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Imaging phosphodiesterase-10a availability in cocaine use disorder with [^{11}C]IMA107 and PET

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Abstract

Phosphodiesterase-10a (PDE10a) is located exclusively in medium spiny neurons (MSN). Rodent studies show an increase in striatal MSN spine density following exposure to cocaine. These increases in MSN spine density are suggested to underlie neurobiological changes which contribute to cocaine self-administration. No postmortem or imaging studies have confirmed this finding in humans. Here, we hypothesized an increase in the MSN marker PDE10a in subjects with cocaine use disorder ("cocaine users") compared to controls. PDE10a availability was measured with [^{11}C]IMA107 and PET in 15 cocaine users and 15 controls matched for age, gender, and nicotine status. Cocaine users with no comorbid psychiatric, medical, or drug abuse disorders were scanned following two weeks of outpatient-monitored abstinence. [^{11}C]IMA107 binding potential relative to nondisplaceable uptake (BP_{ND}) in the regions of interest were derived with the simplified reference tissue method. No significant effect of diagnosis on BP_{ND} was demonstrated using linear mixed modeling with [^{11}C]IMA107 BP_{ND} as the dependent variable and regions of interest as a repeated measure. There were no significant relationships between BP_{ND} and clinical rating scales. To the extent that PDE10a is a valid proxy for MSN spine density, these results do not support its increase in recently abstinent cocaine users.

Keywords

[^{11}C]IMA107; positron emission tomography; phosphodiesterase-10a (PDE 10a); cocaine use disorders; medium spiny neurons

INTRODUCTION

Positron emission tomography (PET) imaging studies have shown lower dopamine $D_{2/3}$ receptor availability, lower baseline dopamine and decreased amphetamine (or methylphenidate)-induced dopamine release in the striatum of cocaine use disorder subjects

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DISCLOSURES

None

compared to matched controls (Martinez et al., 2011; Martinez et al., 2009; Martinez et al., 2007; Volkow et al., 1997). These studies also link lower $D_{2/3}$ receptor availability and decreased dopamine release in the striatum to relapse back to cocaine (Martinez et al., 2004; Martinez et al., 2011; Martinez et al., 2007). PET studies conducted with the vesicular mononamine transporter type 2 radiotracer [^{11}C]-(+)-dihydrotetrabenazine (DTBZ) suggest that a reduction in pre-synaptic dopaminergic terminals may underlie decreased dopamine transmission in cocaine use disorder (Narendran et al., 2012). Given that there are approximately 10-fold more GABA-ergic terminals in the striatum than there are dopaminergic terminals, we were interested in examining chronic cocaine-induced abnormalities in medium spiny neurons (MSN). GABA-ergic MSN represent up to 90–95% of all striatal neurons and can be categorized into two populations: the direct striatonigral and indirect striatopallidal pathway (Yager et al., 2015). D_1 and $D_{2/3}$ receptors dominate the direct and indirect pathway MSN, respectively (Gerfen et al., 1990; Lee et al., 2006). The dendritic trees of MSN are covered with spines, and receive glutamatergic input from the cerebral cortex and thalamus. The neck or dendritic shaft of MSN receive synaptic inputs from midbrain dopamine neurons including the substantia nigra and ventral tegmentum area. Cocaine when administered to rodents has consistently been shown to lead to an increase in the density of thin and mature spines of MSN in the striatum, which includes the nucleus accumbens (see review, Villalba and Smith, 2013). These cocaine-induced alterations to MSN spines have been reported to persist even after 14–30 days of abstinence (Anderson and Self, 2017; Lee et al., 2006). These findings have led investigators to postulate that increased MSN spine density underlies cocaine self-administration. Rodent studies have also shown that dopamine depletion leads to morphological alterations and a loss of spines in MSN (Meredith et al., 1995; Villalba and Smith, 2013). Based on this observation one would expect to find a decrease in MSN spine density in cocaine users because they have blunted dopamine transmission in the striatum. Thus, it is important to clarify the in vivo status of MSN spine density in chronic cocaine abusing humans. PDE10a, which hydrolyzes the second messenger molecules cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), is located exclusively in the post-synaptic membranes of dendrites and spines in MSN (Xie et al., 2006). Recent PET studies with PDE10a radiotracers have taken advantage of its specific, cellular localization to demonstrate a loss in MSN density in Parkinson's disease and Huntington's disease patients (Ahmad et al., 2014; Niccolini et al., 2015a; Niccolini et al., 2015b; Russell et al., 2016). These studies led us to use the PDE10a specific PET radiotracer [^{11}C]IMA107 to examine whether MSN spine density is altered in chronic cocaine users. However, some caution is warranted in using PDE10a PET as a fully quantitative measurement of MSN because no validation data exists on the precise magnitude of change in PDE10a that corresponds to a particular percent increase or decrease in spine density. Furthermore, no rodent studies in the literature have examined and reported an increase in PDE10a to match the alterations in spine density observed following chronic cocaine administration.

The PET radiotracer [^{11}C]IMA107 allows for imaging of PDE10a in both the striatal and extrastriatal regions including the thalamus and substantia nigra. Blocking studies in baboons using [^{11}C]IMA107 and the PDE10a inhibitor MP-10 have demonstrated relatively high specific binding in the striatum (> 85% reduction in binding potential) and identified

the cerebellum as a reference region that can be used to estimate of its non-specific binding (Plisson et al., 2014). [^{11}C]IMA107 BP_{ND} derived using the simplified reference tissue method (SRTM) is highly correlated with results derived using a two tissue compartment kinetic analyses (Searle et al., 2014). The test-retest variability for SRTM BP_{ND} is less than 12% in caudate, putamen, ventral striatum and globus pallidus, 14% in the thalamus, and 25% in the substantia nigra/midbrain (Searle et al., 2014). Recent clinical studies utilizing [^{11}C]IMA107 to investigate Parkinson's disease (PD) and Huntington's disease (HD) have not only reported its ability to demonstrate a decrease in BP_{ND} relative to controls, but also found that such a decrease correlates with diagnosis severity in PD (Niccolini et al., 2015a) and manifests even before onset of clinical symptoms in HD (Niccolini et al., 2015b). These data support the use of imaging PDE10a as a proxy to investigate MSN spine density in neuropsychiatric disorders. Here, we investigated the in vivo availability of PDE10a with [^{11}C]IMA107 in 15 subjects with cocaine use disorder (hereafter, "cocaine users") and 15 healthy controls matched for age, gender, and nicotine status. Since PDE10a is expressed exclusively in MSN, and exposure to cocaine in rodents leads to an increase in spine density —we hypothesized an *increase* in [^{11}C]IMA107 BP_{ND} in cocaine users compared to controls.

MATERIALS AND METHODS

Human Subjects

The Institutional Review Board and Radioactive Drug Research Committee of the University of Pittsburgh approved the study. All subjects provided written informed consent. As there were no prior PDE10a PET studies in cocaine users to compute an effect size for a power calculations, a minimum sample of size of n=15/group was decided to be consistent with published PET investigations.

Cocaine users were recruited through advertisements displayed at local community centers, addiction clinics, buses, newspapers and websites. Study criteria for cocaine dependence were [1] males or females between 18 and 50 years old of all ethnic and racial origins; [2] fulfill DSM-5 criteria for cocaine use disorder as assessed by SCID-5; [3] use of cocaine within the past *thirty days* as confirmed by urine drug screen or review of recent drug use history and/or medical records at initial screening; [4] no other current psychiatric or drug/alcohol use disorder diagnosis other than cocaine use disorder (tobacco use disorder and occasional recreational marijuana/alcohol use were not exclusionary); [5] no serious medical or neurological illness as assessed by a complete physical exam and labs; [6] not currently taking any prescription or psychotropic medications; [7] not currently pregnant or lack of effective birth control during 15 days before the scans; [8] no history of radioactivity exposure from nuclear medicine studies or occupation; and [9] no metallic objects in the body that are contraindicated for magnetic resonance imaging (MRI). Before their PET study, cocaine users completed a minimum of 10 to 14 days of outpatient abstinence, monitored with witnessed urine toxicology (~3 times/week). In order to promote abstinence from cocaine during this two-week period, subjects were paid $20 for each urine sample that was negative for cocaine metabolites. Cocaine users were scheduled for the PET scans after successful completion of the abstinence monitoring protocol. Subjects who did test positive

for cocaine metabolites were offered up to three attempts to re-start the abstinence monitoring protocol before being terminated from the study procedures. This abstinence monitoring protocol ensured that all subjects were abstinent for a minimum of ten days prior to the PET scan. Clinical assessments performed before the PET scans included the Perceived Stress Scale (PSS), Hamilton Anxiety Rating Scale (HAM-A), Fagerstrom Test for Nicotine Dependence (FTND) and Tiffany Cocaine Craving Scale (CCS).

Healthy control subjects matched for age, gender, nicotine status, with no past or present medical or psychiatric disorders including substance use disorders (confirmed by SCID-5, and urine drug screens) were recruited via websites, flyers and newspaper ads. Controls and cocaine users underwent the clinical assessments and scan procedures as outpatients.

Image acquisition and analysis

Before PET imaging, a magnetization prepared rapid gradient echo structural MRI scan was obtained in each subject using a Siemens Biograph mMR scanner for region determination. PET imaging sessions were conducted with the Siemens Biograph64 mCT scanner. The injected mass of [^{11}C]IMA107 was restricted to ≤ 9.0 μg based on the prior studies conducted at Imanova Center for Imaging Sciences, UK. The synthesis of [^{11}C]IMA107 was carried out as previously described (Niccolini et al., 2015a; Niccolini et al., 2015b; Plisson et al., 2014). A low-dose CT scan of the brain was acquired for attenuation correction prior to [^{11}C]IMA107 administration, which was injected intravenously as a bolus. Emission data were acquired for 90 minutes in list mode and data were binned into a sequence of frames of increasing duration. The scan duration of 90 minutes was based on the minimum scanning time previously reported to arrive at stable BP_{ND} values for [^{11}C]IMA107 (Searle et al., 2014). The attenuation corrected PET data were reconstructed by filtered back projection using the camera's built-in software.

The image analysis software PMOD, version 3.802 (PMOD Technologies LLC, Zurich, Switzerland) was used to conduct frame-to-frame motion correction for head movement. The MR-PET image alignment was performed using a normalized mutual information algorithm. Regions of interest were generated for each subject using the built-in brain parcellation work-flow within PMOD's Neuro Tool (PNEURO module) (Douaud G, 2006). Region generation was based off the AAL-VOIs atlas, which is the automatic anatomical labeling result of the spatially normalized (N. Tzourio-Mazoyer, 2002), single subject, high resolution T1 MRI data set provided by the Montreal Neurological Institute (Collins, 1998). Consistent with that reported in prior [^{11}C]IMA107 PET studies, regions of interest included the caudate, putamen, ventral striatum, thalamus, midbrain, and globus pallidus. The cerebellum, which was subsampled to exclude cerebellar white matter and the vermis, was included as a reference region. All regions generated by the brain parcellation tool in PNEURO were visually inspected and manually adjusted as deemed necessary by an image analyst trained in manual region drawing.

Region of interest volumes showed a trend level decrease in the caudate of cocaine users compared to controls (**Table 1).** No group differences in regional volumes were evident in the other regions of interest and the cerebellum. Given the potential to bias the between-group comparison of BP_{ND} in the caudate, we applied a geometric transfer matrix based

partial volume correction method within PMOD on a regional level (point spread parameters: full width half maximum = in plane: 5.0mm; axial: 4.8mm, data was based on the analyses of a 2-point point source phantom) as previously described (Rousset et al., 1998). Regional time-activity curve data generated before and after the correction for partial volume effects were fitted to the simplified reference tissue model to determine BP_{ND} (Lammertsma and Hume, 1996). BP_{ND} derived before and after the correction for partial volume effects are both included in the results section.

Statistical analysis

All statistical analyses were performed with IBM SPSS Statistics v.23. Normality of data were examined using Kolmgorov-Smirnov and Shapiro-Wilkes tests. Group demographic and baseline scan parameter (such as injected dose, mass, plasma clearance) comparisons were performed with unpaired t-tests. Overall group differences in [^{11}C]IMA107 BP_{ND} were analyzed with a linear mixed model analysis performed with regions of interest as a repeated measure and diagnostic group (cocaine use disorder vs. healthy control) as the fixed factor. This test was followed up with post-hoc unpaired t-tests in the individual regions of interest. The relationship between the partial volume corrected regional BP_{ND} that was free of volumetric bias and clinical characteristics (frequency of use, average amount spent per use, years of use, scores on rating scales for cocaine craving, perceived stress, anxiety, etc.) were explored by Pearson product moment correlation coefficient, and controlled for demographic variables (e.g., age) when indicated.

A two-tailed probability value of $p < 0.05$ was selected as the significance level for the linear mixed model analyses. Because our hypothesis was a one-directional increase in PDE10a in the striatal regions, a one-tailed probability value of $p < 0.05$ was selected as the significance level for the post-hoc analyses in the individual regions of interest. In addition, to correct for multiple comparisons in the individual regions of interest, a Bonferroni correction with $\alpha/n = 0.05/6=0.008$ was applied in the post-hoc analyses.

RESULTS

Fifteen individuals with cocaine use disorder were matched with 15 healthy controls on age, gender, ethnicity and nicotine status. Table 2 lists demographics variables and clinical characteristics of the study sample.

[^{11}C]IMA107 baseline scan parameters:

There were no differences in the mean injected dose (cocaine use disorder = 5.8 ± 0.4 mCi; healthy controls = 5.6 ± 0.8 mCi, p=0.39), injected mass (cocaine use disorder = 2.2 ± 1.3 μg; healthy controls = 2.0 ± 0.7 μg, p = 0.55) and specific activity (cocaine use disorder 1525 ± 765 Ci/mmol; healthy controls = 1453 ± 476 Ci/mmol, p = 0.76) between the groups.

BP_{ND} before correction for partial volume effects

Trend level decreases in [^{11}C]IMA107 BP_{ND} were observed in cocaine use disorder compared to healthy controls (linear mixed model, effect of diagnosis, $F(1, 28) = 3.00$, $p = 0.094$; effect of region, $F(5, 140) = 886.31$, $p < 0.001$; region x diagnosis interaction, F (5,

140) = 2.37, p = 0.043). The inclusion of gender or nicotine status as factors in the model did not alter this result (data not shown). The significant region by diagnosis interaction was further examined with post-hoc unpaired t-tests in the individual regions of interest. Post-hoc unpaired t-tests in the individual regions of interest showed **no significant increase** in BP_{ND} between the two groups (Table 3).

BP_{ND} after correction for partial volume effects

No differences in [^{11}C]IMA107 BP_{ND} were observed in cocaine use disorder compared to healthy controls (linear mixed model, effect of diagnosis, F (1, 28) = 2.07, p =0.162; effect of region, F (5, 140) = 456.42, p < 0.001; region x diagnosis interaction, F (5, 140) = 1.11, p = 0.36). The inclusion of gender (linear mixed model, effect of diagnosis, F (1, 27) =2.20, p = 0.15; effect of gender, F (1, 27) = 2.81, p = 0.11) or nicotine status (linear mixed model, effect of diagnosis, F (1, 27) = 1.81, p = 0.19; effect of nicotine, F (1, 27) = 0.19, p = 0.66) as factors in the model did not alter this result. Post-hoc unpaired t-tests in the individual regions of interest showed **no significant increase** in BP_{ND} between the two groups **(see Table 3).**

Effect of age on regional BP_{ND}

Consistent with a recent report (Fazio et al., 2017), we observed a negative relationship between age and BP_{ND} in the caudate (r = - 0.56, p = 0.001), putamen (r = - 0.59, p = 0.001) and globus pallidus (r = - 0.48, p = 0.007) in the combined dataset (i.e., included both cocaine use disorder and controls). This relationship was not evidenced in the ventral striatum (r = - 0.22, p = 0.24), midbrain (r = 0.21, p =0.26) and thalamus (r = 0.19, p = 0.32). Based on these data, we decided to control for the effects of age with partial correlations when examining the relationships between BP_{ND} and clinical measures.

Relationships between BP_{ND} and clinical measures

No significant relationships were observed between regional [^{11}C]IMA107 BP_{ND} and any of the clinical rating scales including perceived stress, anxiety, and cocaine craving.

There were also no relationships between the self-reported severity of cocaine use (frequency and amount of money spent on cocaine) and regional [^{11}C]IMA107 BP_{ND}. The self-reported duration of cocaine use (in years) was positively and negatively correlated with ventral striatum (r = 0.57, p = 0.03) and putamen BP_{ND} (r = - 0.56, p = 0.04), respectively. The negative relationship with duration of cocaine use was also observed in the caudate, but at trend level (r = - 0.50, p = 0.07). No such relationships were noted in the extrastriatal regions (data not shown). None of the significant relationships survived the Bonferroni correction for multiple hypotheses testing.

DISCUSSION

We found no significant increase in [^{11}C]IMA107 BP_{ND} in recently abstinent chronic cocaine users compared controls. To the extent that PDE10a is a valid marker for MSN spine density, these results are inconsistent with the increases reported in chronic cocaine exposed rodents. These negative results can also be viewed as supportive of a prior basic science

study that concluded PDE10a inhibitors such as papaverine are unlikely to have therapeutic potential in cocaine use disorder because they do not extinguish cocaine-induced conditioned placed preference in rodents (Liddie et al., 2012). A secondary observation in these data was that BP_{ND} not corrected for partial volume effects was trend level lower in the globus pallidus (- 9%) and caudate (- 15%) in cocaine users relative to controls **(Table 3).** It was necessary to correct these data for partial volume effects because the caudate, the only striatal subdivision in which we detected lower BP_{ND} in cocaine users was also 10% smaller in patients compared to controls. The decreased volume in the caudate observed in cocaine users in this study was unexpected and has not been observed in previously published imaging studies. The corrected caudate BP_{ND} data, which was free of any volumetric bias, was still ~ 8% lower in cocaine users compared to controls. Partial volume effect correction also negated the trend decrease noted in globus pallidus (uncorrected $p = 0.04$ when using a two-tailed unpaired t-test) despite the fact that BP_{ND} in this region was still lower by the same magnitude (~ 9%, uncorrected $p = 0.10$ when using a two-tailed unpaired t-test) in cocaine users. Partial volume effect correction has the effect to correct for spill-in and spill-out of a particular region, but it also has a tendency to amplify noise in the data and increase variability (Mawlawi et al., 2001). Thus, it is not possible to ascertain whether the reduced statistical size in the globus pallidus resulted from spill-in from surrounding regions or from amplification of noise leading to a smaller effect size following the partial volume correction. The effect size (d) for the partial volume corrected BP_{ND} in the globus pallidus was 0.63. Power calculations ($\beta = 0.8$, unpaired t-tests, alpha error probability =0.008, which is Bonferroni corrected for n= six regions of interest) suggest that [^{11}C]IMA107 PET scans will need to be acquired in 63 subjects/group to confirm the trend level decrease in BP_{ND} in cocaine users. To scan such a large number of subjects to confirm this observation is beyond the scope of this pilot imaging study and remains a question for future imaging studies to address. Nevertheless, given the role of PDE10a in aging and neurodegenerative disorders, it might be worth investigating in older individuals who abuse cocaine as it may suggest accelerated aging of the brain.

Several factors may have contributed to the inability to demonstrate alterations in MSN spine density following chronic cocaine exposure in this human imaging study. They include: *(1) Species differences:* Studies in Parkinson's disease patients and nonhuman primate models have consistently failed to observe the extent and patterns of spine alterations reported in dopamine depleted rodent models (Villalba et al., 2009; Villalba and Smith, 2013). Such species-based differences between rodents and primates/humans exist in the dopaminergic system with chronic cocaine use (Narendran and Martinez, 2008). The lack of human and nonhuman primate studies to confirm the increases in MSN spine density described in cocaine exposed rodents has been raised in the literature as a concern (Villalba and Smith, 2013). Postmortem studies in chronic cocaine abusing primates and humans are necessary to clarify this issue. (2) *MSN spine density is not the only factor that can influence PDE10a* BP_{ND}: PDE10a PET studies that have shown a decrease in striatal BP_{ND} in Huntington's disease support its use as a proxy to measure MSN spine density. Striatal dopamine release leads to increases and decreases in cAMP in the D_1-direct and D_2-indirect MSN respectively (Graybiel, 2000). PDE10a modulates the levels of intracellular cAMP/cGMP levels in these D_1- direct and D_2-indirect MSN. PDE10a expression is likely to be

altered in these D_1- and D_2- MSN (albeit in different directions) to maintain homeostasis in conditions such as cocaine use disorder where dopamine transmission is blunted. This would suggest that PDE10a BP_{ND} in cocaine users is influenced not only by the spine density of MSN, but also its adaptive response to decreased dopamine transmission (Nishi et al., 2008). The relative contribution of these factors to PDE10a BP_{ND} needs to be better understood. Studies with an acute amphetamine or alpha-methyl-para-tyrosine (AMPT) challenge in which BP_{ND} can be measured before and after alterations in dopamine transmission may be helpful in clarifying this issue. Lastly, PDE10a, which controls the response of MSN, is also regulated by cortical glutamatergic input (Siuciak et al., 2006). Thus, the impact of altered glutamate transmission in cocaine users on PDE10a expression may have also impaired our ability to detect an increase in BP_{ND} as hypothesized in this study (Schmaal et al., 2012). Pending further validation work, PDE10a PET studies in disorders where there is altered dopamine and/or glutamate transmission such as cocaine use disorder, schizophrenia, Parkinson's disease, etc., should be interpreted with caution. Future studies should also plan to investigate PDE10a BP_{ND} and amphetamine-induced displacement of [^{11}C]raclopride (dopamine release) in the same subjects to account for the individual differences in dopamine transmission. This may allow for a more nuanced interpretation of MSN spine density in cocaine use disorder. (3) *Duration of abstinence from cocaine:* PDE10a was measured in cocaine users in this study 10 to 14 days after their last use as opposed to when they were in withdrawal (i.e., typically 24–48 hours following their last use). Rodent studies investigating the dendritic spine density of MSN in the ventral striatum have concluded that there is an initial increase in both D_1 and D_2 receptor-containing MSN, but this alteration is maintained only in D_1 receptor-containing neurons after thirty days of cocaine exposure (Scott et al., 2002). Based on this, a normalization in the density of spines in $D_{2/3}$ receptor containing MSN during the abstinence period cannot be ruled out (Anderson and Self, 2017). Such an effect, if any would have diminished the ability to detect between-group differences in this imaging study. The fact that cocaine users had to use cocaine within the 30 days of their initial screening to qualify, and had to abstain for a minimum of 10–14 days before the PET scan did not allow for sufficient variability to test for a relationship between duration of abstinence and BP_{ND}. The prolonged abstinence duration in this study is a major limitation. Future PDE10a imaging studies should measure BP_{ND} in cocaine users during withdrawal to exactly mimic the conditions in which increased spine density has been reported in cocaine exposed rodents. (4) Finally, the possibility of change in the number of PDE10 molecules per dendritic spine and a change in affinity of PDE10a for [^{11}C]IMA107 cannot be excuded as factors that led to the inability to detect an increase in MSN spine density in cocaine users. The latter is relevant as recent studies have shown that the concentration of cAMP alters the affinity of PDE10a for its ligand (Ooms et al., 2016).

The strengths of this study include: imaging of cocaine users with no medical, psychiatric, or drug abuse comorbidity; the matching of controls for age, gender and nicotine status; the confirmation of a minimum of ten days of abstinence from cocaine prior to the imaging; and the use of a well-validated PDE10a PET radiotracer. The results do not support an increase in PDE10a BP_{ND}, and by extension spine density of MSN in recently abstinent human cocaine users. However, alterations in the available PDE10a in response to blunted dopamine transmission in cocaine use disorder may have confounded the ability to detect an

increase in MSN spine density with [^{11}C]IMA107. The negative result of this imaging study further diminishes the prospects for PDE10a inhibitors as a therapeutic target in cocaine use disorder.

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Table 1.

[^{11}C]IMA107 Region of Interest Volume (mm^3)

	Cocaine use disorder	Healthy controls	*p*
Ventral striatum	712 ± 65	697 ± 126	0.69
Caudate	6720 ± 933	7404 ± 970	0.06
Putamen	8132 ± 766	8012 ± 760	0.67
Midbrain	5478 ± 1182	5747 ± 915	0.49
Thalamus	9664 ± 1120	10181 ± 1780	0.35
Globus pallidus	2767 ± 277	2764 ± 327	0.98
Cerebellum	68340 ± 10343	67622 ± 12202	0.86

Values are mean ± SD in subjects with cocaine use disorder (n = 15) and healthy control subjects (n = 15); p is the significance level for unpaired t-test between the groups.

Table 2.

Demographic and clinical characteristics of cocaine use disorder and healthy control subjects (n= 15/group)

	Cocaine use disorder		Healthy controls	
	Mean	**SD**	**Mean**	**SD**
Gender				
Male	4		4	
Female	11		11	
Ethnicity				
African American	5		0	
Caucasian	8		14	
Asian	0		1	
Hispanic	1		0	
More than one race	1		0	
Nicotine use	9		7	
Fagerstrom test for nicotine dependence: Moderate and highly dependent (> 10 cigarettes/day)	4		3	
Positive family history for alcoholism/drug use disorder in first degree relative	11*		0	
Age (years)	39	11	38	11
Age of first use of cocaine (years)	23	8		
Duration of cocaine use (years)	17	9		
Cocaine use frequency per month (days)	15	10		
Amount spent on cocaine per week (dollars)	147	75		
Cocaine Craving Questionnaire (range 0-70)	24	14		
Perceived Stress Scale (range 0-40)	15*	7	6	5
Hamilton Anxiety Scale (range 0-56)	7*	5	1	2

* $p < 0.05$, unpaired-t or Chi-square tests when appropriate

Table 3.

[^{11}C]IMA107 SRTM binding potential relative to nondisplaceable uptake ($BP_{ND,}$ unitless)

	BP_{ND} before correction for partial volume effects		BP_{ND} after correction for partial volume effects	
	Cocaine use disorder	**Healthy controls**	**Cocaine use disorder**	**Healthy controls**
Ventral Striatum	0.94 ± 0.15	0.93 ± 0.21	1.66 ± 0.22	1.67 ± 0.42
Caudate	1.09 ± 0.28	1.26 ± 0.22	1.59 ± 0.29	1.72 ± 0.31
Putamen	2.22 ± 0.25	2.33 ± 0.26	2.44 ± 0.26	2.57 ± 0.34
Midbrain	0.42 ± 0.08	0.42 ± 0.07	0.50 ± 0.13	0.49 ± 0.16
Thalamus	0.31 ± 0.06	0.34 ± 0.05	0.33 ± 0.06	0.36 ± 0.07
Globus Pallidus	2.23 ± 0.29	2.43 ± 0.23	2.47 ± 0.38	2.71 ± 0.38

Values are mean ± SD in cocaine use disorder and healthy control subjects (n = 15/group);

No significant increase in individual regional BP_{ND} are noted in cocaine use disorder compared to healthy controls (Bonferroni-corrected $p > 0.008$ for all between-group contrasts, one-tailed unpaired t-tests)