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Reductions in Brain 5-HT$_{1B}$ Receptor Availability in Primarily Cocaine-Dependent Humans

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Abstract

Background—Preclinical evidence implicates the 5-HT$_{1B}$ receptor in cocaine's effects. This study explores 5-HT$_{1B}$ in humans by examining receptor availability *in vivo* with primary cocaine-dependent (CD) subjects using positron emission tomography (PET).

Methods—Fourteen medically healthy CD subjects (mean age=41±6 yrs) were compared to 14 age-matched healthy control subjects (41±8 yrs) with no past or current history of cocaine or other illicit substance abuse. Participants received an MRI and then a PET scan with the highly selective 5HT$_{1B}$ tracer, [^{11}C]P943, for purposes of quantifying regional binding potential (BP_{ND}). Voxel-based morphometry (VBM) and gray matter masking (GMM) were also employed to control for potential partial volume effects.

Results—[^{11}C]P943 PET imaging data in nine candidate regions (amygdala, anterior cingulate cortex, caudate, frontal cortex, hypothalamus, pallidum, putamen, thalamus and ventral striatum) showed significant or nearly significant reductions of BP_{ND} in CD subjects in three regions,

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including the anterior cingulate (−16%; P<0.01), hypothalamus (−16%, P=0.03) and frontal cortex (−7%, P=0.08). VBM showed significant gray matter reductions in the frontal cortex of CD subjects. After GMM, statistically significant reductions in [^{11}C]P943 BP_{ND} were either retained (anterior cingulate, −14%, p=0.01; hypothalamus, −20%, P<0.01) or achieved (frontal cortex, −14%, p<0.01). Whole brain voxel-wise parameter estimation confirmed these results. Secondary analyses were also significant in some regions for years of cocaine and daily tobacco use.

Conclusions—The reductions found in this study suggest that 5-HT$_{1B}$ receptors may contribute to the etiology and/or expression of cocaine dependence and potentially represent a target for medication development.

Keywords

cocaine; 5-HT$_{1B}$; serotonin; PET; VBM; human

1. Introduction

Cocaine dependence (CD) is a widespread public health problem in the United States and is associated with considerable personal and fiscal costs to both society and the individual. In 2010 the estimated number of current cocaine users in the U.S. was 1.5 million (1). Despite the significant number of users and complications from abuse and dependence, there is no FDA-approved medication treatment for CD. As such, the identification of novel molecular targets that may modulate cocaine's effects in humans remains a priority. In the current study, we focused on one such molecular target, the serotonin receptor 1B subtype (5-HT $_{1B}$).

The 5-HT $_{1B}$ receptor is an inhibitory G protein coupled metabotropic receptor found primarily as presynaptic autoreceptors on 5-HT neurons and as heteroreceptors on non-serotoninergic neurons (2). Administration of drugs with agonistic or antagonistic properties at 5-HT $_{1B}$ receptors will typically inhibit or enhance, respectively, 5-HT activity in the brain (3). Based on autoradiographic work focusing on subcortical structures, the basal ganglia, hippocampus, substantia nigra and entorhinal cortex all have significant 5-HT $_{1B}$ binding, but regional differences in receptor-mediated G-protein activation in these areas have been described (4).

Multiple preclinical studies have investigated the role of the 5-HT $_{1B}$ receptor in mediating the neurobiological effects of cocaine, but the nature of it's role in drug reward remains unclear due to inconsistencies across studies (5). Several studies, however, have suggested potentiation of cocaine's effects by the 5-HT $_{1B}$ receptor (6). This effect is thought to occur via 5-HT $_{1B}$ heteroreceptors that have an inhibitory effect on GABA release in the ventral tegmental area (VTA), thereby disinhibiting dopaminergic activity and amplifying drug reward mechanisms. Studies focusing on cocaine administration have similarly shown a reinforcement of stimulant effects via the 5-HT $_{1B}$ receptor (7, 8). In contrast, 5-HT $_{1B}$ knock-out mice have shown an increased sensitization to cocaine and stimulants that inhibit reinforcement (9), while pharmacologic activation has paradoxically shown a reduction in stimulant use with 5-HT $_{1B}$ receptors in the nucleus accumbens (10). More recent studies have focused on potential explanations for seemingly paradoxical effects, implicating

variables such as drug dose, brain region and length of time since last use as potential explanations (11, 12). Taken together, the preclinical data indicate that 5-HT $_{1B}$ receptor function in brain reward circuitry contributes to cocaine use and cocaine responsiveness, albeit in a complex and incompletely understood fashion.

In humans, genetic studies have found associations between 5-HT $_{1B}$ receptor polymorphisms and substance abuse, suggesting that modified 5-HT $_{1B}$ receptor activity may be a contributing factor to increased susceptibility to addiction (13). In order to better understand the potential role of 5-HT $_{1B}$ receptors in CD, we employed the newly available 5-HT $_{1B}$ PET radioligand [^{11}C]P943 to image receptor availability in CD as compared to healthy control (HC) subjects.

As animal work has indicated that knocking out 5-HT $_{1B}$ receptors in mice is associated with increased cocaine self administration (9) and 5-HT $_{1B}$ receptor over-expression in rats is associated with stress-related stimulant responsiveness (14), there are data to suggest that CD individuals would show either increases or decreases in 5-HT $_{1B}$ receptors. Given this ambiguity and the unknown effects of cocaine on the 5-HT $_{1B}$ receptor in humans, the current work could provide evidence for a mechanism in humans and future development by either showing an increase in 5-HT $_{1B}$ receptor availability in CD, which would support a model of 5-HT $_{1B}$ sensitization in CD, or a decrease that would support a desensitized model of 5-HT $_{1B}$ within reward-related brain regions in chronic CD.

2. Methods and Materials

2.1. Subjects

Fourteen medically healthy, non-treatment seeking CD subjects were compared to previously reported age-matched HC subjects (15, 16). All CD and HC scans took place over three years and the mean scan time between groups was 1 year, 4 months. In the 3 months preceding scans, HC subjects were without significant nicotine (with the exception of one subject), alcohol or illicit substance use. Based on our prior work showing statistically significant effects of age (declining) but not sex or race (17) with [^{11}C]P943 availability, CD and HC subjects were matched as a group for age (41± 6.2 vs. 41± 7.8 years, respectively; p=0.73), but not sex (4/10 vs. 5/9 for females/males) or race (3/9/1/1 vs. 10/3/0/1 for Caucasian/African American/Hispanic/other).

Eligibility for the study was confirmed through comprehensive psychiatric histories and clinical semi structured interviews (e.g., the Mini-International Neuropsychiatric Interview or M.I.N.I.) or SCID-1 (Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Axis I disorders), a physical exam with medical history, routine laboratory studies, pregnancy tests, urine toxicology and electrocardiograms (ECGs). Measures of clinical data for secondary analyses included the Hamilton Depression Rating Scale (HAM-D)(18), Barratt Impulsiveness Scale (BIS-11)(19), the State Trait Anxiety Inventory (STAI)(20), and the Childhood Trauma Questionnaire (CTQ)(21).

Individuals were excluded for evidence of a diagnosis of current or lifetime severe Axis I psychiatric disorder (e.g., schizophrenia or bipolar disorder), current or past serious medical

or neurological illness (including a history of head injury with loss of consciousness), current pregnancy (as documented by pregnancy testing at screening and on the day of the PET imaging study), breast feeding or general MRI exclusion criteria. All subjects were medication-free for a minimum of 6 weeks at the time of scanning.

CD subjects met Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM IV) criteria for cocaine dependence, were between 18 and 50 years of age, used a high-potency, rapid-onset form of cocaine (i.e., smoked or intravenous), reported a history of regular and recent use and provided objective evidence of current use (i.e., benzoylecgonine positivity) on urine toxicology testing before admission into the study. Clinical characteristics of CD participants are shown in Table 1.

The study was performed under protocols approved by the Yale Human Investigation Committee, the Human Subjects Subcommittee of the Veterans Affairs Connecticut Healthcare System, the Yale University Radiation Safety Committee, the Yale-New Haven Hospital Radiation Safety Committee, and the Yale MRI Safety Committee. Subjects were recruited from New Haven and surrounding areas by advertisement and word of mouth referrals. Written informed consent was obtained from all participants after a full explanation of study procedures (including risks and potential benefits).

2.2. Radiochemistry

[^{11}C]P943 (*R*-1-[4-(2-methoxy-isopropyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)benzyl]-pyrrolidin-2-one) was prepared as previously described by *N*-methylation of the precursor with [^{11}C]methyl triflate, using the PETtrace cyclotron and a TRACERLab™FxC automated synthesizer (GE Healthcare, Chalfont St. Giles, United Kingdom) (22). The GE Microlab® was employed in some of the preparations as a source of the requisite [^{11}C]methyl iodide.

2.3. Scanning and Imaging Procedures

PET imaging was performed with the selective 5-HT $_{1B}$ receptor antagonist radiotracer [^{11}C]P943. All scans used a High-Resolution Research Tomograph (HRRT) (Siemens/CTI, Knoxville, TN, USA), which acquired 207 slices (1.2mm slice separation) with a reconstructed image resolution of ~3mm. A transmission scan with a ^{137}Cs point source was obtained before the emission scan. The PET scans were acquired for 120min at rest following a mean (±SD) single bolus intravenous injection of 660 ± 114 MBq with a specific activity of 148 ± 78MBq/nmol.

Structural magnetic resonance images were performed on a Siemens 3-T Trio system (Siemens Medical Solutions, Malvern, Pennsylvania) with a circularly polarized head coil for each subject to exclude individuals with anatomical abnormalities and for coregistration using an MPRAGE pulse sequence. The dimension and voxel size of MR images were 256 × 256 × 176 and 0.98 × 0.98 × 1.0 mm^3, respectively.

Dynamic PET scan data were reconstructed with all corrections (attenuation; normalization; scatter; randoms; deadtime and motion), using the MOLAR algorithm (23) with the following frame timing: 6 × 30sec; 3 × 1min; 2 × 2min; 22 × 5min. Images were smoothed with a Gaussian filter at full width at half maximum (FWHM) of 3 mm and motion was

corrected by either an optical detector (Vicra, NDI Systems, Waterloo, Ontario, Canada) or coregistered to each image frame with an early summed image (0–10 min post injection) using a 6-parameter mutual information algorithm (FLIRT, FSL 3.2, Analysis Group, FMRIB, Oxford, UK). The motion correction approach was added as a covariate in all analyses and no significant differences were found in any of the regions studied. As in previous [^{11}C]P943 studies, the multilinear reference tissue model, MRTM2, was used to produce parametric images of BP_{ND} based on a cerebellum reference given the negligible levels of 5-HT $_{1B}$ in this region(22).

A second summed image (0–10 min after injection) was created from the motion-corrected PET data and nonlinearly registered to the subject's MR image to an MR template (Montreal Neurological Institute or MNI space). All transformations were performed on bioimage suite (version 2.5; http://www.bioimagesuite.com). Regions of interest were based on the Anatomical Automatic Labeling (AAL) template delineated on MR (24) with the exception of a hand-drawn ventral striatum template that was based on guidelines from *Mawlawi et al*. (25)

Given the exploratory nature of the research (and limited sample sizes and, hence power), nine primary regions of interest (ROIs) were selected *a priori (*the amygdala, anterior cingulate cortex, caudate, frontal cortex, hypothalamus, pallidum, putamen, thalamus and ventral striatum) based on the known regional densities of 5-HT $_{1B}$ receptors and brain regions previously implicated as important in mediating cocaine's effects and addiction processes.(26–28) Results were obtained by applying these template regions to individual parametric images that were nonlinearly resliced into template space using the PET to MR and the MR to template transforms.

In order to account for potential partial volume effects, a binary gray-matter mask (GMM) was also employed. Individual MR images were segmented with FAST (FMRIB's Automated Segmentation Tool, v3.1) to obtain gray matter, white matter, and CSF masks. The individual GMM images were then applied to the candidate AAL template regions to obtain the mean regional values limited to gray matter voxels.

Voxel-based morphometry (VBM) was performed with structural data analyzed with FSL-VBM, (http://www.fmrib.ox.ac.uk/fslvbm), an optimized VBM protocol carried out with FSL tools. Structural images were first brain-extracted and gray-matter-segmented before being registered to the MNI 152 standard space using non-linear registration. The resulting images were flipped along the x-axis and averaged to create a left-right symmetric, study-specific gray matter template. Second, all native gray-matter images were non-linearly registered to this study-specific template and "modulated" to correct for local expansion (or contraction) due to the non-linear component of the spatial transformation. The modulated gray-matter images were then smoothed with an isotropic Gaussian kernel with a sigma of 3mm. Finally, voxelwise GLM was applied using permutation-based non-parametric testing, correcting for multiple comparisons across space.

Voxel wise parameter estimation of binding was generated with MRTM2 parametric images using the cerebellum as the reference region. Normalized BP_{ND} maps were statistically

investigated to assess significant contrasts between the groups at every voxel, using independent sample *t* test analysis (SPM8; Wellcome Trust Centre for Neuroimaging, London, UK). The threshold for significant clusters was set to $p < 0.001$ uncorrected. This approach was aimed at confirming *a priori* differences in BP_{ND} at the voxel level without the potential limitations of ROI template placement.

2.5 Statistical Analysis

All outcomes were summarized descriptively and assessed for normality prior to analysis using normal probability plots and Kolmogorov test statistics. All outcomes were approximately normal. Linear mixed models were used to examine the independent and joint effects of group (between-subjects factor) and ROI (within-subjects) on BP_{ND} values. Group contrasts within each region were estimated to explain significant interactions. The best-fitting variance-covariance structure was assessed using information criteria. Secondary (i.e., exploratory) analyses included group comparisons of BP_{ND} levels in frontal subregions and the potential relationship between imaging and clinical measures (executed without adjustment for multiple tests due to small sample size and the exploratory nature of the comparisons). All analyses were conducted using SAS, version 9.1 (Cary, NC).

3. Results

As seen in Figure S1 (supplemental), results of the initial MRTM2 analysis in nine ROIs showed an overall group-by-region effect ($F_{8,208}$= 2.91, P=0.004), with BP_{ND} reductions in CD individuals in the anterior cingulate ($F_{1,208}$ = 7.11, P=0.008; −16%), hypothalamus ($F_{1,208}$ =4.98, P=0.03; −16%) and frontal cortex ($F_{1,208}$ = 3.05, P =0.08; −7%).

Figure 1 is a structural image of the gray matter differences between CD and HC subjects using a VBM analysis (highlighted is the CD-related decrease in gray matter). Table S1 shows the decreases in gray matter in CD subjects found with VBM (all differences found in frontal regions).

Subsequent analyses aimed at minimizing potential partial volume effects through GMM (Figure 2) resulted in similar group-by-region effects ($F_{8,207}$ = 2.94, P=0.004) and emergence of statistically significant findings in the frontal cortex ($F_{1,208}$ = 7.81, P=0.006; −14%) as well as confirmation of a significant difference in the anterior cingulate ($F_{1,207}$ = 6.43, P=0.01; −14%) and hypothalamus ($F_{1,207}$ =8.37, P =0.004; −20%).

Voxel-based results of whole brain analysis are shown in table 2 for each significant region. Whole-brain group-average parametric PET BP_{ND} images of HC and CD subjects (Figure S2) are shown for visual comparison.

In exploratory post-hoc analyses (unadjusted p values), significant decreases were seen in CD subjects in multiple frontal cortical subregions with GMM ($F_{1,130}$ = 7.38, P =0.008) (Figure S3). These results were generalized and non-specific. Within CD individuals, positive associations were observed between years of cocaine use and BP_{ND} in the amygdala (r = − 0.56; p =0.04), putamen (r = − 0.54; p =0.05), and thalamus (r = − 0.54; p = 0.05). Weekly cocaine use (in dollars spent) showed a statistical trend in the anterior cingulate (r =

− 0.52; p = 0.06.). Daily nicotine use was significant in the frontal cortex (r = − 0.69; p = 0.01), putamen (r = − 0.65; p = 0.01) and ventral striatum (r = − 0.59; p = 0.03) with the anterior cingulate close to significance (r= − 0.51; p = 0.07). There was a correlation with the physical abuse subscale of the CTQ in the pallidum (r = − 0.62; p = 0.02) and the state subscale of STAI (r = − 0.61; p = 0.04) in the thalamus, but no other factors examined in measures of past trauma (CTQ), anxiety (STAI), impulsivity (BIS-11), or depression (HAM-D) were significant. In addition, days since last cocaine use and alcohol use were also not correlated with regional brain BP_{ND} availability within this cohort.

4. Discussion

To our knowledge, this study is the first to examine 5-HT $_{1B}$ receptor availability in human cocaine dependence. The results suggest reductions in 5-HT $_{1B}$ receptor availability in the hypothalamus, anterior cingulate, and frontal cortex of CD subjects. In two of these regions (i.e., hypothalamus and anterior cingulate), results were significant whether corrected for gray matter volume or not. In the case of the frontal cortex, initial differences in 5-HT $_{1B}$ availability were non significant ($p<0.08$) but emerged as significant after efforts to minimize potential partial volume effects (a factor that may pertain to some, but not all frontal cortical subregions). Whole brain voxel-wise parameter analysis confirmed these results in frontal cortex and anterior cingulate.

Given that the CD subjects had not used cocaine on average 6 days before the scans, these results could support a down-regulation (or desensitized) model of 5-HT $_{1B}$ in early abstinence cocaine dependence. These decreases are likely not in isolation however, as preclinical work has shown that the 5-HT $_{1B}$ system is largely dependent on the stage of the addiction cycle with cocaine administration and abstinence increasing and reducing 5-HT $_{1B}$ mRNA expression respectively.(29, 30) Mechanistic explanations for these changes are not fully known, but reductions in 5-HT $_{1B}$ receptor availability in CD could be due to 5-HT $_{1B}$ down regulation or also preexisting differences or higher levels of extracellular 5-HT in CD. Any possible preexisting differences in CD could be supported by a host of genetic studies in addiction (13, 31) and inherent 5-HT $_{1B}$ heterogeneity could potentially alter dopamine activity in reward areas by reducing inhibition of GABA release. (30) Potential extracellular 5-HT affects on 5-HT $_{1B}$ are also an important consideration and given that 5-HT levels were increased in a human post-mortem CD sample (32) and [^{11}C]P943 has been shown to be sensitive to endogenous 5-HT in the nonhuman primate (33), elucidation of this possible affect should be made to further interpretations of 5-HT $_{1B}$ in CD.

Clinical work using this same radiotracer, interestingly, found an increase in 5-HT $_{1B}$ receptor availability in the ventral striatum/pallidum in alcohol-dependent subjects (34). Additionally, 5-HT $_{1B}$ receptor availability in the ventral striatum/pallidum, putamen and anterior cingulum correlated positively with problem-gambling severity in pathological gambling (35). These findings are consistent with 5-HT $_{1B}$ receptor involvement in the mesocorticolimbic pathway in addiction, and the ventral striatum, a key area in this pathway, has generally been found to be altered with cocaine and 5-HT $_{1B}$ receptor function (12). Given prior findings, our failure to find differences in the ventral striatum in our CD cohort was surprising. In fact, because of potential limitations of the AAL template (globus

pallidus/nucleus accumbens) with respect to the precise delineation of ventral striatal regions, we specifically applied a hand-drawn ventral striatum template using methods previously validated by other groups for PET radiotracer analyses. Findings were nonetheless negative despite such specialized approaches.

The differences in CD that were found in the current study (i.e. hypothalamus, anterior cingulate and frontal cortex) all showed a decreased $BP_{ND,}$ while the previous studies of alcohol dependence and pathological gambling using the [^{11}C]P943 radiotracer (34, 35) found an increase in 5-HT $_{1B}$ receptor availability in the ventral striatum. These findings are important for multiple reasons. First, It is possible that apparent differences in the studies reflect the time of abstinence (while no differences were found within group with the last day of cocaine use, this study had a short window of abstinence of 6 days vs. 4 weeks for the alcohol-dependence study). Secondly, the current findings may suggest that 5-HT $_{1B}$ receptors contribute uniquely to different addictions, perhaps in a manner related to the specific effects of each drug of abuse. The apparent 5-HT $_{1B}$- receptor-related differences in CD and alcohol-dependent subjects suggest that the findings are not attributable to alcohol use in the CD group, an idea supported by the lack of correlation between ETOH use and 5-HT $_{1B}$ BP_{ND} in this study (it is interesting to note, however, the correlation of active daily nicotine use across multiple brain regions, which could be a proxy for cocaine use or alternatively may provide preliminary evidence that nicotine may be have similar effects on 5-HT $_{1B}$ as cocaine.) Lastly, 5-HT $_{1B}$ receptors may contribute to clinically relevant states relating to cocaine use. For example, given the reductions in 5-HT $_{1B}$ receptor availability observed in major depression (16), 5-HT $_{1B}$- receptor function may contribute to negative affective states observed in cocaine dependence (although we found little evidence for 5-HT $_{1B}$ correlations with clinically based depression, anxiety and trauma measures in this cohort). These factors, alone or in sum, are similar to the differences found to be important in 5-HT $_{1B}$ animal addiction models and could account for the seemingly divergent results of the clinical addiction imaging studies of 5-HT $_{1B}$.

Observations of reduction in 5-HT $_{1B}$ receptor binding in the hypothalamus is a potentially very interesting finding, given the increasing appreciation of this region's role in the neurobiology of addiction. The hypothalamus has high levels of 5-HT $_{1B}$ receptor binding in rats (36), and is also associated with alterations in 5-HT during cocaine self-administration (37) as well as reduced 5-HT $_{1A}$ receptors following cocaine binge behavior (38). Our findings are intriguing given that 5-HT $_{1B}$ knock-out mice have also been found to be hyperreactive to mild stress (39), which is important in cocaine dependence considering the role stress and the hypothalamic–pituitary–adrenal (HPA) axis have in addiction and relapse (40).

Studies have increasingly identified abnormalities in frontal cortical functioning in CD individuals, including abnormalities identified by both functional (e.g., PET) (41) and structural neuroimaging methods. In regards to the latter, structural MRI studies have previously produced contradictory results in regards to gray matter changes, with some suggesting generalized reductions (42), others noting reductions in frontal cortex alone (43, 44) and others failing to find changes altogether (45). Given inconsistencies in the literature, we conducted VBM analyses directly in the current cohort as a prerequisite to potential

partial volume corrections. Our VBM results demonstrated significant and moderate reductions of gray matter in the frontal cortex (including the right superior and inferior gyri, and left inferior gyrus) of CD subjects (in accordance with prior findings (43, 44)).

Based on these results, we applied GMM (using a segmented MRI) to control for between-group differences in frontal cortical gray matter volume (using analyses of unaffected regions as a negative control). Consistent with predictions, BP_{ND} differences emerged as statistically significant in the frontal cortex following GMM (and as importantly, findings in other regions remained unchanged). The whole brain voxel-wise analysis was performed as a confirmatory step and with this and the VBM analyses, we conducted an exploratory post-hoc analysis of frontal cortical subregions (including, inferior, middle, and superior left/right frontal ROIs) in an effort to determine whether 5-HT $_{1B}$ reductions might be confined to areas of gray-matter change. However, results failed to suggest subregional selectivity to these differences (i.e., differences in all frontal subregions were significant post-hoc).

The implications of the anterior cingulate and frontal $5HT_{1B}$ reductions are largely speculative because previous preclinical work has been noticeably silent as to whether cortical 5-HT $_{1B}$ receptor differences exist in CD. Interestingly, however, 5-HT $_{1B}$ receptors have a relatively high density in the frontal brain regions, and a 5-HT $_{1B}$ agonist has been found to reduce aggression and impulsivity in mice when injected into the prefrontal cortex (46). Chronic cocaine users have been shown to have impairments in the cognitive control of these and other executive functions (e.g., error and conflict monitoring, response inhibition, outcome expectancies) and numerous neuroimaging studies have implicated the anterior cingulum and frontal cortex with these deficits in cocaine and stimulant dependence (47).

Lastly, while the current work focused on 5-HT $_{1B}$, this is the first human PET data to investigate serotonin dysfunction in CD of any subtype and these differences should not be interpreted as necessarily exclusive and specific in regards to serotonin. Indeed, the potential importance of other serotonergic mechanisms (e.g., 5-HT $_{2C}$ receptor) in CD and related risk factors (48) corroborates the potential importance of our findings in a growing body of cocaine research focused on serotonin. Future studies could improve upon the current limitations by having prospectively matched controls with corresponding amounts of nicotine use (given the possibility of this confound in the current study) and larger sample sizes. It also remains to be determined whether cognitive differences may be attributable to 5-HT $_{1B}$ receptor function, and future investigations could focus on neuropsychological measures of executive function as well as exploring whether 5-HT $_{1B}$-receptor agonists have an influence on cognitive function. Thus, future studies will be required to more definitively address the nature of potential changes in 5-HT $_{1B}$ regional availability and to directly examine the extent to which the 5-HT $_{1B}$ receptor represents a new and potentially clinically relevant molecular target for the treatment of cocaine dependence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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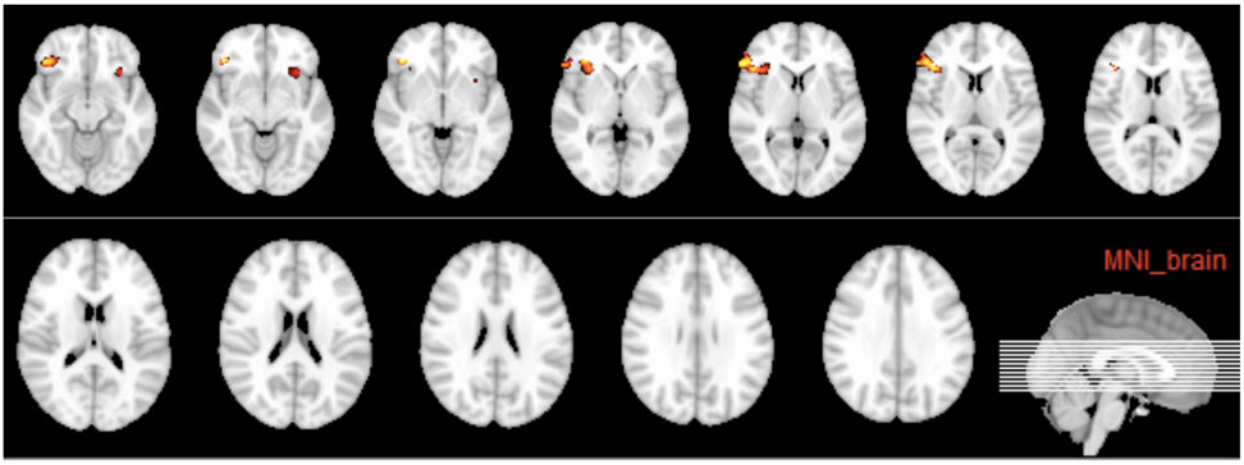

Figure 1.
VBM analysis showing reductions in gray-matter volume in CD individuals (P<0.05, corrected).

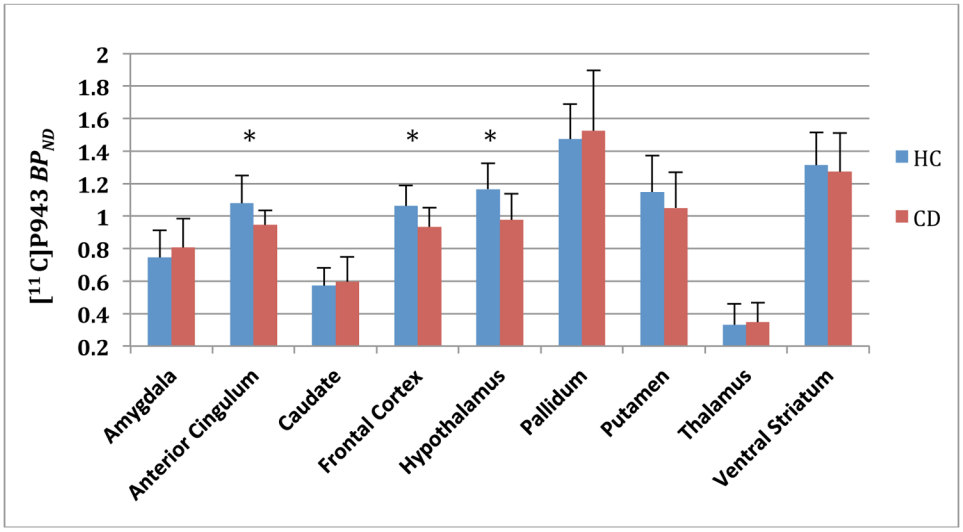

Figure 2.

Region of interest analysis after gray matter masking (GMM) and associated mean [^{11}C]P943 BP_{ND} values for HC (blue) and CD (red) subjects. Asterisks are statistically significant at P=0.01 or better. Error bars denote standard deviation.

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Table 1

Characteristics for cocaine-dependent (CD) subjects

CD Subjects (N=14)	**Demographics**				
Age	41 (6)				
Gender	4 F/10 M				
Ethnicity (Caucasian (C), African-American (AA), Hispanic (H) and other	3 C/9 AA/1 H/1 Other				
Clinical Use Characteristics	**Mean (S.D.)**				
Years of cocaine use	21 (7)				
Weekly cocaine use (US Dollars)	652 (617)				
Weekly cocaine use (grams)	4.6 (4.4)				
Weekly ETOH use (drinks)	16 (13)				
Daily nicotine use (cigarettes)	10 (7)				
Cannabis use in the last week (joints)	3 (7)				
Secondary Measures	**Mean Scores (S.D.)**				
STAI (State Trait Anxiety Inventory) State and Trait Subscales	41 (11)		45 (12)		
BIS-11 (Barratt Impulsiveness Scale)	74 (14)				
HAM-D (Hamilton Rating Scale for Depression)	5 (5)				
CTQ (Childhood Trauma Questionnaire) Raw Scores Emotional (EA), Physical (PA) and Sexual (SA) Abuse Emotional (EN) and Physical (PN) Neglect	EA 11 (4)	PA 10 (4)	SA 7 (4)	EN 13 (4)	PN 10 (4)

Table 2

Voxel based SPM results are shown with brain regions, corresponding Brodmann Areas (BA), T scores of the peak and mean voxels, cluster size (in number of voxels) and Montreal Neurological Institute (MNI) coordinates of the peak voxel for each cluster. Threshold set at P value <0.005 uncorrected and cluster size >50.

Identified brain region	BA	Peak T Value	Mean T Value	Cluster size (voxels)	Peak voxel MNI coordinate (mm)		
					x	y	z
Orbitofrontal Cortex	10,11	5.74	4.05	1454	14	68	0
Superior and Middle Frontal Gyrus	8,9,10	5.03	3.94	523	28	42	36
Cingulate Gyrus	31	4.81	3.90	156	10	−44	34
Temporal and Occipital Gyrus	19,39,22,40,18	4.60	3.80	1168	−58	−72	26
Cingulate Gyrus/Precuneus	31	4.13	3.67	128	−14	−56	24
Inferior and Middle Frontal Gyrus	46,45,10	4.06	3.64	174	50	34	14
Inferior and Middle Frontal Gyrus	46,45,6,8,9	3.81	3.55	238	56	22	22