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Imaging of dopamine D_{2/3} agonist binding in cocaine dependence: A [¹¹C]NPA PET study

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Abstract

Objective—PET studies performed with [¹¹C]raclopride have consistently reported lower binding to D_{2/3} receptors and lower amphetamine-induced dopamine release in cocaine abusers relative to healthy controls. A limitation of these studies that were performed with D_{2/3} antagonist radiotracers such as [¹¹C]raclopride is the failure to provide information that is specific to D_{2/3} receptors configured in a state of high affinity for the agonists (i.e., D_{2/3} receptors coupled to G-proteins, D_{2/3} HIGH). As the endogenous agonist dopamine binds with preference to D_{2/3} HIGH relative to D_{2/3} LOW receptors (i.e., D_{2/3} receptors uncoupled to G-proteins) it is critical to understand the in vivo status of D_{2/3} HIGH receptors in cocaine dependence. Thus, we measured the available fraction of D_{2/3} HIGH receptors in 10 recently abstinent cocaine abusers (CD) and matched healthy controls (HC) with the D_{2/3} antagonist and agonist PET radiotracers [¹¹C]raclopride and [¹¹C]NPA

Methods—[¹¹C]raclopride and [¹¹C]NPA binding potential (BP_{ND}) in the striatum were measured with kinetic analysis using the arterial input function. The available fraction of D_{2/3} HIGH receptors, i.e., % R_{HIGH} available = D_{2/3} HIGH / (D_{2/3} HIGH + D_{2/3} LOW) was then computed as the ratio of [¹¹C]NPA BP_{ND} / [¹¹C]raclopride BP_{ND}.

Results—No differences in striatal [¹¹C]NPA BP_{ND} (HC = 1.00 ± 0.17; CD = 0.97 ± 0.17, p = 0.67) or available % R_{HIGH} (HC = 39% ± 5%; CD = 41% ± 5%, p = 0.50) was observed between cocaine abusers and matched controls

Conclusions—The results of this [¹¹C]NPA PET study do not support alterations in D_{2/3} HIGH binding in the striatum in cocaine dependence.

Keywords

[¹¹C]N-propyl-norapomorphine (NPA); [¹¹C]raclopride; cocaine dependence; Positron emission tomography (PET)

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DISCLOSURES

The authors report no competing interests

INTRODUCTION

Previous imaging studies using endogenous competition techniques and PET have unequivocally demonstrated that the amphetamine (or methylphenidate)-induced displacement of [^{11}C]raclopride binding in the striatum is significantly less (or blunted) in cocaine abusers than healthy controls (Martinez et al., 2007; Volkow et al., 1997). A fundamental question unanswered by the previous imaging studies is whether the blunted displacement of [^{11}C]raclopride following amphetamine in cocaine abusers is caused by pre-synaptic (i.e., less dopamine) or post-synaptic (i.e., lesser affinity of $\text{D}_{2/3}$ receptors for dopamine) factors. A possible explanation for the decreased occupancy of $\text{D}_{2/3}$ receptors by dopamine in chronic cocaine abusers is a reduced activity of dopaminergic neurons following amphetamine exposure. This interpretation is supported by a previous [^{18}F]-6-L-fluorodopa imaging study reporting decreased availability of the dopamine synthesis enzyme DOPA decarboxylase in patients with cocaine abuse relative to controls (Wu et al., 1997). An alternative explanation for the same phenomenon is that the presynaptic dopamine release is essentially normal, but the affinity of $\text{D}_{2/3}$ receptors for dopamine is decreased in chronic cocaine users. In this scenario, relatively normal or even exaggerated release of dopamine following amphetamine in cocaine dependence would be associated with decreased occupancy of $\text{D}_{2/3}$ receptors by dopamine. The available imaging data do not distinguish between pre- and post-synaptic factors, and it is also conceivable that both factors might play a role. This issue is important to the understanding of dopamine transmission abnormalities in cocaine dependence.

As $\text{D}_{2/3}$ receptors are configured in inter-convertible states of high or low affinity for agonists, the affinity of a pool of $\text{D}_{2/3}$ receptors for dopamine will depend not only on the affinity of the high (K_{HIGH}) and low (K_{LOW}) configuration sites, but also on the respective proportion of sites present in high and low configuration. If we assume that the total number of sites in the $\text{D}_{2/3}$ HIGH and $\text{D}_{2/3}$ LOW configurations are R_{HIGH} and R_{LOW} , then $R_{\text{HIGH}} + R_{\text{LOW}} = B_{\text{MAX}}$, where B_{MAX} is the total number of $\text{D}_{2/3}$ receptors. Under this scenario, the binding potential (BP) of a population of $\text{D}_{2/3}$ receptors for a given antagonist radiotracer such as [^{11}C]raclopride is $\text{BP}_{\text{ANTAGONIST}} = \text{BP}_{\text{HIGH}} + \text{BP}_{\text{LOW}} = R_{\text{HIGH}}/K_{\text{HIGH}} + R_{\text{LOW}}/K_{\text{LOW}}$ because antagonists do not distinguish between the D_2 HIGH and D_2 LOW configurations. In contrast the BP for an agonist such as dopamine is $\text{BP}_{\text{AGONIST}} = \text{BP}_{\text{HIGH}} = R_{\text{HIGH}}/K_{\text{HIGH}}$. Therefore a decrease in the proportion of sites configured in the high-affinity state ($\% R_{\text{HIGH}}$) in cocaine dependence would result in a smaller BP for dopamine and lead to a blunted response to amphetamine. To investigate this hypothesis that a lower $\% R_{\text{HIGH}}$ ($= \text{BP}_{\text{AGONIST}}/\text{BP}_{\text{ANTAGONIST}}$) for dopamine contributes to the blunted displacement of [^{11}C]raclopride after amphetamine in cocaine dependence, we measured $\text{D}_{2/3}$ antagonist and $\text{D}_{2/3}$ agonist BP in cocaine abusers and matched controls with the PET radiotracers [^{11}C]raclopride and [^{11}C]NPA.

MATERIALS AND METHODS

Human Subjects

Twenty subjects were enrolled in this study who were either cocaine dependent ($n=10$) or healthy comparison ($n=10$) subjects. The study was conducted under the University of Pittsburgh Institutional Review Board. All subjects provided written informed consent. Cocaine abusers were recruited through flyers displayed at local community centers, buses, and addiction medicine clinics. Study criteria for cocaine abusers were [1] males or females between 18 and 50 years old, of all ethnic and racial origins; [2] fulfill DSM-IV criteria for cocaine dependence as assessed by SCID; [3] a positive urine screen for cocaine; [4] no DSM IV Axis I disorder other than cocaine abuse or dependence including abuse or dependence to alcohol or other drugs (nicotine dependence was allowed); [5] no current (as

confirmed by urine drug screen at screening) use of opiates, cannabis, sedative-hypnotics, amphetamines, MDMA, and PCP [6] not currently on any prescription or over the counter medications; [7] no current or past severe medical or neurological illnesses (including glaucoma, seizure disorders) as assessed by a complete medical history and physical; [8] not currently pregnant; [9] no history of significant radioactivity exposure (nuclear medicine studies or occupational exposure); [10] no metallic objects in the body that are contraindicated for MRI. All eligible cocaine dependent subjects completed a minimum of twelve days of outpatient abstinence monitored with witnessed urine toxicology (all subjects underwent urine drug screens for cocaine and other recreational drugs three times/week for two consecutive weeks). Following the twelve-day outpatient abstinence period subjects were admitted to an inpatient research unit for two days prior to the PET scan. This combined outpatient and inpatient monitoring protocol ensured that all subjects were abstinent for a minimum of two weeks prior to the PET scan. Healthy control subjects with no past or present neurological or psychiatric illnesses including substance abuse (confirmed by urine drug screen both at screening and the day of the PET scan) underwent the PET scan as outpatients.

Imaging methods

MRI acquisition—Prior to PET imaging, a spoiled gradient recalled sequence (SPGR) magnetic resonance imaging (MRI) scan was obtained using a GE Signa 1.5 Tesla scanner for determination of regions of interest as previously described (Narendran et al., 2009b; Narendran et al., 2010)

PET acquisition—[¹¹C]raclopride and [¹¹C]NPA were synthesized using the methodology reported previously (Halldin et al., 1991; Hwang et al., 2000). PET imaging sessions were conducted with the ECAT EXACT HR+ camera. The [¹¹C]raclopride PET scan was always followed by the [¹¹C]NPA PET scan in both patients and controls. Following a 10 minute transmission scan, [¹¹C]raclopride or [¹¹C]NPA was injected intravenously over a 45 second period and emission data were collected in the 3D mode for 60 minutes consistent with previous studies for these radiotracers in humans (Narendran et al., 2009b; Narendran et al., 2010). Also, consistent with previous evaluations the maximum injected mass for [¹¹C]raclopride and [¹¹C]NPA were restricted to 6 µg and 2 µg (Mawlawi et al., 2001; Narendran et al., 2009a) to be at tracer dose, i.e., less than 5% receptor occupancy.

Input function measurement—Following radiotracer injection, arterial samples were collected manually approximately every 6s for the first two min and thereafter at longer intervals. A total of 35 samples were obtained per scan. Following centrifugation, plasma was collected in 200 µL aliquots and activities were counted in a gamma counter. To determine the plasma activity representing unmetabolized parent compound for [¹¹C]raclopride (collected at 8, 12, 20, 30, 40, 50 and 60 min) and [¹¹C]NPA (collected at 4, 8, 12, 16, 20, 40, 50) seven samples were further processed using high performance liquid chromatogram methods described previously for both the radiotracers (Mawlawi et al., 2001; Narendran et al., 2009a). For [¹¹C]raclopride, the seven measured parent fractions were fitted using a sum of two exponentials (Narendran et al., 2004). For [¹¹C]NPA the parent fractions were fitted to a Hill Plot model (Narendran et al., 2009a). The input function was then calculated as the product of total counts and interpolated parent fraction at each time point. The measured input function values were fitted to a sum of three exponentials from the time of peak plasma activity and the fitted values were used as the input to the kinetic analysis. The clearance of the parent compound (C_L expressed in liter/hour) was calculated as the ratio of the injected dose to the area under the curve of the input function (Abi-Dargham et al., 1994). The determination of the plasma free fraction (f_p) for both

[¹¹C]raclopride and [¹¹C]NPA were performed using ultrafiltration units (Gandelman et al., 1994).

Image analysis—All region drawing and image analysis was performed blind to the subject diagnosis with MEDx (Sensor Systems, Inc., Sterling, Virginia) and SPM2 (Statistical parametric mapping). The primary region of interest (ROI), the striatum was divided into five anatomical ROIs and three functional subdivisions using published criteria (Martinez et al., 2003). The three functional subdivisions of the striatum include the limbic striatum, LST (includes the ventral striatum VST), the associative striatum, AST (includes the precommisural caudate preDCA, precommisural putamen preDPU and postcommisural caudate postCA) and sensorimotor striatum, SMST (included the postcommisural putamen, postPU). The cerebellum was used as a reference region for both radiotracers (Narendran et al., 2010). Correction for head movement and co-registration of the PET data to the MR were done using previously described methods (Narendran et al., 2010).

Outcome measures—In this section we describe outcome variables using the consensus nomenclature for in vivo imaging of reversibly binding radioligands (Innis et al., 2007). Baseline D_{2/3} receptor availability for the antagonist and agonist radiotracers, [¹¹C]raclopride and [¹¹C]NPA were estimated using the PET outcome measure BP_{ND}, i.e., binding potential relative to non-displaceable uptake. As the concentration of D_{2/3} receptors in the cerebellum is relatively low compared to the striatum, we assumed that the V_T in the cerebellum (V_{T CER}) is largely representative of the free and nonspecifically bound radiotracer. In other words, we assumed that V_{T CER} is equal to the non-displaceable distribution volume (V_{ND}).

[¹¹C]raclopride and [¹¹C]NPA regional distribution volumes (V_T, mL of plasma/cm³ of tissue) were derived with kinetic analysis and the arterial input function. A one and two-tissue compartment model was used to describe the kinetics in the cerebellum and striatal subdivisions for [¹¹C]raclopride (Lammertsma et al., 1996). A two-tissue compartment model described the kinetics in both the cerebellum and striatal subdivisions for [¹¹C]NPA (Narendran et al., 2009a). Following, which the [¹¹C]raclopride or [¹¹C]NPA BP_{ND} was derived using the formula

$$BP_{ND} = \frac{V_T - V_{ND}}{V_{ND}} \quad \text{Eq. 1}$$

The primary outcome measure for the study, which was computed as the ratio of [¹¹C]NPA BP_{ND} to [¹¹C]raclopride BP_{ND} in cocaine abusers and healthy controls provided an estimate of the fraction of the D_{2HIGH} sites not occupied by dopamine at baseline (or available for endogenous competition), that is

$$\%R_{HIGH} \text{ available} = \frac{D_{2/3 \text{ HIGH}}}{D_{2/3 \text{ HIGH}} + D_{2/3 \text{ LOW}}} = \frac{[^{11}\text{C}]NPA \text{ BP}_{ND}}{[^{11}\text{C}]raclopride \text{ BP}_{ND}} \quad \text{Eq. 2}$$

Statistical analysis

Group differences in baseline scan parameters (such as injected dose, mass, plasma clearance, V_{ND}) and dependent variables ([¹¹C]raclopride BP_{ND}, [¹¹C]NPA BP_{ND} and [¹¹C]NPA/[¹¹C]raclopride ratio) were performed with unpaired t tests. A probability value of 0.05 was selected as significance level for all analyses.

RESULTS

Ten cocaine dependent subjects (3 women and 7 men, mean age 44 ± 8 years) and 10 healthy comparison subjects (3 women and 7 men, mean age 42 ± 8 years) were enrolled in this study. All twenty individuals completed the [^{11}C]raclopride scan, but only 9/10 individuals in both the patient and control groups completed the [^{11}C]NPA scans (n=1 radiochemistry failure; n=1 dropped out because of back spasms). Subjects were matched on smoking status (5 smokers/group) and ethnicity (cocaine abusers: 7 African American and 3 Caucasian; healthy controls: 4 African American and 6 Caucasian) as best as possible. The cocaine abusers reported smoking crack cocaine on average of 17 ± 8 years and were spending $\$728 \pm 650$ weekly.

Scan parameters

Critical PET scan parameters are listed in Table 1 (n=10 subjects/group for [^{11}C]raclopride and n=9 subjects/group for [^{11}C]NPA). The mean injected dose, specific activity at time of injection, and injected mass did not differ between the cocaine dependent and healthy comparison groups for both [^{11}C]raclopride and [^{11}C]NPA. In addition, no significant between-group differences were observed in [^{11}C]raclopride and [^{11}C]NPA rate of clearance from the plasma compartment, or cerebellum distribution volume (V_{ND})

Regional volumes

No significant between-group differences were found in ROI or reference region volumes (Table 2) suggesting lack of measurable volumetric changes in the human striatum after chronic cocaine abuse.

D_{2/3} receptor binding potential as measured using [^{11}C]raclopride and [^{11}C]NPA

The results of [^{11}C]raclopride BP_{ND} and [^{11}C]NPA BP_{ND} in cocaine abusers in the striatal subdivisions relative to healthy controls are shown in Table 3. Also shown in Table 3 are the effect sizes (d) for between group difference for [^{11}C]raclopride BP_{ND} and [^{11}C]NPA BP_{ND} in the striatal subdivisions.

Fraction of D_{2/3} high receptors available (% R_{HIGH} available)

No between-group differences were observed for the available % R_{HIGH} in the striatal subdivisions (Figure 1).

DISCUSSION

Previous PET studies performed with the D_{2/3} antagonist radiotracers [^{11}C]raclopride and [^{18}F]NMSP have consistently reported decreased D_{2/3} receptor availability in the striatum of cocaine abusers (11–38%) which persisted following abstinence (Martinez et al., 2004; Martinez et al., 2007; Volkow et al., 1993; Volkow et al., 1990; Volkow et al., 1997). The [^{11}C]raclopride results of this study were consistent with these previous data in suggesting both trend level and significant decreases in the subdivisions of the striatum in cocaine abusers relative to healthy controls (Table 3). Thus, the overall data on this topic are in agreement that there is less D_{2/3} antagonist (D_{2/3} HIGH and D_{2/3} LOW) binding in cocaine abusers relative to healthy comparison subjects. No previous in vitro postmortem or in vivo imaging studies have investigated and reported on the availability of the physiologically more relevant D_{2/3} agonist binding (as D_{2/3} HIGH, and not D₂ LOW are the sites accessed by dopamine) in cocaine dependent humans. We were interested in this particular issue for two reasons (1) it was critical to understand whether the blunted displacement of [^{11}C]raclopride after amphetamine in cocaine dependence can be attributed to post-synaptic factors, i.e., a lower fraction of D_{2/3} receptors configured in a state of high affinity for the agonists and (2)

previous reports in rodents suggest that chronic exposure to psychostimulant drugs such as cocaine and amphetamine lead to a higher (~ 150%), not lower fraction of D_{2/3} HIGH receptors (Briand et al., 2008; Seeman, 2009; Seeman et al., 2007; Seeman et al., 2002), which was contradictory to our predicted hypothesis. Thus, in this human imaging study, we investigated both the D_{2/3} antagonist and D_{2/3} agonist binding potential in a group of subjects who regularly abused cocaine for nearly two decades and found neither an increase nor a decrease in the available % R_{HIGH} relative to healthy comparison subjects. This particular observation was a consequence of the lack of difference in D_{2/3} agonist BP_{ND} rather than D_{2/3} antagonist BP_{ND} as shown in Table 3. Furthermore, as the effect size for [¹¹C]NPA in the striatal subdivisions was relatively small (0.06 to 0.47; Table 3), we found no reason to continue with the study. For example, at the observed effect size of 0.86 in the striatum for [¹¹C]raclopride, the study would have required a sample size of 22 subjects/group to detect a significant difference between cocaine abusers and controls (p < 0.05; power 0.8). In contrast, at the observed effect size of only 0.22 in the striatum for [¹¹C]NPA, the same clinical study would have required us to recruit and scan 325 subjects/group to detect a between-group difference.

One reason for the failure to observe an increase in the available % R_{HIGH} in chronic cocaine exposed humans may be related to the differences in baseline dopamine levels between the control and cocaine groups that impact the in vivo PET measures in humans but not necessarily the in vitro binding measures in rodents (Martinez et al., 2009). Nevertheless, a more likely explanation is that chronic cocaine exposure leads to paradoxical changes in dopamine transmission and associated parameters (such as D_{2/3} receptors, D_{2/3} HIGH receptors, dopamine transporters, vesicular monoamine transporter, type 2, etc.) in rodents and humans for unclear reasons as reviewed in (Narendran and Martinez, 2008). Future [¹¹C]NPA PET studies following the depletion of synaptic dopamine with alpha-methyl-para-tyrosine (AMPT) in cocaine abusers and micro-PET studies in rodents exposed to chronic cocaine are necessary to clarify these issues. Another factor that needs to be considered in the interpretation of the available % R_{HIGH} that was arrived at via comparison of the agonist [¹¹C]NPA and antagonist [¹¹C]raclopride in this study is the difference in D₃/D₂ affinity ratio between these radiotracers. For example, a decrease or increase in D₃ receptor availability in cocaine dependent patients compared to controls may have masked an abnormally higher or lower % R_{HIGH} as [¹¹C]NPA demonstrates modest preference for D₃ over D₂ receptors compared to [¹¹C]raclopride (Narendran et al., 2009b). Future studies with the D₃-receptor preferring agonist radiotracer [¹¹C]PHNO and a selective D₃ antagonist drug in cocaine dependence are necessary to investigate this issue (Searle et al., 2010). Finally, recent PET imaging studies with both D_{2/3} antagonist (such as [¹¹C]raclopride and [¹¹C]FLB 457) and agonist radiotracers (such as [¹¹C]NPA and [¹¹C]PHNO) suggest a small but significant fraction of D_{2/3} specific binding in the cerebellum (Narendran et al., 2004; Narendran et al., 2011; Narendran et al., 2010; Rabiner et al., 2009; Searle et al., 2010), the region that is typically used as an estimate of free plus non-specific binding for the derivation of BP_{ND}. Thus, one cannot discount the possibility that differences in the fraction of D_{2/3} specific binding between the agonist and antagonist radiotracer could have biased the % R_{HIGH} measured in this clinical study as we assumed that there is no specific binding in the cerebellum for both these radiotracers. In summary, despite the limitations of the imaging paradigm used we found no evidence for abnormal D_{2/3} HIGH binding in cocaine abusers relative to healthy controls, thereby raising questions as to whether it plays a critical role in cocaine dependence in humans.

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Figure 1. Shows no significant difference between controls (white bars) and cocaine abusers (black bars) in the available fraction of D_{2/3} high receptors (% R_{HIGH}) in the striatal subdivisions.

Scan parameters

Table 1

Scan Parameter	¹¹ C]raclopride scans (n=10/group)		¹¹ C]NPA scans (n=9/group)	
	Controls	Cocaine abusers	Controls	Cocaine abusers
Injected dose (mCi)	10.3 ± 0.9	10.5 ± 0.3	9.8 ± 1.4	10.3 ± 1.0
Specific activity (Ci/mmoles)	2139 ± 601	2063 ± 408	2416 ± 875	2724 ± 1220
Injected Mass (µg)	1.9 ± 0.9	1.9 ± 0.5	1.3 ± 0.4	1.3 ± 0.4
Plasma Free Fraction (f _p , %)	11 ± 2	12 ± 3	10 ± 2	12 ± 3
Clearance (L/h)	22.8 ± 6.3	23.0 ± 5.9	139.2 ± 41.9	113.4 ± 29.4
Cerebellum V _{ND} (mL cm ⁻³)	0.43 ± 0.06	0.45 ± 0.07	3.35 ± 0.87	3.50 ± 0.92

Comparisons between controls and cocaine abusers for both scan parameters all p > 0.05, two-tailed, unpaired t-test

Table 2

Regional Volumes (denoted in mm3)

Functional subdivision	Anatomical subdivision	Controls	Cocaine abusers	p-value
LST	VST	1786 ± 287	1729 ± 315	0.68
AST		7543 ± 585	7580 ± 678	0.90
	Pre-DCA	3333 ± 404	3534 ± 425	0.29
	Post-CA	2019 ± 290	1916 ± 501	0.58
	Pre-DPU	2192 ± 417	2130 ± 505	0.77
SMST	Post-PU	4825 ± 954	4894 ± 558	0.85
Striatum		14155 ± 1440	14203 ± 845	0.93

Values are Mean ± SD, n = 10 per group
LST-limbic striatum; AST-associative striatum; SMST-sensorimotor striatum; STR-Striatum; VST-ventral striatum; pre-DCA-precommissural caudate; post-CA postcommissural caudate; pre-DPU-precommissural putamen; post-PU-postcommissural putamen
p-values are from two-tailed, unpaired t tests

Table 3

Regional [¹¹C]raclopride and [¹¹C]NPA binding potential (BP_{ND}) in healthy controls and chronic cocaine abusers

Striatal subdivision		[¹¹ C]raclopride scans (n = 10/group)			[¹¹ C]NPA scans (n=9/group)		
Functional	Anatomical	Controls	Cocaine abusers	Effect size	Controls	Cocaine abusers	Effect size
LST	VST	2.38 ± 0.26	2.24 ± 0.29	0.53	1.02 ± 0.16	1.01 ± 0.19	0.07
AST		2.36 ± 0.21	2.14 ± 0.23 *	1.06	0.86 ± 0.16	0.81 ± 0.16	0.35
	Pre-DCA	2.38 ± 0.20	2.12 ± 0.25 *	1.22	0.85 ± 0.16	0.77 ± 0.18	0.47
	Post-CA	1.76 ± 0.22	1.63 ± 0.32	0.51	0.59 ± 0.17	0.57 ± 0.19	0.12
	Pre-DPU	2.86 ± 0.23	2.62 ± 0.23 *	1.13	1.14 ± 0.20	1.05 ± 0.19	0.47
SMST	Post-PU	3.02 ± 0.26	2.81 ± 0.35	0.69	1.22 ± 0.18	1.21 ± 0.19	0.06
Striatum		2.58 ± 0.21	2.39 ± 0.26 †	0.86	1.00 ± 0.17	0.97 ± 0.17	0.22

LST-limbic striatum; AST-associative striatum; SMST-sensorimotor striatum; STR-Striatum; VST-ventral striatum; pre-DCA-precommisural caudate; post-CA postcommisural caudate; pre-DPU-precommisural putamen; post-PU-postcommisural putamen

* p < 0.05,

† p < 0.1 on two-tailed, unpaired t-test;

Effect size is Cohen's d derived using pooled standard deviation for two independent samples