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Imaging glutamate homeostasis in cocaine addiction with the mGluR5 PET radiotracer [¹¹C]ABP688 and Magnetic Resonance Spectroscopy

Diana Martinez, M.D.¹, Mark Slifstein, Ph.D.¹, Nabeel Nabulsi, Ph.D.², Alexander Grassetti, B.A.¹, Nina Urban, M.D.¹, Audrey Perez, R.N.¹, Fei Liu, Ph.D.¹, Shu-fei Lin, Ph.D.², Jim Ropchan, Ph.D.², Xiangling Mao, M.S.³, Lawrence S. Kegeles, M.D., Ph.D.¹, Dikoma C. Shungu, Ph.D.³, Richard E. Carson, Ph.D.², and Yiyun Huang, Ph.D.²

¹Department of Psychiatry, Columbia University College of Physicians and Surgeons and the New York State Psychiatric Institute, New York, NY, USA

²The Department of Psychiatry, Yale PET Center, Yale University School of Medicine, New Haven, Connecticut, USA

³Department of Radiology, Weill Medical College of Cornell University, New York, NY, USA

Abstract

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 (PET) imaging with the radiotracer [¹¹C]ABP688 was used to measure mGluR5 binding and magnetic resonance spectroscopy (MRS) was used to measure glutamate-glutamine levels in the striatum of cocaine addicted participants (n=15) compared to healthy controls (n=15). Following the scans, the cocaine addicted volunteers performed cocaine self-administration sessions in order 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 20–22% reduction in [¹¹C]ABP688 binding in the striatum. A secondary analysis of cortical and subcortical regions other than the striatum showed a similar reduction in [¹¹C]ABP688 binding, suggesting that the decrease is widespread. No between-group differences were seen in the MRS

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Corresponding Author Diana Martinez, M.D., New York State Psychiatric Institute, 1051 Riverside Drive, Box #31, New York, NY 10032, Telephone: (212) 543-6628, Fax: (212) 568-6171.

Conflict of interest.

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

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measures of glutamate-glutamine in the left striatum. In addition, no correlation was seen between [11C]ABP688 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 to matched healthy controls and suggests that this receptor may serve as a viable target for treatment development for this disorder.

Keywords

addiction; cocaine; magnetic resonance spectroscopy; positron emission tomography; metabotropic glutamate receptor 5; cocaine self-administration

Introduction

The metabotropic glutamate receptor subtype 5 (mGluR5) is a predominantly post-synaptic 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 to controls (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 to control subjects, using Positron Emission Tomography (PET) and the radiotracer [11C]ABP688 (3-(6-methylpyridin-2-ylethynyl)-cyclohex-2-enone-O-carbon-11-methyl-oxime), 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 extra-synaptic 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, in order 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

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 10–14 days prior to the scans. The healthy control subjects (HC) 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 [^{11}C]ABP688 were performed at the Yale University Positron Emission Tomography Research Center. [^{11}C]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 (HRRT, Siemens/CTI, Knoxville, TN) in 3D mode for 90 minutes with collection of the arterial input function.

Each subject had a T1-weighted structural MRI scan for identification of the regions of interest (ROIs). The primary hypothesis in this study was limited to the striatum, which was divided into 5 subdivisions: 1) the caudate (rostral and caudal); 2) the putamen (rostral and caudal); and 3) the ventral striatum (VST), which includes 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 is included in the supplementary information.

Magnetic Resonance Spectroscopy scans

The MRS scans were performed on a GE Signa EXCITE 3T scanner (GE Medical Systems, Milwaukee, WI) at the New York State Psychiatric Institute. Glx and GABA data were acquired with a receive-only 8-channel phased-array head coil using a standard PRESS sequence with a volume-selective J-editing difference method (22) as modified by Sailasuta et al (23). The MRS data were processed as previously described (24) (see supplementary information for details).

Cocaine self-administration sessions—The cocaine using participants completed cocaine self-administration sessions using methods previously described (25) (additional details in supplementary information). The subjects underwent two separate sessions with

either 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 (LMM), with regions of interest as repeated measure and diagnostic group and regions as a 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 (see table 4) 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 association between the number of times cocaine was chosen (over money) and BP_{ND} was performed as follows: 1) using the ROI analysis; 2) using a linear mixed modeling; and 3) with correlation maps performed with SPM2 software. Additional details of the statistical analyses are included in the supplementary information.

Results

Fifteen cocaine addicted (CA) 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 $\$356 \pm 149/\text{week}$ (about $3.2 \pm 1.3/\text{week}$) 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 the supplemental data.

PET data: [^{11}C]ABP688 BP_{ND}

Cocaine addiction was associated with lower values for [^{11}C]ABP688 BP_{ND} in each of the striatal subregions, as shown in table 2, following false discovery rate correction multiple comparisons. Following Bonferroni correction, the ventral striatum and putamen, but not the caudate, remained significant. The analysis of the remaining non-striatal ROIs showed that cocaine addiction was associated with lower values for [^{11}C]ABP688 BP_{ND} in these regions as well (LMM, effect of diagnosis, $F(1,27) = 6.7$, $p = 0.015$; effect of region, $F(8,27) = 127.5$, $p < 0.001$; region by diagnosis interaction, $F(8,27) = 2.9$, $p = 0.018$). The values for BP_{ND} in the remaining ROIs are shown in table 3. This is illustrated in figure 1, which shows a map of BP_{ND} for [^{11}C]ABP688 for each group, generated using the basis function method for each voxel (26). No between group differences were seen in cerebellum VT

(VT_{CER} controls 2.64 ± 1.12 ; cocaine addicted 2.40 ± 1.12 , $p = 0.6$) indicating that differences in non-specific binding did not explain these findings.

MRS data

As shown in table 4, no differences were seen between 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. ANCOVA 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), which did not change these 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 [^{11}C]ABP688 BP_{ND} and Glx/W for each subject in the left striatum; no significant associations were detected.

Cocaine self-administration sessions

One CA subject chose to leave the study prior to the cocaine self-administration sessions, so that this analysis included 14 subjects. The 6 mg dose of smoked cocaine was chosen an average of 1.3 ± 1.8 times, which was greater than the average choice for the 0 mg dose (0.21 ± 0.6 times, $p = 0.04$). Thus, the 6 mg condition differed from the control condition. However, no significant associations were detected between BP_{ND} of the ROIs and the choice for cocaine at the individual ROI level or globally using the linear mixed model. The SPM map contained no clusters that survived FDR correction for multiple comparisons. No significant correlations were seen between BP_{ND} of the VST 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 [^{11}C]ABP688 BP_{ND} , is reduced in cocaine addicted subjects compared to 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 [^{11}C]ABP688 BP_{ND} in the ventral striatum and putamen compared to controls. However, a secondary analysis of the brain regions outside the striatum (anterior cingulate, prefrontal and temporal cortex, thalamus, and occipital cortex) showed that [^{11}C]ABP688 BP_{ND} 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 [^{11}C]ABP688 BP_{ND} 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 controls.

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 show a reduction in receptor expression (11–13) another 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) and 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 recently published study reporting that cigarette smoking, but not cocaine abuse, is associated with lower [11C]ABP688 BP_{ND} compared to controls (28). However, there are some key differences between the study of Hulka et al (28) and the present one. The subjects included in that study were lighter users of cocaine than those of the present study (estimated 1.5 ± 1.4 gm/week vs 3.2 ± 1.3 gm/week). They had also used cocaine for fewer years (10 ± 6 years vs 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 (< 3 days vs 10–14 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 to non-smokers (29). That study also showed a global effect: mGluR5 BP_{ND} 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 vs 17 ± 5 in Akkus et al and 12 ± 11 in Hulka et al). 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 (ROI) 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 BP_{ND} was small (0.0065 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, $F(1,27.295) = 5.901$, $p = 0.022$; effect of ROI, $F(8,27) = 127.481$, $p < 0.001$; effect of smoking, $F(1,26.016) = 4.479$, $p = 0.044$; diagnosis by ROI interaction, $F(8,27) = 2.905$, $p = 0.018$). As a result, we conclude that cocaine addiction itself is associated with a decrease in mGluR5 BP_{ND} measured with [11C]ABP688, which is also associated cigarette smoking. Notably, previous human imaging 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 break point 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 10–14 days of abstinence, and this time point was chosen for two reasons. The first 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 two 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 down-regulated 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 useful in identifying neurobiological targets for treatment development, future studies are needed to determine the direct effect of modulating mGluR5 receptor signaling on cocaine addiction.

The radiotracer [^{11}C]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 displaceable 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 [^{11}C]ABP688 in the cerebellum in rodents (20), another study showed there was a small decrease 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 [^{11}C]ABP688. A previous study reported a high test/re-test variability for [^{11}C]ABP688 BP_{ND} in healthy human volunteers, in which BP_{ND} increased in the second scan compared to the first (46). Since this effect was not seen in test/re-test studies performed in anesthetized non-human 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 BP_{ND}) compared to the second PET scan (45). With respect to the present study, both cocaine addicted subjects and healthy controls underwent only one PET scan each, such that it might be expected that their stress levels would have been 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 to controls. 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); 3) in our study, the cocaine addicted subjects underwent MRS scans following 10–14 days of abstinence, whereas in the monkeys 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 that this might have normalized following a period of abstinence.

In this study, we saw no correlation between [^{11}C]ABP688 BP_{ND} 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 that 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 that 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Average [^{11}C]ABP688 BPND (calculated per voxel) images in the healthy volunteers (top row) and cocaine addicted subjects (second row) for each group. SRTM maps were generated in each subject's native image space using the basis function method. Each subject's MRI was then nonlinearly transformed into MNI space using SPM2 software and the resultant transformation parameters were applied to the BPND maps. Maps were then averaged across subjects. The color bar shows the values for BPND. The bottom row shows a representative MRI with cross hairs to indicated the locations of the coronal and transverse slices. These images illustrate that cocaine addiction is associated with a decrease in [^{11}C]ABP688 BPND compared to healthy volunteers.

Table 1

Group demographics of the healthy control and cocaine addicted (CA) subjects

	Controls	CA subjects	p
Age (mean $\pm$ SD, in years)	41 $\pm$ 4	43 $\pm$ 3	0.2 ^a
Gender (Male/Female)	13M/1F	14M/1F	-
Ethnicity (African-American/Caucasian not Hispanic)	12AA/2C	13AA/2C	0.94 ^b
Smoking status (Yes/No)	9Y/5N	12Y/3N	0.60 ^b
Number of cigarettes per day in smokers (mean $\pm$ SD)	4 $\pm$ 7	6 $\pm$ 5	0.67 ^a

Abbreviations:

^a unpaired t-test;^b chi-squared tests.

Table 2

Comparison of [¹¹C]ABP688 BPND in the striatal subregions between the healthy control and cocaine addicted (CA) subjects. 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 results in all BPND remaining significant. However, with Bonferroni correction, the differences in BPND remain significant in the limbic striatum and putamen (anterior and posterior), but not the caudate (anterior and posterior).

Region of Interest	Controls (n= 14)		CA subjects (n=15)		p
	mean	sd	mean	sd	
Limbic Striatum	1.07	0.23	0.83	0.19	0.005
Anterior Putamen	1.01	0.20	0.80	0.19	0.006
Posterior Putamen	0.72	0.15	0.56	0.13	0.005
Anterior Caudate	0.88	0.21	0.69	0.19	0.018
Posterior Caudate	0.40	0.17	0.25	0.14	0.017

Table 3

Comparison of [¹¹C]ABP688 BPND in the additional ROIs between the healthy control and cocaine addicted (CA) subjects. 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).

Region of Interest	Controls (n=14)		CA subjects (n=15)		p
	mean	sd	mean	sd	
Anterior cingulate	1.20	0.26	0.99	0.21	0.03
Dorsolateral Prefrontal cortex	1.04	0.20	0.84	0.18	0.009
Medial Prefrontal cortex	1.10	0.25	0.90	0.21	0.02
Orbitofrontal cortex	0.97	0.22	0.76	0.17	0.008
Medial Temporal cortex	0.70	0.16	0.59	0.15	0.07
Temporal cortex	0.93	0.21	0.77	0.21	0.06
Occipital cortex	0.84	0.15	0.72	0.16	0.04
Thalamus	0.43	0.12	0.31	0.13	0.02

Table 4

Ratio of metabolite and tissue composition results in cocaine addicted (CA) and control subjects using magnetic resonance spectroscopy (MRS) in the left striatum. 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.

Metabolite ratio	Controls (n=12)	CA subjects (n=14)	
	Mean (SD)	Mean (SD)	p
Glx/water	$5.15 (1.62) \times 10^{-3}$	$5.24 (1.71) \times 10^{-3}$	0.8
GABA/water	$8.56 (1.12) \times 10^{-3}$	$7.83 (2.77) \times 10^{-3}$	0.4
Choline/water	$2.21 (.39) \times 10^{-2}$	$2.37 (.32) \times 10^{-2}$	0.3
Creatine /water	$2.76 (.31) \times 10^{-2}$	$2.75 (.53) \times 10^{-2}$	0.9
NAA/water	$3.77 (.48) \times 10^{-2}$	$4.23 (.50) \times 10^{-2}$	0.03
Tissue Type			
Gray Matter %	40.0 (3.8) %	39.7 (3.8)%	0.8
White Matter %	55.0 (4.1)%	56.3 (3.6)%	0.4
Cerebrospinal Fluid %	4.9 (1.4)%	4.0 (1.5)%	0.1

Abbreviations: GABA = gamma-aminobutyric acid; Glx = glutamate-glutamine; NAA = N acetylaspartate.