

# Nigrostriatal and Mesolimbic D<sub>2/3</sub> Receptor Expression in Parkinson's Disease Patients with Compulsive Reward-Driven Behaviors

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The nigrostriatal and mesocorticolimbic dopamine networks regulate reward-driven behavior. Regional alterations to mesolimbic dopamine D<sub>2/3</sub> receptor expression are described in drug-seeking and addiction disorders. Parkinson's disease (PD) patients are frequently prescribed D<sub>2</sub>-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<sub>2/3</sub> 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 [<sup>18</sup>F]fallypride, a high affinity D<sub>2</sub>-like receptor ligand that can measure striatal and extrastriatal D<sub>2/3</sub> nondisplaceable binding potential (BP<sub>ND</sub>). Striatal differences between ICB+/ICB− patients localized to the ventral striatum and putamen, where ICB+ subjects had reduced BP<sub>ND</sub>. In this group, self-reported severity of ICB symptoms positively correlated with midbrain D<sub>2/3</sub> receptor BP<sub>ND</sub>. Group differences in regional D<sub>2/3</sub> BP<sub>ND</sub> relationships were also notable: ICB+ (but not ICB−) patients expressed positive correlations between midbrain and caudate, putamen, globus pallidus, and amygdala BP<sub>ND</sub>s. These findings support the hypothesis that compulsive behaviors in PD are associated with reduced ventral and dorsal striatal D<sub>2/3</sub> 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 [<sup>18</sup>F]fallypride, allowing quantification of D<sub>2/3</sub> receptors throughout the mesocorticolimbic network. We demonstrate widespread differences in dopaminergic networks, including (1) D<sub>2</sub>-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<sub>2/3</sub> 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<sub>2</sub>-like (D<sub>2</sub>/D<sub>3</sub>) 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<sub>2/3</sub> 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<sub>2/3</sub> receptor levels are linked to established patterns of addictive behavior (Nader et al., 2006). D<sub>2/3</sub> receptors are also important in the ventral midbrain, where decreased D<sub>2/3</sub> (auto)receptor binding is associated with greater impulsivity in healthy humans (Buckholtz et al., 2010).

Pramipexole and ropinirole, D<sub>3</sub> preferring D<sub>2/3</sub> agonists (DAgonists), produce improvements in the motor symptoms of Parkinson's disease (PD; Piercey, 1998). However, these D<sub>2/3</sub>-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<sub>2/3</sub> levels in PD patients with ICB symptoms provides an opportunity to examine the role of D<sub>2/3</sub> 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 [<sup>11</sup>C]raclopride (Steeves et al., 2009) and [<sup>11</sup>C]-(+)-PHNO (Payer et al., 2015) have reported reduced baseline D<sub>2/3</sub> receptor levels in the ventral striatum in ICB+ patients; this finding may be due to either decreased ventral striatal D<sub>2/3</sub> receptor expression, or increased ventral striatal extracellular dopamine levels, which could in theory reduce the number of available D<sub>2/3</sub> receptors. Due to its moderate affinity for the D<sub>2/3</sub> receptor, [<sup>11</sup>C]raclopride provides an estimate of striatal D<sub>2/3</sub> receptor levels but has not typically been used to estimate extrastriatal D<sub>2/3</sub>. [<sup>11</sup>C]-(+)-PHNO, a higher affinity D<sub>3</sub>-preferring D<sub>2/3</sub> agonist radioligand, can be used to estimate D<sub>2/3</sub> 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 [<sup>11</sup>C]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 [<sup>11</sup>C]FLB-457 can be used to estimate extrastriatal D<sub>2/3</sub> 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<sub>2/3</sub> receptor levels in the midbrain, striatal, limbic, and cortical regions of the reward circuit, or the relationships between regional D<sub>2/3</sub> 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). [<sup>18</sup>F]fallypride is a high-affinity D<sub>2/3</sub> radioligand that can provide accurate estimates of binding in both striatal and extrastriatal regions, allowing for quantification of dopamine D<sub>2/3</sub> receptor levels [i.e., nondisplaceable binding potential (BP<sub>ND</sub>)] 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<sub>2/3</sub> BP<sub>ND</sub> differences, thus determining the relationship between D<sub>2/3</sub> receptor levels and self-reported severity of reward-based behaviors. We hypothesized that D<sub>2/3</sub> BP<sub>ND</sub> 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<sub>2/3</sub> receptor expression and receptor expression throughout the nigrostriatal and mesolimbic networks.

## Materials and Methods

**Participants.** Subjects ( $n = 35$ ; sex = 11 F/24 M; age =  $61.8 \pm 8.5$  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

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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 premonitory 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 [<sup>18</sup>F]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 (wash-out 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<sub>1</sub>-weighted (MPRAGE; spatial resolution = 1 × 1 × 1 mm<sup>3</sup>; TR/TE = 8.9/4.6 ms), and (2) T<sub>2</sub>-weighted FLAIR (spatial resolution = 1 × 1 × 1 mm<sup>3</sup>; TR/TE = 4000/120 ms).

**Fallypride PET data acquisition.** [<sup>18</sup>F]fallypride [(S)-N-[(1-allyl-2-pyrrolidinyl)methyl]-5-(3-[<sup>18</sup>F]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 Application 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 [<sup>18</sup>F]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 T<sub>1</sub> 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<sub>1</sub>-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<sub>ND</sub> 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<sub>ND</sub> images were registered to Montreal Neurological Institute space using FSL's FNIRT (FSL v5.0.2.1, FMRIB).

Regional DA D<sub>2/3</sub> levels were estimated using the simplified reference region method (Lammertsma et al., 1996) performed in PMOD software (PMOD Technologies) to measure [<sup>18</sup>F]fallypride binding potential (BP<sub>ND</sub>; the ratio of specifically bound [<sup>18</sup>F]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 PXM0D module of PMOD. The rate constants were specified by the user as k<sub>2a</sub> minimum = 0.006 min<sup>-1</sup> and k<sub>2a</sub> maximum = 0.6 min<sup>-1</sup>. The cerebellum was selected as the reference region due to its relatively limited expression of D<sub>2/3</sub> receptors in the cerebellum (Camps et al., 1989), it was selected as the reference region (Kessler et al., 2009). ROI BP<sub>ND</sub> values were determined by evaluating the average BP<sub>ND</sub> 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  $\chi^2$  test. To test the hypothesis that ICB+ patients have different dopamine D<sub>2/3</sub> receptor expression in striatal and extrastriatal areas, mean group regional [<sup>18</sup>F]fallypride BP<sub>ND</sub> was analyzed via a general linear regression model (GLM), where within-ROI BP<sub>ND</sub> 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<sub>2/3</sub> receptor status (Mukherjee et al., 2002). UPDRS-II was also specified as a covariate, as PD severity has been shown to influence D<sub>2/3</sub> 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<sub>2/3</sub> BP<sub>ND</sub> 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<sub>2/3</sub> 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+	<i>p</i>
<i>N</i>	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 sub-categories; 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

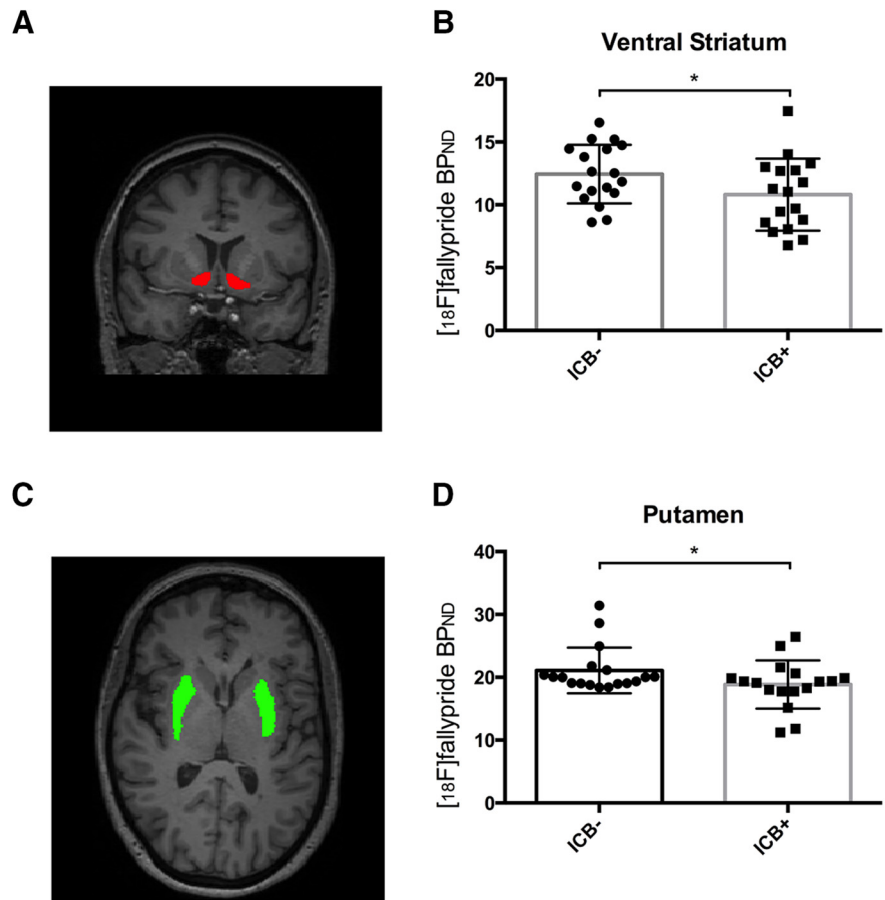
observed in the caudate (unstandardized  $B = -0.71$ ;  $p = 0.031$ ), putamen (unstandardized  $B = -0.79$ ;  $p = 0.024$ ), globus pallidus (unstandardized  $B = -0.65$ ;  $p = 0.044$ ), and amygdala (unstandardized  $B = -0.60$ ;  $p = 0.047$ ). The ICB+ group expressed significant positive  $BP_{ND}$  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 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

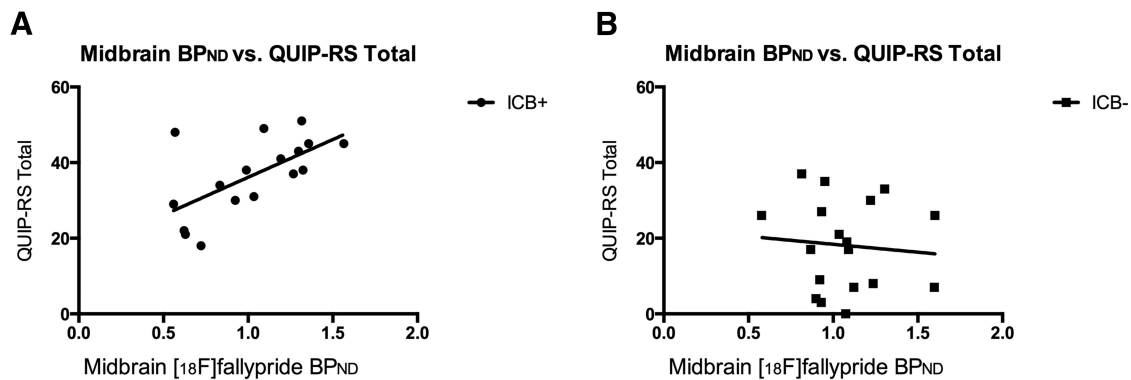
The ventral striatum is a crucial structure to reinforcement learning in the initial stages of addiction (O'Doherty et al., 2004; Everitt and Robbins, 2005). Ventral striatal dopamine transmission mediates the maintenance of both the psychostimulant and reinforcement effects of drugs of abuse (Pettit 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 (Trifileff 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 (Cromptley et al., 2008)



**Figure 2.** Midbrain [ $^{18}\text{F}$ ]fallypride binding potential versus QUIP-RS. **A**, Scatterplot of [ $^{18}\text{F}$ ]fallypride  $\text{BP}_{\text{ND}}$  in the substantia nigra ( $x$ -axis) versus scores on the QUIP-RS ( $y$ -axis) fit with a linear regression. A significant correlation between midbrain  $\text{BP}_{\text{ND}}$  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  $\text{BP}_{\text{ND}}$  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  $\text{D}_{2/3}$  receptor levels (Steeves et al., 2009; Payer et al., 2015), unaltered striatal  $\text{D}_1$  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  $\text{D}_{2/3}$  binding precedes, or emerges after, dopamine-related treatment. Preclinical models of addiction support the former hypothesis, where decreased ventral striatal  $\text{D}_{2/3}$  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  $\text{D}_2$  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  $\text{D}_{2/3}$  receptor levels in the nucleus accumbens/ventral striatum (Engber et al., 1993).

### The dorsal striatum and habitual behavior

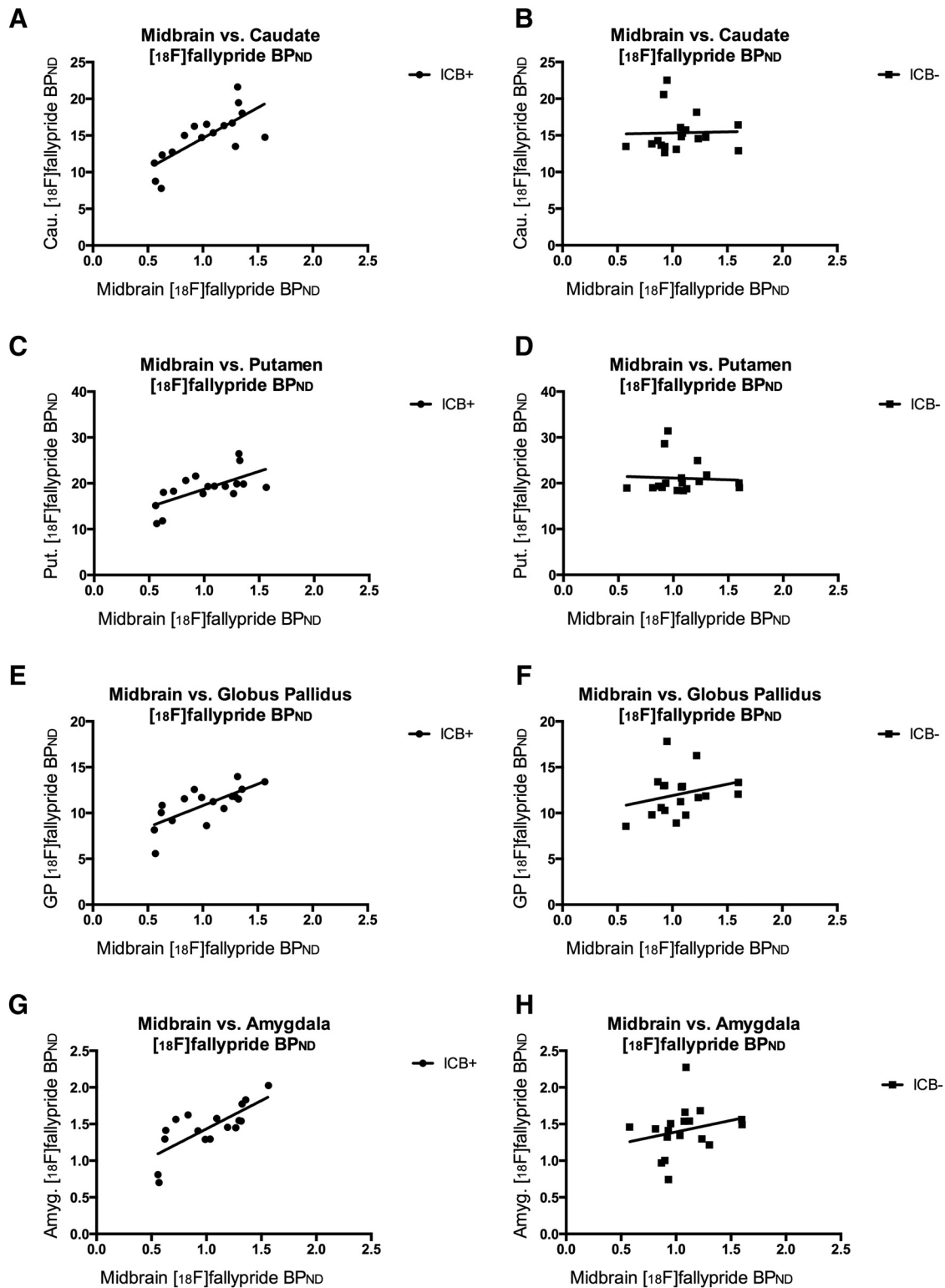
Previous studies in PD have not observed altered dorsal striatal  $\text{D}_{2/3}$   $\text{BP}_{\text{ND}}$  in relation to ICB status. Whereas the ventral striatum is associated with anticipation of future rewards and reward-related drug reinforcement, the dorsal striatum maintains compulsive habitual 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  $\text{D}_{2/3}$  receptor  $\text{BP}_{\text{ND}}$  occur after an action becomes habitual (Nader et al., 2006; Dalley et al., 2007). Dorsal striatal reductions in  $\text{D}_{2/3}$  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  $\text{D}_{2/3}$  receptors (associated with reward-related impulsivity) cause signaling changes that over time evolve into dorsal  $\text{D}_{2/3}$  reductions (linked to compulsive reward driven behavior). Together, we interpret reduced [ $^{18}\text{F}$ ]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  $\text{D}_{2/3}$   $\text{BP}_{\text{ND}}$  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 [ $^{18}\text{F}$ ]fallypride  $\text{BP}_{\text{ND}}$  and the severity of reward seeking behaviors (QUIP-RS), in ICB+ but not ICB- patients. This parallels a past [ $^{11}\text{C}$ ]-(+)-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  $\text{D}_{2/3}$  (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  $\text{D}_{2/3}$  receptors function as inhibitory autoreceptors at both axonal and somatodendritic areas, and the negative correlation between midbrain  $\text{D}_{2/3}$   $\text{BP}_{\text{ND}}$  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  $\text{D}_{2/3}$   $\text{BP}_{\text{ND}}$  and QUIP-RS scores would therefore appear to be unexpected. However, the total level of ventral midbrain  $\text{D}_{2/3}$  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 [<sup>18</sup>F]fallypride binding potential versus [<sup>18</sup>F]fallypride binding potential in other regions. **A–G**, Scatterplots of midbrain BP<sub>ND</sub> (*x*-axis) versus BP<sub>ND</sub> in regions where a significant group × BP<sub>ND</sub> 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<sub>ND</sub> 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 × BP<sub>ND</sub> 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 [ $^{11}\text{C}$ ]FLB-457 study was performed following pramipexole administration, which has been shown to produce significant changes in ventral midbrain dopamine  $D_{2/3}$   $\text{BP}_{\text{ND}}$  that were not present in the ventral striatum (Ray et al., 2012; Deuschländer 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  $D_{2/3}$   $\text{BP}_{\text{ND}}$  and the caudate, putamen, globus pallidus, and amygdala significantly differ between groups. Using [ $^{18}\text{F}$ ]fallypride, significant positive  $\text{BP}_{\text{ND}}$  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, denervation

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  $\text{BP}_{\text{ND}}$  differences are manifestations of ICB-related distinctions in  $D_{2/3}$  receptor expression. Changes in apparent [ $^{18}\text{F}$ ]fallypride  $\text{BP}_{\text{ND}}$ s can also be produced by differences in extracellular dopamine levels, which compete with [ $^{18}\text{F}$ ]fallypride in binding to  $D_{2/3}$  receptors. However, previous studies examining the relationship between shifts in striatal extracellular dopamine levels and changes in [ $^{11}\text{C}$ ]raclopride binding have indicated a 44:1 ratio, where a 44% increase in extracellular dopamine produces a 1% decrease in  $\text{BP}_{\text{ND}}$  (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 [ $^{18}\text{F}$ ]fallypride  $\text{BP}_{\text{ND}}$  would require an ~750% higher extracellular dopamine level. Therefore, it is unlikely that the entire difference in ventral striatal [ $^{18}\text{F}$ ]fallypride  $\text{BP}_{\text{ND}}$  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 [ $^{18}\text{F}$ ]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  $\text{BP}_{\text{ND}}$ , as well as a relationship between midbrain  $\text{BP}_{\text{ND}}$  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 [ $^{18}\text{F}$ ]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.



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