Neurobiology of Disease

Nigrostriatal and Mesolimbic D$_{2/3}$ Receptor Expression in Parkinson's Disease Patients with Compulsive Reward-Driven Behaviors

Adam J. Stark,[1] Christopher T. Smith,[2] Ya-Chen Lin,[3,4] Kalen J. Petersen,[1] Paula Trujillo,[1] Nelleke C. van Wouwe,[1] Hakmook Kang,[3,4] Manus J. Donahue,[1,5,6] Robert M. Kessler,[7] David H. Zald,[2,6] and Daniel O. Claassen[1]

[1]Neurology, Vanderbilt University Medical Center, Nashville, Tennessee 37232, [2]Psychology, Vanderbilt University, Nashville, Tennessee 37240, [3]Biostatistics, Vanderbilt University Medical Center, Nashville, Tennessee 37203, [4]Center for Quantitative Sciences, Vanderbilt University Medical Center, Nashville, Tennessee 37232, [5]Radiology and Radiological Sciences, Vanderbilt University Medical Center, Nashville, Tennessee 37232, [6]Psychiatry, Vanderbilt University Medical Center, Nashville, Tennessee 37212, and [7]Radiology, University of Alabama at Birmingham School of Medicine, Birmingham, Alabama 35233

The nigrostriatal and mesocorticolimbic dopamine networks regulate reward-driven behavior. Regional alterations to mesolimbic dopamine D$_{2/3}$ receptor expression are described in drug-seeking and addiction disorders. Parkinson's disease (PD) patients are frequently prescribed D$_2$-like dopamine agonist (DAgonist) therapy for motor symptoms, yet a proportion develop clinically significant behavioral addictions characterized by impulsive and compulsive behaviors (ICBs). Until now, changes in D$_{2/3}$ receptor binding in both striatal and extrastriatal regions have not been concurrently quantified in this population. We identified 35 human PD patients (both male and female) receiving DAgonist therapy, with ($n = 17$) and without ($n = 18$) ICBs, matched for age, disease duration, disease severity, and dose of dopamine therapy. In the off-dopamine state, all completed PET imaging with [^{18}F]fallypride, a high affinity D$_2$-like receptor ligand that can measure striatal and extrastriatal D$_{2/3}$ nondisplaceable binding potential (BP$_{ND}$). Striatal differences between ICB+/ICB− patients localized to the ventral striatum and putamen, where ICB+ subjects had reduced BP$_{ND}$. In this group, self-reported severity of ICB symptoms positively correlated with midbrain D$_{2/3}$ receptor BP$_{ND}$. Group differences in regional D$_{2/3}$ BP$_{ND}$ relationships were also notable: ICB+ (but not ICB−) patients expressed positive correlations between midbrain and caudate, putamen, globus pallidus, and amygdala BP$_{ND}$s. These findings support the hypothesis that compulsive behaviors in PD are associated with reduced ventral and dorsal striatal D$_{2/3}$ expression, similar to changes in comparable behavioral disorders. The data also suggest that relatively preserved ventral midbrain dopaminergic projections throughout nigrostriatal and mesolimbic networks are characteristic of ICB+ patients, and may account for differential DAgonist therapeutic response.

Key words: dopamine; impulse control disorder; impulsive compulsive behaviors; mesocorticolimbic; Parkinson's disease; positron emission tomography

---

Significance Statement

The biologic determinants of compulsive reward-based behaviors have broad clinical relevance, from addiction to neurodegenerative disorders. Here, we address biomolecular distinctions in Parkinson's disease patients with impulsive compulsive behaviors (ICBs). This is the first study to image a large cohort of ICB+ patients using positron emission tomography with [18F]fallypride, allowing quantification of D$_{2/3}$ receptors throughout the mesocorticolimbic network. We demonstrate widespread differences in dopaminergic networks, including (1) D2-like receptor distinctions in the ventral striatum and putamen, and (2) a preservation of widespread dopaminergic projections emerging from the midbrain, which is associated with the severity of compulsive behaviors. This clearly illustrates the roles of D$_{2/3}$ receptors and medication effects in maladaptive behaviors, and localizes them specifically to nigrostriatal and extrastriatal regions.

Introduction

Altered dopaminergic signaling in the nigrostriatal and mesolimbic circuits is the focus of many investigations of the pathophysiologic basis of addictive behaviors, such as drug seeking, compulsive gambling, and binge eating (Haber and Knutson, 2010). Within these networks, dopamine release from ventral midbrain projections is implicated in both the development and maintenance of addiction (Pettit et al., 1984; Yin et al., 2004). Reductions in striatal dopamine D_2-like (D_2/D_3) receptor binding are consistently observed in patients with alcohol, cocaine, methamphetamine, opiate, and nicotine abuse (Trifilieff and Martinez, 2014). Moreover, ventral striatal decreases in $D_{2/3}$ receptor expression are associated with impulsive behaviors, a risk factor for the development of addiction (Dalley et al., 2007), whereas decrements in dorsal striatal $D_{2/3}$ receptor levels are linked to established patterns of addictive behavior (Nader et al., 2006). $D_{2/3}$ receptors are also important in the ventral midbrain, where decreased $D_{2/3}$ (auto)receptor binding is associated with greater impulsivity in healthy humans (Buckholtz et al., 2010).

Pramipexole and ropinirole, D_3 preferring $D_{2/3}$ agonists (DAgonists), produce improvements in the motor symptoms of Parkinson's disease (PD; Piercey, 1998). However, these $D_{2/3}$-preferring medications can also induce impulsive and compulsive behaviors (ICBs), distinguished by an aberrant focus on reward-driven activities including gambling, shopping, sex, eating, and hobbies (Voon et al., 2007), as well as heightened novelty seeking (Voon et al., 2011). The causal nature of this effect is emphasized by the clinical finding that discontinuation or reduction of DAgonist in ICB+ individuals can result in symptom improvement (Claassen et al., 2013). Due to the receptor-level specificity of DAgonist compounds, investigation of mesocorticolimbic $D_{2/3}$ levels in PD patients with ICB symptoms provides an opportunity to examine the role of $D_{2/3}$ receptors in maladaptive reward-seeking behaviors in PD patients.

Dopaminergic projections from the ventral midbrain to striatal, limbic, and cortical regions in the brain reward circuit are critical for reward network function (Haber and Knutson, 2010). A small number of PET studies using [11C]raclopride (Steeves et al., 2009) and [11C]-(+)-PHNO (Payer et al., 2015) have reported reduced baseline $D_{2/3}$ receptor levels in the ventral striatum in ICB+ patients; this finding may be due to either decreased ventral striatal $D_{2/3}$ receptor expression, or increased ventral striatal extracellular dopamine levels, which could in theory reduce the number of available $D_{2/3}$ receptors. Due to its moderate affinity for the $D_{2/3}$ receptor, [11C]raclopride provides an estimate of striatal $D_{2/3}$ receptor levels but has not typically been used to estimate extrastriatal $D_{2/3}$. [11C]-(+)-PHNO, a higher affinity D_3-preferring $D_{2/3}$ agonist radioligand, can be used to estimate $D_{2/3}$ receptor levels in striatal and select extrastriatal regions (a relatively low signal-to-noise ratio in most cortical regions re-

stricts extrastriatal use; Hall et al., 1989; Egerton et al., 2010). One [11C]FLB-457 study noted increased binding in the anterior cingulate cortex and midbrain of ICB+ patients during a control task and gambling task, respectively (Ray et al., 2012). However, although [11C]FLB-457 can be used to estimate extrastriatal $D_{2/3}$ levels, it does not provide accurate binding estimates in the striatum (Farde et al., 1997). To date, no single study of ICBs in PD patients has concurrently evaluated $D_{2/3}$ receptor levels in the midbrain, striatal, limbic, and cortical regions of the reward circuit, or the relationships between regional $D_{2/3}$ mediated neurotransmission in this network.

An approach capable of concurrently evaluating striatal and extrastriatal areas could provide a greater understanding regarding the interaction between important components of the reward network (including the ventral midbrain, striatum, and the orbitofrontal, prefrontal, and anterior cingulate cortices). [18F]fallypride is a high-affinity $D_{2/3}$ radioligand that can provide accurate estimates of binding in both striatal and extrastriatal regions, allowing for quantification of dopamine $D_{2/3}$ receptor levels [i.e., nondisplaceable binding potential (BP_{ND})] throughout the mesocorticolimbic network (Kessler et al., 2000; Mukherjee et al., 2002). We assessed a cohort of PD patients (with and without ICB and matched for disease severity) to examine the localization of $D_{2/3}$ BP_{ND} differences, thus determining the relationship between $D_{2/3}$ receptor levels and self-reported severity of reward-based behaviors. We hypothesized that $D_{2/3}$ BP_{ND} reductions in ICB+ patients would localize to the ventral striatum, with distinctions in the midbrain and anterior cingulate cortex (Steeves et al., 2009; Ray et al., 2012; Payer et al., 2015). Finally, in an effort to examine putative differences in the reward-network between groups and to better understand the interaction between the dopaminergic system in the midbrain and in terminal field locations, we evaluated the relationship between midbrain $D_{2/3}$ receptor expression and receptor expression throughout the nigrostriatal and mesolimbic networks.

Materials and Methods

Participants. Subjects ($n = 35$; sex = 11 F/24 M; age = 61.8 ± 8.5 years) were recruited from the Movement Disorders Clinic at Vanderbilt University Medical Center, and provided written, informed consent in accordance with the Vanderbilt Institutional Review Board. We screened patients diagnosed with idiopathic PD (meeting UK Brain Bank criteria), who were taking DAgonist medication (including pramipexole, ropinirole, and rotigotine) with or without concomitant levodopa therapy. A clinical determination of active ICB symptoms was based on behavioral interview with the patient care partner (Mestre et al., 2013). ICBs were defined as clinically problematic compulsive behaviors with onset following DAgonist administration according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association, 2000), with specific attention toward the previously reported categories of compulsive shopping, eating (with modified DSM-IV-TR criteria for binge-eating disorder including overeating as well as episodes of binge-eating), hypersexuality, gambling, and hobbyism (Voon et al., 2007; Weintraub et al., 2012). Before the interview, participants completed the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS). As per the methods of Weintraub et al. (2009), answers to QUIP-RS items could be used to guide the clinical interview, but were not used to singularly define an explicit cutoff mark in the diagnosis of ICB. As a result, certain patients within the ICB− group may have expressed an increased proclivity toward shopping, eating, sexual behavior, gambling, or hobbyism relative to others in the same group; however, these behaviors were not deemed clinically problematic in these subjects. Although previous investigations of ICB have often concentrated on compulsive gambling, recruitment efforts were

not limited to a single subcategory, and reflected the distribution in the local population.

Patients completed the self-reported Movement Disorders Society-United Parkinson's Disease Rating Scale (MDS-UPDRS) part II (an assessment of the impact of PD on activities of daily living; Goetz et al., 2008; Weintraub et al., 2012). Cognitive impairment was assessed with the Montreal Cognitive Assessment (MoCA), and premorbid intelligence screened using the American version of the National Adult Reading Test (AMNART; Grober and Sliwinski, 1991; Nasreddine et al., 2005). Depression symptoms were screened using the Center for Epidemiological Studies Depression Scale Revised (CESD-R; Radloff, 1977). Patients were excluded if (1) they had an implanted deep brain stimulator; (2) were prescribed psychoactive medications that could alter dopamine receptor availability; (3) were demented, or suffered from comorbid neuropsychiatric, cerebrovascular, or cardiovascular disease; (4) scored <22 in the MoCA (to exclude possible cognitive impairment); or (5) had contraindications for MRI or PET. Levodopa and DAgonist dosages were converted to levodopa-equivalent dose using accepted criteria (Tomlinson et al., 2010). From the pool of individuals who had completed the initial screening visit, subjects were selectively enrolled in the imaging portion of the study based on the determination of ICB status and matched by UPDRS-II severity, to ensure size-matched groups. From the 90 PD patients who had completed the initial screening and behavioral interview, 17 ICB+ and 18 ICB− patients were ultimately included in the study.

The structural MRI and [18F]fallypride PET scan were completed in the off-dopamine (levodopa and DAgonist) state. Of note, in the Off condition, patients refrained from all dopaminergic medications (washout was at least 40 h for DAgonist and 16 h for Levodopa) before assessments, as this period is sufficient to eliminate DAgonist effects while minimizing patient discomfort (the half-life of levodopa and immediate-release DAgonists are ~1.5 and 6 h respectively; Fabbrini et al., 1987; Tompson and Oliver-Willwong, 2009).

Magnetic resonance imaging. Structural MRI scans were completed before PET scans. Patients were scanned at 3.0T (Philips) using body coil transmission and 8-channel SENSE reception. All underwent a multimodal imaging protocol consisting of the following scans: (1) T_1-weighted (MPRAGE; spatial resolution = $1 \times 1 \times 1$ mm^3; TR/TE = 8.9/4.6 ms), and (2) T_2-weighted FLAIR (spatial resolution = $1 \times 1 \times 1$ mm^3; TR/TE = 4000/120 ms).

Fallypride PET data acquisition. [18F]fallypride [(S)-N-[(1-allyl-2-pyrrolidinyl)methyl]-5-(3[18F]fluoropropyl)-2,3-dimethoxybenzamide] was synthesized in the radiochemistry laboratory adjacent to the PET unit, in alignment with the synthesis and quality control procedures outlined by U.S. Food and Drug Administration Investigational New Drug Applicaiton 47245 and 120035. Data were collected on a GE Discovery STE PET/CT scanner. Serial scan acquisition began simultaneously with a 5.0 mCi slow bolus injection of [18F]fallypride (specific activity >3000 Ci/mmol). Arterial blood sampling was not performed. CT scans were collected before each of the three emissions scans for the purpose of attenuation correction. Together, the scans lasted ~3.5 h with two breaks of 15–20 min (beginning ~70 and 135 min after the beginning of the scan, respectively) included for patient comfort

Fallypride PET data processing. Following attenuation correction and decay correction, serial PET scans were coregistered with each other using the Statistical Parametric Mapping software (SPM8, Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm/software/) to correct for motion across scanning periods with the last dynamic image of the first series as the reference image. The mean PET image produced by realignment was then coregistered to the subject's corresponding high-resolution T1 MRI image using FSL's FLIRT with 6 degrees of freedom (FSL v5.0.2.1, FMRIB). Regions-of-interest (ROIs), including the caudate, putamen, globus pallidus, ventral striatum, amygdala, midbrain, thalamus, and cerebellum, were manually segmented on the T_1-weighted MRI scans by a neuroradiologist (R.M.K.) and neurologist (D.O.C.) experienced in PET and MRI data analysis, and transferred to the coregistered PET images through the FLIRT FSL transformation matrix. These regions were selected due to their importance in the nigrostriatal and mesolimbic circuits (Haber and Knutson, 2010), implicating them as areas

where ICB-related differences in dopaminergic signaling could be evident. Manual segmentation methods followed established anatomical criteria, capturing the central portion of the selected region to gather the most representative sample and avoid partial volume effects, and were applied so as to avoid the potential confound of intersubject structural variability.

The caudate, putamen, and globus pallidus were manually drawn on axial slices ~2–12 mm above the ACPC line. The ventral striatum was segmented on coronal slices with the criteria of Mawlawi et al. (2001). The amygdala can be identified on axial slices 6–20 mm below the ACPC line, 12–28 mm lateral to the midline, and 2–12 mm behind the plane of the anterior commissure (Schaltenbrand and Wahren, 1998). To avoid contamination by signals from striatal regions with high BP$_{ND}$ because of partial volume averaging, amygdala ROIs were defined 10–16 mm beneath the ACPC plane. The midbrain was drawn on axial slices in the ventral midbrain 9–14 mm below the ACPC line, and the thalamus was segmented 2–12 mm above the ACPC line (Schaltenbrand and Wahren, 1998). The cerebellar ROI was drawn centrally within the structure to avoid partial voluming of midbrain or cortical signal, and contained an approximately equal distribution of gray and white matter. To account for potentially divergent structure size between groups, ROI volumes were collected and preserved for statistical analysis. For voxelwise analyses, subject-space BP$_{ND}$ images were registered to Montreal Neurological Institute space using FSL's FNIRT (FSL v5.0.2.1, FMRIB).

Regional DA D$_{2/3}$ levels were estimated using the simplified reference region method (Lammertsma et al., 1996) performed in PMOD software (PMOD Technologies) to measure [18F]fallypride binding potential (BP$_{ND}$; the ratio of specifically bound [18F]fallypride to its nondisplaceable concentration as defined under equilibrium conditions. Voxelwise estimates were generated using a published basis function fitting approach (Gunn et al., 1997) conducted in the PXMOD module of PMOD. The rate constants were specified by the user as k_{2a} minimum = 0.006 min^{-1} and k_{2a} maximum = 0.6 min^{-1}. The cerebellum was selected as the reference region due to its relatively limited expression of D$_{2/3}$ receptors in the cerebellum (Camps et al., 1989), it was selected as the reference region (Kessler et al., 2009). ROI BP$_{ND}$ values were determined by evaluating the average BP$_{ND}$ within an ROI overlaid on the subject-space voxelwise map, which was generated in the previous PET processing steps.

Experimental design and statistical analysis. Group differences between ICB+ (n = 17; sex = 11 M/6 F) and ICB− subjects (n = 18; sex = 13 M/5 F) in demographic and clinical parameters, ROI volume, and the proportion of levodopa daily dose (LEDD) accounted for by DAgonists were evaluated using Mann–Whitney U tests. We also examined whether scores on the QUIP-RS were significantly correlated with LEDD for either group. Sex and DAgonist regimen differences were evaluated with a χ^2 test. To test the hypothesis that ICB+ patients have different dopamine D$_{2/3}$ receptor expression in striatal and extrastriatal areas, mean group regional [18F]fallypride BP$_{ND}$ was analyzed via a general linear regression model (GLM), where within-ROI BP$_{ND}$ was the dependent variable and ICB status was the primary independent variable. Age was included as a covariate, due to previous evidence of an effect of age on D$_{2/3}$ receptor status (Mukherjee et al., 2002). UPDRS-II was also specified as a covariate, as PD severity has been shown to influence D$_{2/3}$ binding (Kaasinen et al., 2000). UPDRS-II was selected because of past indications that it accurately tracks disease severity, and the fact that measurements of short term motor symptoms fluctuate and are highly sensitive to medication status (Harrison et al., 2009). Although study design led to equivalent age and UPDRS-II values between groups, these factors were included as covariates to account for residual confounding effects. A separate model was used to test mean differences in each ROI. A voxelwise analysis completed using SPM8 assessed group differences in D$_{2/3}$ BP$_{ND}$ across cortical regions, given that this was an exploratory analysis that sought to capture distinctions in subregions of larger structures. Age was included as a covariate in this analysis. Subcortical areas were excluded through the use of an explicit cortical mask in the voxelwise analysis, to improve statistical power and to ensure that the considerable difference in D$_{2/3}$ density between the basal ganglia and cortex did not serve as a confounding factor (Joyce et al., 1991). Significance criteria

Table 1. Demographic and clinical evaluation from the two participant groups

Variables	PD ICB−	PD ICB+	p
N	18	17	
Sex, M/F	13/5	11/6	0.72
Age, years	62.7 ± 10.1	60.9 ± 6.6	0.17
Disease duration, years	6.1 ± 4.5	5.7 ± 3.2	0.99
CES-D	15.1 ± 7.2	16.3 ± 10.3	0.89
MDS-UPDRS Part II	23.2 ± 7.7	20.3 ± 7.7	0.19
QUIP-RS total	18.1 ± 11.9	36.5 ± 10.1	<0.0001*
ICB symptom distribution (based on semistructured behavioral interview)			
Hobbyism	n/a	12/17	
Eating	n/a	11/17	
Sex	n/a	11/17	
Shopping	n/a	4/17	
Gambling	n/a	0/17	
Laterality score (− = left worse, + = right worse)	−3.1 ± 9.6	−1.8 ± 12.0	0.74
Dopamine replacement therapy			
Total LEDD, mg/d	693.9 ± 406.3	673.8 ± 440.0	0.69
Agonist single-dose equivalent, mg/d	135.4 ± 76.4	103.9 ± 65.1	0.19

Data are shown as mean ± SD.

*Indicates uncorrected $p < 0.05$.

No significant group difference observed in the type of DAgonist prescribed (Table 1-3 available at https://doi.org/10.1523/JNEUROSCI.3082-17.2018.t1-3) or the fraction of LEDD accounted for by DAgonist as opposed to levodopa ($p = 0.99$; Table 1-1 available at https://doi.org/10.1523/JNEUROSCI.3082-17.2018.t1-1). PET acquisition parameters were similar (Table 1-2 available at https://doi.org/10.1523/JNEUROSCI.3082-17.2018.t1-2).

PD ICB+, PD with symptoms consistent with ICB; PD ICB−, PD without ICBs.

consisted of an uncorrected $p < 0.001$, and multiple-comparisons correction was accomplished by controlling cluster-level False discovery rate (FDR) at 0.05.

A secondary analysis investigated associations between $D_{2/3}$ receptor binding in each ROI and scores on the QUIP-RS, a clinical measure of ICB severity. A partial Pearson's correlation was used to examine these relationships, specifying age and UPDRS-II score as covariates. As an exploratory method, we examined whether the relationship between midbrain BP_{ND} and BP_{ND} in other regions differed in ICB+ patients. Because the midbrain provides key dopaminergic inputs to the nigrostriatal and mesolimbic tracts, and midbrain binding potential significantly correlates with binding potential in other components of the reward circuit (Zald et al., 2010), this analysis served to probe potential differences in dopaminergic network integrity. To accomplish this, we used a linear regression model including midbrain BP_{ND} as the dependent variable, age and UPDRS-II scores as covariates, and ICB status, BP_{ND} of the other six ROIs, and the interaction between ICB status and BP_{ND} of the other six ROIs (caudate, putamen, ventral striatum, globus pallidus, thalamus, and amygdala) as independent variables. To avoid overfitting, the first principal component of age and UPDRS-II was used as a single covariate. A separate model was used for the caudate, putamen, ventral striatum, globus pallidus, and thalamus, where the variables of non-midbrain ROI BP_{ND} and interaction between group status and non-midbrain ROI BP_{ND} were present for one ROI at a time in a pairwise manner. For ROIs where a significant interaction was observed, midbrain-ROI correlations were examined using a Pearson's partial correlation test with age and UPDRS-II as covariates. FDR was controlled at 0.1 to correct for multiple comparisons in the ROI-based GLM and correlation analyses, and all reported results survived this correction threshold. All analyses were performed using SPSS Statistics 24 (IBM) and R (R Foundation for Statistical Computing, 2016).

Results
Demographic and clinical features
Demographic and clinical features for patients meeting the ICB inclusion criteria ($n = 17$) and those without ICBs ($n = 18$) are presented in Table 1. QUIP-RS scores were significantly greater in ICB+ patients after correction for multiple comparisons ($p <$

0.0001). DAgonist and levodopa equivalent daily doses in the On condition were comparable across groups. No significant group difference was observed in the type of DAgonist prescribed (Table 1-3 available at https://doi.org/10.1523/JNEUROSCI.3082-17.2018.t1-3) or the fraction of LEDD accounted for by DAgonist as opposed to levodopa ($p = 0.99$), and PET acquisition parameters were similar (Tables 1-1 available at https://doi.org/10.1523/JNEUROSCI.3082-17.2018.t1-1 and 1-2 available at https://doi.org/10.1523/JNEUROSCI.3082-17.2018.t1-2, respectively). LEDD did not significantly correlate with QUIP-RS scores for either group. Hypersexuality, compulsive eating, compulsive shopping, and hobbyism were all included among the expressed ICB subcategories; no subjects were identified as participating in pathological gambling.

Mean regional fallypride binding potential
When we examined group differences in mean regional BP_{ND} using a GLM with age and UPDRS-II specified as covariates, [^{18}F]fallypride binding was significantly lower in the bilateral ventral striatum (unstandardized $B = 1.99$; df = 31; $p = 0.023$) and putamen (unstandardized $B = 2.43$; df = 31; $p = 0.026$) of ICB+ ($n = 17$) compared with the ICB− ($n = 18$) patients, surviving FDR correction. There were no significant ROI volume differences between the ICB+ and ICB− groups; therefore ROI size was not considered as a confounding factor. The voxelwise analysis did not reveal any significant clusters in cortical regions. Figure 1 presents the age- and UPDRSII-adjusted mean regional BP_{ND}s for the ventral striatum and putamen. Visualization of the segmentation protocol for all regions is displayed in Fig. 1-1 (available at https://doi.org/10.1523/JNEUROSCI.3082-17.2018.f1-1) alongside a full description of ROI volumes and within-ROI BP_{ND} values (Figs. 1-2 available at https://doi.org/10.1523/JNEUROSCI.3082-17.2018.f1-2 and 1-3 available at https://doi.org/10.1523/JNEUROSCI.3082-17.2018.f1-3, respectively).

Relationships between regional [^{18}F]fallypride BP_{ND}s and clinical measures
When all regional BP_{ND} values were compared with QUIP-RS scores, a significant positive correlation between midbrain BP_{ND} and QUIP-RS scores was observed for the ICB+ group ($r = 0.633$; df = 13; $p = 0.011$), surviving FDR correction. This association was not present in the ICB− group ($r = -0.129$; df = 13; $p = 0.634$). To better define whether the relationship between QUIP-RS and midbrain BP_{ND} was significantly different between groups, a post hoc analysis was conducted using a linear regression model including midbrain BP_{ND} as the dependent variable, the first principal component of age and UPDRS-II score as a covariate, and ICB status, QUIP-RS score, and the interaction between ICB status and QUIP-RS score as independent variables. A significant interaction term was present for this analysis ($p = 0.009$). For both groups, no significant correlation was observed between BP_{ND} and QUIP-RS in any other ROI (see Fig. 2-1 available at https://doi.org/10.1523/JNEUROSCI.3082-17.2018.f2-1 for a full listing of correlation coefficients). Figure 2 displays a scatterplot of BP_{ND} versus QUIP-RS and a representative segmentation for the midbrain.

Regional [^{18}F]fallypride BP_{ND} relationships
When we examined the relationship between binding in the midbrain and binding in other reward-related regions (df = 30), significant group differences in the midbrain-ROI correlation (FDR corrected; defined by significant interaction term) were

observed in the caudate (unstandardized $B = -0.71$; $p = 0.031$), putamen (unstandardized $B = -0.79$; $p = 0.024$), globus pallidus (unstandardized $B = -0.65$; $p = 0.044$), and amygdala (unstandardized $B = -0.60$; $p = 0.047$). The ICB+ group expressed significant positive BP_{ND} correlations (df = 13) between the midbrain BP_{ND} and caudate ($r = 0.706$, $p = 0.003$), putamen ($r = 0.589$, $p = 0.021$), globus pallidus ($r = 0.668$, $p = 0.007$), and amygdala ($r = 0.709$, $p = 0.003$) BP_{ND}s. There were no significant correlations (df = 14) between BP_{ND}s in in these regions and the midbrain for the ICB− group (caudate: $r = 0.001$, $p = 0.99$; putamen: $r = -0.126$, $p = 0.643$; globus pallidus: $r = 0.262$, $p = 0.328$; amygdala: $r = 0.243$, $p = 0.364$). Figure 3 presents scatterplots of midbrain BP_{ND} versus BP_{ND} in the regions where a significant interaction term was observed for the ICB+ and ICB− groups. Scatterplots in ROIs where no significant difference was observed are presented in Fig. 3-1 (available at https://doi.org/10.1523/JNEUROSCI.3082-17.2018.f3-1).

Discussion

Because the clinical phenotype of compulsive participation in reward-based behaviors is causally linked to DAgonist use, investigating how $D_{2/3}$ receptors relate to behavioral symptoms could prove useful to the broader study of dopamine and compulsive behaviors. Our main finding replicates and extends previous work in the neurobiology of addiction, where PD patients with ICB have reduced $D_{2/3}$ BP_{ND}, localizing to the ventral striatum and putamen. In these patients, we observe a significant positive relationship between midbrain $D_{2/3}$ BP_{ND} levels and the severity of reward-seeking behavior (QUIP-RS), and positive correlations between $D_{2/3}$ receptor levels in the midbrain, striatum, and amygdala. These results indicate that $D_{2/3}$ receptor status in PD patients may play a key role in the manifestation of DAgonist-induced ICBs. The precise mechanism of this influence may include premorbid, PD-related, or treatment-related changes to $D_{2/3}$ receptor number and function, ultimately influencing how a patient can regulate reward-based behavior.

Ventral striatal dopamine and ICB status

The ventral striatum is a crucial structure to reinforcement learning in the initial stages of addiction (O'Doherty et al., 2004; Everitt and Robbins, 2005). Ventral striatal dopamine transmission mediates the maintenance of both the psychostimulant and reinforcement effects of drugs of abuse (Pettit et al., 1984; Caine and Koob, 1994) and a number of previous studies demonstrate reduced $D_{2/3}$ levels in human psychostimulant, alcohol, and opiate addiction (Trifilieff and Martinez, 2014). However, this association has not been universally observed across the spectrum of maladaptive reward-seeking behavior, where reductions are no-
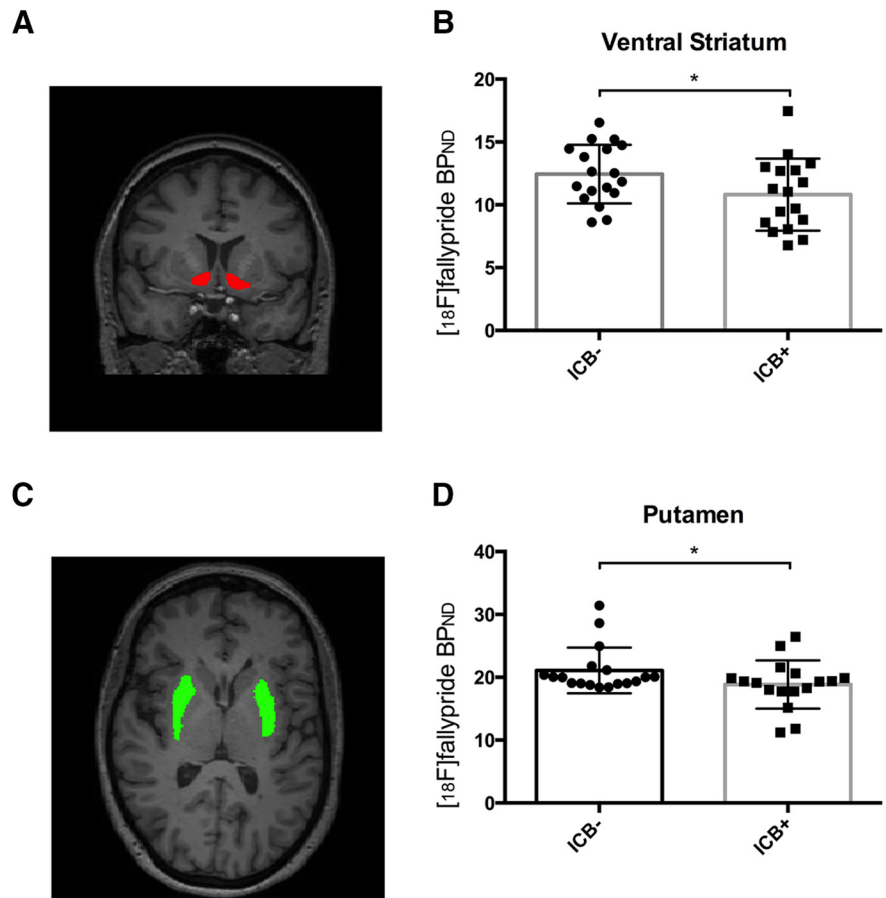
Figure 1. Mean regional [^{18}F]fallypride binding potential analysis. *A, C*, Representative coronal and axial slices for a single subject show an example of the manual segmentation routine for two different structures, including (*A*) ventral striatum and (*C*) putamen. *B, D*, Bar graphs of the mean [^{18}F]fallypride BP_{ND} in each corresponding region, with error bars representing the SD of the mean, and scatterplots representing individual regional means. There were significant differences in mean regional BP_{ND} between the ICB+ and ICB− groups in the ventral striatum (*A, B*) and putamen (*C, D*). Visualization of the segmentation protocol for all regions is displayed in Figure 1-1 (available at https://doi.org/10.1523/JNEUROSCI.3082-17.2018.f1-1) alongside a full description of ROI volumes and within-ROI BP_{ND} values (Figures 1-2 available at https://doi.org/10.1523/JNEUROSCI.3082-17.2018.f1-2 and 1-3 available at https://doi.org/10.1523/JNEUROSCI.3082-17.2018.f1-3, respectively). *$p < 0.05$, survival of FDR correction for multiple comparisons.

tably absent in primary gambling addiction (Nutt et al., 2015). Our findings are consistent with previous reports of decreased baseline ventral striatal $D_{2/3}$ BP_{ND} in PD patients with ICB, as reported with [^{11}C]raclopride (Steeves et al., 2009) and [^{11}C]-(+)-PHNO (Payer et al., 2015). Although these radioligands have differing affinities for D_2 and D_3 receptors, lower $D_{2/3}$ receptors in the ventral striatum are clearly associated with PD patients who develop behavioral changes over the course of treatment (Narendran et al., 2006; Tziortzi et al., 2011).

Within the ventral striatum, $D_{2/3}$ receptors localize to both presynaptic mesolimbic terminal autoreceptors and postsynaptic indirect-pathway medium spiny neurons (Anzalone et al., 2012; Kenny et al., 2013). The decreased ventral striatal $D_{2/3}$ receptor levels observed in substance abuse, extreme obesity, and impulsive disorders have been associated with decreased function of the indirect pathway, which mediates behavioral flexibility and avoidance learning in response to novel stimuli (Kenny et al., 2013; Nakanishi et al., 2014). In contrast, the direct pathway is characterized by the expression of dopamine D_1 receptors, which are involved in reward motivation (Kenny et al., 2013; Nakanishi et al., 2014). Notably, PET studies of D_1 receptor expression in PD have reported no differences in the striatum (Cropley et al., 2008)
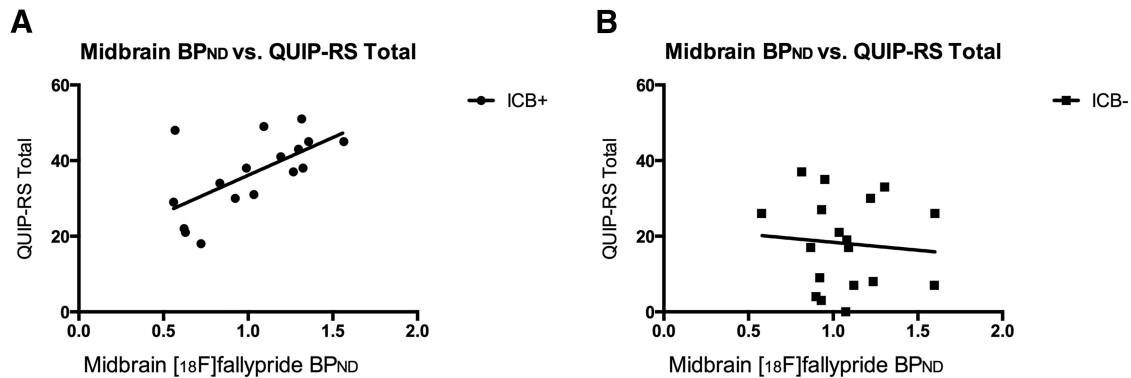
Figure 2. Midbrain [^{18}F]fallypride binding potential versus QUIP-RS. **A**, Scatterplot of [^{18}F]-fallypride BP$_{ND}$ in the substantia nigra (x-axis) versus scores on the QUIP-RS (y-axis) fit with a linear regression. A significant correlation between midbrain BP$_{ND}$ and QUIP-RS score was observed for the ICB + group ($r = 0.633$, $p = 0.011$), but not the ICB − group ($r = -0.129$, $p = 0.634$). No significant correlation was observed between BP$_{ND}$ and QUIP-RS in any other region. **B**, Representative axial slice for a single subject show an example of the manual segmentation routine for the midbrain. A full listing of correlation coefficients and p values for all analyzed ROIs is provided in Figure 2-1 (available at https://doi.org/10.1523/JNEUROSCI.3082-17.2018.f2-1).

emphasizing dissimilar direct pathway effects. Therefore, the findings of decreased ventral striatal D$_{2/3}$ receptor levels (Steeves et al., 2009; Payer et al., 2015), unaltered striatal D$_1$ receptor levels (Cropley et al., 2008), and increased ventral striatal extracellular dopamine (Steeves et al., 2009) suggest that when an imbalance between the direct and indirect pathways in the ventral striatum is coupled with increased DA release in response to rewarding stimuli, increased reward motivation in the setting of decreased avoidance learning could lead to the manifestation of ICBs in PD.

A key unanswered question is whether the lower ventral striatal D$_{2/3}$ binding precedes, or emerges after, dopamine-related treatment. Preclinical models of addiction support the former hypothesis, where decreased ventral striatal D$_{2/3}$ receptor expression in animals is associated with greater trait impulsivity (as indexed by the ability to withhold premature motor responses) as well as drug-taking behavior in rodents and nonhuman primates (Nader et al., 2006; Dalley et al., 2007). By contrast, overexpression of ventral striatal D$_2$ increases motivation for long-term effortful outcomes over short-term reward (Trifilieff et al., 2013), as well as reducing drug intake (Thanos et al., 2008). However, divergent patterns of PD neurodegeneration or cellular responses to medication could also effect the manifestation of group differences, through PD-related dopaminergic denervation of nigrostriatal projections (Rinne et al., 1990) or mechanisms of agonist-induced receptor internalization, respectively (Itokawa et al., 1996). In particular, animal studies suggest that DAgonist administration can selectively decrease dopamine D$_{2/3}$ receptor levels in the nucleus accumbens/ventral striatum (Engber et al., 1993).

The dorsal striatum and habitual behavior
Previous studies in PD have not observed altered dorsal striatal D$_{2/3}$ BP$_{ND}$ in relation to ICB status. Whereas the ventral striatum is associated with anticipation of future rewards and reward-related drug reinforcement, the dorsal striatum maintains compulsive habitual responding to reward-based behaviors (O'Doherty et al., 2004; Everitt and Robbins, 2005). Indeed, dorsal striatal dopamine release is necessary to maintain habit-based learning in addiction paradigms (Yin et al., 2004; Vanderschuren et al., 2005), where reductions in dorsal D$_{2/3}$ receptor BP$_{ND}$ occur after an action becomes habitual (Nader et al., 2006; Dalley et al., 2007). Dorsal striatal reductions in D$_{2/3}$ receptors are observed in patients with long-term cocaine, methamphetamine, alcohol, nicotine, and opiate abuse (Trifilieff and Martinez, 2014). In this manner, an impulsive behavior becomes compulsive, as dopaminergic ab-

normalities that initially occur in the ventral striatum, extend dorsally via the feedforward striato–nigro–striatal loop (Haber and Knutson, 2010). At the receptor level, low ventral striatal D$_{2/3}$ receptors (associated with reward-related impulsivity) cause signaling changes that over time evolve into dorsal D$_{2/3}$ reductions (linked to compulsive reward driven behavior). Together, we interpret reduced [^{18}F]fallypride binding in both ventral and dorsal striatum of ICB patients as a neurobiological manifestation of both impulsive, and compulsive behaviors, paralleling previous findings in substance abuse disorders.

The midbrain and impulsive-compulsive behavioral symptoms
Although differences in mean ventral midbrain D$_{2/3}$ BP$_{ND}$ in ICB have not been reported by the current or a previous study (Ray et al., 2012) a positive relationship was observed in the current study between midbrain [^{18}F]fallypride BP$_{ND}$ and the severity of reward seeking behaviors (QUIP-RS), in ICB+ but not ICB− patients. This parallels a past [^{11}C]-(+)-PHNO PET study that described a similar relationship between pathological gambling severity and midbrain binding (Boileau et al., 2013). In healthy humans, impulsivity has been positively correlated with antero-ventral striatal dopamine release and negatively correlated with ventral midbrain D$_{2/3}$ (Buckholtz et al., 2010). Similarly, PD patients with DAgonist-induced pathological gambling demonstrated increased ventral striatal dopamine release during performance on a gambling task relative to those without this side-effect (Steeves et al., 2009); in addition, increased ventral striatal dopamine release has also been reported following presentation of reward-related visual cues associated with individual ICBs in ICB+ patients (O'Sullivan et al., 2011; Wu et al., 2015). Combined, these studies suggest that state impulsivity in younger healthy subjects and ICBs in PD bear a common association with increased ventral striatal dopamine release.

Given that ventral midbrain D$_{2/3}$ receptors function as inhibitory autoreceptors at both axonal and somatodendritic areas, and the negative correlation between midbrain D$_{2/3}$ BP$_{ND}$ and state impulsivity seen in healthy subjects (Mercuri et al., 1992; Khan et al., 1998; Buckholtz et al., 2010), the positive correlation between ventral midbrain D$_{2/3}$ BP$_{ND}$ and QUIP-RS scores would therefore appear to be unexpected. However, the total level of ventral midbrain D$_{2/3}$ receptors includes those expressed on axons innervating the dorsal as well as the ventral striatum, in addition to other brain structures. Although postmortem studies of
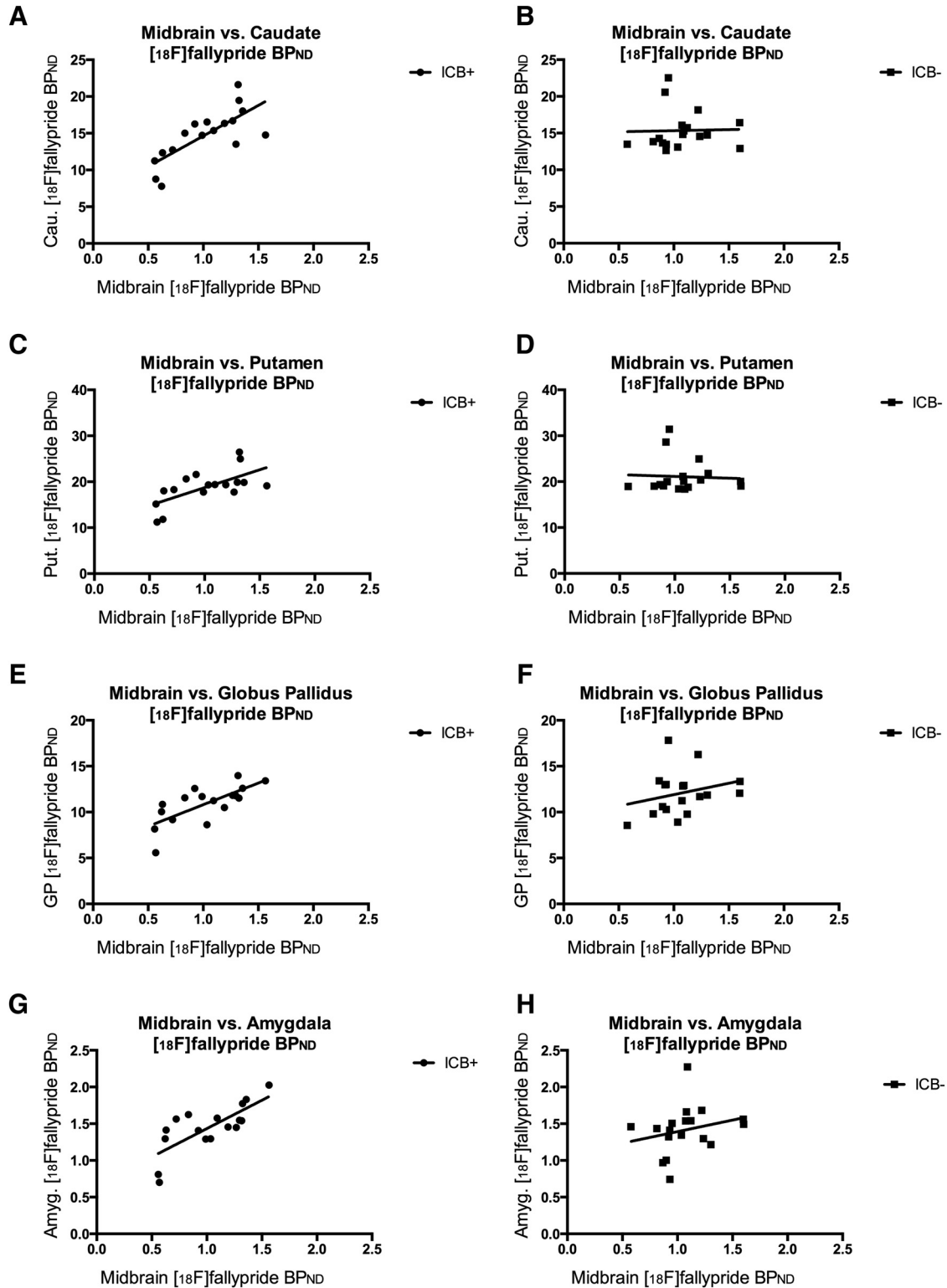
Figure 3. Midbrain [^{18}F]fallypride binding potential versus [^{18}F]fallypride binding potential in other regions. **A–G**, Scatterplots of midbrain BP$_{ND}$ (x-axis) versus BP$_{ND}$ in regions where a significant group $\times$ BP$_{ND}$ interaction was observed (y-axis) fit with a linear regression for the ICB+ and ICB− groups. This effect appeared in the (**A**, **B**) caudate (ICB+: $r = 0.706$, $p = 0.003$; ICB−: $r = 0.001$, $p = 0.99$), (**C**, **D**) putamen (ICB+: $r = 0.589$, $p = 0.021$; ICB−: $r = -0.126$, $p = 0.643$), (**E**, **F**) globus pallidus (ICB+: $r = 0.668$, $p = 0.007$; ICB−: $r = 0.262$, $p = 0.328$), and (**G**, **H**) amygdala (ICB+: $r = 0.709$, $p = 0.003$; ICB−: $r = 0.243$, $p = 0.364$), indicating a divergent BP$_{ND}$ relationship between the structures. Figure 3-1 (available at https://doi.org/10.1523/JNEUROSCI. 3082-17.2018.f3-1) includes a visualization of scatterplot results, in addition to a listing of correlation coefficients and p values for ROIs that were not associated with a significant group $\times$ BP$_{ND}$ interaction term.

early to middle stage PD have shown that dopaminergic projections to the motor striatum are more severely affected by denervation (Gibb and Lees, 1991), the fraction of $D_{2/3}$ receptors expressed on neurons projecting to the ventral striatum likely still represents a small minority of the total ventral midbrain $D_{2/3}$ content. The lack of difference in total level of ventral midbrain $D_{2/3}$ receptors may therefore not be informative as to the status of neurons projecting to the ventral striatum. If the number of $D_{2/3}$ receptors on individual dopamine neurons projecting to the ventral striatum remains relatively constant between ICB+ and ICB− subjects, then the positive correlation seen in this study may reflect a relatively more intact dopaminergic innervation of the ventral striatum consistent with the increased ventral striatal dopamine release seen in previous studies.

One prior study of DAgonist-induced pathological gambling has also observed distinctions in the ventral midbrain, where performance of a gambling task produced greater apparent dopamine release in ICB− compared with ICB+ subjects (Ray et al., 2012). The authors concluded that this apparent decreased DA release reflected altered $D_{2/3}$ autoreceptor function leading to the previously reported increase in ventral striatal dopamine release. However, this PET [^{11}C]FLB-457 study was performed following pramipexole administration, which has been shown to produce significant changes in ventral midbrain dopamine $D_{2/3}$ BP_{ND} that were not present in the ventral striatum (Ray et al., 2012; Deutschländer et al., 2016). Combined with the finding that dopamine release within the midbrain is crucial in producing therapeutic psychostimulant effects in related psychiatric phenotypes, such as attention deficit/hyperactivity disorder (del Campo et al., 2013) it is likely that individual differences in both midbrain $D_{2/3}$ survival and drug sensitivity are involved in the manifestation of ICB. As a result, the interaction between pramipexole binding and changes in autoreceptor function requires further study. The positive correlation of midbrain $D_{2/3}$ receptor levels with dopamine agonist induced altered reward behaviors in PD seen in the current study suggests the possibility that ICB+ PD subjects may have relatively greater preservation of ventral striatal dopaminergic innervation than ICB− subjects.

Relationships between dopamine receptors in the midbrain and other reward related-regions

Correlations between midbrain $D_{2/3}$ BP_{ND} and the caudate, putamen, globus pallidus, and amygdala significantly differ between groups. Using [^{18}F]fallypride, significant positive BP_{ND} correlations between midbrain, striatum, and amygdala (Zald et al., 2010) are evident in healthy humans. A positive correlation across multiple regions may reflect similar types of $D_{2/3}$ receptors (e.g., autoreceptors), concerted influence of nigrostriatal and mesolimbic dopamine release or DAgonist effects on $D_{2/3}$ expression (Itokawa et al., 1996; Haber and Knutson, 2010), or the relative integrity of midbrain-based dopaminergic networks. Although the comparison of interregional correlations is cautiously interpreted given the older age of our subjects (Zald et al., 2010), ICB+ patients appear more similar to healthy controls. The ventral midbrain is known to contain several heterogeneous subpopulations, with unique patterns of anatomical projection, pharmacological and cellular properties, and relevance to behavior (Lammel et al., 2008; Haber and Knutson, 2010). Furthermore, past evidence using presynaptic biomarkers such as FDOPA indicates that dopaminergic projections undergo differential rates of PD-related degeneration, where the loss of dorsal striatal innervation is known to precede the same process in the ventral striatum (Gibb and Lees, 1991; Kumakura et al., 2010). Consequently, denerva-

tion that uniquely spares cells that regulate dopamine release to the dorsal striatum, globus pallidus, or amygdala could also be involved in producing ICBs. This result could also be affected by similar expression, but altered dynamic function of $D_{2/3}$ in ICB+ patients. Chronic DAgonist administration can induce midbrain D_2 autoreceptor desensitization in rodents (Chernoloz et al., 2009), and differences in this response, or PD-related changes to receptor functionality could also play a role. Regardless of the mechanism, ICB appears to be associated with greater functional preservation of midbrain dopaminergic terminal fields in ICB+ compared with ICB− subjects. Increased integrity of midbrain dopamine neuron subpopulations and the extended reward network, in combination with decreased ventral striatal and putamen dopamine $D_{2/3}$ receptor levels, may result in a DAgonist "overdose" of the reward circuit that drives the development of compulsive reward-driven behaviors with impaired inhibitory behavioral control.

Limitations and future directions

Interpretation of the present work relies on the assumption that BP_{ND} differences are manifestations of ICB-related distinctions in $D_{2/3}$ receptor expression. Changes in apparent [^{18}F]fallypride BP_{ND}s can also be produced by differences in extracellular dopamine levels, which compete with [^{18}F]fallypride in binding to $D_{2/3}$ receptors. However, previous studies examining the relationship between shifts in striatal extracellular dopamine levels and changes in [^{11}C]raclopride binding have indicated a 44:1 ratio, where a 44% increase in extracellular dopamine produces a 1% decrease in BP_{ND} (Breier et al., 1997). In the current study, ICB+ patients have ventral striatal $D_{2/3}$ receptor levels 17.1% lower than those seen in ICB− patients, adjusted for covariates; such a difference in [^{18}F]fallypride BP_{ND} would require an ~750% higher extracellular dopamine level. Therefore, it is unlikely that the entire difference in ventral striatal [^{18}F]fallypride BP_{ND} is due to increased extracellular dopamine levels. Although some studies have expressed differences in stimuli-induced acute dopamine release in ICB+ subjects (Steeves et al., 2009; Ray et al., 2012), no reports have described synaptic dopamine concentrations at rest. Therefore, the topics of ICB-related dopamine release and reward-circuit preservation demand further exploration by other experimental modalities, such as [^{18}F]fallypride with concurrent pharmacological challenge. Animal models are needed to test mechanistic hypotheses relating to medication use and altered ventral striatal $D_{2/3}$ receptor levels. In addition, whereas the cohort included in the present study was composed mostly of ICB+ subjects defined by hypersexuality and compulsive eating, some previous studies have exclusively examined pathological gamblers (Steeves et al., 2009; Ray et al., 2012); although similarities are apparent between the two samples (including reduced ventral striatal BP_{ND}, as well as a relationship between midbrain BP_{ND} and impulsivity) differences are also present (such as the lack of cortical findings in the present work). Overall, these findings emphasize a distinct association between medication-induced reward-driven-behaviors and altered expression of $D_{2/3}$ receptors in key striatal and midbrain components of reward networks in PD patients. Further validation of this relationship could eventually lead to the use of [^{18}F]fallypride as a screening measure for personalization of treatment regimens, and a better understanding of which individuals respond best to the long-term prescription of DAgonist medication.

References

American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders: DSM-IV-TR, Ed 4, text revision. Washington, DC: American Psychiatric Association.

Anzalone A, Lizardi-Ortiz JE, Ramos M, De Mei C, Hopf FW, Iaccarino C, Halbout B, Jacobsen J, Kinoshita C, Welter M, Caron MG, Bonci A, Sulzer D, Borrelli E (2012) Dual control of dopamine synthesis and release by presynaptic and postsynaptic dopamine D2 receptors. J Neurosci 32: 9023–9034. CrossRef Medline

Boileau I, Payer D, Chugani B, Lobo D, Behzadi A, Rusjan PM, Houle S, Wilson AA, Warsh J, Kish SJ, Zack M (2013) The $D_{2/3}$ dopamine receptor in pathological gambling: a positron emission tomography study with $[^{11}C]$-(+)-propyl-hexahydro-naphtho-oxazin and $[_{11}C]$raclopride. Addiction 108:953–963. CrossRef Medline

Breier A, Su TP, Saunders R, Carson RE, Kolachana BS, de Bartolomeis A, Weinberger DR, Weisenfeld N, Malhotra AK, Eckelman WC, Pickar D (1997) Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method. Proc Natl Acad Sci U S A 94:2569–2574. CrossRef Medline

Buckholtz JW, Treadway MT, Cowan RL, Woodward ND, Li R, Ansari MS, Baldwin RM, Schwartzman AN, Shelby ES, Smith CE, Kessler RM, Zald DH (2010) Dopaminergic network differences in human impulsivity. Science 329:532. CrossRef Medline

Caine SB, Koob GF (1994) Effects of mesolimbic dopamine depletion on responding maintained by cocaine and food. J Exp Anal Behav 61:213–221. CrossRef Medline

Camps M, Cortés R, Gueye B, Probst A, Palacios JM (1989) Dopamine receptors in human brain: autoradiographic distribution of D_2 sites. Neuroscience 28:275–290. CrossRef Medline

Chernoloz O, El Mansari M, Blier P (2009) Sustained administration of pramipexole modifies the spontaneous firing of dopamine, norepinephrine, and serotonin neurons in the rat brain. Neuropsychopharmacology 34:651–661. CrossRef Medline

Claassen DO, Kanoff K, Wylie SA (2013) Dopamine agonists and impulse control disorders in Parkinson's disease. US Neurol 9:13–16. CrossRef

Cropley VL, Fujita M, Bara-Jimenez W, Brown AK, Zhang XY, Sangare J, Herscovitch P, Pike VW, Hallett M, Nathan PJ, Innis RB (2008) Pre- and post-synaptic dopamine imaging and its relation with frontostriatal cognitive function in parkinson disease: PET studies with $[^{11}C]NNC$ 112 and $[^{18}F]FDOPA$. Psychiatry Res 163:171–182. CrossRef Medline

Dalley JW, Fryer TD, Brichard L, Robinson ES, Theobald DE, Lääne K, Peña Y, Murphy ER, Shah Y, Probst K, Abakumova I, Aigbirhio FI, Richards HK, Hong Y, Baron JC, Everitt BJ, Robbins TW (2007) Nucleus accumbens $D_{2/3}$ receptors predict trait impulsivity and cocaine reinforcement. Science 315:1267–1270. CrossRef Medline

del Campo N, Fryer TD, Hong YT, Smith R, Brichard L, Acosta-Cabronero J, Chamberlain SR, Tait R, Izquierdo D, Regenthal R, Dowson J, Suckling J, Baron JC, Aigbirhio FI, Robbins TW, Sahakian BJ, Müller U (2013) A positron emission tomography study of nigro-striatal dopaminergic mechanisms underlying attention: implications for ADHD and its treatment. Brain 136:3252–3270. CrossRef Medline

Deutschländer A, la Fougère C, Boetzel K, Albert NL, Gildehaus FJ, Bartenstein P, Xiong G, Cumming P (2016) Occupancy of pramipexole (Sifrol) at cerebral dopamine D2/3 receptors in Parkinson's disease patients. Neuroimage Clin 12:41–46. CrossRef Medline

Egerton A, Hirani E, Ahmad R, Turton DR, Brickute D, Rosso L, Howes OD, Luthra SK, Grasby PM (2010) Further evaluation of the carbon11-labeled $D_{2/3}$ agonist PET radiotracer PHNO: reproducibility in tracer characteristics and characterization of extrastriatal binding. Synapse 64: 301–312. CrossRef Medline

Engber TM, Marin C, Susel Z, Chase TN (1993) Differential effects of chronic dopamine D_1 and D_2 receptor agonists on rotational behavior and dopamine receptor binding. Eur J Pharmacol 236:385–393. CrossRef Medline

Everitt BJ, Robbins TW (2005) Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nat Neurosci 8:1481–1489. CrossRef Medline

Fabbrini G, Juncos J, Mouradian MM, Serrati C, Chase TN (1987) Levodopa pharmacokinetic mechanisms and motor fluctuations in Parkinson's disease. Ann Neurol 21:370–376. CrossRef Medline

Farde L, Suhara T, Nyberg S, Karlsson P, Nakashima Y, Hietala J, Halldin C

(1997) A PET-study of $[^{11}C]FLB$ 457 binding to extrastriatal D_2-dopamine receptors in healthy subjects and antipsychotic drug-treated patients. Psychopharmacology (Berl) 133:396–404. CrossRef Medline

Gibb WR, Lees AJ (1991) Anatomy, pigmentation, ventral and dorsal subpopulations of the substantia nigra, and differential cell death in Parkinson's disease. J Neurol Neurosurg Psychiatry 54:388–396. CrossRef Medline

Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stern MB, Dodel R, Dubois B, Holloway R, Jankovic J, Kulisevsky J, Lang AE, Lees A, Leurgans S, LeWitt PA, Nyenhuis D, Olanow CW, et al. (2008) Movement disorder society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 23:2129–2170. CrossRef Medline

Grober E, Sliwinski M (1991) Development and validation of a model for estimating premorbid verbal intelligence in the elderly. J Clin Exp Neuropsychol 13:933–949. CrossRef Medline

Gunn RN, Lammertsma AA, Hume SP, Cunningham VJ (1997) Parametric imaging of ligand-receptor binding in PET using a simplified reference region model. Neuroimage 6:279–287. CrossRef Medline

Haber SN, Knutson B (2010) The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology 35:4–26. CrossRef Medline

Hall H, Ogren SO, Köhler C, Magnusson O (1989) Animal pharmacology of raclopride, a selective dopamine D_2 antagonist. Psychopharmacol Ser 7:123–130. Medline

Harrison MB, Wylie SA, Frysinger RC, Patrie JT, Huss DS, Currie LJ, Wooten GF (2009) UPDRS activity of daily living score as a marker of Parkinson's disease progression. Mov Disord 24:224–230. CrossRef Medline

Itokawa M, Toru M, Ito K, Tsuga H, Kameyama K, Haga T, Arinami T, Hamaguchi H (1996) Sequestration of the short and long isoforms of dopamine D_2 receptors expressed in chinese hamster ovary cells. Mol Pharmacol 49:560–566. Medline

Joyce JN, Janowsky A, Neve KA (1991) Characterization and distribution of $[^{125}I]$epidepride binding to dopamine D_2 receptors in basal ganglia and cortex of human brain. J Pharmacol Exp Ther 257:1253–1263. Medline

Kaasinen V, Någren K, Hietala J, Oikonen V, Vilkman H, Farde L, Halldin C, Rinne JO (2000) Extrastriatal dopamine D_2 and D_3 receptors in early and advanced Parkinson's disease. Neurology 54:1482–1487. CrossRef Medline

Kenny PJ, Voren G, Johnson PM (2013) Dopamine D_2 receptors and striatopallidal transmission in addiction and obesity. Curr Opin Neurobiol 23:535–538. CrossRef Medline

Kessler RM, Woodward ND, Riccardi P, Li R, Ansari MS, Anderson S, Dawant B, Zald D, Meltzer HY (2009) Dopamine D_2 receptor levels in striatum, thalamus, substantia nigra, limbic regions, and cortex in schizophrenic subjects. Biol Psychiatry 65:1024–1031. CrossRef Medline

Kessler R, Mason N, Jones C, Ansari M, Manning R, Price R (2000) N-allyl-5-fluoropropylepidepride (fallypride): radiation dosimetry, quantification of striatal and extrastriatal dopamine receptors in man. Neuroimage 11:S32.

Khan ZU, Mrzljak L, Gutierrez A, de la Calle A, Goldman-Rakic PS (1998) Prominence of the dopamine D_2 short isoform in dopaminergic pathways. Proc Natl Acad Sci U S A 95:7731–7736. CrossRef Medline

Kumakura Y, Danielsen EH, Gjedde A, Vernaleken I, Buchholz HG, Heinz A, Gründer G, Bartenstein P, Cumming P (2010) Elevated $[^{18}F]FDOPA$ utilization in the periaqueductal gray and medial nucleus accumbens of patients with early Parkinson's disease. Neuroimage 49:2933–2939. CrossRef Medline

Lammel S, Hetzel A, Häckel O, Jones I, Liss B, Roeper J (2008) Unique properties of mesoprefrontal neurons within a dual mesocorticolimbic dopamine system. Neuron 57:760–773. CrossRef Medline

Lammertsma AA, Bench CJ, Hume SP, Osman S, Gunn K, Brooks DJ, Frackowiak RS (1996) Comparison of methods for analysis of clinical $[^{11}C]$ raclopride studies. J Cerebl Blood Flow Metab 16:42–52. CrossRef Medline

Mawlawi O, Martinez D, Slifstein M, Broft A, Chatterjee R, Hwang DR, Huang Y, Simpson N, Ngo K, Van Heertum R, Laruelle M (2001) Imaging human mesolimbic dopamine transmission with positron emission tomography: I. accuracy and precision of D_2 receptor parameter measurements in ventral striatum. J Cereb Blood Flow Metab 21:1034–1057. CrossRef Medline

Mercuri NB, Calabresi P, Bernardi G (1992) The electrophysiological actions of dopamine and dopaminergic drugs on neurons of the substantia

nigra pars compacta and ventral tegmental area. Life Sci 51:711–718. CrossRef Medline

Mestre TA, Strafella AP, Thomsen T, Voon V, Miyasaki J (2013) Diagnosis and treatment of impulse control disorders in patients with movement disorders. Ther Adv Neurol Disord 6:175–188. CrossRef Medline

Mukherjee J, Christian BT, Dunigan KA, Shi B, Narayanan TK, Satter M, Mantil J (2002) Brain imaging of ^{18}F-fallypride in normal volunteers: blood analysis, distribution, test–retest studies, and preliminary assessment of sensitivity to aging effects on dopamine D-2/D-3 receptors. Synapse 46:170–188. CrossRef Medline

Nader MA, Morgan D, Gage HD, Nader SH, Calhoun TL, Buchheimer N, Ehrenkaufer R, Mach RH (2006) PET imaging of dopamine D_2 receptors during chronic cocaine self-administration in monkeys. Nat Neurosci 9:1050–1056. CrossRef Medline

Nakanishi S, Hikida T, Yawata S (2014) Distinct dopaminergic control of the direct and indirect pathways in reward-based and avoidance learning behaviors. Neuroscience 282:49–59. CrossRef Medline

Narendran R, Slifstein M, Guillin O, Hwang Y, Hwang DR, Scher E, Reeder S, Rabiner E, Laruelle M (2006) Dopamine ($D_{2/3}$) receptor agonist positron emission tomography radiotracer [^{11}C]-(+)-PHNO is a D_3 receptor preferring agonist in vivo. Synapse 60:485–495. CrossRef Medline

Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H (2005) The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 53:695–699. CrossRef Medline

Nutt DJ, Lingford-Hughes A, Erritzoe D, Stokes PR (2015) The dopamine theory of addiction: 40 years of highs and lows. Nat Rev Neurosci 16:305–312. CrossRef Medline

O'Doherty J, Dayan P, Schultz J, Deichmann R, Friston K, Dolan RJ (2004) Dissociable roles of ventral and dorsal striatum in instrumental conditioning. Science 304:452–454. CrossRef Medline

O'Sullivan SS, Wu K, Politis M, Lawrence AD, Evans AH, Bose SK, Djamshidian A, Lees AJ, Piccini P (2011) Cue-induced striatal dopamine release in Parkinson's disease-associated impulsive-compulsive behaviours. Brain 134:969–978. CrossRef Medline

Payer DE, Guttman M, Kish SJ, Tong J, Strafella A, Zack M, Adams JR, Rusjan P, Houle S, Furukawa Y, Wilson AA, Boileau I (2015) [^{11}C]-(+)-PHNO PET imaging of dopamine $D_{2/3}$ receptors in Parkinson's disease with impulse control disorders. Mov Disord 30:160–166. CrossRef Medline

Pettit HO, Ettenberg A, Bloom FE, Koob GF (1984) Destruction of dopamine in the nucleus accumbens selectively attenuates cocaine but not heroin self-administration in rats. Psychopharmacology (Berl) 84:167–173. CrossRef Medline

Piercey MF (1998) Pharmacology of pramipexole, a dopamine D3-preferring agonist useful in treating Parkinson's disease. Clin Neuropharmacol 21:141–151. Medline

Radloff LS (1977) The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1:385–401. CrossRef

Ray NJ, Miyasaki JM, Zurowski M, Ko JH, Cho SS, Pellecchia G, Antonelli F, Houle S, Lang AE, Strafella AP (2012) Extrastriatal dopaminergic abnormalities of DA homeostasis in Parkinson's patients with medication-induced pathological gambling: a [^{11}C] FLB-457 and PET study. Neurobiol Dis 48:519–525. CrossRef Medline

Rinne UK, Laihinen A, Rinne JO, Någren K, Bergman J, Ruotsalainen U (1990) Positron emission tomography demonstrates dopamine D_2 receptor supersensitivity in the striatum of patients with early Parkinson's disease. Mov Disord 5:55–59. CrossRef Medline

Schaltenbrand G, Wahren W (1998) Atlas for stereotaxy of the human brain: with an accompanying guide (2nd ed. rev). Stuttgart, Germany: Thieme.

Steeves TD, Miyasaki J, Zurowski M, Lang AE, Pellecchia G, Van Eimeren T, Rusjan P, Houle S, Strafella AP (2009) Increased striatal dopamine release in parkinsonian patients with pathological gambling: a [^{11}C] raclopride PET study. Brain 132:1376–1385. CrossRef Medline

Thanos PK, Michaelides M, Umegaki H, Volkow ND (2008) D2R DNA transfer into the nucleus accumbens attenuates cocaine self-administration in rats. Synapse 62:481–486. CrossRef Medline

Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE (2010) Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 25:2649–2653. CrossRef Medline

Tompson D, Oliver-Willwong R (2009) Pharmacokinetic and pharmacodynamic comparison of ropinirole 24-hour prolonged release and ropinirole immediate release in patients with Parkinson's disease. Clin Neuropharmacol 32:140–148. CrossRef Medline

Trifilieff P, Martinez D (2014) Imaging addiction: D_2 receptors and dopamine signaling in the striatum as biomarkers for impulsivity. Neuropharmacology 76:498–509. CrossRef Medline

Trifilieff P, Feng B, Urizar E, Winiger V, Ward RD, Taylor KM, Martinez D, Moore H, Balsam PD, Simpson EH, Javitch JA (2013) Increasing dopamine D_2 receptor expression in the adult nucleus accumbens enhances motivation. Mol Psychiatry 18:1025–1033. CrossRef Medline

Tziortzi AC, Searle GE, Tzimopoulou S, Salinas C, Beaver JD, Jenkinson M, Laruelle M, Rabiner EA, Gunn RN (2011) Imaging dopamine receptors in humans with [^{11}C]-(+)-PHNO: dissection of D3 signal and anatomy. Neuroimage 54:264–277. CrossRef Medline

Vanderschuren LJ, Di Ciano P, Everitt BJ (2005) Involvement of the dorsal striatum in cue-controlled cocaine seeking. J Neurosci 25:8665–8670. CrossRef Medline

Voon V, Potenza MN, Thomsen T (2007) Medication-related impulse control and repetitive behaviors in Parkinson's disease. Curr Opin Neurol 20:484–492. CrossRef Medline

Voon V, Sohr M, Lang AE, Potenza MN, Siderowf AD, Whetteckey J, Weintraub D, Wunderlich GR, Stacy M (2011) Impulse control disorders in Parkinson disease: a multicenter case-control study. Ann Neurol 69:986–996. CrossRef Medline

Weintraub D, Hoops S, Shea JA, Lyons KE, Pahwa R, Driver-Dunckley ED, Adler CH, Potenza MN, Miyasaki J, Siderowf AD, Duda JE, Hurtig HI, Colcher A, Horn SS, Stern MB, Voon V (2009) Validation of the questionnaire for impulsive-compulsive disorders in Parkinson's disease. Mov Disord 24:1461–1467. CrossRef Medline

Weintraub D, Mamikonyan E, Papay K, Shea JA, Xie SX, Siderowf A (2012) Questionnaire for impulsive-compulsive disorders in Parkinson's disease-rating scale. Mov Disord 27:242–247. CrossRef Medline

Wu K, Politis M, O'Sullivan SS, Lawrence AD, Warsi S, Bose S, Lees AJ, Piccini P (2015) Single versus multiple impulse control disorders in Parkinson's disease: an ^{11}C-raclopride positron emission tomography study of reward cue-evoked striatal dopamine release. J Neurol 262:1504–1514. CrossRef Medline

Yin HH, Knowlton BJ, Balleine BW (2004) Lesions of dorsolateral striatum preserve outcome expectancy but disrupt habit formation in instrumental learning. Eur J Neurosci 19:181–189. CrossRef Medline

Zald DH, Woodward ND, Cowan RL, Riccardi P, Ansari MS, Baldwin RM, Cowan RL, Smith CE, Hakyemez H, Li R, Kessler RM (2010) The interrelationship of dopamine D2-like receptor availability in striatal and extrastriatal brain regions in healthy humans: a principal component analysis of [^{18}F]fallypride binding. Neuroimage 51:53–62. CrossRef Medline