Premorbid brain size is a determinant of functional reserve in abstinent crack-cocaine and crack-cocaine–alcohol-dependent adults

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Abstract

Studies of Alzheimer’s disease patients show that individuals with larger premorbid brains have a later onset of disease, or a lessened severity of cognitive impairment, or both. This may be due to a “functional reserve” associated with the greater number of neurons and synapses available in larger brains. We used magnetic resonance imaging and the MicroCog Assessment of Cognitive Functioning to examine the association between intracranial volume (premorbid brain size) and neuropsychological function in abstinent crack-cocaine and crack-cocaine–alcohol dependent individuals. There were no significant differences between the crack-only and the crack–alcohol dependent participants in neuropsychological performance or in intracranial volume. The abstinent cocaine-dependent individuals (both crack-only and crack–alcohol) were significantly impaired in many neuropsychological domains. Intracranial volume accounted for a significant proportion of the variance in neuropsychological performance. This result is consistent with the finding in the Alzheimer’s literature that larger brains can maintain function to a greater degree, or for a longer period of time, in the face of cerebral disease or insult. Functional reserve may be a heretofore little recognized protective mechanism of the brain that has consequences for the severity of expression of cerebral disease or insult throughout life. (JINS, 1998, 4, 559–565.)

Keywords: Crack, Cocaine, Magnetic resonance imaging, Neuropsychological performance

INTRODUCTION

The larger brain has a greater number of neurons and synapses (Haug, 1987). This additional capacity may act as a functional reserve ameliorating cognitive decline due to neurological insult or disease. Katzman et al. (1988), in a study of 137 nursing home residents, found 10 individuals whose postmortem revealed a quantity of neocortical plaques comparable to that of the demented patients with Alzheimer’s disease (AD), but whose cognitive performance was comparable or better than that of nondemented control individuals without AD. In addition, the brain weights and number of large neurons in these high plaque–cognitively normal individuals were significantly greater than those of the control group. Katzman concluded that these high plaque–cognitively normal individuals had incipient AD, but were cognitively intact due to a greater reserve of neurons associated with their larger than average brains. Other authors have investigated the relation between premorbid brain size and the onset and progression of AD. That work builds on the intimate association between mature brain size and either intracranial volume (ICV), or head circumference (since skull growth is driven by brain growth; Blatter et al., 1995; Davis & Wright, 1977; Van Valen, 1974). Schofield et al. (1995), in a computerized tomography study of 28 female patients with probable AD, showed that age of onset of AD was significantly correlated with premorbid brain size. Schofield hypothesized that cognitive functions stayed within the reserve capacity of the larger brains for a longer period of time, thereby delaying the onset of dementia. Mori et al. (1997), in a magnetic resonance imaging (MRI) study of 60 patients with probable AD, found that many of the cog-
nitive functions tested were significantly and positively correlated with premorbid brain volume; these associations were independent of the effects of age, sex, and education. Although Mori, unlike Schofield, did not find a relation between age of onset of AD and premorbid brain size, he did conclude that premorbid brain volume was a determinant of reserve capacity and postulated a threshold concept (i.e., that dementia emerges after the exhaustion of the functional reserve capacity). Graves et al. (1996) investigated the relation between head circumference and cognitive function in 52 probable AD patients, 31 possible AD patients, and 117 controls. There was a highly significant relation between premorbid brain size and cognitive impairment in the prob-

able AD group (after adjustment for age, sex, and education differences). Graves postulated:

While the initial size of the brain is likely to be irrelevant to the cognitive status of individuals without an ongoing AD pathological process, it may be important in determining reserve capacity which can modify the clinical presentation of the process, once [that process] is well established.

Differences in brain size may entirely reflect normal variability among individuals. However, mature brain size may also reflect the effect of poor prenatal or early childhood environment on the brain. Individuals subjected to these developmental risks can develop smaller brains, which may make them more vulnerable to the morbid effects of later cerebral disease or insult (such as substance abuse). For example, maternal addiction to alcohol or heroin during pregnancy has a persistent, deleterious effect on brain-head size (Chasnoff et al., 1986; Day et al., 1994; Feng, 1993). Severe maternal psychosocial stress may also reduce the head circumference of the newborn (Lou et al., 1994). In early childhood, malnutrition and psychosocial deprivation may also retard brain-head growth (Cole & Cole, 1993; Stoch et al., 1982).

Many studies document the persistent cognitive deficits found in abstinent alcoholics (reviewed in Fein et al., 1990). There are only a few well-controlled studies of cognitive function in cocaine dependence, most of which find evidence of neuropsychological (NP) impairments in early abstinence (Beatty et al., 1995; O'Malley et al., 1992; O'Malley & Gawin, 1990; Volkow et al., 1992). However, the relationship of premorbid brain size to cognitive performance has not been investigated in either the cocaine or the alcohol abuse literature. We used MRI and the MicroCog Assessment of Cognitive Functioning (Powell et al., 1993) to examine the association between ICV (premorbid brain size) and NP functioning in a sample of abstinent crack-cocaine and crack-cocaine–alcohol dependent persons to determine whether larger premorbid brain size ameliorates the deleterious effects of cocaine abuse on NP performance.

METHODS

Research Participants

Participants (Table 1) met DSM–III–R (American Psychiatric Association, 1987) criteria for crack-cocaine dependence, or crack-cocaine and alcohol dependence (the majority of cocaine abusers also abuse alcohol; Grant & Harford, 1990). No participant met DSM–III–R criteria for dependence on any substance other than crack-cocaine or alcohol. Participants were also screened using DSM–III–R criteria to exclude those with any major psychiatric or neuro-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crack-only dependent (N = 19)</th>
<th>Crack–alcohol dependent (N = 28)</th>
<th>Controls (N = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>M (SD)</td>
</tr>
<tr>
<td>Sex</td>
<td>39.2 (7.0)</td>
<td>41.4 (7.2)</td>
<td>35.3 (8.0)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>16 M, 3 F</td>
<td>23 M, 5 F</td>
<td>14 M, 5 F</td>
</tr>
<tr>
<td>Education***</td>
<td>17 AA, 2 W</td>
<td>19 AA, 9 W</td>
<td>8 AA, 11 W</td>
</tr>
<tr>
<td>Peak alcohol dose (drinks per month)</td>
<td>88.4 (128.5)</td>
<td>543.1 (263.1) (N = 21)</td>
<td>N/A</td>
</tr>
<tr>
<td>Peak alcohol duration (months)</td>
<td>99.0 (101.3) (N = 22)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Lifetime alcohol dose (drinks per month)</td>
<td>26.9 (43.7)</td>
<td>317.0 (222.1)</td>
<td>11.3 (10.8)</td>
</tr>
<tr>
<td>Lifetime alcohol duration (months)</td>
<td>267.9 (89.5)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Peak crack dose (dollars per month)</td>
<td>2029 (1900)</td>
<td>2297 (2865)</td>
<td>N/A</td>
</tr>
<tr>
<td>Peak crack duration (months)</td>
<td>26.2 (27.3)</td>
<td>39.9 (36.9)</td>
<td>N/A</td>
</tr>
<tr>
<td>Lifetime crack dose (dollars per month)</td>
<td>799 (768)</td>
<td>688 (671) (N = 24)</td>
<td>N/A</td>
</tr>
<tr>
<td>Lifetime crack duration (months)</td>
<td>148.2 (66.4)</td>
<td>176.1 (64.7)</td>
<td>N/A</td>
</tr>
<tr>
<td>Weeks abstinent*</td>
<td>10.3 (9.4)</td>
<td>13.6 (10.2)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*AA = African American, W = White
b data not presented because less than half the participants were able to recall this information
c some subjects not able to recall this information
verified by urine screen at least weekly
*significantly impaired relative to controls: *p ≤ .05, **p ≤ .01, ***p ≤ .001.
logic disorder except those secondary to cocaine or cocaine-alcohol dependence. Controls were not substance dependent and were negative for any lifetime DSM-III-R psychiatric or neurologic disorder. Participants and controls were excluded for loss of consciousness associated with head trauma (it was not possible to ascertain if the participants suffered loss of consciousness associated with head trauma during "blackouts")

The controls had a larger proportion of Whites versus African Americans than the cocaine-dependent group ($\chi^2 = 7.23, p = .007$). The controls were also younger ($r(64) = 2.59, p = .02$) and more educated than the cocaine-dependent sample ($r(64) = 4.68, p < .0001$). The substance abuse and control groups did not differ in the proportion of males and females ($\chi^2 = .74, p = .39$).

Crack-cocaine and crack-cocaine–alcohol–dependent participants were either inpatients on the Substance Abuse Inpatient Unit (SAIU) at the San Francisco Department of Veterans Affairs Medical Center, or were recruited from substance abuse outpatient treatment centers throughout the surrounding area. Random urine screens to verify abstinence were performed on a weekly basis by the outpatient treatment centers, and every other day at the SAIU. Urine screens for cocaine, amphetamines, benzodiazepines, and opiates were performed on both substance abusers and controls on the days of NP testing and MRI to verify abstinence. Substance abusers and controls were determined to be HIV negative by polymerase chain reaction (PCR). All female participants were tested to assure that they were not pregnant at the time of the study. All procedures used in this study were approved by the University of California at San Francisco Committee on Human Research, and all participants signed an informed consent form.

Neuropsychological Assessment

Both substance abusers and controls underwent the computerized MicroCog Assessment of Cognitive Functioning (Standard version; Powell et al., 1993). The MicroCog takes 45 to 90 min; 18 subtests are used to assess performance in the domains of attention, abstraction, spatial processing, memory, learning, and reaction time. We also computed a global clinical impairment score (GCIS) for each of these NP domains from the age and education-adjusted $z$ scores averaged across subtests within the domain. The averaged $z$ scores were converted into percentiles; clinical impairment scores were then assigned to these percentiles. A clinical impairment score of zero was assigned if a percentile was greater than 15, a clinical impairment score of 1 was assigned if a percentile was between 15 and 6, and a clinical impairment score of 2 was assigned to percentiles of 5 or less. The clinical impairment scores (0, 1, or 2) were then summed across domains to yield the GCIS.

Intracranial Volume on MRI

Axial spin–echo studies were performed on a Siemens 1.5 Tesla system. The spin–echo sequence ($TR/TE_1/TE_2 = 2500/45$ to 90 min; 18 subtests are used to assess performance in the abstraction, spatial abilities, memory, and learning domains (Table 2). The domains of attention and reaction time exhibited a trend to-

Statistical Analysis

There were no differences between the crack-cocaine and crack-cocaine–alcohol–dependent samples in any domain of NP performance, or in head size; therefore, the two samples were combined into a single “cocaine-dependent” group in all subsequent analyses. The association of head size and NP performance was assessed using regression analysis and analysis of covariance. For these analyses we used either the GCIS, or the age and education-adjusted NP domain average $z$ scores. NP domain $z$ scores were used rather than the percentile scores, as $z$ scores more closely meet the normality assumptions of the analysis procedures.

We first examined the degree to which NP impairment covaried with head size. Next we determined whether this covariation differed between males and females, or between African Americans and Whites (due to possible sex and racial differences in head size). We also examined whether this covariation was affected by age, education, crack-cocaine use variables, or alcohol use variables. Secondary analyses were then performed to determine whether head size in the cocaine-dependent sample was comparable to head size in controls (reflecting normal variation in head size), or whether cocaine-dependent participants had reduced head size compared to controls (possibly as a result of prenatal or early developmental insult). The head size comparisons between cocaine-dependent and control samples were performed separately for males and females, and for African American and White samples.

RESULTS

The NP performance of crack-cocaine–only dependent participants did not differ from crack-cocaine–alcohol–dependent participants on any of the NP domains, or on the GCIS (all $p > .2$ except the attention domain, where $p = .13$). Cocaine-dependent participants (the combined crack-cocaine and crack-cocaine–alcohol group) were significantly impaired compared to controls on the GCIS ($r(64) = 4.09, p < .0001$), and in the abstraction, spatial abilities, memory, and learning domains (Table 2). The domains of attention and reaction time exhibited a trend to-
ward reduced performance in the cocaine-dependent sample ($p < .13$).

We performed an analysis of covariance (ANCOVA) with education as a covariate, and two-way ANOVAs of Group X Ethnicity, and Group X Sex to determine if the differences in NP performance between the cocaine-dependent participants and controls were independent of these potentially confounding demographic variables. The Group X Education interaction effect was nonsignificant, thus meeting the assumptions of the analysis of covariance. When we removed the variance in the NP measures due to education, the differences in NP performance between the cocaine-dependent sample and the controls were only marginally affected. The two-way ANOVAs by ethnicity, and by sex, revealed nonsignificant interaction effects of Ethnicity X Group, and Sex X Group, indicating that the group differences in NP performance were comparable in African Americans and Whites, and in males and females.

We performed analyses to assess the effects of age, education, ethnicity, duration of abstinence, and crack-cocaine and alcohol use variables on NP performance within the cocaine-dependent sample; only peak cocaine dose had a significant effect on any of the NP measures. Peak cocaine dose accounted for 19.7% of the variance of the GCIS ($p = .002$), and from 9.3% (attention) to 22% (spatial abilities) of the variance of the specific NP domain summary scores (Table 2).

The head size of crack-cocaine-only dependent participants did not differ from the head size of crack-cocaine-alcohol-dependent participants ($p = .75$). Within the cocaine-dependent participants, head size accounted for significant variance of the GCIS (14.1% of variance, $p = .009$). Head size also accounted for significant variance of NP performance for each of the specific NP domains within the cocaine-dependent sample (ranging from 6.2% of the variance for the learning domain to 16.7% of the variance for the attention domain; Table 2). Within the control group, head size accounted for a significant proportion of the variance in performance in the attention domain ($p = .04$), and showed trends toward an association in the abstraction, spatial abilities, and reaction time domains (all $p < .22$). The associations of head size and NP performance within the cocaine-dependent group and within the control group were only minimally affected when the potentially modulating effects of age, education, sex, and ethnicity were examined by ANCOVA.

Given the effect of peak crack-cocaine dose on NP performance, we computed NP impairment score residuals after removing the variance attributable to peak cocaine dose. We then examined the strength of the association of these residual NP impairment scores and head size. The association of head size to these NP residual scores was larger than that reported above for the raw NP scores. Head size accounted for 21.2% of the variance in GCIS ($p = .001$), and from 7.8% of the variance for the learning domain to 23.0% of the variance for the spatial abilities domain when the vari-

### Table 2. The relation of neurophysiological (NP) test results to head size

<table>
<thead>
<tr>
<th>NP domain</th>
<th>Crack users</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z score M ± SD (percentile)</td>
<td>Z score M ± SD (percentile)</td>
<td>Z score M ± SD (percentile)</td>
</tr>
<tr>
<td>Attention</td>
<td>-0.80 ± 0.60 (50.0)***</td>
<td>-0.80 ± 0.60 (50.0)***</td>
</tr>
<tr>
<td>Abstraction</td>
<td>-0.47 ± 0.71 (31.9)***</td>
<td>-0.47 ± 0.71 (31.9)***</td>
</tr>
<tr>
<td>Memory</td>
<td>-0.63 ± 0.64 (76.5)***</td>
<td>-0.63 ± 0.64 (76.5)***</td>
</tr>
<tr>
<td>Learning</td>
<td>-0.56 ± 0.79 (59.3)***</td>
<td>-0.56 ± 0.79 (59.3)***</td>
</tr>
<tr>
<td>Reaction time</td>
<td>-0.34 ± 0.80 (56.7)***</td>
<td>-0.34 ± 0.80 (56.7)***</td>
</tr>
<tr>
<td>Global Clinical Impairment Score</td>
<td>0.04 ± 0.22**</td>
<td>0.04 ± 0.22**</td>
</tr>
</tbody>
</table>

*There were no significant differences between crack only and crack-alcohol dependent participants on any NP domain, therefore they are considered as a combined cocaine-dependent group for these analyses.

Methods: 54% of comparisons between cocaine-dependent participants and controls were computed on the average z scores across each domain; percentile scores corresponding to the mean z scores are presented. means ± SD, and comparisons between cocaine-dependent participants and controls were computed on the average z scores across each domain; percentile scores corresponding to the mean z scores are presented. SD, and comparisons between cocaine-dependent participants and controls were computed on the average z scores across each domain; percentile scores corresponding to the mean z scores are presented. SD, and comparisons between cocaine-dependent participants and controls were computed on the average z scores across each domain; percentile scores corresponding to the mean z scores are presented. SD, and comparisons between cocaine-dependent participants and controls were computed on the average z scores across each domain; percentile scores corresponding to the mean z scores are presented. SD, and comparisons between cocaine-dependent participants and controls were computed on the average z scores across each domain; percentile scores corresponding to the mean z scores are presented. SD, and comparisons between cocaine-dependent participants and controls were computed on the average z scores across each domain; percentile scores corresponding to the mean z scores are presented. SD, and comparisons between cocaine-dependent participants and controls were computed on the average z scores across each domain; percentile scores corresponding to the mean z scores are presented. SD, and comparisons between cocaine-dependent participants and controls were computed on the average z scores across each domain; percentile scores corresponding to the mean z scores are presented.
ance due to peak cocaine dose was removed (Figure 1; Table 2).

Finally, we compared the head size of the control group to that of the cocaine-dependent group. There were too few participants for comparison of female samples. African American males showed no difference in head size between controls and the cocaine-dependent sample \( r(34) = .16, p = .87 \). White male controls showed a strong trend to have larger ICVs than the cocaine-dependent sample \( r(14) = 1.77, p = .10 \).

**DISCUSSION**

Head size accounted for more than 20% of the variance in the global clinical impairment score in the cocaine-dependent sample. Head size also accounted for more than 20% of the variance in the specific NP domains of attention and spatial abilities and 14.3% of the variance in the domain of abstraction in these participants. These effects were very large. For example, effect sizes of approximately 14.0% of the variance are comparable to the magnitude of difference between the mean IQ of Ph.D. graduates versus typical college freshman, between college graduates and individuals with only a 50–50 chance of passing in an academic high school curriculum, or between the mean difference in height in 13-year-old versus 18-year-old girls (Cohen, 1988).

Our results suggest that larger brains may be able to maintain function to a greater degree, or for a longer period of time, in the face of the cerebral insult associated with crack-cocaine dependence. This is most likely due to the greater number of neurons and synapses available to assume the function of neurons damaged or lost due to the cerebral effects of cocaine dependence (i.e., an increased functional reserve). This assumes, of course, the same neuronal and synaptic density among individuals. We are currently testing the hypothesis that regional atrophic changes in the brains of these cocaine-dependent individuals are related to their NP impairments (Di Sclafani et al., 1997). However, the import of the significant relationship between brain size and NP impairments presented here is not dependent on an elucidation of the substrate of reduced cerebral function.

We believe that the significant NP impairments found in this sample of abstinent crack-cocaine and crack-cocaine-alcohol-dependent individuals (Table 2) did not exist before these individuals became crack cocaine-dependent. There was no association in the cocaine-dependent sample between educational level and NP performance or between educational level and head size (either of which may be consistent with preexisting impairments); conversely, there was a significant correlation between peak crack-cocaine use and NP impairment. Moreover, although the severity of the NP impairments in the cocaine-dependent sample was not as-

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Fig. 1. Scatter plot of global clinical impairment score residual (after removing variance attributable to crack-cocaine peak dose) versus intracranial volume (head size) within the cocaine-dependent sample. The regression line showing the association between global clinical impairment score and head size is displayed.
associated with length of abstinence in this study (2.5–3.5 months), longitudinal data on a larger sample (of which this sample is a subset) shows a partial recovery of NP deficits at 6 months of abstinence (Fein & Tolou-Shams, manuscript submitted for publication).

In addition to documenting significant NP impairments in this sample of abstinent cocaine-dependent individuals, we also noted a trend for these participants to have a smaller head size than controls in the White male subsample. This suggests the possibility that some factor that reduces head size may have been operative in the cocaine-dependent group but not in the control group. This comparison should be viewed as no more than suggestive, given that we saw no difference in the head sizes of African American cocaine-dependent participants versus controls, the small sample sizes studied, and the lack of population-based samples. Because there is little in the literature on the import of differences in brain size due to normal variability among individuals, there is substantial documentation of the consequences of developmental factors that reduce head–brain growth (Andreasen et al., 1993; Van Valen, 1974). Many authors find that negative prenatal or early childhood influences (such as maternal substance abuse, poor nutrition during pregnancy, and malnutrition or psychosocial deprivation in early childhood) can result in a smaller mature brain (Chasnoff et al., 1986; Day et al., 1994; Feng, 1993). Although there are far fewer studies of whether these adverse developmental influences also result in long-term NP deficits (due to the greater difficulties in obtaining longitudinal data), some of these investigations reveal long-term reductions in varying NP functions (Chasnoff et al., 1986; Feng, 1993; Stoch et al., 1982).

If early developmental environments detrimental to brain growth do have consequences for the severity of expression of cognitive impairment due to later substance abuse, this connection is part of a synergistic nexus of risk for the poor. Deficient prenatal care, early childhood malnutrition, and early childhood psychosocial deprivation are often associated with poverty. Poverty and substance abuse often affect the same inner-city populations. In the United States, female-headed households are the hardest hit. The poverty rates for these single mothers and their children (under the age of 6 years) are 60.5% for Whites, 71.8% for Hispanics, and 73.1% for African Americans (DiNitto, 1995).

There is also the possibility that many of the parents of the cocaine-dependent sample are likely to have been substance dependent themselves (due to the strong genetic contribution to substance dependence). This would further increase the possibility of poor nutrition and substance abuse during pregnancy, and of a less than thriving environment for the young child. The worst case scenario is that these children, who already suffer NP developmental deficits, may complete the generational cycle by becoming substance dependent teenagers or adults. In that case, the early developmental deficits and the morbid effects of substance dependence are analogous to a “second strike” situation for the brain—the “third strike” may be the morbid effects of a cerebral disease such as AD, or even the cerebral effects of normal aging.

Both this study and the findings in the Alzheimer’s literature indicate that larger brains may be able to maintain function to a greater degree, or for a longer period of time, in the face of cerebral disease or insult (Katzman et al., 1988; Mori et al., 1997; Schofield et al., 1995). In addition, our data revealed a trend for the White male cocaine-dependent sample to have a smaller head size than White male controls. This finding (substantially leavened by the appropriate caveats) raises the question of whether some factor that reduces mature brain size was operative in the cocaine-dependent sample but not in the controls. If true, this finding of reduced adult head size may be due to negative prenatal and early childhood influences that reduce brain growth.

The establishment of premorbid brain size as a marker for the magnitude of functional reserve (and, therefore, for the amelioration of the NP consequences of cerebral disease or insult) will require appropriate population-based samples of adequate size, and estimates of premorbid function. An important question is whether the mechanism of functional reserve is operative only in specific types of cerebral disease or insult (such as AD or crack-cocaine dependence), or whether it is a general mechanism operative in all types of cerebral disease and insult. It is also possible that brain size has some impact on functional performance in healthy individuals but becomes more crucial in the case of cerebral disease or insult. This possibility is supported by the similarity of the pattern of association between head size and performance in specific NP domains between our control group and the cocaine-dependent group (Table 2). However, the appearance of this pattern in the control group, or conversely, the failure of any of the relations between head size and NP performance to achieve significance in this group may be due to the small size of the control sample.

This study is the first (of which we know) to investigate the concept of functional reserve outside the field of AD. We hope that our positive results will inspire further investigation of the relation of brain size to NP function in syndromes with cerebral morbidity. Functional reserve may be a general protective mechanism of the brain that has consequences for the severity of expression of cerebral disease or insult throughout life.

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Brain size in former drug abusers

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