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[^{18}F]fallypride characterization of striatal and extrastriatal $D_{2/3}$ receptors in Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is characterized by widespread degeneration of monoaminergic (especially dopaminergic) networks, manifesting with a number of both motor and non-motor symptoms. Regional alterations to dopamine $D_{2/3}$ receptors in PD patients are documented in striatal and some extrastriatal areas, and medications that target $D_{2/3}$ receptors can improve motor and non-motor symptoms. However, data regarding the combined pattern of $D_{2/3}$ receptor binding in both striatal and extrastriatal regions in PD are limited. We studied 35 PD patients off-medication and 31 age- and sex-matched healthy controls (HCs) using PET imaging with [^{18}F] fallypride, a high affinity $D_{2/3}$ receptor ligand, to measure striatal and extrastriatal $D_{2/3}$ nondisplaceable binding potential (BP_{ND}). PD patients completed PET imaging in the off medication state, and motor severity was concurrently assessed. Voxel-wise evaluation between groups revealed significant BP_{ND} reductions in PD patients in striatal and several extrastriatal regions, including the locus coeruleus and mesotemporal cortex. A region-of-interest (ROI) based approach quantified differences in dopamine $D_{2/3}$ receptors, where reduced BP_{ND} was noted in the globus pallidus, caudate, amygdala, hippocampus, ventral midbrain, and thalamus of PD patients relative to HC subjects. Motor severity positively correlated with $D_{2/3}$ receptor density in the putamen and globus pallidus. These findings support the hypothesis that abnormal $D_{2/3}$ expression occurs in regions related to both the motor and non-motor symptoms of PD, including areas richly invested with noradrenergic neurons.

1.1. Introduction

D_2 and D_3 receptors are expressed in high abundance in the striatum and ventral midbrain, and in lower levels in certain limbic and cortical regions (Gurevich and Joyce, 1999). Dopamine agonists that preferentially target these $D_{2/3}$ receptors improve motor symptoms in Parkinson's disease (PD) (Shannon et al., 1997), and have been suggested to also reduce certain non-motor symptoms, such as depression (Barone et al., 2006). Early in the course of PD, striatal $D_{2/3}$ binding potential (BP_{ND}) increases (Rinne et al., 1993; Rinne et al., 1995), potentially due to reduced receptor occupancy by endogenous dopamine, or post-synaptic sensitization induced increases in receptor expression (Knudsen et al., 2004). This upregulation of $D_{2/3}$ receptors is more extensive in the putamen than the caudate nucleus, consistent with the earlier and more prominent dopaminergic denervation of the putamen in PD (Gibb and Lees, 1991). With longer disease duration, $D_{2/3}$ expression diminishes throughout the striatum (Antonini et al., 1997). Less attention has been devoted to the effects of PD on extrastriatal $D_{2/3}$ expression. Some studies have reported a decrease in $D_{2/3}$ BP_{ND} later in the course of PD, including in the medial thalamus as well as anterior cingulate, inferior temporal, and ventromedial/dorsolateral prefrontal cortices (Kaasinen et al., 2003; Kaasinen et al., 2000; Ko et al., 2013).

Abbreviations: BP_{ND}, Binding potential (nondisplaceable); CES-D, Center for Epidemiologic Studies Depression Scale; LEDD, Levodopa Daily Dose; MDS-UPDRS, Movement Disorders Society-United Parkinson's disease Rating Scale; MoCA, Montreal Cognitive Assessment; HC, Healthy controls; PD, Parkinson's disease; PET, Positron emission tomography; ROI, Region of Interest

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Due to intrinsic differences in properties of SPECT and PET radioligands, few studies have been capable of concurrently examining striatal and extrastriatal $D_{2/3}$ binding in PD patients. The fact that most radioligands are best suited towards quantitation of binding in striatal or extrastriatal sites, but not both at the same time, makes a comprehensive understanding of the relative magnitude of PD-induced $D_{2/3}$ BP_{ND} changes across areas compared to healthy subjects difficult to capture. [^{11}C]raclopride is effective at measuring striatal (and to an extent thalamic) $D_{2/3}$ levels but cannot provide reliable estimates in most extrastriatal areas, while [^{11}C]FLB-457 can assess extrastriatal regions but is not able to quantify binding in the striatum (as it does not reach equilibrium in a reasonable timeframe) (Farde et al., 1997; Hall et al., 1989). The D_3 preferring ligand [^{11}C]-(+)-PHNO has infrequently been used to estimate dopamine receptor binding in PD (Boileau et al., 2009; Payer et al., 2015), but cannot provide full characterization of limbic and cortical regions (Egerton et al., 2010).

[^{18}F]fallypride ((*S*)-N-[(1 allyl-2-pyrrolidinyl)methyl]-5-(3[18F]fluoropropyl)-2,3-dimethoxybenzamide) is a high-affinity $D_{2/3}$ radioligand that can provide accurate estimates of binding in both striatal and extrastriatal regions, allowing for concurrent estimation of dopamine $D_{2/3}$ receptor levels (i.e. nondisplaceable binding potential, BP_{ND}) throughout the brain (Kessler et al., 2000; Mukherjee et al., 2002). Furthermore, [^{18}F]fallypride has been successfully applied in a PD cohort (Deutschlander et al., 2016). We examined regional [^{18}F]fallypride binding in a large cohort of PD patients and age-matched healthy control (HC) subjects in order to simultaneously determine differences in striatal and extrastriatal $D_{2/3}$ BP_{ND}, with the goal of providing cortical and subcortical binding potentials that can be directly compared. As a secondary objective, we assessed if $D_{2/3}$ BP_{ND} reflected motor severity in PD patients.

1.2. Methods

1.2.1. Participants

PD participants were recruited from the Movement Disorders Clinic at Vanderbilt University Medical Center. All met UK Brain Bank criteria for a diagnosis of PD and were prescribed levodopa and DA agonist medications (including pramipexole, ropinirole, and rotigotine) for relief of motor symptoms. Daily doses of dopamine replacement therapy were converted to levodopa equivalent dose (Tomlinson et al., 2010). Patients were excluded if they had an implanted deep brain stimulator, received antipsychotic treatments, suffered from comorbid neuropsychiatric, cerebrovascular, or cardiovascular disease, could not tolerate a brain MRI/PET study, or dopaminergic medication withdrawal. HC subjects (Dang et al., 2017; Dang et al., 2016) did not have a history of psychiatric illness, head trauma, substance abuse, diabetes, or medical condition that precluded MRI collection, nor could they use tobacco. No participants took psychostimulant or psychotropic medications (with an exception for occasional use of benzodiazepines as sleep medication) over the preceding 6 months, and did not consume excessive alcohol. Urine drug tests were administered to all participants to ensure the absence of amphetamine, barbiturates, cocaine, marijuana, or opiates.

A neurologic exam was performed on all participants, in order to exclude parkinsonism in HC subjects. PD patients completed part II of the Movement Disorders Society-United Parkinson's disease Rating Scale (MDS-UPDRS) (a self-reported assessment of the impact of PD on activities of daily living), and part III (an assessment of motor function in PD) in the Off-medication condition (Goetz et al., 2008; Weintraub et al., 2012). Dopamine medications were withheld for > 40 h prior to PET imaging for DA agonists and > 16 h for levodopa prior to PET imaging (the half-life of levodopa, ropinirole, and pramipexole are approximately 1.5, 6, and 8–12 h respectively (Bennett Jr and Piercey, 1999; Fabbrini et al., 1987; Tompson and Oliver-Willwong, 2009; Wright et al., 1997). Cognitive screening was performed using the Montreal Cognitive Assessment (MoCA) to rule out patients with frank dementia (Nasreddine et al., 2005), requiring a score of at least 22. In PD patients, depression was screened using the Center for Epidemiologic Studies Depression Scale Revised (CESD-R) (Radloff, 1977). The presence of medication-induced impulsive compulsive behaviors (ICBs) as a potential confounding factor was also assessed using a semi-structured interview with patient and partner.

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

Variables	PD	HC	*p*-Value
N	35	31	
Sex (M/F)	24/11	21/10	0.94
Age (years)	61.8 ± 8.5	58.1 ± 11.3	0.17
Disease duration (years)	5.9 ± 3.9	n/a	–
CES-D	15.7 ± 8.7	n/a	–
Laterality score (− = left worse, + = right worse)	−2.45 ± 10.7	n/a	–
Left worse/right worse (individual)	22/13		
MDS-UPDRS			
Part II	21.8 ± 7.7	n/a	–
Part III (OFF)	30.0 ± 11.1	n/a	–
Dopamine replacement therapy			
Total LEDD (mg/day)	632.7 ± 418.7	n/a	–
Agonist single dose equivalent (mg/day)	103.9 ± 71.6	n/a	–

Data are shown as mean ± standard deviation.
MDS-UPDRS Part III conducted off medication (36 h for DAgonist and 16 for LDOPA).
PD: Parkinson's Disease.
AMNART: American version of the National Adult Reading Test.
CES-D: Center for Epidemiologic Studies Depression Scale.
MDS-UPDRS: Movement Disorders Society-United Parkinsons Disease Rating Scale.
BIS: Barratt Impulsivity Scale.
LEDD: Levodopa Daily Dose.

Demographic and clinical features for PD patients (n = 35), as well as HC subjects (n = 31) are presented in Table 1. Both groups had a similar average age and sex distribution. The side of symptom severity (both onset and based on motor testing) was more prominent in the left hemi-body of PD patients, who expressed moderate PD progression with an average disease duration of 5.9 ± 3.9 years. Of this cohort, 17 had symptoms of Impulsive Compulsive Behaviors.

Written informed consent was obtained from all subjects, and the study was performed in accordance with the Institutional Review Board at Vanderbilt University, adhering to the ethical standards stipulated by the Declaration of Helsinki and its amendments.

1.2.2. Magnetic resonance imaging

MRI scans were completed prior to PET scans in order to provide high-resolution structural delineation. Both PD and HC subjects were scanned at 3.0T (Philips, Best, The Netherlands) using body coil transmission and 8-channel SENSE reception. All underwent a T_1-weighted high-resolution anatomical scan (MPRAGE; spatial resolution = 1 × 1 × 1 mm^3; TR/TE = 8.9/4.6 ms).

1.2.3. Fallypride PET data acquisition

[^{18}F]fallypride was synthesized in the radiochemistry laboratory consistent with the synthesis and quality control procedures outlined by US Food and Drug Administration INDs 47,245 and 120,035. 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 [^{18}F] fallypride (specific activity > 3000 Ci/mmol). CT scans were collected prior to each of the three emissions scans for the purpose of attenuation correction. Together, the scans lasted approximately 3.5 h with two breaks of 15–20 min (beginning approximately 70 min and 135 min after the beginning of the scan, respectively) included for patient