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RESEARCH ARTICLE

Abstinent chronic crack-cocaine and crack-cocaine/alcohol abusers evidence normal hippocampal volumes on MRI despite persistent cognitive impairments

VICTORIA DI SCLAFLANI,1 DIANA L. TRURAN,1 COURTNEY BLOOMER,1 MARINA TOLOU-SHAMS,1 H. WESTLEY CLARK,1,3 DAVID NORMAN,2 DAVID HANNAUER1 & GEORGE FEIN1,2,3

Departments of 1Psychiatry, 2Radiology, University of California, San Francisco, and 3San Francisco Veterans Affairs Medical Center, California, USA

Abstract
We measured hippocampal volumes and cognitive functioning in crack-cocaine and crack-cocaine/alcohol-dependent subjects (abstinent approximately 10-12 weeks) compared to age-matched controls. Cognitive function was evaluated using the computerized MicroCog Assessment of Cognitive Functioning (which includes tests of explicit, declarative memory subserved by the hippocampus). The hippocampal volumes were quantified on T1-weighted MRIs and were expressed as a proportion of intracranial vault volume. Both subjects and controls showed the larger right versus left hippocampal volume expected in normal anatomy, but we found no differences in hippocampal volume between any of the groups. However, both abstinent cocaine-dependent subjects and abstinent cocaine/alcohol-dependent subjects showed persistent cognitive impairments, including deficits in explicit memory. Our results suggest that either: (1) the hippocampus is resistant to structural volume loss in young and middle-aged cocaine or cocaine/alcohol-dependent subjects, (2) the hippocampal volume loss suffered by young and middle-aged cocaine or cocaine/alcohol-dependent subjects resolves after approximately 3 months of abstinence, or (3) hippocampal atrophy is obscured by the process of gliosis. Further, the cognitive impairments persisting in these abstinent cocaine and cocaine/alcohol-dependent samples may (1) be unrelated to hippocampal function or (2) be associated with abnormal hippocampal function that is not reflected in MRI measures of overall hippocampal atrophy.

Introduction
There are approximately 2 million cocaine abusers in the United States, yet there is relatively little research on the long-term effects of cocaine on the human brain. Moreover, the potential magnitude of central nervous system (CNS) effects has increased dramatically over the past 10 years due to the introduction of a new route of administration: cocaine smoked as the free base, also called "crack". Smoking crack is comparable to intravenous injection for obtaining rapid systemic absorption and high brain concen-
trations. Unlike intravenous injection, repeat dosing is very easy with crack. Crack addicts go on “missions”, a 3–4 day binge during which they smoke almost constantly (3–50 “rocks” a day), and rarely eat or sleep. The street purity of crack is over 95% (compared to the average 58% street purity of intranasally administered cocaine hydrochloride), increasing the potential magnitude of CNS effects.

The literature on the neuropsychological (NP) consequences of chronic crack-cocaine abuse is both limited and contradictory. Beatty et al., in a study of chronic cocaine (mostly crack) abusers abstinence for 3–5 weeks, found the abusers to be impaired in most measures of learning and explicit memory but normal in measures of sustained attention in comparison to matched controls. In contrast, Volkow et al. compared the NP performance of 21 chronic crack-cocaine abusers abstinence for 1–6 weeks to the NP performance of 18 matched controls; cocaine abusers showed minimal NP impairment. O’Malley et al. found explicit memory and concentration to be impaired in abstinent chronic cocaine (mostly crack) abusers in comparison to matched controls. She postulated a relationship between the length of abstinence and recovery of NP function similar to that seen in alcoholics. O’Malley’s model is based on data from two samples of chronic cocaine abusers; one sample abstinence an average of 23 days and the other abstinent an average of 135 days. O’Malley found that cocaine abusers with longer abstinence had better NP performance than cocaine abusers with less abstinence; however, with regard to explicit memory, the cocaine abusers with the longer abstinence still showed a deficit in retaining nonverbal material. The only caveat to O’Malley’s results is that she did not report any verification of the abstinence of the sample abstinent 135 days other than self-report. Additional literature on the effects of chronic crack-cocaine abuse on NP performance is difficult to evaluate due to insufficiently stringent inclusion/exclusion criteria for subjects and controls and/or comparisons to inadequately defined control samples.

The majority of cocaine abusers also abuse alcohol. Like cocaine abuse, alcohol abuse impairs explicit memory in humans. Long-term, high dosage alcohol consumption is associated with a significant loss of hippocampal pyramidal cells and dendrites in animal studies, however, only a few studies have quantified atrophy of the hippocampus in abstinent alcoholics. Jernigan et al. found atrophy in the medial temporal lobe region (which includes the hippocampus) in middle-aged alcoholics abstinence for approximately 1 month; these alcoholics performed significantly poorer than controls on some explicit memory tests (the Rey Auditory Verbal Learning Test and Story Recall). Sullivan et al. found hippocampal atrophy in older alcoholics abstinent approximately for 1 month; surprisingly, these abstinent alcoholics did not differ from controls on their performance on the Wechsler Memory Scale.

While there has been some focus on explicit memory impairments in chronic cocaine abusers, there have been no published investigations on the effects of chronic cocaine use on the human hippocampus, the cerebral structure subserving explicit, declarative memory. In order to assess the effect of cocaine-only abuse/dependence and the joint effect of co-existing cocaine and alcohol abuse/dependence on cognitive function and hippocampal volume, we measured NP performance (including explicit, declarative memory) and hippocampal volumes in age-matched abstinent cocaine-only and cocaine/alcohol-dependent subjects and controls.

**Methods**

**Subjects**

Subjects (Table 1) met DSM-III-R (APA, 1987) criteria for cocaine and/or alcohol dependence; no subject met DSM-III-R criteria for dependence on any substance besides cocaine or alcohol. One (cocaine/alcohol) subject used intravenous cocaine; all other subjects were crack-cocaine users. Subjects were also screened using DSM-III-R criteria to exclude those with any major psychiatric or neurological disorder except those secondary to chronic cocaine or cocaine/alcohol dependence. Subjects were excluded for episodes of head trauma with loss of consciousness. Controls were non-substance abusing individuals and negative for any life-time DSM-III-R psychiatric or neurological disorder; they reported no head trauma with loss of consciousness. All female participants were tested to ensure that they were not pregnant at the time of the study.

Cocaine and cocaine/alcohol-dependent subjects were either inpatients on the Substance Abuse Inpatient Unit (SAUI) at the San Francisco Department of Veterans Affairs Medical
Hippocampal volumes and cognition in crack abusers

Table 1. Subject demography

<table>
<thead>
<tr>
<th></th>
<th>Cocaine-only-dependent (n = 19)</th>
<th>Cocaine/alcohol-dependent (n = 18)</th>
<th>Controls (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>M ± SD</td>
<td>M ± SD</td>
<td>M ± SD</td>
</tr>
<tr>
<td>Gender</td>
<td>16M, 3F</td>
<td>13M, 5F</td>
<td>12M, 6F</td>
</tr>
<tr>
<td>Alcohol use (drinks per month)</td>
<td>16AA, 2C, 1As</td>
<td>13AA, 4C, 1H</td>
<td>8AA, 8C, 1H, 1As</td>
</tr>
<tr>
<td>Peak cocaine dosage (dollars per month)</td>
<td>2166 ± 1870</td>
<td>1939 ± 2762</td>
<td>N/A</td>
</tr>
<tr>
<td>Peak cocaine duration (months)</td>
<td>23.6 ± 21.9</td>
<td>37.5 ± 36.4</td>
<td>N/A</td>
</tr>
<tr>
<td>Life-time cocaine dosage (dollars per month)**</td>
<td>813 ± 759</td>
<td>572 ± 558</td>
<td>N/A</td>
</tr>
<tr>
<td>Life-time cocaine duration (months)</td>
<td>146.8 ± 67.3</td>
<td>177.9 ± 69.0</td>
<td>N/A</td>
</tr>
<tr>
<td>Weeks abstinent</td>
<td>9.9 ± 9.6</td>
<td>11.9 ± 9.6</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*AA = African-American; C = Caucasian; H = Hispanic; As = Asian.

**Weighted average of total dose and peak dose.

Neuropsychological assessment

Both subjects and controls underwent the computerized MicroCog Assessment of Cognitive Functioning (standard version). The MicroCog takes 45–90 minutes; 18 subtests are used to assess performance in attention, abstraction, spatial processing, memory, learning and reaction time. The tests of memory in the MicroCog Assessment evaluate explicit, declarative memory (primarily working and short-term memory). Age and education-adjusted standard scores for each of the 14 NP domains were averaged and converted into percentiles. A clinical impairment score of 0 was assigned to domain Z-scores falling above the 15th percentile, a clinical impairment score of 1 was assigned to domain Z-scores falling at or below the 15th and above the 5th percentile, and a clinical impairment score of 2 was assigned to domain Z-scores falling at or below the 5th percentile. The clinical impairment scores (0, 1 or 2) were then summed across domains to yield a Global Clinical Impairment Score (GCIS).

Hippocampal volumes on MRI

T1-weighted coronal MP-RAGE studies were performed on a Siemens 1.5 Tesla system. The 3D (no slice gap) whole brain studies were angulated orthogonal to the optic nerve; 164 1.4 mm thick slices resulted, with an in-plane resolution of 1 x 1 mm, a flip angle of 15 degrees and a TR/TE of 10/4 msec. The images were reformatted to be perpendicular to the long axis of the hippocampus in each subject; the reformatting was done separately for measurement of the left and right hippocampus (Fig. 1).

Hippocampal areas on each MRI slice were drawn using the methods and anatomical boundaries described by Watson et al. The first visible anterior portion of the hippocampal head (the pes hippocampus) was marked on each of the first two 1.4 mm slices. The body of the hippocampus was marked on 2.8 mm averaged slices and includes the subicular complex, hippocampus proper, dentate gyrus, alveus and fimbria. The most posterior aspect of the hippocampus (the hippocampal tail) was outlined on each of the last two 1.4 mm slices at the point of the separation of the crus of the fornix from the fimbria of the hippocampus (excluded at this level are the crus of the fornix, the isthmus of the cingulate gyrus and the parahippocampal gyrus). Approximately 28 1.4 mm slices were included in the volume of the hippocampus. Finally, the hippocampi were divided into anterior and pos-
terior volumes using the same criteria as Sullivan et al., that is, the anterior and posterior portions of the hippocampus were designated by dividing the total number of slices in half. When the total slice number was an odd number, the "extra" slice was assigned to the anterior division. The inter-operator intraclass correlation coefficient for this hippocampal voluming method was 0.81 (across 20 scans, including both subjects and controls); however, this study was done by a single operator.

Results
Subject demography
Cocaine-only-dependent, cocaine/alcohol-dependent, and control subjects did not differ significantly on age ($F_{2,28} = 1.33, p = 0.27$); subjects and controls were generally in their late thirties and early forties (Table 1). Subjects and controls were predominantly males. Subjects were mainly African Americans; about half the controls were African American and about half were Caucasian. Cocaine-only and cocaine/alcohol-dependent samples did not differ on cocaine use variables ($p > 0.17$) or in abstinence duration ($p = 0.77$).

Hippocampal volumes
Hippocampal volume measurements uncorrected for head size showed a significant difference between the cocaine/alcohol group and the controls in right hippocampus volume ($p = 0.05$) and exhibited trends toward a difference between the cocaine/alcohol group and controls in right posterior hippocampal volume, right anterior hippocampal volume, left anterior hippocampal volume, left hippocampal volume and total hippocampal volume (left hippocampal volume plus right hippocampal volume) ($0.05 < all ps < 0.13$). There were no other significant differences in uncorrected hippocampal volume measurements between the groups (all $p > 0.3$; Table 2). However, left, right and total hippocampal volume measurements were positively correlated.
Table 2. Hippocampal volumes and intracranial vault volume ("head size")

<table>
<thead>
<tr>
<th></th>
<th>Cocaine-only-dependent</th>
<th>Cocaine/alcohol-dependent</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=19)</td>
<td>(n=18)</td>
<td>(n=18)</td>
</tr>
<tr>
<td>Total hippocampus</td>
<td>9877 ± 1092</td>
<td>9591 ± 967</td>
<td>10195 ± 906</td>
</tr>
<tr>
<td></td>
<td>(right plus left; mm³)</td>
<td>(right plus left; mm³)</td>
<td>(right plus left; mm³)</td>
</tr>
<tr>
<td>Right hippocampus</td>
<td>5039 ± 617</td>
<td>4849 ± 510</td>
<td>5191 ± 482</td>
</tr>
<tr>
<td>Anterior</td>
<td>3066 ± 387</td>
<td>2973 ± 372</td>
<td>3184 ± 355</td>
</tr>
<tr>
<td>Posterior</td>
<td>1972 ± 314</td>
<td>1876 ± 241</td>
<td>2007 ± 227</td>
</tr>
<tr>
<td>Left hippocampus</td>
<td>4839 ± 530</td>
<td>4742 ± 498</td>
<td>5004 ± 491</td>
</tr>
<tr>
<td>Anterior</td>
<td>2920 ± 322</td>
<td>2832 ± 295</td>
<td>3015 ± 365</td>
</tr>
<tr>
<td>Posterior</td>
<td>1919 ± 271</td>
<td>1910 ± 260</td>
<td>1989 ± 251</td>
</tr>
<tr>
<td>Intracranial vault</td>
<td>1345 ± 135</td>
<td>1289 ± 109</td>
<td>1366 ± 139</td>
</tr>
<tr>
<td>volume (cm³)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*There were no statistically significant differences among groups on any hippocampal measure presented in this table (all ps > 0.3). Intracranial vault volume in the combined cocaine-only dependent and cocaine/alcohol dependent groups showed a strong trend to be smaller than the intracranial vault volume of controls (p = 0.07).

Neuropsychological impairment
We determined that there were no significant differences between the cocaine-only and cocaine/alcohol groups in any NP domain (Table 4); thereafter, we considered the cocaine-only and cocaine/alcohol samples as a combined group in all analyses. The combined cocaine-only and cocaine/alcohol groups had a significantly higher mean GCIS score than controls (t₁₈ = 44.6, p = 0.0001). They also showed impairment in all NP domains compared to controls (all ps < 0.017 without correction for multiple comparisons).

Table 3. Hippocampal volumes as a percentage of intracranial vault volume ("head size")

<table>
<thead>
<tr>
<th></th>
<th>Cocaine-only-dependent</th>
<th>Cocaine/alcohol-dependent</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=19)</td>
<td>(n=18)</td>
<td>(n=18)</td>
</tr>
<tr>
<td>Total hippocampus</td>
<td>0.74 ± 0.08</td>
<td>0.75 ± 0.07</td>
<td>0.75 ± 0.08</td>
</tr>
<tr>
<td>(right plus left)</td>
<td>(right plus left)</td>
<td>(right plus left)</td>
<td>(right plus left)</td>
</tr>
<tr>
<td>Right hippocampus</td>
<td>0.38 ± 0.04</td>
<td>0.38 ± 0.04</td>
<td>0.38 ± 0.05</td>
</tr>
<tr>
<td>Anterior</td>
<td>0.23 ± 0.03</td>
<td>0.23 ± 0.03</td>
<td>0.23 ± 0.03</td>
</tr>
<tr>
<td>Posterior</td>
<td>0.15 ± 0.02</td>
<td>0.15 ± 0.02</td>
<td>0.15 ± 0.02</td>
</tr>
<tr>
<td>Left hippocampus</td>
<td>0.36 ± 0.04</td>
<td>0.37 ± 0.04</td>
<td>0.37 ± 0.04</td>
</tr>
<tr>
<td>Anterior</td>
<td>0.22 ± 0.02</td>
<td>0.22 ± 0.02</td>
<td>0.22 ± 0.03</td>
</tr>
<tr>
<td>Posterior</td>
<td>0.14 ± 0.02</td>
<td>0.15 ± 0.02</td>
<td>0.15 ± 0.02</td>
</tr>
</tbody>
</table>

*There were no statistically significant differences among groups on any measures presented in this table (all ps > 0.66).
Figure 2. Right plus left hippocampal volume as a percentage of intracranial vault volume (head size).

Table 4. Neuropsychological test results

<table>
<thead>
<tr>
<th>Test Domain</th>
<th>Cocaine-only-dependent (n = 19)</th>
<th>Cocaine/alcohol-dependent (n = 18)</th>
<th>Controls (n = 18)</th>
<th>Combined cocaine-only and cocaine/alcohol groups &lt;controls**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Z-score M ± SD (percentile)*</td>
<td>Z-score M ± SD (percentile)*</td>
<td>Z-score M ± SD (percentile)*</td>
<td></td>
</tr>
<tr>
<td>Attention</td>
<td>-0.34 ± 0.68 (36.8)</td>
<td>-0.78 ± 0.86 (21.8)</td>
<td>-0.03 ± 0.71 (48.7)</td>
<td>p = 0.022</td>
</tr>
<tr>
<td>Abstraction</td>
<td>-0.48 ± 0.74 (31.5)</td>
<td>-0.70 ± 0.69 (24.1)</td>
<td>0.19 ± 0.46 (57.7)</td>
<td>p = 0.0001</td>
</tr>
<tr>
<td>Spatial process</td>
<td>-0.76 ± 0.63 (22.3)</td>
<td>-0.59 ± 0.68 (27.7)</td>
<td>0.03 ± 0.34 (51.1)</td>
<td>p = 0.0001</td>
</tr>
<tr>
<td>Memory</td>
<td>-0.98 ± 0.93 (16.3)</td>
<td>-0.94 ± 1.1 (17.2)</td>
<td>-0.20 ± 0.73 (42.0)</td>
<td>p = 0.006</td>
</tr>
<tr>
<td>Learning</td>
<td>-0.56 ± 0.78 (28.8)</td>
<td>-0.50 ± 0.62 (30.9)</td>
<td>-0.06 ± 0.57 (47.5)</td>
<td>p = 0.017</td>
</tr>
<tr>
<td>Reaction time</td>
<td>-0.20 ± 0.66 (42.2)</td>
<td>-0.70 ± 0.92 (24.3)</td>
<td>0.20 ± 0.59 (57.9)</td>
<td>p = 0.005</td>
</tr>
<tr>
<td>Global clinical impairment score</td>
<td>2.2 ± 1.8</td>
<td>2.7 ± 3.0</td>
<td>0.22 ± 0.54 (57.9)</td>
<td>p = 0.0001</td>
</tr>
</tbody>
</table>

*Means, SDs and comparisons between cocaine-dependent subjects and controls were computed on the domain Z-scores. Percentile scores corresponding to the mean Z-scores are presented to help put the Z-scores into a clinical perspective.

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

Discussion
Middle-aged chronic crack-cocaine and crack-cocaine/alcohol abusers abstinent for 10–12 weeks did not show evidence of hippocampal atrophy, despite demonstrating persistent explicit memory and other cognitive impairments. These results suggest that: (1) the hippocampus is resistant to structural volume loss in young and middle-aged cocaine or cocaine/alcohol-dependent subjects, (2) the hippocampal volume loss suffered by young and middle-aged cocaine or cocaine/alcohol-dependent subjects resolves
after approximately 3 months abstinence, or (3) hippocampal atrophy is obscured by the process of gliosis. Further, the cognitive impairments persisting in these abstinent cocaine and cocaine/alcohol-dependent samples may (1) be unrelated to hippocampal function or (2) be associated with abnormal hippocampal function that is not reflected in MRI measures of hippocampal atrophy.

If hippocampal atrophy sufficient to be detected by standard structural MRI did exist in the cocaine and cocaine/alcohol-dependent samples, we are confident that our implementation of the Watson et al. voluming method is sensitive enough to detect the reductions. Not only did this hippocampal voluming method detect the normal anatomic asymmetry between the left and right hippocampus in the current study, but this method has been used successfully to quantitate hippocampal atrophy in Alzheimer's Disease (AD) and medial temporal lobe epilepsy (mTLE). We are not aware of any literature documenting the effects of chronic cocaine abuse on the hippocampus, but Sullivan et al. documented hippocampal atrophy in abstinent alcoholics. Jernigan et al. documented mesial temporal lobe atrophy (which includes the hippocampus), also in abstinent alcoholics. (Both Sullivan et al. and Jernigan et al. corrected hippocampal volumes for head size; although with a different method than we used in this study.) The negative hippocampal volume results of this study are not necessarily at odds with the Sullivan et al. or the Jernigan et al. studies. Although our alcoholic sample drank twice as much as the Sullivan sample (life-time alcohol dose = 2597 ± 2120 kg vs. 1285 ± 868 kg) our sample was abstinent about 2.5 times as long (approximately 2.5–3 months vs. approximately 1 month). Our sample drank approximately three-quarters the amount of Jernigan's sample (11 ± 7 drinks per day vs. 15 ± 10 drinks per day) and averaged about 15 years of abusive drinking compared to 12 years for the Jernigan sample; but again our sample was abstinent about 2.5 times as long. In addition, Sullivan found hippocampal atrophy primarily in older alcoholics (unrelated to disease duration or life-time alcohol dose), not in the middle-aged alcoholics that resembled our sample. While Jernigan did not address the relationship of age and degree of atrophy within her sample, her sample on average was about 10 years older than our sample. Neither Sullivan nor Jernigan reported the ethnicity of their subject samples, so it is impossible to compare our study to theirs in that regard. It is possible that hippocampal atrophy is present primarily in older alcoholics and/or that detectable hippocampal atrophy resolves by 10–12 weeks of abstinence in middle-aged samples. There is no cocaine literature on hippocampal atrophy, but both animal and human studies document the resolution of atrophy associated with long-term alcohol exposure and withdrawal. Animal studies document both neuronal loss and dendritic loss in the hippocampus following long-term alcohol exposure and withdrawal; dendritic reorganization occurred after extended abstinence from alcohol. MRI studies of alcoholics have found significant reversal of brain volume decreases in alcoholics who remained abstinent. It is also possible that hippocampal neuronal loss occurred in our cocaine-only and cocaine/alcohol-dependent subjects, but was partially or wholly obscured from standard structural MRI by the process of gliosis. Proton MR Spectroscopy (MRSI), which can be used to measure N-acetyl aspartate (NAA), an amino acid found only in neurons, has been able to detect neuronal degeneration and loss when atrophy has not been found on structural MRI. Knowlton et al. documented hippocampal atrophy in the majority of mTLE patients. However, when focusing on mTLE patients without MRI evidence of hippocampal atrophy, he found NAA reductions in the hippocampus of the seizure focus. In studying Alzheimer's Disease (AD), Schuff et al. found that hippocampal volumes and NAA concentrations were highly correlated yet made independent contributions to the discrimination between AD patients and controls. To the degree that the process of gliosis has obscured early hippocampal neuron loss in our cocaine-only and cocaine/ alcohol-dependent individuals, NAA measurement may reveal such effects. In addition to MRSI, a more sensitive structural imaging technique, such as phased-array surface coil MRI, may provide the high anatomic detail and contrast resolution needed to detect effects limited to substructures of the hippocampus.

The explicit memory deficits shown by these abstinent cocaine and cocaine/alcohol abusers is in agreement with most of the alcohol abuse and cocaine abuse literature. A possible basis for these persistent explicit memory deficits does exist if hippocampal atrophy in these subjects was
obscured by gliosis or was limited to atrophy not detectable by standard imaging. If, however, hippocampal atrophy did not occur in these subjects or resolved by 10–12 weeks of abstinence (the time of the MRD), what could account for explicit memory deficits in the cocaine and cocaine/alcohol abusing subjects? The memory deficits in these subjects could be associated with (a) functional or neurochemical abnormalities in the hippocampus or (b) abnormalities in other regions of the brain that result in abnormal or delayed input to or output from the hippocampus.

Changes in hippocampal neurons at the electrophysiological and neurochemical level have been documented in chronic alcohol abuse. These changes may predate atrophy and be the substrate of the cognitive deficits seen in the cocaine and cocaine/alcohol abusers. We have reported abnormal amplitude and suppression of the auditory P30 event-related potential in cocaine-only and cocaine/alcohol-dependent subjects. In the context of Freedman et al.'s demonstration that the hippocampus is the primary site for P30 inhibitory control, our P30 findings provide further suggestive evidence of abnormal hippocampal functioning in the cocaine-only and cocaine/alcohol dependent subjects.

Neurochemical abnormalities in the hippocampus may be present with or without associated neuronal loss. Inhibition of cholinergic function and loss of cholinergic neurons in various parts of the brain (including the hippocampus) as a result of chronic alcohol consumption have been documented in the alcohol literature. It has been postulated that the memory disruption and cognitive impairment associated with long-term alcohol intake is a consequence of the depression of brain cholinergic activity. In addition, neurochemical damage to the hippocampus may be a function of the elevated glucocorticoids of prolonged stress caused by alcohol intoxication, since the hippocampus is a site-specific target for glucocorticoids. Glucocorticoids inhibit glucose uptake; neurons are particularly vulnerable to reduced energy supply. Neurons already in this weakened state may be further insulted by additional neurological sequelae to alcoholism (such as hypoxia and/or ischemia and seizure) which, through a variety of mechanisms, may lead to neuronal degeneration and death.

Abnormalities in other regions of the brain may result in abnormal or delayed input to or output from the hippocampus. We recently reported very large delays in the latency and reductions in the amplitude of the P3A event-related potential component in the auditory and visual modalities in both the abstinent cocaine-only and cocaine/alcohol-dependent samples. The P3A component indexes a frontal cortex mediated orientating response to rare novel stimuli that occur during a target detection paradigm. Literature on P3A suggests that amplitude effects implicate frontal cortex abnormalities, while latency effects implicate impaired or delayed inputs to the frontal cortex from subcortical and other cortical regions. Thus, the P3A results suggest abnormalities in frontal cortex and in frontal white matter that may result in deficient input to or output from the hippocampus.

Finally, the persistent cognitive deficits in our crack-cocaine and crack-cocaine/alcohol-dependent subjects may reflect a combination (or a synergy, as multiple systems are affected) of all of the above factors, i.e. electrophysiological or neurochemical abnormalities in the hippocampus, abnormalities in other regions of the brain that result in abnormal or delayed input to or output from the hippocampus, or atrophy of the hippocampus not detectable by standard structural imaging. It is also possible that at least some of the cognitive impairments in this sample pre-dated cocaine and alcohol abuse and may be due to genetic factors and/or a poor perinatal environment. For example, fetal alcohol syndrome, once considered a clinical constellation of brain anomalies and mental retardation, is now thought to be composed of a continuum of neurological abnormalities involving subtle morphological changes. Animal studies have shown alterations in hippocampal morphology, including a reduction in dendrites, in very young animals whose mothers were exposed to alcohol perinatally. A persistent, deleterious effect on brain/head size is also associated with maternal alcohol abuse during pregnancy. In this sample, the cocaine/alcohol groups showed a strong trend toward a smaller premorbid brain size (inferred from intracranial vault volume) than the controls. In a larger sample (of which the sample presented here is a subset) we have suggestive evidence that both the crack-cocaine and crack-cocaine/alcohol groups have a smaller premorbid brain size than controls. This finding strengthens the possibility that at least some of the cognitive impairments shown by these abstinent
cocaine and cocaine/alcohol abusers predated their substance abuse and resulted from early developmental factors.37

Acknowledgements

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