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A PRELIMINARY STUDY OF DOPAMINE $D_{2/3}$ RECEPTOR AVAILABILITY AND SOCIAL STATUS IN HEALTHY AND COCAINE DEPENDENT HUMANS IMAGED WITH [^{11}C](+)PHNO

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Abstract

Background—Previous work in healthy non-human primates and humans has shown that social status correlates positively with dopamine 2/3 receptor ($D_{2/3}$ R) availability imaged with antagonist radioligands and positron emission tomography (PET). Further work in non-human primates suggests that this relationship is disrupted by chronic cocaine administration. This

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Conflict of interest statement

The authors report no conflicts of interest with respect to the content of this manuscript

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exploratory study examined the relationship between social status and $D_{2/3}R$ availability in healthy (HH) and cocaine dependent (CD) humans using the D_3-preferring, agonist radioligand, [^{11}C](+)PHNO.

Methods—Sixteen HH and sixteen CD individuals completed the Barratt Simplified Measure of Social Status (BSMSS) and underwent [^{11}C](+)PHNO scanning to measure regional brain $D_{2/3}R$ binding potentials (BP_{ND}). Correlations between BP_{ND} and BSMSS scores were then assessed within each group.

Results—Within HH and CD groups, inverse associations between BSMSS score and BP_{ND} were observed in the substantia nigra/ventral tegmental area (SN/VTA) and the ventral striatum, and for the CD group alone, the amygdala. After adjusting for body mass index and age, negative correlations remained significant in the SN/VTA for HH and in the amygdala for CD subjects.

Conclusion—These preliminary data utilizing a dopamine agonist tracer demonstrate, for the first time, an inverse association between social status and $D_{2/3}R$ availability in the D_3R rich extrastriatal regions of HH and CD humans.

Keywords

dopamine; cocaine; social status; PET imaging; [^{11}C](+)PHNO

1. INTRODUCTION

Social status is an important factor relating to health and behaviors in mammals, including humans (Adler et al., 1994; Tamashiro et al., 2005). Particularly, dopaminergic function in the brain has been found to relate to social status in different species (Grant et al., 1998; Hall et al., 1998; Morgan et al., 2000). In healthy humans, greater social status as measured by the Barratt Simplified Measure of Social Status (BSMSS; Barratt, 2006), a comprehensive instrument which quantifies social status based on educational and occupational environment, has been associated with higher striatal dopamine subtype 2/3 receptor ($D_{2/3}R$) availability when imaged with the antagonist positron emission tomography (PET) radioligand, [^{11}C]raclopride (Martinez et al., 2010). This finding is consistent with earlier PET work in nonhuman primates that utilized a social status corollary, social dominance, to show that social dominance was positively associated with striatal $D_{2/3}R$ availability in substance-naïve cynomolgus macaques when measured by [^{18}F]fluoroclebopride (Morgan et al., 2002). Although novel, those previous studies were both done utilizing similar non-selective dopamine $D_{2/3}R$ antagonist tracers either shown to be unreliable outside of the striatum (Graff-Guerrero et al., 2008) or examined the basal ganglia as a whole (Morgan et al., 2002), thus important somatodendritic $D_{2/3}R$ regions within the basal ganglia, such as the substantia nigra / ventral tegmental area (SN/VTA), have not been examined. Additionally, the aforementioned antagonist tracers bind to both “high” affinity (i.e., the D_3R and certain active forms of the D_2R) and “low” affinity (i.e., the non-active forms of the D_2R) dopamine $D_{2/3}R$ receptors (George et al., 1985; Leff, 1995) with equal preference. Consequently, this lack of preference limits the degree to which the relative distribution of dopamine receptor subtype (i.e., D_2R vs. D_3R) and isoform (i.e., “high” vs. “low” affinity D_2R) can be examined in certain regions. However, with an agonist tracer it has been shown

that D_3R predominates in the SN/VTA (as opposed to the dorsal striatum where D_2R is predominant)(Graff-Guerrero et al., 2008; Narendran et al., 2006; Searle et al., 2010; Tziortzi et al., 2011). Thus, to date, no studies have examined social status and $D_{2/3}R$ receptor availability in a non-substance abusing healthy human population with an agonist dopamine tracer, both within and outside the striatum.

Given the role of dopamine in mediating cocaine effects, investigators have sought to understand potential relationships between social status, cocaine, and brain dopamine function. Morgan and colleagues found that the vulnerability to self-administer cocaine was associated with lower social status in cynomolgus macaques (Morgan et al., 2002). Follow-up work from the same group showed that after an extended period (between 5 and 45 months) of cocaine self-administration the positive association between social dominance and striatal $D_{2/3}R$ availability in socially housed nonhuman primates was lost (Czoty et al., 2004; for a complete review of social status and cocaine administration paradigms in nonhuman primates see Nader and Banks, 2014). Thus, current nonhuman primate evidence suggests a potentially complex relationship between the vulnerability to abuse cocaine, social status, and striatal dopamine function - a relationship that has yet to be examined in brain regions of clinical populations.

In light of these prior works (Czoty et al., 2004; Martinez et al., 2010; Morgan et al., 2002), this preliminary study looks, for first time, to utilize the D_3-preferring agonist tracer [^{11}C](+)PHNO to examine the association between social status and 1) striatal and extrastriatal (e.g., SN/VTA) $D_{2/3}R$ availability in non-substance abusing healthy humans (HH) humans and 2) investigate these same relationships in cocaine dependent (CD) humans for the first time with a radioligand.

2. PARTICIPANTS AND METHODS

2.1 Participants

Sixteen HH participants without a clinical history of illicit substance use and sixteen medically healthy, non-treatment-seeking CD participants were studied. Subject eligibility was confirmed by comprehensive medical and psychiatric histories, physical examination, neurological and mental status exam, routine laboratory studies, electrocardiogram, and semi-structured (Sheehan et al., 1998) or structured clinical interview (American Psychiatric Association. and American Psychiatric Association Task Force on DSM-IV, 2000).

CD participants were between the ages of 18 and 50 years, met DSM-IV criteria for cocaine dependence, used cocaine as their primary drug of choice via a rapid-onset (e.g., intravenous or smoked) route, and had a history of regular and recent cocaine use (e.g., as evidenced by benzoylecgonine positivity on urine toxicology testing). Three of the CD participants have been previously reported (Matuskey et al., 2014). Demographic and clinical features of all participants are shown in Table 1.

Participants were excluded based on evidence of a current or lifetime major psychiatric illness (e.g., schizophrenia or bipolar disorder), current or past serious medical or neurological illness (e.g., 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 contraindications to magnetic resonance imaging (MRI).

Once determined eligible, participants completed the BSMSS (Barratt, 2006), a comprehensive measure of social status based on the Hollingshead index (Hollingshead, 1975). The BSMSS and the Hollingshead index are similar in that they both generate a single comprehensive score of social status taking into account education and occupation of the research participant, their parents, and their spouse. The comprehensive score of the BSMSS is weighted in favor of the scores of the research participant and significant others over that of the parents. Subject screening records (e.g., occupation and education) were reviewed to confirm an accurate BSMSS report. One potential CD subject was excluded for providing incongruent information.

Participants were recruited from the greater New Haven area by advertisement, word of mouth and referral. Informed consent was obtained from all participants after a thorough explanation of the study procedures by a research assistant, study coordinator, or study investigator. This study was performed under protocols approved by the Yale Human Investigation, Yale University Radiation Safety, Yale-New Haven Hospital (YNHH) Radiation Safety, and Yale MRI Safety Committees.

2.2 Radiochemistry, Scanning, and Imaging Procedures

Carbon 11-labeled (+)-4-propyl-9-hydroxynaphthoxazine [[11C](+)PHNO] is a $D_{2/3}R$ agonist radiotracer that has D_3R preferring properties and was prepared as previously reported (Gallezot et al., 2012). Injection information and radioactivity data for both HH and CD participants are shown in Table 2.

All scans used a high-resolution research tomograph (Siemens/CTI, Knoxville, TN, USA), which acquired 207 slices (1.2mm slice separation) with a reconstructed image resolution of ~3mm over 120 minutes at rest. A transmission scan with a ^{137}Cs point source was obtained before the emission scan.

Structural MRI was performed on a 3 Tesla Trio system (Siemens Medical Solutions, Malvern, Pennsylvania) with a circularly polarized head coil for purposes of excluding individuals with anatomical abnormalities and anatomically coregistering with PET scans. The dimension and voxel size of MR images were 256 × 256 × 176 voxels and 0.98 × 0.98 × 1.0 mm^3, respectively.

Motion correction was based on an optical detector (Vicra, NDI Systems, Waterloo, Ontario, Canada). Dynamic PET scan data were reconstructed with all corrections (attenuation; normalization; scatter; randoms; deadtime and motion), using the MOLAR algorithm (Carson, 2003) with the following frame timing: 6 × 30 sec; 3 × 1 min; 2 × 2 min; 22 × 5 min.

PET data were used to produce a time–activity curve for the cerebellum, which has minimal $D_{2/3}R$ binding and was used as the reference region as in previous studies (Boileau et al., 2012; Ginovart et al., 2007; Matuskey et al., 2014; Mizrahi et al., 2011; Payer et al., 2014; Searle et al., 2010). A summed image (0–10 min after injection) was created from the

motion-corrected PET data and registered to the subject's MR image, which in turn was nonlinearly registered to a MR template in Montreal Neurological Institute space. All transformations were performed using Bioimagesuite (version 2.5; http://www.bioimagesuite.com). Parametric images of binding potentials (BP_{ND}), which are linearly proportional to the density of available $D_{2/3}$Rs under conditions of comparable non-specific tracer binding, were computed using a simplified reference tissue model (2-parameter version: SRTM2). This method has been previously validated for [^{11}C](+)PHNO (Gallezot et al., 2014b; Wu and Carson, 2002) and was used to optimize the statistical quality of the SRTM applied in prior studies by reducing noise of the functional images (Matuskey et al., 2014).

Regions of interest (ROI) included the amygdala, caudate, hypothalamus, pallidum, putamen, SN/VTA, thalamus, and ventral striatum (VST) and, with the exception of the SN/VTA and VST, were based on the Anatomical Automatic Labeling (AAL) template delineated on MR (Tzourio-Mazoyer et al., 2002). Specifically, the SN/VTA was manually delineated on BP_{ND} images in template space as noted in the supplement of work done by Gallezot and colleagues (Gallezot et al., 2014b), and the VST template was based on guidelines previously described (Mawlawi et al., 2001). ROIs were applied to the BP_{ND} images to extract individual values.

2.3 Statistical Considerations

Between-group differences in BSMSS scores, education, mass dose, and radioactivity parameters were analyzed using independent t-tests. Potential associations between BSMSS scores, clinical characteristics, and demographics with ROIs were estimated using Pearson correlation coefficients and subsequently adjusted for body mass index (BMI) and age due to known influences of these variables on $D_{2/3}$R (Caravaggio et al., 2013; Correa, 2014; Ishibashi et al., 2009; Kessler et al., 2014; Kim et al., 2011; Volkow et al., 2000; Wang et al., 2001). Analysis of covariance (ANCOVA) models were used to test whether associations differed between groups. All analyses were considered significant at the two-tailed $\alpha<0.05$ threshold and were conducted using SPSS, version 19 (Armonk, NY). Correlations were not adjusted for multiple tests given the exploratory nature of these analyses.

3. RESULTS

Means and standard deviations of demographic, clinical characteristic, and injection parameter data for both HH and CD participants are shown in Tables 1 and 2. There were no significant associations between daily cigarette intake or weekly alcohol consumption and regional measures of BP_{ND} in either group.

Mean BSMSS scores for HH (44.8±10.1, range 30–62) and CD participants (30.2±7.1, range 15–44) differed significantly ($p<0.001$). Years of education were not statistically correlated with regional measures of BP_{ND} in either group; however, a statistical trend was observed in the SN/VTA ($r=-0.49$, $p=0.06$) in CD participants.

In HH participants, a significant inverse association was observed between BSMSS score and regional BP_{ND} in the SN/VTA (r=−0.67, p<0.01), as well as a statistical trend in the VST (r=−0.44, p=0.086) (Figure 1). In CD participants, significant negative correlations were observed in the amygdala (r=−0.60, p=0.014), SN/VTA (r=−0.50, p=0.048), and VST (r=−0.50, p=0.049)(Figure 1). No other regions emerged as statistically significant in either group and no region would have survived multiple comparison correction. Separate ANCOVA models revealed no differences in the above results between groups.

The association between BSMSS score and regional BP_{ND} in the SN/VTA retained significance after adjusting for BMI and age (corrected, r=−0.55, p=0.04) in HH participants. Similarly, the association remained significant in the amygdala among CD participants after adjustment for BMI and age (corrected, r=−0.55, p=0.04). Other associations lost significance after BMI and age adjustment. Additionally, injection parameters had no effects on correlations when examined with all participants.

A summary of both unadjusted and adjusted correlations between BSMSS score and all ROI BP_{ND} values for both HH and CD participants are shown in Tables 3 and 4. Between-group comparisons of BP_{ND} were outside the scope of this manuscript and thus not completed here, however, they will be reported as part of a larger cohort in a future publication.

4. DISCUSSION

To our knowledge, the current study is the first to examine the relationship between social status and extrastriatal $D_{2/3}R$ availability in humans using the D_3-preferring agonist radioligand, [^{11}C](+)PHNO. This work found two major findings. The first was an inverse association between social status and $D_{2/3}R$ availability in the SN/VTA of HH participants. This relationship retained significance after adjusting for the known effects of age (Correa, 2014; Ishibashi et al., 2009; Kim et al., 2011; Volkow et al., 2000) and BMI (Caravaggio et al., 2013; Kessler et al., 2014; Wang et al., 2001) on $D_{2/3}R$ availability. Secondly, this study is the first to examine social status and $D_{2/3}R$ availability in a human CD population utilizing PET. Interestingly, similar inverse associations were observed between social status and $D_{2/3}R$ availability in the amygdala, SN/VTA, and VST of CD participants, findings that remained significant in the amygdala alone after age and BMI correction.

Our findings in HH participants suggest a negative association between social status and extrastriatal $D_{2/3}R$ availability whereas prior work focusing on the striatum suggested $D_{2/3}R$ availability was positively correlated with social status and years of education in HHs (Martinez et al., 2010) and social dominance in non-human primates (Czoty et al., 2010; Morgan et al., 2002). Several factors may be responsible for these differences, but perhaps most notably, our study employed a different radiotracer with unique properties compared with prior work.

As discussed previously, [^{11}C](+)PHNO has been shown to have a preference for binding to the D_3R subtype as compared to the D_2R subtype. This preference, along with excellent signal to noise properties, enables the visualization/quantification of dopamine receptors in a number of important extrastriatal regions such as the SN/VTA, where the D_3R predominates

(Graff-Guerrero et al., 2008; Narendran et al., 2006; Searle et al., 2010; Tziortzi et al., 2011). Thus, our findings here are the first to report on social status in this region, and the negative correlation observed may be accounted for by relatively different roles of D_3R vs. D_2R subtypes with respect to the trait. Moreover, from a neuroanatomic perspective, the SN/VTA contains dopamine cell bodies that project to the striatum and differences in the regulation of somatodendritic $D_{2/3}$Rs as compared to those in nerve terminal regions, such the striatum, could also exist in relation to social status.

In addition, "high-affinity" forms of the $D_{2/3}$R, for which [11C](+)PHNO has a specific preference, may be regulated differently in relation to social status compared to the total $D_{2/3}$R binding as imaged by antagonist tracers in prior studies. In fact, prior studies in healthy and CD humans suggest differences in striatal $D_{2/3}$R availability as imaged by antagonist vs. agonist tracers (Narendran et al., 2011; Payer et al., 2014). Another potential explanation for discrepancies between this and prior studies relates to ligand-related differences in vulnerability to competition from endogenous dopamine. As an agonist tracer, [^{11}C](+)PHNO has been shown to be considerably more sensitive to endogenous dopamine fluctuations and PET tracer displacement than [^{11}C]raclopride (Gallezot et al., 2014a; Ginovart et al., 2006; Shotbolt et al., 2012; Willeit et al., 2008). In fact, in the absence of other pharmacologic interventions such as the depletion of dopamine by the tyrosine-hydroxylase inhibitor, alpha-methly-para-tyrosine (AMPT; Abi-Dargham et al., 2000; Caravaggio et al., 2014; Laruelle et al., 1997; Martinez et al., 2009), BP_{ND} measures reflect tracer binding to available receptors (i.e., those not currently bound by endogenous transmitters (Innis et al., 2007)). As such, our receptor availability findings in the SN/VTA could be a reflection, in whole or in part, of higher levels of endogenous dopamine displacing the tracer (evidenced by lower BP_{ND}) and thus providing preliminary evidence that social status might influence dopamine neurotransmitter synthesis/release, a finding that [^{11}C]raclopride within the striatum might not be able to detect due to the differences in tracers (i.e., antagonist vs. agonist) and anatomy (i.e., striatum vs. SN/VTA)

In addition to tracer effects, characteristics of the study cohorts may also be contributing to the observed differences. For example, average BSMSS scores were considerably higher in our HH participants (45 ± 10) as compared to those in prior work (33 ± 5; Martinez et al., 2010). Additionally, age-related differences between the present work and the work of Martinez and colleagues (40±9 years old vs. 30±4, respectively; Martinez et al., 2010)) could also have had an effect (Correa, 2014; Ishibashi et al., 2009; Kim et al., 2011; Volkow et al., 2000).

This work in CD, the first in humans, demonstrated an inverse association between social status and $D_{2/3}$R availability in the VST, the SN/VTA, and the amygdala prior to adjusting for age and BMI. We corrected for these potential influences based on prior findings (Caravaggio et al., 2013; Correa, 2014; Ishibashi et al., 2009; Kessler et al., 2014; Kim et al., 2011; Volkow et al., 2000; Wang et al., 2001) and statistical significance was retained in the amygdala alone. No significant interactions were seen with HH and CD cohorts using ANCOVA models however, allowing the possibility that no differences exist between these groups in relation to social status and regional BP_{ND} values. While the amygdala finding is

intriguing with respect to social status in CD, caution is warranted given the low BP_{ND} values (i.e., low signal to noise) and the exploratory context of this study.

Prior work in nonhuman primates indicated that chronic periods of cocaine self-administration might obscure the preexisting relationship between social status and $D_{2/3}R$ availability in striatal areas (Czoty et al., 2004). Even though we also found no relationship in the dorsal striatum in CD, it is difficult for direct comparisons between these works for two reasons, including 1) the previously discussed absence of a relationship between social status and striatal $D_{2/3}R$ availability in our human HH cohort and 2) the focus on a clinical population. The latter has important caveats such as modifications in experimental procedures and environmental control. Nonhuman studies have the ability to control cocaine access and social interactions as well as to obtain more direct measurements of social status, constraints not possible in clinical studies.

There are several potential limitations of our methods that merit discussion. The first is the use of the BSMSS as a measure of social status. The BSMSS was developed as a 1989 update to the earlier Hollingshead index (Hollingshead, 1975); as a result, several occupations queried by the BSMSS are obsolete (e.g., typist) or not reflective of current professions (e.g., webmaster or software engineer, etc.). Thus, updated versions of the scale and/or alternative measures/approaches to assessing social status may benefit future studies of the relationship between social status and $D_{2/3}R$ availability. The second limitation could be the confounding effects of nicotine and alcohol consumption. Although prior work utilizing [^{11}C](+)PHNO has demonstrated that both alcohol (Erritzoe et al., 2014) and nicotine (Le Foll et al., 2014) influence [^{11}C](+)PHNO binding, we failed to find any associations between daily nicotine intake (i.e., cigarettes smoked) or weekly alcohol consumption and regional measures of BP_{ND} in either cohort, suggesting the specificity of associations between BSMSS score and regional BP_{ND}. Notwithstanding, we did observe a correlation between weekly alcohol consumption and BSMSS scores within the CD but not HH cohort. However, this correlation was driven by three CD participants who reported drinking alcohol in excess of three standard deviations from the mean as compared to the rest of the cohort (i.e., those three subjects reported drinking between 32 and 109 drinks per week whereas the mean for the rest of the CD cohort was 4 ± 4 drinks per week). If these individuals are removed from the cohort this correlation is no longer observed, while the negative linear association between social status and $D_{2/3}R$ availability persists. This suggests alcohol consumption is not a crucial variable in our main study findings of BSMSS scores and BP_{ND}. That stated, future work would benefit from more rigorous matching of subjects for alcohol and nicotine to definitively rule-out such confounds. The third limitation involves the use in the current study of a single radiotracer, thus complicating direct comparisons with previous studies using different radioligands and leaving unresolved questions. Future studies employing multiple tracers in a within-subject design (e.g., where the same subjects are scanned with both [^{11}C](+)PHNO and [^{11}C]raclopride) will help improve our understanding of how $D_{2/3}R$ availability relates to social status. Finally, pharmacological interventions (e.g., AMPT) that eliminate the potentially confounding influence of endogenous dopamine on PET measures of radiotracer binding/receptor availability may also shed light on such relationships. In combination, such approaches

would constitute a rigorous design for assessing how social status relates to endogenous dopamine brain levels in different clinical and non-clinical samples.

In summary, this study is the first to examine the relationship between social status and $D_{2/3}R$ availability in HH and CD humans with the D_3-preferring, $D_{2/3}R$ agonist radioligand, [^{11}C](+)PHNO. These data demonstrate that inverse associations exist between social status and extrastriatal $D_{2/3}R$ availability in both HH (SN/VTA) and CD individuals (amygdala) when adjusting for age and BMI. Although this work is exploratory in nature and warrants replication in larger, more statistically powered cohorts, these results suggest novel relationships not previously observed between social factors and brain reward pathways, a finding congruent with the notion of the human brain as a "social organ" (Cozolino, 2014). Furthermore, this finding implies that social status is an important variable that should be considered when investigating reward system deficiencies such as addiction.

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Highlights

- This paper examines social status and $D_{2/3}R$ availability in humans
- Healthy and cocaine dependent individuals were studied with the tracer [^{11}C](+)PHNO
- Inverse associations between social status and $D_{2/3}R$ availability were observed
- These areas included D_3R rich brain reward areas in both groups
- These findings demonstrate a novel relationship between social status and $D_{2/3}R$

Figure 1a.

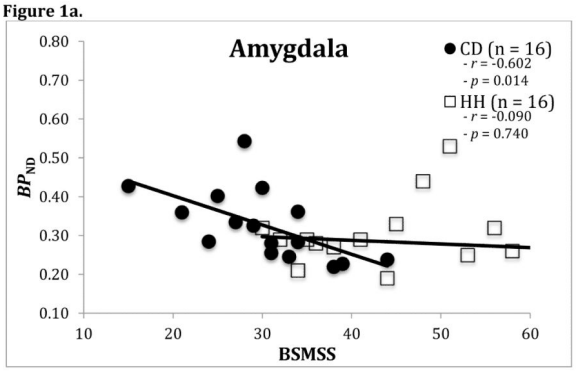

Figure 1b.

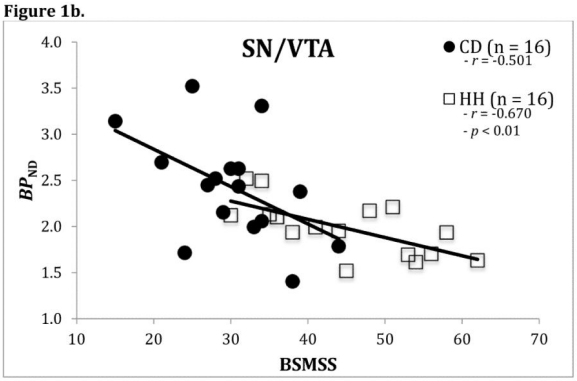

Figure 1c.

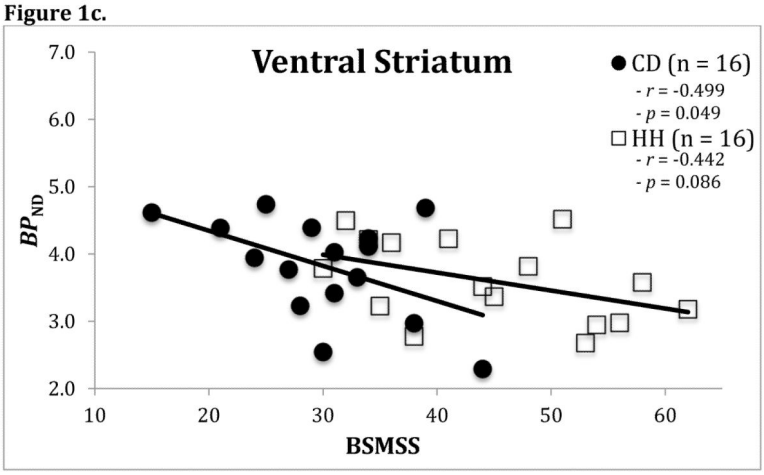

Figure 1.

Correlations between BSMSS and [11C](+)PHNO BP_{ND} in both CD and HH participants for the amygdala (Figure 1a), the substantia nigra/ventral tegmental (SN/VTA) area (Figure 1b), and the ventral striatum (Figure 1c). Correlations shown are not BMI and age-adjusted.

Table 1

Demographic and clinical characteristics of HH and CD participants. Mean values (and standard deviation) are shown. AA = African American, C = Caucasian, C-H = Caucasian-Hispanic, SM = Smoke, IN = Intranasal, IV = Intravenous

	HH	CD
Number of participants	16	16
Age in years	40.3 (9.3)	41.9 (5.4)
Gender	13 M, 3 F	12 M, 4 F
Race	11 AA, 5 C	10 AA, 5 C 1 C-H
Body mass index (kg/m^2)	29.7 (6.7)	30.6 (7.0)
Years of Education	15.3 (2.0)	12.6 (1.4)
Years of cocaine use	-	19.9 (5.9)
Weekly cocaine use in $USD	-	$409 ($321)
Weekly alcohol use (in standard drinks)	3.1 (6.1)	15.1 (28.6)
Daily nicotine use (in cigarettes)	0.6 (2.5)	9.1 (6.5)
Weekly cannabis use (in joints rolled)	-	<1
Days from last cocaine use to PET scan	-	7.8 (5.1)
Route(s) of cocaine administration	-	4 SM and IN 10 SM Only 2 SM, IN, and IV

Table 2

Injection information and radioactivity data for HH and CD participants. Means and standard deviations (in parenthesis) are shown.

	HH	CD
Mass dose (ug/kg)	0.024 (0.007)	0.024 (0.006)
Specific activity (MBq/nmol)	57.9 (31.8)	52.0 (16.5)
Radioactive Dose (MBq)	408.8 (140.4)	406.9 (156.8)

Table 3

Unadjusted and BMI and age-adjusted correlations between BSMSS and [^{11}C](+)PHNO *BP*ND in HH participants

	Amygdala	Caudate	Hypothalamus	Pallidum	Putamen	SN/VTA	Thalamus	Ventral Striatum
BP_{ND} Mean (S.D.)	0.28 (0.10)	1.90 (0.31)	1.20 (0.28)	3.55 (0.53)	2.58 (0.38)	1.98 (0.30)	0.38 (0.10)	3.60 (0.61)
Unadjusted Pearson *r*	−0.09	−0.38	−0.26	0.02	−0.30	**−0.67**	−0.34	−0.44
Unadjusted *p* Value	0.74	0.15	0.34	0.94	0.27	**<0.01**	0.20	0.09
Adjusted Pearson *r*	−0.08	−0.29	0.07	0.31	−0.14	**−0.55**	−0.27	−0.25
Adjusted *p* Value	0.80	0.31	0.80	0.28	0.63	**0.04**	0.34	0.39

Table 4

Unadjusted and BMI and age-adjusted correlations between BSMSS and [^{11}C](+)PHNO BP_{ND} in CD participants

	Amygdala	Caudate	Hypothalamus	Pallidum	Putamen	SN/VTA	Thalamus	Ventral Striatum
BP_{ND} Mean (S.D.)	0.33 (0.09)	1.70 (0.45)	1.42 (0.42)	3.53 (0.51)	2.32 (0.33)	2.43 (0.58)	0.36 (0.09)	3.82 (0.75)
Unadjusted Pearson *r*	**−0.60**	−0.35	−0.37	−0.28	−0.39	**−0.50**	−0.35	**−0.50**
Unadjusted *p* Value	**0.01**	0.18	0.16	0.30	0.13	**0.05**	0.19	**0.05**
Adjusted Pearson *r*	**−0.55**	−0.17	−0.33	−0.19	−0.26	−0.41	−0.28	−0.38
Adjusted *p* Value	**0.04**	0.57	0.25	0.53	0.36	0.15	0.34	0.18