Imaging Glutamate Homeostasis in Cocaine Addiction with the Metabotropic Glutamate Receptor 5 Positron Emission Tomography Radiotracer $^{11}$CABP688 and Magnetic Resonance Spectroscopy

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Background: Preclinical studies demonstrate that glutamate homeostasis in the striatum is disrupted following cocaine exposure, including a decrease in metabotropic glutamate receptor type 5 (mGluR5) expression and reduced glutamate turnover. The goal of this study was to use imaging of the human brain to investigate alterations in the glutamate signaling in cocaine addiction.

Methods: Positron emission tomography imaging with the radiotracer $^{11}$CABP688 was used to measure mGluR5 binding and magnetic resonance spectroscopy was used to measure glutamate-glutamine levels in the striatum of cocaine-addicted participants ($n = 15$) compared with healthy control subjects ($n = 15$). Following the scans, the cocaine-addicted volunteers performed cocaine self-administration sessions to investigate the correlation between cocaine-seeking behavior and mGluR5 receptor binding.

Results: The results of the study showed that cocaine addiction was associated with a 20% to 22% reduction in $^{11}$CABP688 binding in the striatum. A secondary analysis of cortical and subcortical regions other than the striatum showed a similar reduction in $^{11}$CABP688 binding, suggesting that the decrease was widespread. No between-group differences were seen in the magnetic resonance spectroscopy measures of glutamate-glutamine in the left striatum. In addition, no correlation was seen between $^{11}$CABP688 binding in the striatum and the choice to self-administer cocaine.

Conclusions: Overall, these results show that long-term cocaine use is associated with a decrease in mGluR5 availability compared with matched healthy control subjects and suggests that this receptor may serve as a viable target for treatment development for this disorder.

Key Words: Addiction, cocaine, cocaine self-administration, magnetic resonance spectroscopy, metabotropic glutamate receptor 5, positron emission tomography

The metabotropic glutamate receptor subtype 5 (mGluR5) is a predominantly postsynaptic receptor that contains both orthosteric and allosteric binding sites (1). The mGluR5 are mostly located on the periphery of the synapse, where they regulate ionotropic glutamate receptor activity and play an important role in synaptic plasticity (1). Preclinical studies show that modulation of the mGluR5 receptor affects the reinforcing efficacy of cocaine. The administration of an mGluR5 antagonist to rodents reduces the reinforcing properties of cocaine (2–7) and similar results have been reported in rhesus monkeys (8,9). On the other hand, activation of the mGluR5 with the administration of a positive allosteric modulator has been shown to improve extinction learning following cocaine self-administration in rodents (10).

Studies in rodents have also investigated the effect of cocaine exposure followed by withdrawal on mGluR5 expression in the striatum, and overall, these show a reduction in mGluR5 receptor levels compared with control animals (11–13). In addition, the decrease in mGluR5 surface expression is associated with elevated levels of Homer1b/c protein, which is thought to contribute to increased sequestration of the mGluR5 from the membrane surface (13). Based on these studies, we tested the hypothesis that cocaine addiction in human volunteers would be associated with a reduction in mGluR5 receptor availability in the striatum compared with control subjects, using positron emission tomography (PET) and the radiotracer 3-(6-methylpyridin-2-ylethynyl)-cyclohex-2-enone-O-carbon-11-methyl-oxime ($^{11}$C ABP688), which binds to the allosteric site of the mGluR5.

Preclinical studies have also shown that cocaine exposure disrupts glutamate neurotransmitter levels in the striatum. Glutamate turnover is decreased in the nucleus accumbens following cocaine self-administration in rodents (14) and long-term cocaine exposure decreases basal extrasynaptic glutamate levels (15). Therefore, in addition to PET imaging, magnetic resonance spectroscopy (MRS) studies were obtained to measure glutamate + glutamine (Glx) levels in the striatum.

Lastly, to investigate the relationship between cocaine-seeking behavior and mGluR5 receptor availability, the cocaine-addicted subjects completed cocaine self-administration sessions following the PET scans. Our hypothesis was that lower mGluR5 availability would correlate with higher levels of cocaine self-administration.
Methods and Materials

The cocaine-addicted (CA) volunteers were medically healthy individuals who fulfilled DSM-IV criteria for current cocaine dependence, with no other current Axis I diagnosis, including abuse or dependence to other substances (classified per DSM-V they met criteria for substance use disorder, moderate to severe). The CA volunteers were actively using smoked cocaine at study entry (verified by urine toxicology) and could not be seeking treatment for their cocaine use. Admission began 10 to 14 days before the scans. The healthy control subjects were required to be medically healthy with no current or past DSM-IV Axis I disorder. The study was approved by the Institutional Review Boards of the New York State Psychiatric Institute and the Yale University School of Medicine.

Positron Emission Tomography Scans

The PET scans with [11C]ABP688 were performed at the Yale University Positron Emission Tomography Research Center. [11C]ABP688 was administered as a bolus with constant infusion (Kbol = 75 min, determined from initial bolus studies). The PET scans were acquired on the High Resolution Research Tomograph (Siemens/CTI, Knoxville, Tennessee) in three-dimensional mode for 90 minutes with collection of the arterial input function.

Each subject had a T1-weighted structural magnetic resonance imaging scan for identification of the regions of interest (ROIs). The primary hypothesis in this study was limited to the striatum, which was divided into subdivisions: 1) the caudate (rostral and caudal); 2) the putamen (rostral and caudal); and 3) the ventral striatum, which included the nucleus accumbens, ventral caudate, and ventral putamen, using criteria described previously (16). Given the wide distribution of the mGluR5 receptor in the human brain, the following additional subcortical and cortical regions were included for a secondary analysis: anterior cingulate, dorsolateral prefrontal cortex, medial prefrontal cortex, orbitofrontal cortex, medial temporal cortex (comprised of the amygdala, hippocampus, parahippocampal gyrus, entorhinal cortex, and uncus combined), temporal cortex (excluding the structures included of the medial temporal lobe), occipital cortex, and thalamus. These ROIs were identified using criteria previously described (16,17). The cerebellum served as the reference region, based on previous studies (18–21). Additional data regarding the acquisition and analysis of the PET scans are included in Supplement 1.

Magnetic Resonance Spectroscopy Scans

The MRS scans were performed on a GE Signa EXCITE 3T scanner (GE Medical Systems, Milwaukee, Wisconsin) at the New York State Psychiatric Institute. Glutamate + glutamine and gamma-aminobutyric acid data were acquired with a receive-only 8-channel phased-array head coil using a standard point resolved spectroscopy sequence with a volume-selective J-editing difference method (22) as modified by Sallasuta et al. (23). The MRS data were processed as previously described (24) (see Supplement 1 for details).

Cocaine Self-Administration Sessions

The cocaine-using participants completed cocaine self-administration sessions using methods previously described (25) (additional details in Supplement 1). The subjects underwent two separate sessions with 0 mg or 6 mg smoked cocaine. Each subject underwent one 0 mg and one 6 mg dosing session. The 0 mg session served as the control. The outcome measure for the self-administration sessions was the number of times a dose of cocaine was chosen over the money option (range 0–5).

Statistical Analysis

Group demographic comparisons were performed with chi-square or unpaired t tests. The primary analysis was performed on the striatal ROIs using unpaired t tests with correction for multiple observations. A secondary analysis of the remaining ROIs was performed with linear mixed modeling, with regions of interest as repeated measure and diagnostic group and regions as fixed factors (SPSS Statistics, Chicago, Illinois).

For the MRS data, the primary outcome measure was the ratio of Glx to water in the left striatum, and the between-subject comparison was made using an unpaired t test. A secondary analysis was performed for the additional outcome measures with unpaired t tests. Correction for tissue heterogeneity was made by entering voxel tissue proportion as a covariate in the group comparison when this quantity differed between the diagnostic groups.

Analysis of the association between the number of times cocaine was chosen (over money) and binding potential (specific to nonspecific equilibrium partition coefficient, BPND) was performed as follows: 1) using the ROI analysis; 2) using linear mixed modeling; and 3) with correlation maps performed with SPM2 software (Wellcome Trust Centre for Neuroimaging, University College London, United Kingdom). Additional details of the statistical analyses are included in the supplementary information.

Results

Fifteen cocaine-addicted subjects and 15 control subjects completed this study. The CA subjects had been using cocaine for an average of 18 ± 7 years and were currently spending an average of $356 ± $149 per week (about 3.2 ± 1.3 gm/week) on smoked cocaine. One healthy control subject was found to have an Axis I disorder, and was removed from the analysis. Two additional control subjects and one cocaine-addicted subject did not undergo the MRS scans due to either scheduling conflicts or technical issues. The demographic data are shown in Table 1, with additional details provided in Supplement 1.

PET Data: [11C]ABP688 BPND

Cocaine addiction was associated with lower values for [11C]ABP688 BPND in each of the striatal subregions, as shown in Table 2, following false discovery rate correction for multiple

### Table 1. Group Demographics of the Healthy Control and Cocaine-Addicted Subjects

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects</th>
<th>CA Subjects</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean ± SD, in Years)</td>
<td>41 ± 4</td>
<td>43 ± 3</td>
<td>.2*</td>
</tr>
<tr>
<td>Gender (Male/Female)</td>
<td>13M/1F</td>
<td>14M/1F</td>
<td>–</td>
</tr>
<tr>
<td>Ethnicity (African American/Caucasian not Hispanic)</td>
<td>12AA/2C</td>
<td>13AA/2C</td>
<td>.94*</td>
</tr>
<tr>
<td>Smoking Status (Yes/No)</td>
<td>9Y/5N</td>
<td>12Y/3N</td>
<td>.60*</td>
</tr>
<tr>
<td>Number of Cigarettes per Day in Smokers (Mean ± SD)</td>
<td>4 ± 7</td>
<td>6 ± 5</td>
<td>.67*</td>
</tr>
</tbody>
</table>

*Unpaired t test.
*Chi-squared test.
A decrease in BPND was seen in each of the subdivisions. The values presented are mean and standard deviation (SD) and the p values were obtained with a two-tailed unpaired t test (not corrected for multiple observations). False discovery rate correction resulted in all BPND remaining significant. However, with Bonferroni correction, the differences in BPND remained significant in the limbic striatum and putamen (anterior and posterior) but not the caudate (anterior and posterior).

BPND, binding potential; CA, cocaine-addicted.

comparisons. Following Bonferroni correction, the ventral striatum and putamen, but not the caudate, remained significant. The analysis of the remaining nonstriatal ROIs showed that cocaine addiction was associated with lower values for [11C]ABP688 BPND in these regions as well (linear mixed modeling, effect of diagnosis, F1,27 = 6.7, p = .015; effect of region, F8,27 = 127.5, p < .001; region by diagnosis interaction, F8,27 = 2.9, p = .018). The values for BPND in the remaining ROIs are shown in Table 3. This is illustrated in Figure 1, which shows a map of BPND for [11C]ABP688 for each group, generated using the basis function method for each voxel (26). No between-group difference were seen in cerebellum VT (total volume of distribution) (VTCER control subjects 2.64 ± 1.12; cocaine-addicted 2.40 ± 1.12, p = .6) indicating that differences in non-specific binding did not explain these findings.

MRS Data

As shown in Table 4, no differences were seen in the Glx/water ratio between the cocaine-addicted (n = 14) and control subjects (n = 12). In addition, no differences were seen between the two groups with respect to the remaining outcome measures (following correction for multiple observations), also shown in Table 4. Analysis of covariance with cerebrospinal fluid percent of the voxel volume as covariate was performed, since this quantity differed at trend level (p = .10) between the groups (Table 4) but did not change the results. In addition, tissue composition did not differ by group in the striatal voxel (Table 4). A post hoc analysis was performed investigating the correlation between [11C]ABP688 BPND and Glx/water for each subject in the left striatum; no significant associations were detected.

Cocaine Self-Administration Sessions

One CA subject chose to leave the study before the cocaine self-administration sessions, so this analysis included 14 subjects. The 6 mg dose of smoked cocaine was chosen as an average of 1.3 ± 1.8 times, which was greater than the average choice for the 0 mg dose (21 ± 0.6 times, p = .04). Thus, the 6 mg condition differed from the control condition. However, no significant associations were detected between BPND of the ROIs and the choice for cocaine at the individual ROI level or globally using the linear mixed model. The statistical parametric map contained no clusters that survived false discovery rate correction for multiple comparisons. No significant correlations were seen between BPND of the ventral striatum or striatum and years of abuse, self-reports of craving for cocaine, or amount of cocaine use at study entry.

Discussion

The results of this study demonstrate that mGluR5 receptor availability, measured as [11C]ABP688 BPND, is reduced in cocaine-addicted subjects compared with matched healthy volunteers. Our primary hypothesis was that mGluR5 binding would be reduced in the striatum, and the results showed that cocaine addiction was associated with a decrease in [11C]ABP688 BPND in the ventral (limbic) striatum and putamen compared with control subjects. However, a secondary analysis of the brain regions outside the striatum (anterior cingulate, prefrontal and temporal cortex, thalamus, and occipital cortex) showed that [11C]ABP688 BPND was also reduced in these regions, suggesting that the decrease in mGluR5 binding is widespread. Within the cocaine-addicted volunteers, the association between the reinforcing effects of cocaine, measured as cocaine self-administration, and [11C]ABP688 BPND was investigated, and no correlation was seen. In addition, magnetic resonance spectroscopy was used to measure the glutamate/water ratio in the left striatum, and no differences were seen between the cocaine-addicted subjects and control subjects.

The finding of reduced striatal mGluR5 is largely in agreement with studies in rodents. Previous studies have investigated the effect of cocaine exposure on striatal mGluR5, and while some studies showed a reduction in receptor expression (11–13) another study did not (27). The studies showing a decrease in mGluR5 expression used both extended access to cocaine and extinction following self-administration. The decrease in mGluR5 was shown in the nucleus accumbens (11–13). These studies have also shown reduced functional mGluR5 activity (12) and increased Homer1b/c protein levels, which would be expected to increase internalization of the surface mGluR5 (13). The study of Hao et al. (12) also reported a downward trend in mGluR5 expression outside the striatum, in the medial prefrontal cortex and hippocampus.

The results of this study are not in agreement with a recently published study reporting that cigarette smoking, but not cocaine abuse, is associated with lower [11C]ABP688 BPND compared with control subjects (28). However, there are some key differences between the study of Hulkia et al. (28) and the present study. The

Table 2. Comparison of [11C]ABP688 BPND in the Striatal Subregions between the Healthy Control and Cocaine-Addicted Subjects

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Control Subjects (n = 14)</th>
<th>CA Subjects (n = 15)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Limbic Striatum</td>
<td>1.07</td>
<td>.23</td>
<td>.83</td>
</tr>
<tr>
<td>Anterior Putamen</td>
<td>1.01</td>
<td>.20</td>
<td>.80</td>
</tr>
<tr>
<td>Posterior Putamen</td>
<td>.72</td>
<td>.15</td>
<td>.56</td>
</tr>
<tr>
<td>Anterior Caudate</td>
<td>.88</td>
<td>.21</td>
<td>.69</td>
</tr>
<tr>
<td>Posterior Caudate</td>
<td>.40</td>
<td>.17</td>
<td>.25</td>
</tr>
</tbody>
</table>

The values presented are mean and standard deviation (SD) and the p values were obtained with a two-tailed unpaired t test (not corrected for multiple observations).

BPND, binding potential; CA, cocaine-addicted; ROI, region of interest.

Table 3. Comparison of [11C]ABP688 BPND in the Additional ROIs between the Healthy Control and Cocaine-Addicted Subjects

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Control Subjects (n = 14)</th>
<th>CA Subjects (n = 15)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Anterior Cingulate</td>
<td>1.20</td>
<td>.26</td>
<td>.99</td>
</tr>
<tr>
<td>Dorsolateral Prefrontal Cortex</td>
<td>1.04</td>
<td>.20</td>
<td>.84</td>
</tr>
<tr>
<td>Medial Prefrontal Cortex</td>
<td>1.10</td>
<td>.25</td>
<td>.90</td>
</tr>
<tr>
<td>Orbitofrontal Cortex</td>
<td>.97</td>
<td>.22</td>
<td>.76</td>
</tr>
<tr>
<td>Medial Temporal Cortex</td>
<td>.70</td>
<td>.16</td>
<td>.59</td>
</tr>
<tr>
<td>Temporal Cortex</td>
<td>.93</td>
<td>.21</td>
<td>.77</td>
</tr>
<tr>
<td>Occipital Cortex</td>
<td>.84</td>
<td>.15</td>
<td>.72</td>
</tr>
<tr>
<td>Thalamus</td>
<td>.43</td>
<td>.12</td>
<td>.31</td>
</tr>
</tbody>
</table>

The values presented are mean and standard deviation (SD) and the p values were obtained with a two-tailed unpaired t test (not corrected for multiple observations).
subjects included in that study were lighter users of cocaine than those in the present study (estimated 1.5 ± 1.4 gm/week versus 3.2 ± 1.3 gm/week). They had also used cocaine for fewer years (10 ± 6 years versus 18 ± 7 years in this study) and mostly used intranasal cocaine, whereas all the subjects in this study used smoked cocaine. Lastly, they had been abstinent for less time ($\leq 3$ days versus 10 to 14 days). Although the extent of use most likely contributes to this difference between the two studies, it is also possible that cocaine use is associated with a decrease in mGluR5 receptor binding only after days of abstinence.

Additionally, another study has shown that mGluR5 receptor binding is reduced in smokers and ex-smokers compared with nonsmokers (29). The study also showed a global effect: mGluR5 BPND was reduced by 20.6% across brain regions, which is similar to the finding by Hulka et al. (28). Our study controlled for tobacco smoking and the amount of cigarette use was much lower than that reported by Akkus et al. (29) and Hulka et al. (28) (6 ± 5 per day in this study versus 17 ± 5 in Akkus et al. [29] and 12 ± 11 in Hulka et al. [28]). Yet, we conducted a post hoc analysis using a linear mixed model with the cigarettes smoked per day as a covariate. The two-way interactions between smoking and diagnosis or region of interest were not significant, and the model with main effects of smoking added to the previous model was a more parsimonious method. The main effect of smoking was significant, although the effect of smoking itself on BPND was small (.0065 decrease per cigarette per day), and the main effect of diagnosis, as well as the ROI by diagnosis interaction, continued to be significant (effect of diagnosis, $F_{1,27,295} = 5.901, p = .022$; effect of ROI, $F_{8,27} = 127.481, p < .001$; effect of smoking, $F_{1,26,016} = 4.479, p = .044$; diagnosis by ROI interaction, $F_{8,27} = 2.905, p = .018$). As a result, we conclude that cocaine addiction itself is associated with a decrease in mGluR5 BPND measured with $[^{11}C]$ABP688, which is also associated with cigarette smoking. Notably, previous human imaging

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**Table 4. Ratio of Metabolite and Tissue Composition Results in Cocaine-Addicted and Control Subjects Using Magnetic Resonance Spectroscopy in the Left Striatum**

<table>
<thead>
<tr>
<th>Metabolite Ratio</th>
<th>Control Subjects (n = 12)</th>
<th>CA Subjects (n = 14)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glx/Water</td>
<td>$5.15 (1.62) \times 10^{-3}$</td>
<td>$5.24 (1.71) \times 10^{-3}$</td>
<td>.8</td>
</tr>
<tr>
<td>GABA/Water</td>
<td>$8.56 (1.12) \times 10^{-3}$</td>
<td>$7.83 (2.77) \times 10^{-3}$</td>
<td>.4</td>
</tr>
<tr>
<td>Choline/Water</td>
<td>$2.21 (3.9) \times 10^{-2}$</td>
<td>$2.37 (3.2) \times 10^{-2}$</td>
<td>.3</td>
</tr>
<tr>
<td>Creatine/Water</td>
<td>$2.76 (3.1) \times 10^{-2}$</td>
<td>$2.75 (5.3) \times 10^{-2}$</td>
<td>.9</td>
</tr>
<tr>
<td>NAA/Water</td>
<td>$3.77 (4.8) \times 10^{-2}$</td>
<td>$4.23 (5.0) \times 10^{-2}$</td>
<td>.03</td>
</tr>
<tr>
<td>Tissue Type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gray Matter %</td>
<td>40.0 (3.8)%</td>
<td>39.7 (3.8)%</td>
<td>.8</td>
</tr>
<tr>
<td>White Matter %</td>
<td>55.0 (4.1)%</td>
<td>56.3 (3.6)%</td>
<td>.4</td>
</tr>
<tr>
<td>Cerebrospinal Fluid %</td>
<td>4.9 (1.4)%</td>
<td>4.0 (1.5)%</td>
<td>.1</td>
</tr>
</tbody>
</table>

No significant difference was seen between the two groups (following correction for multiple observations). Tissue composition also did not differ by group in the striatal voxel.

CA, cocaine-addicted; GABA, gamma-aminobutyric acid; Glx, glutamate + glutamine; NAA, N-acetylaspartate.
studies have also shown that other receptor systems are affected similarly across addictions, such as the dopamine type 2 receptor, which is decreased in the striatum in both nicotine and cocaine addiction (30,31), and the serotonin transporter, which is increased in both types of addiction (32,33).

In addition to receptor expression, preclinical studies have also investigated the effect of blocking the mGluR5 on cocaine-seeking behavior. These studies show that the administration of an mGluR5 antagonist reduces cocaine self-administration, conditioned place preference, the breakpoint for cocaine, and the cue-induced reinstatement of cocaine self-administration (2–7). In monkeys, mGluR5 antagonist administration attenuates cocaine self-administration, cocaine-induced reinstatement of drug-seeking behavior, and the discriminative stimulus effects of cocaine (8,9). However, recent studies in rodents have also shown that activation of the mGluR5 improves the acquisition and consolidation of extinction learning following cocaine exposure (10,34). Thus, while these studies show that mGluR5 antagonism reduces cocaine self-administration in animal models, activation of the receptor appears to improve extinction learning.

Currently, effective pharmacotherapies for cocaine addiction do not exist, and the question arises as to how or whether this imaging study, combined with the preclinical literature, might inform future treatment. In the present study, PET scans were obtained after 10 to 14 days of abstinence, and this time point was chosen for two reasons. The first reason was to avoid the acute effects of cocaine on the mGluR5 and to ensure that all subjects were scanned after a standard period of abstinence, since all were actively using cocaine at study entry. The second reason was to obtain a measure of neurochemistry at a time point that has clinical significance, since previous studies have shown that cocaine-addicted subjects who achieve 2 weeks of abstinence have a better treatment response, whereas those who do not tend to have worse treatment outcomes (35,36). Yet, it remains possible that this duration of abstinence adds a selection bias, since only subjects willing to be hospitalized for this time period could be enrolled in this study.

Insofar as reduced receptor availability reflects reduced receptor activation in the human brain, these findings indicate that future studies targeting the mGluR5 receptor may serve as a viable treatment approach for cocaine addiction. But it is not known whether the reduction in mGluR5 binding potential reflects a need for activation at this receptor or whether the receptor is downregulated in response to excess glutamate levels, suggesting that receptor blockade would be a more appropriate approach. Animal models of cocaine addiction show both an increase and a decrease in striatal glutamate levels (37–41). Additionally, as described above, animal studies have shown that both agonists and antagonists may be beneficial in preventing relapse to cocaine use. Therefore, while the imaging data can be used to identify neurobiological targets for treatment development, future studies are needed to determine the direct effect of modulating mGluR5 receptor signaling on cocaine addiction.

The radiotracer [11C]ABP688 has not yet been used extensively in clinical populations, but it has a number of characteristics that make it useful for imaging the mGluR5 in psychiatric disorders. Its pharmacokinetic properties allow for a relatively short scan time, it is specific for an allosteric site on the mGluR5 (42), and reference tissue modeling has been validated in human imaging (21). In this study, we used reference tissue modeling, which requires a brain region (reference region) without displacable binding of the radiotracer to the receptor. The cerebellum was used for this purpose, which has been shown in one study to lack mGluR5 receptors (measured with immunoreactivity) (18), although other studies have shown low binding of mGluR5 radiotracers to receptors in human cerebellum (43,44). However, both of these studies showed that the mGluR5 density was much lower than that of the cortical and subcortical brain regions. Additionally, while one study showed that blocking the mGluR5 does not affect binding of [11C]ABP688 in the cerebellum in rodents (20), another study showed there was a small decrease in the cerebellum in baboons (45). Nevertheless, recent studies show that reference tissue modeling for this radiotracer is appropriate using the cerebellum (20,21). In the present study, no group differences were seen in the volume of distribution in the cerebellum, suggesting that the differences seen in mGluR5 availability was not due to a group difference in global non-specific binding.

Nonetheless, there are some methodological issues that arise with the use of [11C]ABP688. A previous study reported a high test/retest variability for [11C]ABP688 BPND in healthy human volunteers, in which BPND increased in the second scan compared with the first scan (46). Since this effect was not seen in test/retest studies performed in anesthetized nonhuman primates (19,45), the authors suggested that, in the control subjects, the first PET scan may have been associated with greater stress and higher levels of extracellular glutamate (and thus a lower value for BPND) compared with the second PET scan (45). With respect to the present study, both cocaine-addicted subjects and healthy control subjects underwent only one PET scan each. It could be expected that their stress levels were similar across groups, although this question was not specifically investigated.

Previous MRS imaging studies in cocaine users have reported a decrease in glutamate in the rostral anterior cingulate (47) and an increase in glutamate in the dorsal anterior cingulate cortex (48). A recent study in squirrel monkeys showed that chronic cocaine administration resulted in an increase in glutamate and glutamine (relative to creatine) in the putamen (49). In the present study, we measured the Glx/water ratio in the striatum (caudate and putamen) using MRS but did not see a difference in the cocaine-addicted subjects compared with control subjects. A post hoc analysis using the ratio of Glx/creatine also showed no between-group difference. This could result from a few sources: 1) in this study, the caudate and putamen were measured together; 2) the monkey study used a higher field strength scanner (9.4T vs. 3T in our human study); and 3) in our study, the cocaine-addicted subjects underwent MRS scans following 10 to 14 days of abstinence, whereas in the monkey study, the animals were scanned hours after the last dose of cocaine. Therefore, it is possible that alterations in glutamate do occur in cocaine-addicted humans, but this might have normalized following a period of abstinence.

In this study, we saw no correlation between [11C]ABP688 BPND and the choice to self-administer cocaine. In a previous study, we showed that dopamine release, measured with PET imaging, correlated with the choice to self-administer cocaine in the laboratory (50). The reason for this lack of a correlation in the present study is unclear and could result from a lack of sensitivity in the PET or the behavioral data. Alternatively, this data could indicate that the mGluR5 receptor is reduced in cocaine addiction, but this decrease may be associated with aspects of cocaine addiction other than reward-related behavior. Preclinical studies have shown that the dopamine and glutamate signaling in the striatum are intertwined in mediating cocaine self-administration, but glutamate signaling at the mGluR5 is more closely related to...
learning processes (10,34). Thus, a behavioral measure that probes cognition may be more closely associated with mGluR5 binding.

This study was supported by the National Institute on Drug Addiction Public Health Service Grants RC1 DA028033 and K02 DA026525. This publication was also made possible by Clinical and Translational Science Award Grant No. UL1 RR024139 from the National Center for Research Resources and the National Center for Advancing Translational Science, components of the National Institutes of Health (NIH), and NIH roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the view of NIH.

We thank the staff of the Yale University Positron Emission Tomography Center for their excellent technical support and nursing care. In addition, the research was made possible by support of the New York State Psychiatric Institute and the inpatient staff where the participants were admitted in addition to the Marian W. Fischman Cocaine Research Laboratory. We also thank Rawad Ayoub and Xiaoyan Xu for their excellent work in image analysis and J. John Mann and Ramin V. Parsey for their help with the radiotracer. Our thanks to Richard Foltin, Ph.D., for his review and editing of the manuscript.

The authors report no biomedical financial interests or potential conflicts of interest.

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.biopsych.2013.06.026.


