Decreased Gray Matter Concentration in the Insular, Orbitofrontal, Cingulate, and Temporal Cortices of Cocaine Patients

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Background: Structural deficiencies within limbic and prefrontal regions may contribute to the characteristic drug-seeking and drug-taking behaviors that prevail in persons dependent on cocaine. To date, a focal structural analysis of the brains of cocaine patients has not been undertaken.

Methods: We used voxel based morphometry in conjunction with statistical parametric mapping on the structural magnetic resonance images of cocaine-dependent (n = 13) and cocaine-naive individuals (n = 16) to assess differences between the two groups in gray and white matter concentration.

Results: We report a decrease in gray matter concentration in the ventromedial orbitofrontal, anterior cingulate, anteroventral insular, and superior temporal cortices of cocaine patients in comparison to controls (p < .01 corrected for multiple comparisons). The average percentage decrease in gray matter concentration within a region ranged from 5% to 11%. White matter concentration did not differ between groups.

Conclusions: We conclude that the brains of cocaine patients are structurally dissimilar from those of nondrug-using controls. The differences were detected in regions involved in decision-making, behavioral inhibition and assignation of emotional valence to environmental stimuli and, hence, may contribute to some of the behavioral deficits characteristic of chronic cocaine users. Biol Psychiatry 2002;51:134–142 © 2002 Society of Biological Psychiatry

Key Words: Voxel based morphometry, structural MRI, cocaine, insular cortex, orbitofrontal cortex

Introduction

Despite continued efforts, a medication that can effectively treat cocaine dependence and prevent relapse remains elusive. Knowledge of the differences between the brains of cocaine users and nonusers is critical to identifying possible pharmacotherapies to treat this disorder. One line of evidence implicating select brain regions in pathologic drug use has been derived from observations that discretely brain-damaged and drug-dependent individuals exhibit similar behavioral deficits (Bechara et al 1994; Bechara et al 1999; Bechara 2000; Grant et al 2000; Rogers et al 1999). Select regions in the brains of cocaine users show functional, neurochemical, and structural abnormalities as well.

Functional abnormalities in cocaine-dependent (COC) patients have been observed in the orbitofrontal cortex (OFC), the insula, and other limbic-related regions (Llondon et al 2000; Strickland et al 1993; Volkow and Fowler 2000; Volkow et al 1991; Holman et al 1991). For example, using the method of positron emission tomography (PET) and [18F]-fluorodeoxyglucose, changes in brain glucose metabolism were observed in the OFC and basal ganglia of COC patients versus controls (Volkow et al 1991; Volkow et al 1992). In other studies, using 15O-labeled water and PET, baseline scans revealed significant hypoperfusion in the anterior cingulate (Childress et al 1999) and the OFC (Childress et al in press) in COC patients relative to a nondrug-using group.

Chronic cocaine also affects neurotransmitter systems. Considerable evidence exists for altered function of the mesolimbic dopamine system. Cocaine self administration studies in animals report decreases in DA receptor binding sites (Moore et al 1998a; Moore et al 1998b) and various, difficult to interpret, changes in DA transporter binding (Arroyo et al 2000; Letchworth et al 2001; Tella et al 1997; Wilson et al 1994), implying dysregulation of the dopaminergic system. Likewise, studies in chronic cocaine users report down regulation of postsynaptic dopamine (DA) sites (Volkow et al 1993) and increased DA trans-

Structural deficits may accompany the functional and neurochemical deficits observed in the limbic and prefrontal brain regions of COC individuals. Indeed, a volumetric assessment of the prefrontal and temporal lobes of primarily COC subjects showed decreased volumes in comparison with a control group (Liu et al 1998). Another study observed accelerated age-related gray matter volume changes in the temporal lobes of COC subjects compared with control subjects (Bartzokis et al 2000). More recently available tools, such as voxel-based morphometry (VBM), examine changes in the concentration of gray or white matter rather than volume changes (Ashburner and Friston 2000; Bullmore et al 1999; Woermann et al 1999). Thus, damage within a region that does not alter the structure's size can be ascertained. This is contrasted with volume of interest (VOI) or region of interest (ROI) studies that provide information on the area contained by a structure without providing specific information on possible deficiencies within that structure. In this study, we used VBM to test the hypothesis that the brains of cocaine patients show structural deficiencies in regions involved in decision-making processes and autonomic arousal such as the ventromedial orbitofrontal (VMOF), anterior cingulate (AC), and anteroventral insular (AVI) cortices.

Methods and Materials

Subjects

Structural magnetic resonance images (MRIs) from a previous PET study and an ongoing functional MRI (fMRI) study were examined. Twenty-nine right-handed, HIV(−) adult male subjects participated in the study procedures; n = 16 control subjects reporting lifelong abstinence from cocaine and n = 13 COC patients meeting DSM-IV criteria for cocaine dependence (American Psychiatric Association, 1994). For all patients, “crack” smoking was the primary mode of cocaine administration. Within the COC group, the mean years of cocaine use was approximately 13 (SD = 6.5), and the average number of days of cocaine used during the last 30 was 15 (SD = 7.3). Patients reported spending roughly $106.00 (SD = $154.40) within a cocaine binge. The mean age of the COC group was 42 (SD = 6.3), reporting approximately 12 years of education (SD = 1.1). The control group mean age was 32 (SD = 6.9), reporting 17 years of education (SD = 2.6). All persons in the COC group were black American and the control group was comprised of six black Americans, nine white Americans, and one Asian American. Subjects were medically and psychologically screened and were required to be free of current alcohol or other drug (except nicotine) dependence, past or current use of opiates, gross neurologic abnormalities (as determined by the structural MRI), history of serious head injury or unconscious periods lasting more than 3 min, presence of metallic objects in the body, and clinically significant neurologic or medical illness (including DSM-IV Axis-I or Axis-II disorders).

Stringent criteria were imposed upon study candidates to reduce the contribution of comorbid illness. To this end, approximately five patients were screened for each subject accepted into the study. Likely candidates received a complete medical examination and participated in a psychosocial screening, which included the Cocaine Selective Severity Assessment (CSSA), the Beck Depression Inventory (BDI), and the Addiction Severity Index (ASI). A licensed doctoral level psychologist administered the Schedule of Affective Disorders and Schizophrenia – Lifetime (SADS-L) interview to determine DSM-IV diagnoses and Global Assessment of Functioning (GAF) ratings.

The Institutional Review Board of the University of Pennsylvania approved all work and all participants provided written informed consent. Cocaine-dependent patients were recruited from the Treatment Research Center of the University of Pennsylvania School of Medicine and were housed in an inpatient facility for 3 to 5 days before the MRI session.

MRI Scanning Protocol

T1-weighted MRI scans were obtained from a 1.5 T GE scanner (Milwaukee, WI). An inversion recovery-prepared 3D spoiled gradient echo (IRP-SPGR) sequence (Tr/Te/FOV/Nex/flip angle/matrix size = 35 msec/5 msec/24 cm/135°/256 × 192) with 128 contiguous axial slices and a slice thickness of 1 mm was used for analysis.

Analysis of Structural MRI Data in SPM ’99

Data were analyzed on a Sun SPARC 10 workstation (Sun Microsystems, Palo Alto, CA) using SPM 99 software (Wellcome Department of Cognitive Neurology, London, UK), according to the method described by Ashburner and Friston (2000). Voxel-based morphometry analysis requires 1) spatial normalization of all images into the same stereotactic space, 2) gray/white/CSF matter segmentation, 3) smoothing, and 4) statistical parametric comparisons. These steps are described in more detail below.

SPATIAL NORMALIZATION. MRI data were interpolated to 0.9375 mm³ voxels and stored as axial slices. To correct for global brain shape differences, the individual T1-weighted MRI volume acquisitions were transformed into a standard 3D space (Montreal Neurologic Institute [MNI], provided by SPM 99). The images were coregistered to an MNI atlas template, using affine transformations and nonlinear warping (7 × 8 × 7 basis functions). The resulting spatially normalized images had isotropic voxels of 2 mm.
Table 1. Regions of Decreased Gray Matter Density in the Cocaine-Dependent Group in Comparison with the Control Group

<table>
<thead>
<tr>
<th>Region</th>
<th>z Score</th>
<th>P Values</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Mean % Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anteroventral insular cortex (AVI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>5.00</td>
<td>&lt;.001</td>
<td>36</td>
<td>12</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Left</td>
<td>4.46</td>
<td>&lt;.001</td>
<td>36</td>
<td>6</td>
<td>-8</td>
<td>7</td>
</tr>
<tr>
<td>Ventromedial orbitofrontal cortex (VMOF)</td>
<td>4.74</td>
<td>&lt;.001</td>
<td>-34</td>
<td>20</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Anterior cingulate (AC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>4.77</td>
<td>&lt;.001</td>
<td>6</td>
<td>40</td>
<td>-12</td>
<td>7</td>
</tr>
<tr>
<td>Left</td>
<td>4.20</td>
<td>.008</td>
<td>-8</td>
<td>48</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Superior temporal cortex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>4.52</td>
<td>.004</td>
<td>60</td>
<td>-26</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Left</td>
<td>4.39</td>
<td>.005</td>
<td>-50</td>
<td>2</td>
<td>-4</td>
<td>11</td>
</tr>
</tbody>
</table>

Coordinates are given for the maximally significant voxel in each area, where x defines the lateral placement from the midline (left = negative), y defines the anteroposterior displacement relative to the anterior commissure (posterior = negative) and z defines the vertical position relative to the anteroposterior commissural line (down = negative). P values are corrected for multiple comparisons at P < .01 (df = 26). Extent threshold: k = 95 voxels. The z score (refers to the number of standard deviations away from the mean) and coordinates are in Montreal Neurological Institute (MNI) space. Mean % change refers to the average percentage change in gray matter density after masking with the statistic image from SPM99 to show only those regions that were significantly different.

**SEGMENTATION.** A clustering algorithm that identifies voxel intensities of particular tissue types (gray or white matter, cerebrospinal fluid, and three other background classes) was applied to the normalized MRIs. This technique compares each brain voxel with voxels from a set of previously normalized probability images. The probability images determine the likelihood that each voxel belongs to a particular tissue class (Evans et al 1994). Repeated determinations are made as to the category of tissue class for a particular voxel, based on the mean and variance of the developing tissue clusters of the brain under analysis. This tissue classification method includes a correction for image intensity nonuniformity that arises in MR imaging (Ashburner and Friston 2000).

**SMOOTHING.** The normalized, segmented, and transformed images were smoothed by convolving with an isotropic FWHM 12 mm Gaussian kernel. This reduces the effects of image noise and conditions the data for subsequent statistical tests performed in SPM99. The images were then logit transformed to render them more normally distributed.

**STATISTICAL ANALYSES.** Groups (COC and control) of images were contrasted voxel by voxel using SPM99 software. Each voxel was compared between groups using analysis of covariance. Because it is known that brain structure changes with age (Gur et al 1991; Luft et al 1999; Passe et al 1997; Salonen et al 1997), age was included in the design matrix as a confounding covariate, parcellating out effects due to age. The result is a statistical parametric map of the t statistic. Statistically significant differences between sets of data were assessed at each voxel with a threshold of p < .001. To correct for multiple comparisons, clusters of voxels that survived this threshold were further assessed using the theory of random Gaussian fields (Worsley et al 1996), which calculated the significance of clusters based on their peak height and spatial extent. It has been suggested that the cluster size threshold is inaccurate, giving a number of false-positive results (Ashburner and Friston 2000). To correct for this effect, the threshold on the clusters was made tighter than normal, with a significance threshold of p < .01.

With this technique, differences in automatically segmented gray and white matter between the cocaine patients and nondrug-using controls were assessed, and statistical parametric images were generated showing significant regional differences between groups. In addition, images of percentage difference in gray matter concentration were constructed, masked by the statistic image from SPM99 to show only those regions showing significant differences.

**Results**

Statistical parametric mapping analyses revealed significant gray matter concentration decreases in the VMOF, AC, AVI, and superior temporal cortices of the COC group in comparison with the control group at p < .01 corrected (see Table 1). The anatomical locations of these regions are clearly delineated in representative axial slices taken from a high resolution T1-weighted structural MRI (see Figure 1). In contrast, there were no areas of increased gray matter concentration in the cocaine brains compared with controls, and no differences between groups in white matter concentration were observed.

The results of SPM image analysis were displayed on 3D group map renderings to allow visual inspection of the differences in gray matter between groups. Figure 2 depicts eight such 3D images showing the degree of decreased gray matter concentration in the COC group. The color scale represents the t value from 3.43 (red) to 5.5 (white). The continuous colored band visible in the sagittal section of Figure 1 (top left image) indicates gray matter decreases throughout the VMOF and the AC. The decreased gray matter concentration in the COC group is
Figure 1. Representative high resolution magnetic resonance imaging (MRI) structural axial slices showing the anatomical location of the regions in which gray matter differences were observed. The \( z \) value indicates the difference in mm below or above the plane of the anterior and posterior commissures. Top: Slice taken from \( z = -18 \) mm showing the ventromedial orbital frontal (VMOF) region and the superior temporal cortices (Sup TC). Bottom: Slice taken from \( z = 0 \) showing the anterior cingulate (AC), the anteroventral insular cortex (AVI), and the superior temporal cortices.

Individual significant differences were overlaid on T1-weighted averaged MNI axial brain slices provided by SPM'99 to facilitate anatomical location of the decreases (see Figure 3). Nine slices are shown, in neurologic convention (right side = right side), using the \( z \) value convention: slices are numbered according to the number of millimeters (mm) above (+) or below (−) the plane of the anterior and posterior commissures. Only even numbered slices are shown from \( 14 \) mm to \( 2 \) mm. The degree of difference in gray matter density is shown after masking with the statistic image from SPM99 to show only those regions that were significantly different. The percentage scale (which runs from 0%−14%) shows the least percentage of gray matter density difference in a region (black) to the most (white).

The COC group was 100% black American and the control group was 38% black American, 56% white American, and 6% Asian American. The use of this unmatched control group was dictated by the available demography at the site of the data collection center. Acquiring a demographically matched group of individuals without a cocaine history in the vicinity of the treatment facility (West Philadelphia) is almost impossible; however, groups (black and white American) of images from the control group were contrasted voxel by voxel using SPM99 with age included in the model as a confounding covariate and no differences in gray matter concentration were seen between ethnic groups. The one Asian subject was not included in this analysis.

Although we used a relaxed \( P \) value (\( p < .05 \)), there still were no significant correlations between density decreases in the COC group and dollar amount spent during a cocaine binge, years of cocaine use, or number of days used out of the last 30.

Discussion

We provide neuroanatomical evidence that select limbic and cortical regions of COC patients are structurally dissimilar in comparison to a nondrug-using group. When controlling for age-related decreases in gray matter which have been shown to occur in studies measuring volume (Gur et al 1991; Luft 1999; Passe et al 1997), and intensity (Salonen et al 1997), deficits were observed in the AVI, VMOF, AC, and the superior temporal cortices in COC patients compared with a group of cocaine-naive individuals. These findings are the first, either animal or human, to report discrete gray matter differences in chronic cocaine subjects. We suggest that these focal decreases in gray matter concentration, ranging from 5% to 11%, reflect decreased neuronal tissue, and result in deficiencies in these specific regions that may underlie the hypoactivity observed in PET studies of metabolism (Volkow et al 1991; Volkow et al 1992), or cerebral blood flow (Childress et al in press; Childress et al 1999). These abnormalities emerge in regions that are importantly involved in behaviors such as decision making (OFC, AC and AVI: Bechara et al 1999), behavioral inhibition (OFC and AC: Devinsky et al 1995; Knight 1999), and assigning emotional valence (AC and AVI: Cechetto and Saper 1990; Devinsky et al 1995; Knutson et al 2000).

Our findings are consistent with studies showing similar behavioral deficits among discretely brain-damaged and drug-dependent individuals. Drug-dependent patients and OF patients both perform poorly on the gambling task, which is designed to measure deficits that characterize OFC impairment (Bechara et al, 1994). Another study showed that drug abusers perform only half as well as control subjects on the gambling task (Grant et al 2000).
Similarly, impaired performance on the gambling task was associated with defective somatic signaling, a proposed insular function, in drug-dependent patients (Bechara et al 1999; Bechara 2000). Our results are also consistent with a study in which amphetamine abusers exhibited poor performance, correlated with years of amphetamine use, compared with a nondrug-using control group on the Rogers decision-making task (Rogers et al 1999). This task measures a construct similar to the gambling task (Monterosso et al 2001).

As mentioned, COC persons often exhibit deficiencies in behaviors associated with the regions in which gray matter decreases were found, and these deficiencies are also observed in patients with OF or insular damage. Both groups choose immediate gratification over long-term rewards in several decision-making tasks (Bechara et al 1994; Bechara et al 1999; Grant et al 2000). This tendency to make poor decisions may underlie the propensity of COC individuals to risk shelter, relationships, work, health, and even their lives for cocaine. Orbitofrontal dysfunction has also been linked to behavioral disinhibition, perseveration, and the inability to modulate stimulus-reward behavior (Jentsch and Taylor 1999). Accordingly, it is common for COC individuals to have extreme difficulty terminating a binge, even in the face of seriously negative consequences. VMOF and insula lesions also lead to deficits in the ability to respond autonomically to situations involving risk (Bechara et al 2000). A normal autonomic response to danger may help gauge the level of risk involved when contemplating a future behavior, while blunted autonomic responding may permit participation in potentially dangerous behaviors. Cocaine-dependent individuals regularly engage in risky behaviors, particularly when attempting to obtain cocaine (Hudgins et al 1995; Hwang et al 2000). The AC is purported to be involved in all of the above behaviors (Devinsky et al 1995). Temporal cortices are involved in mediating emotionality (Breiter et al 1997; Liotti et al 2000). We suggest that the decreased gray matter concentration found here within select brain regions may contribute to interrupted or imbalanced information processing. In light of the proposed functionality of the interconnected VMOF, AC, AVI and superior temporal cortex, this faulty processing may partially underlie the characteristic behavioral patterns of cocaine-dependent individuals. In such individuals, the immediate gratification guaranteed with the use of cocaine repeatedly outweighs the future negative consequences of using the drug.

This study employed automated segmentation and voxel-by-voxel comparison of gray matter in COC and control subjects based on their structural MRIs. This method has advantages and disadvantages over previous ROI and VOI approaches to examining brain structure. The segmentation step is fast and rater independent as opposed to manual and semiautomated segmentation used.
in other approaches, which can take several hours and may reflect investigator bias. Another feature of this technique is that it is independent of \textit{a priori} hypotheses that may limit the analysis to specific regions. The entire brain can be examined quickly and relatively efficiently. On the other hand, this does not preclude \textit{a priori} hypotheses or hypothesis-driven studies. The primary disadvantage of this technique is that small or subtle abnormalities may be excluded during the normalization, segmentation, or smoothing steps of the SPM analysis. These essential preprocessing steps (Ashburner and Friston 2000) limited the effective spatial resolution to approximately 4mm to 5 mm in this study. Furthermore, we applied a stringent criterion for statistical significance to avoid Type-I errors that may occur because of the large number of statistical tests performed on the clusters. This criterion may have further limited the identification of subtle gray matter differences. Future studies in our laboratory include an ROI analysis on the same data set to determine if any effects in smaller regions were concealed by the preprocessing steps or restrictive significance level.

Limitations of the study include possible contributions from other psychiatric diagnoses. For example, one study reported that 32% of substance dependent patients met criteria for attention-deficit/hyperactivity disorder (ADHD) (Clure et al 1999), whereas epidemiologic studies using standardized diagnostic criteria report a 3%–6% ADHD diagnosis in the general population (Goldman et al 1998). Region of interest MRI studies on ADHD subjects report reduced volumes in some regions of the frontal lobes and basal ganglia relative to comparison subjects (Castellanos et al 1996; Swanson et al 1998 (although volume differences do not necessarily equate with gray matter differences). Despite the fact that a thorough psychological examination was included here that excluded Axis-I and Axis-II disorders, many traits of ADHD are similar to behaviors common in chronic cocaine users. Its sagacious diagnosis in this population would benefit from a full battery of ADHD diagnostic tools, not included here. Ongoing studies in our lab include a thorough neuropsychological examination to investigate the relationship between brain and behavioral dysfunction in COC patients.

Antisocial personality disorder (ASP) is also often comorbid with drug dependence, and both groups exhibit deficits in behavioral inhibition and decision-making capabilities. Reductions in prefrontal gray matter volume by ROI analysis have been attributed to ASP (Raine et al 2000); however, approximately 70% of the ASP subjects in that study were cocaine dependent. Furthermore, as mentioned, volume and concentration are not to be considered interchangeable measurements. It would be beneficial to study separate ASP and COC groups using both types of analyses. In light of our findings, in a COC population without ASP symptomology, the reduced gray matter volume findings of the Raine et al 2000 study may be a partial reflection of the high percentage of cocaine dependence in the ASP group.

As with most studies in treatment populations, this study cannot address the etiology of the structural abnormalities. The observed differences may be related to preexisting dysfunction, either environmentally or genetically determined, or a result of the effects of chronic cocaine assault. These possibilities are not mutually exclusive and evidence exists for both cocaine-inflicted damage and predisposed hypoplasia.

For example, one study found lesions that appear to be related to cocaine-induced arterial vasoconstriction (Bartokis et al 1999). Lesions were predominant in insular white matter, consistent with reports that the majority of infarctions presenting in cocaine patients were due to middle cerebral artery blockade, which provides the major blood supply to the insula (Daras et al 1994; Jacobs et al 1989). Furthermore, animal data has shown that transient middle cerebral artery occlusion causes insular damage (Young et al 1997). These data, combined with ours, showing decreased gray matter in the insula and reciprocally connected regions, suggest that cocaine’s vasoconstrictive properties could account for the differences.

An alternative explanation for cocaine-inflicted damage is indicated by preclinical evidence that cocaine stimulates excessive glutamate release in select brain regions (Bell et al 2000; Pierce et al 1996), resulting in glutamate toxicity (Rockhold 1998). Neuronal cell death and responses to cocaine administration, such as tachycardia, acute and chronic myocardial damage, and sudden cardiac death, all processes associated with glutamate toxicity, can be prevented with excitatory amino acid antagonists (Rockhold 1991; Rappolt et al 1977). These and other lines of evidence point to a cocaine-induced destruction of gray matter (for a review of cocaine-induced neurotoxicity and neuropathy, see Majewska 1996).

Other findings indicate possible preexisting brain dysfunction in COC individuals. As mentioned, there exists a high prevalence of ADHD in COC patients (Clure et al 1999). Coincidentally, other ADHD studies report decreased gray matter in some regions of the frontal lobes (Castellanos et al 1996) and hypofrontality in patients performing a motor task during fMRI (Rubia et al 1999). These deficits in ADHD individuals could indicate preexisting dysfunction that may increase the likelihood of dependence. An additional line of evidence found a correlation between D2 receptor levels and subjective responses to the psychostimulant and reuptake blocker, methylphenidate, in subjects without a history of drug use (Volkow et al 1999). Those who liked the effects of
methylenphenidate had lower D2 receptor levels than those who disliked the effects. Indeed, the D2 receptor levels in the controls who liked methylenphenidate were as low as those documented previously for chronic cocaine users (Volkow et al 1993), and may, in both populations, reflect a preexisting or predisposing factor for cocaine dependence. The fact that we did not see correlations between gray matter concentration decreases and measures of cocaine use are potential evidence that the differences reflect a preexisting condition; however, a larger sample size may reveal a relationship between gray matter deficits and one or more measures of severity of cocaine dependence.

Finally, the regions showing decreased gray matter closely parallel regions activated by cocaine-related stimuli in several studies of cue-induced craving (OF, AVI, and AC) (Childress et al 1999; Grant et al 1996; Maas et al 1998; Stapleton et al 1995). Craving is often cited as a reason for subsequent participation in drug-seeking and drug-taking activities (Childress et al 1993; Wallace 1989). The overlap in structural insufficiencies in regions involved in behavioral inhibition, decision-making, attributing emotional valence, and those activated during cue-induced craving may result in an overwhelming desire to seek and use drugs ungnoverned by the prospect of future negative consequences. The subsequent poor decision to use cocaine at an immediate moment despite future costs is a core feature of addiction and may be related to the structural deficits reported here.

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