-slice volume centered on the anterior commissure was used for data quantification. Volumes were computed by summing the products of each cross-sectional area with the slice thickness. Frontal and temporal gray and white matter were measured while excluding subcortical gray and white matter and insular cortex (Figure 1). Test–retest (scan–rescan) reliabilities for the regions of interest were good; the

Table 1. Correlations[a] of Brain Volumes versus Age in Cocaine Dependent (CD) and Normal Control Subjects, aged 19–47

	CD (n = 37)		Control subjects (n = 52)		Significance of difference	
	r	p	r	p	z test	p
Total WM	−.02	.89	.55	.0001	2.82	.005
Frontal WM	−.001	.99	.52	.0001	2.55	.011
Temporal WM	−.07	.67	.54	.0001	2.30	.02
Total GM	−.55	.0005	−.31	.028	1.32	.19
Frontal GM	−.59	.0002	−.34	.014	1.43	.15
Temporal GM	−.42	.01	−.21	.13	.94	.35

WM, white matter; GM, gray matter.
[a]Controlling for height.

reliability coefficients (r_{xx}) were .85 and .86 for total temporal and frontal lobe volume, respectively, and .82 and .90 for the temporal and frontal white matter, respectively (Bartzokis et al 1993). Interrater reliabilities between the two raters were also high (based on a sample of 10 subjects) with intraclass reliability coefficients (r_{xx}) of .99 and .98 for total temporal and frontal lobe volumes, respectively, and .84 and .92 for frontal and temporal white matter volumes, respectively.

Data Analysis

The primary interest was to evaluate the changes in white and gray matter volumes in the 19 to 47 age range in which normal brain maturation is still occurring (Bartzokis et al 2001). Therefore, analyses were conducted on CD and normal control subgroups of subjects aged 47 or younger. Pearson product–moment correlation analyses were used to evaluate the relationship between age and brain volumes. Height was statistically controlled (partial correlation) in all the analyses to adjust for variations in body size on the brain and its regions (Skullerud 1985) and control for the "secular effect" (the progressive trend toward increased body height and brain weight in the 20th century). Demographic factors such as years of education and race can have potential effects on the brain. The control group was significantly more educated than the CD group (mean = 16.9 years, SD = 2.5; mean = 13.2 years, SD = 1.5, respectively; $t = 8.7$, $df = 83.2$, $p = .0001$), and the distribution of race among the groups (dichotomized into blacks and nonblacks) also differed significantly ($\chi^2 = 27.2$, $p = .001$). Additional analyses were performed partialling these variables to determine if any significant findings might be attributable to demographic differences. Investigation of the influence of length of exposure to cocaine and days abstinent from cocaine use on brain variables did not reveal any significant associations ($p > .17$); therefore, they were not controlled in subsequent statistical analyses. Differences between the groups were tested by transforming the partial correlations using Fisher's z transform and then applying the normal curve test. Comparisons of group differences between the slopes (i.e., absolute rates of change per year in brain volumes) were also done using multiple regression analyses, again controlling for height, education, and race.

Results

The results are tabulated in Table 1. Highly significant positive correlations between white matter volume and age were observed in both the frontal and temporal lobes of the normal group. The findings remain highly significant when education and race were partialled out in addition to height ($r = .46$, $p = .001$ and $r = .55$, $p = .0001$, frontal and temporal lobes, respectively); however, CD subjects did not demonstrate any age-related increase in white matter volume in this age range; in fact, the relationships were slightly in the opposite direction for both frontal ($r = -.001$; $p = .99$) and temporal ($r = -.07$; $p = .67$) lobes (Table 1).

There was a striking difference in the pattern of frontal and temporal white matter volume changes with age between the CD and control groups (Figure 2a and 2b). Multiple regression analysis showed significant age by diagnosis interactions for the frontal ($F = 6.0$, $df = 1, 85$, $p = .016$) and temporal white matter volumes ($F = 9.9$, $df = 1, 85$, $p = .002$). When height, education, and race were included in the multiple regression model, the age by diagnosis interaction remained significant for both frontal white matter and temporal white matter volumes ($F = 4.7$, $df = 1, 82$, $p = .03$, and $F = 8.1$, $df = 1, 82$, $p = .006$, respectively).

As depicted in Table 1, both the CD and normal control groups demonstrated age-related gray matter volume decrements as expected from the literature (Jernigan et al 1991; Lim et al 1992; Passe et al 1997; Pfefferbaum et al 1994; Raz et al 1997; Sullivan et al 1995; Figure 3a and 3b). In this age range, both total and frontal lobe gray matter regions exhibited highly significant age-related volume loss when height, education, and race were partialled out ($r = -0.38$, $df = 84$, $p = .0003$ for both groups combined).

Because of the potential influence of alcohol dependence on brain variables, additional analyses were con-

Fig. 2a

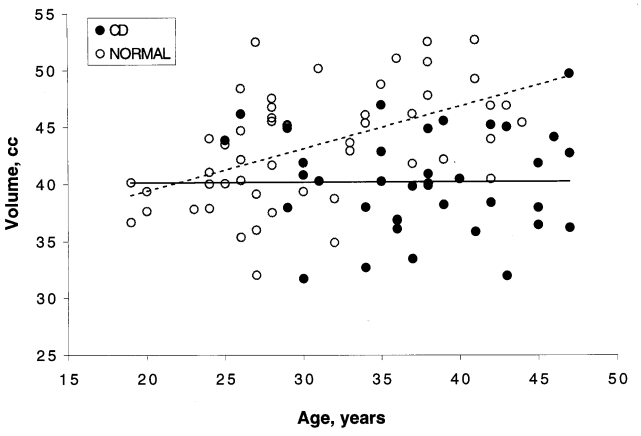

Fig. 2b

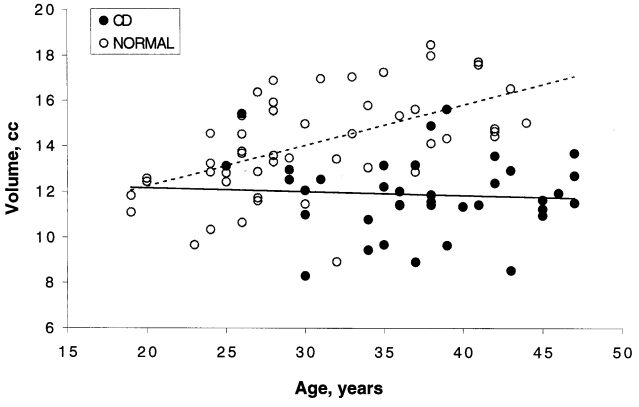

Figure 2. Regression of **(a)** frontal and **(b)** temporal lobe white matter volume on age in a sample of 37 male CD patients and 52 normal adult men. CD, cocaine dependent.

Fig. 3a

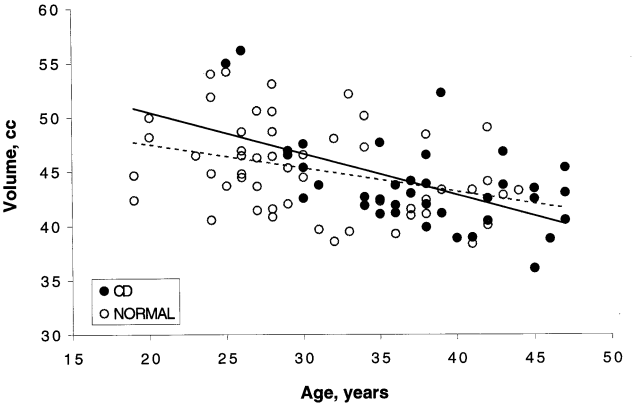

Fig. 3b

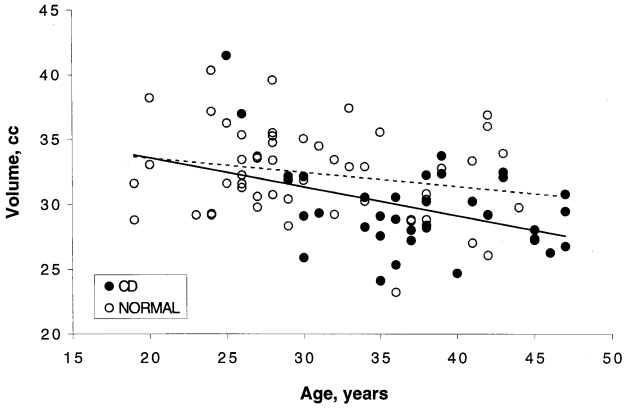

Figure 3. Regression of **(a)** frontal and **(b)** temporal lobe gray matter volume on age in a sample of 37 male CD patients and 52 normal adult men. CD, cocaine dependent.

ducted dividing the CD group into those patients with history of alcohol dependence ($n = 16$) and those without ($n = 21$; mean age = 38.2, SD = 5.2 and mean age = 36.6, SD = 7.1, respectively; $t = .77$, $df = 35.0$, $p = .45$). The brain volumes of the two subgroups did not differ ($p > .17$), and both subgroups demonstrated similar negative age–brain volume associations in the gray matter regions but no significant age–brain relationships in the white matter regions. The addition of alcohol dependence history (dichotomized as present or absent) as a statistical control variable did not alter the age–volume relationships presented above. Finally, excluding the three active alcohol dependent subjects from the analysis also did not meaningfully alter the results. The above analyses were also repeated by dividing the CD group into patients with marihuana dependence history ($n = 12$; mean age = 36.3, SD = 5.9) and those without ($n = 25$; mean age = 38.1, SD = 6.2; $t = .81$, $df = 35$, $p = .42$) and again, this did not meaningfully alter the results.

Discussion

This is the first anatomic evidence that cocaine abuse may suppress the normal maturation of the frontal and temporal lobes of adults (Bartzokis et al 2001; Yakovlev and Lecours 1967). Similar effects of cocaine have been described in the brain of animal and human newborns (Ferriero 1998; Hajnal et al 1995).

This observation has important potential implications for brain function in CD patients. The speed of neural transmission depends on the structural properties of the connecting fibers, including axon diameter and the thickness of the insulating myelin sheath (Aboitiz et al 1992). An increase in myelination could improve the interconnectivity of the frontal and temporal lobes and facilitate the synchronous integration of information across the many spatially segregated associative neocortex regions involved in higher cognitive functions (Gould et al 1999; Srinivasan 1999). Liu et al (1998) reported smaller pre-

frontal lobe volume in polysubstance abusers. Regions of the frontal cortex involved in inhibitory response control are directly affected by long-term exposure to drugs of abuse (Jentsch and Taylor 1999), and higher neurocognitive functions involving prefrontal cortex are poorly performed by CD individuals when compared with matched control subjects (Bolla et al 2000). The apparent absence of white matter maturation in the frontal lobes of chronic CD individuals also has face validity because lack of impulse control resulting in continued drug use, despite known substantial negative consequences, is a cardinal feature of addiction to cocaine (DSM-IV).

The loss of gray matter volume in this age range is consistent with imaging studies demonstrating that after early adolescence, when maximum gray matter volume is reached (Giedd et al 1999), cortical gray matter volume continues to decrease throughout the life span (Gur et al 1999; Lim et al 1992; Passe et al 1997; Pfefferbaum et al 1994; Raz et al 1997; Sullivan et al 1995). Postmortem data suggest that this gray matter volume decrease is primarily a result of large neuron shrinkage with minimal if any neuronal cell loss before the age of 55 (Haug 1987; Pakkenberg and Gundersen 1997; Peters et al 1998; Terry et al 1987).

Several limitations of this study must be acknowledged before further interpretation of the data. First, the sample was composed solely of men under age 48, thus limiting the generalizability of the results to women and older populations. Second, only a sample of the total frontal and temporal lobes was measured and results may differ if the lobes were measured in their entirety; however, unlike prior studies of addicted populations that used axial images, on which the demarcation of the posterior boundaries of these lobes is difficult (Danos et al 1998; Evans et al 1989; Pascual-Leone et al 1991; Pezawas et al 1998; Pfefferbaum et al 1998), we used coronal images to measure consistently demarcated volumes focusing on the regions known to undergo continued myelination in adulthood (Bartozkis et al 1993; Yakovlev and Lecours 1967). Third, the CD and control groups were not matched in age and race, which could have influenced the results; however, statistically controlling for these variables did not alter the results, suggesting that they did not have an overt influence. Finally, a large proportion (43%) of the CD subjects had either a current or past history of alcohol dependence, which could have increased the rate of gray matter loss compared with the normal control group (Pfefferbaum et al 1998); however, additional analyses did not support this possibility, and statistically controlling for alcohol history did not alter the present findings.

Conclusions about causality cannot be directly drawn from cross-sectional studies such as this one because factors such as sampling could markedly influence the results. Epidemiologic data have shown that rates of illicit drug dependence change markedly with age, with younger people (aged 19–29) demonstrating the highest risk for dependence (17%), dropping to 4% for ages 30 to 59, and virtually disappearing in those over 60 years old (Miller 1991). It is therefore probable that with age, the sample in this study was enriched with CD subjects who were unable to achieve sobriety. This would suggest that CD subjects with lower white matter volumes are least likely to achieve sobriety irrespective of the mechanism resulting in the reduced white matter volume.

The mechanism underlying the apparent absence of the normal white matter maturation in CD is unknown and could be due to cocaine effects or factors associated with the lifestyle of cocaine users such as nutrition, cigarette smoking, and so forth. Evidence from animals and newborn humans suggests that arrests or delays in myelination can result from cocaine exposure during gestation (Ferriero 1998). This disruption of early brain development could be caused by cocaine's interference with the serotonin system's neurotrophic effects (Whitaker-Azmitia 1998), but whether such effects persist in adult neurogenesis is unclear (Aboitiz et al 1992).

Another possibility is that the vascular effects of cocaine interfere with the continued myelination of the normal adult brain, which retains oligodendroglial progenitors with extensive myelination capacity (Yakovlev and Lecours 1967; Scolding et al 1999; Zhang et al 1999). In human cocaine users, cocaine has substantial effects on brain perfusion, reducing global cerebral blood flow even after single experimental intravenous cocaine infusions (Herning et al 1999; Kaufman et al 1997; Wallace et al 1996). The vasoconstrictive effects of cocaine may have an especially damaging effect in the white matter (Bartzokis et al 1999). Cocaine addicts have widespread and frequent (70%–100%) perfusion defects (Strickland et al 1993; Tumeh et al 1990; Volkow et al 1988; Weber et al 1993) that can be observed even after months of verified abstinence (Herning et al 1997; Strickland et al 1993). Chronic hypoperfusion can be preferentially damaging to myelin (Kurumatani et al 1998; Schäbitz et al 2000) and thus may reduce or arrest the process of continued myelination of the frontal and temporal lobes (Bartzokis et al 2001; Yakovlev and Lecours 1967). The data could be interpreted to imply that pharmacologic interventions able to prevent or reverse hypoperfusion and preserve myelin or interventions that promote myelination should be considered. Such interventions are already available and could be more fully investigated (Demerens et al 1999; Herning et al 1995; Schäbitz et al 2000; Thomas 2000).

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